2025 Gynecological Cancers SPORE Investigators Meeting

Oct. 16 & 17, 2025

OU Health | Stephenson Cancer Center
The UNIVERSITY of OKLAHOMA

OU Health Stephenson Cancer Center | 800 NE 10th St., Room 5058, OKC, OK 73104

This event is co-sponsored by the Translational Research Program of the Division of Cancer Treatment and Diagnosis at the National Cancer Institute (NCI) and OU Health Stephenson Cancer Center.

Route 66 Endometrial Cancer SPORE

OU Health | Stephenson Cancer Center
The UNIVERSITY of OKLAHOMA

2025 Gyn SPORE Investigators Meeting Agenda – in Brief

Day 1: Thursday, October 16, 2025

7:30 – 8:15 am	Breakfast & Registration
8:15 – 8:20 am	Logistics
8:20 – 8:35 am	Welcome
8:35 – 8:45 am	Report on the Status of the GYN Cancers SPORE portfolio
8:45 – 9:55 am	**Session 1:** Overview of Gynecologic Cancer SPOREs
9:55 – 10:05 am	Break
10:05 – 10:50 am	**Special Talk**
10:50 – 12:30 pm	**Session 2:** Artificial Intelligence and New Technology
12:30 – 1:30 pm	Lunch and Poster Session
1:30 – 2:30 pm	**Working Group 1**: Sharing Novel Technologies
2:30 – 3:50 pm	**Session 3**: Tumor Biology, Early Detection, and Prevention
3:50 – 4:00 pm	Break
4:00 – 4:20 pm	**Special Session**: Patient Advocates
4:20 – 4:50 pm	**Session 4**: Early-Stage Investigators
6:00 – 8:30 pm	Evening Reception

Day 2: Friday, October 17, 2025

8:00 – 9:00 am	Breakfast
9:00 – 10:30 am	**Session 5:** Combination Therapies and Immunotherapy
10:30 – 10:50 am	Investigators Transitioning to Endometrial Cancer Research
10:50 – 11:00 am	Break
11:00 – 12:00 pm	**Working Group 2**: Optimizing time to activation of clinical trials
12:00 – 12:10 pm	Meeting Summary & Future Directions
12:10 – 12:15 pm	Concluding Remarks & Adjournment
12:15 – 1:15 pm	Lunch to go

Route 66 Endometrial Cancer SPORE

OU Health | Stephenson Cancer Center
The UNIVERSITY of OKLAHOMA

2025 Gyn SPORE Investigators Meeting Agenda

October 16–17, 2025
800 NE 10th St, 5th Floor Conference Room, Oklahoma City, OK 73104

Meeting website: https://www.ouhealth.com/stephenson-cancer-center/cancer-research/cancer-shared-resources-services/research-conferences-events/2025-gynecological-cancers-spore-investigators-m

Virtual link:
https://oklahoma.zoom.us/j/92806356058?pwd=13GhX7HpoSEZAAmzlp7fV5rENpHxsJ.1

Meeting ID: 928 0635 6058
Passcode: 51243077

Agenda times are in CST.

Day 1: Thursday, October 16, 2025

7:30 – 8:15 am	Breakfast & Registration	
8:15 – 8:20 am	Logistics	Doris M. Benbrook, Ph.D.
8:20 – 8:35 am	Welcome	Toby T. Hecht, Ph.D.
8:35 – 8:45 am	Report on the Status of the GYN Cancers SPORE portfolio	Naveena Basa Janakiram, Ph.D.

Session 1: Overview of Gynecologic Cancer SPOREs

Chair – Naveena Basa Janakiram, Ph.D.

8:45 – 8:55 am	**Kimberly Leslie, M.D.**	University of New Mexico (Route 66)
8:55 – 9:05 am	**Tzyy-Choou Wu, M.D., Ph.D., M.P.H.**	Johns Hopkins University
9:05 – 9:15 am	**Scott H. Kaufmann, M.D., Ph.D.**	Mayo Clinic
9:15 – 9:25 am	**Anil Sood, M.D.**	MD Anderson Cancer Center
9:25 – 9:35 am	**Kirsten Moysich, Ph.D.**	Roswell/University of Chicago
9:35 – 9:45 am	**Ronald J. Buckanovich, M.D., Ph.D.**	University of Pittsburgh
9:45 – 9:55 am	**Ie-Ming Shih, M.D., Ph.D.**	Johns Hopkins University/UPenn

9:55 – 10:05 am Break

Special Talk

Introduction by Scott H. Kaufmann, M.D., Ph.D.

10:05 – 10:50 am **Fergus Couch, Ph.D.** Mayo Clinic
"Comprehensive functional analysis of ovarian cancer susceptibility genes at the nucleotide level"

Session 2: Artificial Intelligence and New Technology

Moderators – Anil Sood, M.D., Ph.D. and Ronald J. Buckanovich, M.D., Ph.D.

10:50 – 11:10 am **Han Liang, Ph.D.** MD Anderson Cancer Center
"Computational algorithms, bioinformatics tools"

11:10 – 11:30 am **Rikki Cannioto, Ph.D., Ed.D., M.S.** Roswell Park/UIC
"Leveraging two image-based technologies to unravel the obesity paradox and identify novel prognostic factors in epithelial ovarian cancer"

11:30 – 11:50 am **Mara Steinkamp, Ph.D.** University of New Mexico (Route 66)
"Humanized mouse models"

11:50 – 12:10 pm **Nagarajan Kannan, Ph.D., M.S.** Mayo Clinic
"Lessons from studies of normal Fallopian tube organoid biology and applications of cellular barcoding technology"

12:10 – 12:30 pm **Ie-Ming Shih, M.D., Ph.D.** Johns Hopkins University
"The Fallopian Tube Precancer Atlas"

12:30 – 1:30 pm Lunch and Poster Session

Working Group 1

Moderators – Kirsten Moysich, Ph.D. and Ronald J. Buckanovich, M.D., Ph.D.

1:30 – 2:30 pm **Sharing Novel Technologies**

Session 3: Tumor Biology, Early Detection, and Prevention

Moderators – Jamie Bakkum-Gamez, M.D. and Doris M. Benbrook, Ph.D.

2:30 – 2:50 pm **Kimberly Levinson, M.D., M.P.H.** Johns Hopkins University
"Therapeutic HPV vaccination in patients with HPV16-positive low-grade cervical dysplasia"

2:50 – 3:10 pm **Doris M. Benbrook, Ph.D.** University of Oklahoma HSC (Route 66)
"Targeting endometrial cancer vulnerabilities"

3:10 – 3:30 pm **Siddhartha Yadav, M.B.B.S., M.D.** Mayo Clinic
"Genomics of hereditary breast and ovarian cancer in the South Asian population"

3:30 – 3:50 pm **Nadine Hempel, Ph.D.** University of Pittsburgh
"Cancer metastasis"

3:50 – 4:00 pm Break

Special Session: Patient Advocates

Introductions by Doris M. Benbrook, Ph.D.

4:00 – 4:10 pm Katie Keyser
4:10 – 4:20 pm Diana Lasswell

Session 4: Early-Stage Investigators

Moderators – Nadine Hempel, Ph.D. and Kimberly Levinson, M.D., M.P.H.

4:20 – 4:30 pm Rajani Rai, Ph.D., CEP, University of Oklahoma (Route 66)
4:30 – 4:40 pm Vishal Chandra, Ph.D., CEP, University of Oklahoma (Route 66)
4:40 – 4:50 pm Bethany Hannafon, Ph.D., Pilot Project University of Oklahoma (Route 66)

Evening Reception

Stephenson Cancer Center – First Floor

6:00 – 6:20 pm Opening Remarks – Robert Mannel, M.D.
Drinks and Networking
6:20 – 6:50 pm OK Pow Wow Club – Native American Dance Troupe
6:50 – 8:30 pm Dinner

Day 2: Friday, October 17, 2025

8:00 – 9:00 am Breakfast

Session 5: Combination Therapies and Immunotherapy

Moderators – Kimberly Leslie, M.D. and Scott H. Kaufmann, M.D., Ph.D.

9:00 – 9:20 am **Matthew Powell, M.D.** Washington University (Route 66)
"NRG Combination Immunotherapy Trials"

9:20 – 9:40 am **Arun Kanakkanthara, Ph.D.** Mayo Clinic

"PARPi/ALKi combinations for ovarian cancer"

9:40 – 10:10 am **Rugang Zhang, Ph.D.** MD Anderson Cancer Center
"Leveraging epigenetic vulnerabilities to overcome PARP inhibitor resistance induced by acidic tumor microenvironment"

10:10 – 10:30 am **Marion Curtis, Ph.D.** Mayo Clinic
"Cryptic antigens (PMID: 39970218, Science Advances 2025)"

10:30 – 10:50 am Investigators Transitioning to Endometrial Cancer Research

Moderators – Kimberly Leslie, M.D. and Scott H. Kaufmann, M.D., Ph.D.

10:30 – 10:40 pm Deirdre Hill, M.P.H., Ph.D., University of New Mexico
10:40 – 10:50 pm Xiang Xue, Ph.D. University of New Mexico (Route 66)

10:50 – 11:00 am Break

Working Group 2

Moderators – Andrea Hagemann, M.D., Danuta Kozbor, Ph.D.

11:00 – 12:00 pm **Optimizing time to activation of clinical trials**

12:00 – 12:10 pm **Meeting Summary & Future Directions** Anil Sood, M.D. and Doris M. Benbrook, Ph.D.

12:10 – 12:15 pm **Concluding Remarks & Adjournment** Naveena Basa Janakiram, Ph.D.

12:15 – 1:15 am Lunch to go

Day 1

Thursday, October 16, 2025

OU Health | Stephenson Cancer Center
The UNIVERSITY of OKLAHOMA

Naveena B. Janakiram, Ph.D.

Naveena B. Janakiram, PhD, serves as a Program Director at the Translational Research Program within the Division of Cancer Treatment and Diagnosis at the National Cancer Institute (NCI). She manages Specialized Programs of Research Excellence (SPOREs) focused on ovarian, endometrial, cervical, neuroendocrine and breast cancer and is also a member of the Uterine Serous Cancer and PDX Models Working Group. Dr. Janakiram earned her Ph.D. in Microbiology in India before moving to the University of Oklahoma Health Sciences Center (OUHSC) in Oklahoma City for postdoctoral research training. She later advanced to the position of Associate Professor in the Department of Medicine at the Stephenson Cancer Center at OUHSC. Over her 12 years of experience in translational research for drug development, Dr. Janakiram has developed scientific and technical expertise in colon, pancreatic, and ovarian cancers. Her specific focus has been on understanding the immune modulation, inflammation, and molecular changes that occur during the initiation and progression of cancer to identify specific immune cell functions and genes that serve as promising targets for drug development to inhibit tumor growth and spread. Additionally, her research has addressed the modulation of immune mechanisms related to T cells, NK cells, and NKT cells in the context of colon and pancreatic carcinogenesis. Dr. Janakiram has also worked as a Research Physiologist at the Walter Reed National Military Medical Center and as an Associate Professor in the Department of Surgery at the Uniformed Services University of Health Sciences in Bethesda. She has published over 55 peer-reviewed research articles and four book chapters.

REPORT ON THE STATUS OF THE GYN CANCERS SPORE PORTFOLIO

Naveena Basa Janakiram, Ph.D.

Program Director, Translational Science Program, DCTD, National Cancer Institute, NIH, Rockville, MD

Dr. Basa Janakiram will provide a brief overview of the SPORE program and present updates on the SPORE portfolio. Further, she will highlight the accomplishments that have emerged from the SPORE funding and the collaborative efforts of the Gyn Cancers SPORE investigators.

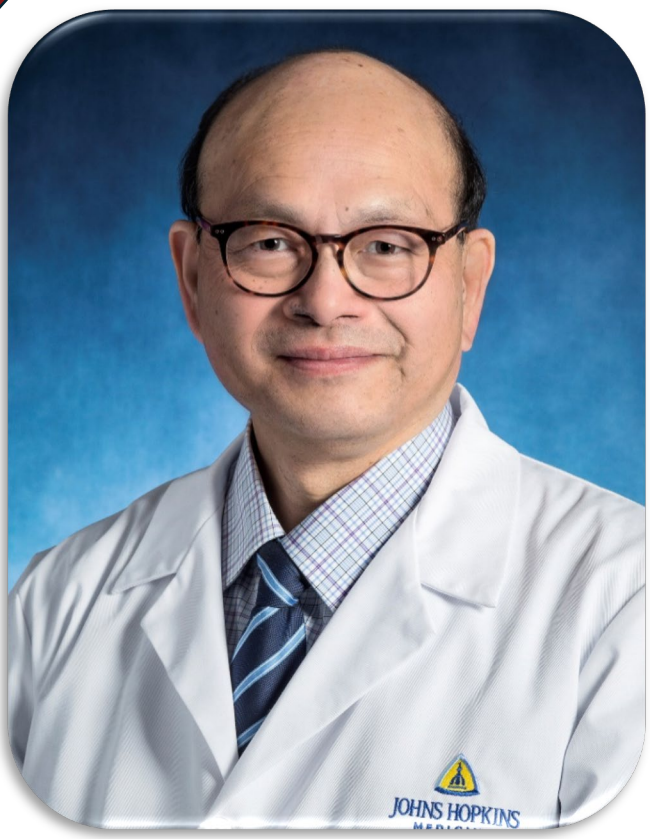
Session 1: Overview of Gynecologic Cancer SPOREs

Chair – Naveena Basa Janakiram, Ph.D.

8:45 – 8:55 am	**Kimberly Leslie, M.D.**	University of New Mexico (Route 66)
8:55 – 9:05 am	**Tzyy-Choou Wu, M.D., Ph.D., M.P.H.**	Johns Hopkins University
9:05 – 9:15 am	**Scott H. Kaufmann, M.D., Ph.D.**	Mayo Clinic
9:15 – 9:25 am	**Anil Sood, M.D.**	MD Anderson Cancer Center
9:25 – 9:35 am	**Kirsten Moysich, Ph.D.**	Roswell/University of Chicago
9:35 – 9:45 am	**Ronald J. Buckanovich, M.D., Ph.D.**	University of Pittsburgh
9:45 – 9:55 am	**Ie-Ming Shih, M.D., Ph.D.**	Johns Hopkins University/UPenn

Kimberly Leslie, M.D.

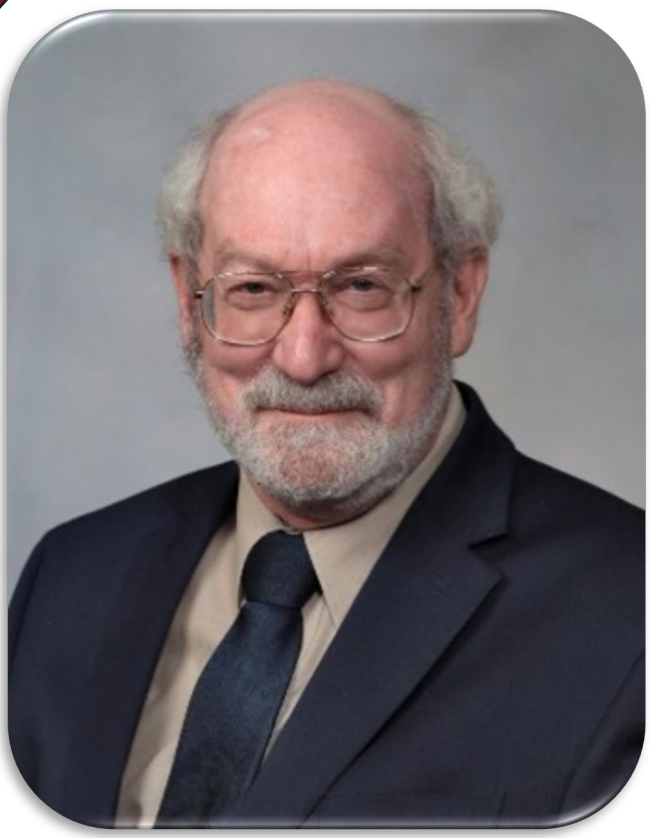
Kimberly K. Leslie, M.D. is Professor of Molecular Medicine and Director of Faculty Development at the University of New Mexico Comprehensive Cancer Center. She is MPI of the Route 66 Endometrial Cancer SPORE and PI of multiple additional federal grants including the newly awarded P01, Advancing Hormone Therapy for Endometrial Cancer. Dr. Leslie is an active physician scientist originally trained through the NIH Reproductive Scientist Development Program. She is Chair Emeritus of the University of Iowa Department of Obstetrics and Gynecology, a former American Board of Obstetrics and Gynecology Examiner, a member of multiple NIH study sections and a member of the NIH NICHD Council and the NIH Director's Council of Councils. Dr. Leslie has been continuously funded by NIH since 1991 for basic and translational research relating to the molecular mechanisms of diseases in the reproductive tract. Dr. Leslie's more than 170 publications include work in the field of oncology with an emphasis on preventing and improving the treatment of endometrial cancer through novel and personalized hormonal and targeted therapies.



Tzyy-Choou Wu, M.D., Ph.D., M.P.H.

Dr. T.-C. Wu is an internationally recognized leader in gynecologic pathology, viral oncogenesis, and cancer immunotherapy, with over three decades of pioneering research in human papillomavirus (HPV)-associated malignancies. He received his MD from the National Taiwan University College of Medicine, followed by an MPH in Epidemiology and a PhD in Molecular Virology from Johns Hopkins University. He completed residency and fellowship training in anatomic and gynecologic pathology at The Johns Hopkins Hospital and has been on the Johns Hopkins faculty since 1995, achieving the rank of full professor in 2003.

Since 2003, Dr. Wu has served as **Principal Investigator of the Johns Hopkins Cervical Cancer SPORE (Specialized Program of Research Excellence)**, leading multidisciplinary teams in translational research to improve prevention, detection, and treatment of HPV-associated cancers. As Director of Gynecologic Pathology at Johns Hopkins since 2016, he has guided research programs focused on the molecular pathogenesis of gynecologic malignancies, pioneering DNA- and RNA-based therapeutic cancer vaccines targeting HPV oncogenes and advancing several of these strategies toward early-phase clinical trials. His work has also investigated tumor immune evasion, biomarker discovery, and personalized immunotherapy approaches.



Scott H. Kaufmann, M.D., Ph.D.

Scott H. Kaufmann, M.D., Ph.D., is Professor Pharmacology and Medicine in the Mayo Clinic College of Medicine and Science and the Helen C. Levitt Professor of the Mayo Foundation for Education and Research. He is a co-leader of the Novel Therapeutics and Therapeutic Modalities Program of the Mayo Clinic Comprehensive Cancer Center and Associate Director of the Medical Scientist (M.D.-Ph.D.) Training Program.

Dr. Kaufmann and his team conduct research designed to improve the therapy of ovarian cancer, with a particular focus on understanding of how anticancer treatments kill susceptible cells and what goes awry to make cancer cells resistant to targeted therapies. Among the targeted agents his lab studies are TOP1 poisons, inhibitors of DNA damage response pathway components (PARP1, ATR, CHK1, and WEE1), and BH3 mimetics. He leads the Mayo Clinic Specialized Program of Research Excellence (SPORE) in Ovarian Cancer, a team science grant investigating novel strategies for improving prevention, detection and treatment of ovarian cancer. His work on ovarian cancer has also been funded by additional grants from the National Cancer Institute, Ovarian Cancer Research Alliance, Stand Up to Cancer, and the Department of Defense Congressionally Mandated Research Program. This work has led to numerous articles, which have been published in *Cell*, *Nature*, *Molecular Cancer* and *Nature Communications*, among others. In addition, he is an editorial board member for several journals, including *Clinical Cancer Research* and *Molecular Cancer Research*.

Anil Sood, M.D.

Dr. Anil K. Sood is Professor in the Department of Gynecologic Oncology and Reproductive Medicine at the UT MD Anderson Cancer Center. He serves as Director of the multi-disciplinary Blanton-Davis Ovarian Cancer Research Program, and co-lead of the Ovarian Cancer Moon Shot Program.

Dr. Sood earned his medical degree from the University of North Carolina at Chapel Hill. His research focuses on understanding human cancer biology and translating laboratory discoveries into novel therapeutics. His team has made seminal contributions in tumor microenvironment, nanomedicine, and the neuroendocrine regulation of cancer. He has received recognition for his research accomplishments including the Hunter Award, and the GCF/Claudia Cohen Research Foundation Prize for Outstanding Gynecologic Cancer Researcher. He is an elected member of the American Society for Clinical Investigation (ASCI), the American Association for the Advancement of Science (AAAS), and the Association of American Physicians (AAP). Dr. Sood was selected as an American Cancer Society Research Professor in 2017 and was elected to the National Academy of Medicine (NAM) in 2021.

Kirsten Moysich, Ph.D.

Dr. Moysich joined the staff of Roswell Park Comprehensive Cancer Center in 1998 and was appointed as Professor of Oncology and Full Member in the Department of Cancer Prevention and Control in 2009. She also serves as Professor and Academic Program Chair, Department of Cancer Pathology and Prevention and Professor, Department of Social and Preventive Medicine at the State University of New York at Buffalo. Dr. Moysich earned her doctoral degree in Epidemiology and Community Health and completed a postdoctoral fellowship in Social and Preventative Medicine at SUNY Buffalo.

Dr. Moysich has authored or co-authored more than 340 peer-reviewed journal publications. She is an ad-hoc reviewer for more than 30 journals and has participated in over 50 local and national study sections since 2003. Dr. Moysich served and serves on numerous national and international advisory committees, including the Scientific Advisory Board for the Sister Study, National Institute of Environmental Health Sciences and the Scientific Advisory Board, Exposure and Human Health Committee, U.S. Environmental Protection Agency. She is an active member of the Ovarian Cancer Association Consortium, where she held administrative leadership positions. Dr. Moysich has been continuously funded since her initial faculty appointment at Roswell Park in 1998 and currently serves as the contact MPI of the Roswell Park – University of Chicago Ovarian Cancer SPORE. In that role, she co-leads the Administrative Core, the Career Enhancement Program, the Developmental Research Program and Individual Research Project 4.

Ronald Buckanovich, M.D., Ph.D.

Ronald Buckanovich graduated from Cornell University in 1990 with a B.S. in Genetics and Biochemistry. He then completed the Medical Scientist Training Program and started his life-long study of ovarian cancer. He received his Ph.D. in 1996 from the Rockefeller University and his M.D. in 1998 from Cornell University. Dr. Buckanovich then went on to complete an Internal Medicine residency and a Hematology-Oncology fellowship at the Hospital of the University of Pennsylvania. During his fellowship he continued his research on ovarian cancer, identifying dozens of novel clinical targets and helped to develop a novel therapeutic to enhance tumor vaccine therapy. Dr. Buckanovich joined the University of Michigan as an Assistant Professor of Internal Medicine in 2006. There he identified a novel population of cancer stem-like cells (CSCs) which may be responsible for ovarian cancer metastasis, chemotherapy resistance and ultimately disease recurrence. His laboratory is now studying the factors which regulate these CSCs including regulators of asymmetric division and quiescence. His laboratory has identified two novel compounds which directly target cancer stem cells; one which blocks the ability of these cells to metastasize, and a second which selectively kills the cancer stem-like cells. Both of these drugs are now being developed for first in human clinical trials.

Ie-Ming Shih, M.D., Ph.D.

Dr. Ie-Ming Shih is the *Richard W. TeLinde* Distinguished Professor of Gynecologic Pathology in the Department of Gynecology and Obstetrics and is the director of the TeLinde inter-departmental gynecologic disease research program at the Johns Hopkins Medical Institutions. Dr. Shih also co-directs the *Women's Malignancy Group* at the *Sidney Kimmel Comprehensive Cancer Center* at Johns Hopkins. Dr. Shih completed his PhD study at the University of Pennsylvania before his clinical training at the Johns Hopkins Hospital. After completing a residency, clinical fellowship, and research fellowship at Hopkins, Dr. Shih became a faculty member there in 2000. His research focuses on exploring diagnostic and molecular landscapes and pathogenesis in different types of ovarian cancers. Dr. Shih currently serves as a senior editor of *Cancer Research*. He is also an editorial member of the current *World Health Organization (WHO) Classification of Female Genital Tumors*. He was the recipient of the *Rosalind Franklin Prize for Excellence in Ovarian Cancer*.

Special Talk

Fergus Couch, Ph.D.

OU Health | Stephenson Cancer Center
The UNIVERSITY of OKLAHOMA

Fergus Couch, Ph.D.

Fergus Couch is the Zbigniew and Anna M. Scheller Professor of Medical Research and Chair of the Division of Experimental Pathology and Laboratory Medicine at the Mayo Clinic. Dr. Couch has over 650 publications with an H-index of 114 and a D-index of 137 relating primarily to the clinical characterization of inherited genetic variants in cancer susceptibility genes. He is the director of the Mayo Clinic Breast Cancer Registry and a founder and contributor to the CIMBA and BCAC consortia that have identified common genetic variants associated with breast cancer risk and developed polygenic risk scores for breast cancer risk assessment. He is the founder of the CARRIERS study that established population-based risks of breast cancer for variants in cancer predisposition genes. He is also a co-founder of the ENIGMA consortium and has focused on the use of functional studies for classification of variants of uncertain significance (VUS) in cancer predisposition genes including recent large CRISPR/cas9 saturation genome editing studies. He is also the co-leader of the NIH/ClinGen Hereditary Breast, Ovarian and Pancreatic (HBOP) cancer variant curation expert panel (VCEP) for cancer predisposition genes. He works closely with many collaborators in academia and industry. He holds several grants, including an R35 outstanding investigator award from the National Cancer Institute, and has received a number of awards in recognition of his work including the Mayo Clinic Distinguished Investigator Award, the AACR Outstanding Investigator Award for Breast Cancer Research, the Basser Global Prize and the Brinker Award for Basic Science.

Session 2: Artificial Intelligence and New Technology

Moderators – Anil Sood, M.D., Ph.D. and Ronald J. Buckanovich, M.D., Ph.D.

Han Liang, Ph.D.

MD Anderson Cancer Center

10:50 – 11:10 am

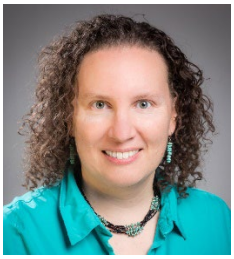
"Computational algorithms, bioinformatics tools"

Rikki Cannioto, Ph.D., Ed.D., M.S.

Roswell Park/UIC

11:10 – 11:30 am

"Leveraging standard-of-care CT scans and immune biomarkers to identify body composition phenotypes predictive of epithelial ovarian cancer survival"



Mara Steinkamp, Ph.D.

University of New Mexico (Route 66)

11:30 – 11:50 am

"Humanized mouse models"

Nagarajan Kannan, Ph.D., M.S.

Mayo Clinic

11:50 – 12:10 pm

"Lessons from studies of normal Fallopian tube organoid biology and applications of cellular barcoding technology"

Ie-Ming Shih, M.D., Ph.D.

Johns Hopkins University

12:10 – 12:30 pm

"The Fallopian Tube Precancer Atlas"

LEVERAGING AI AND BIG DATA TO ADVANCE OVARIAN CANCER RESEARCH

Han Liang, Ph.D.

Cancer omics data have been generated at an unprecedented pace, yet translating this wealth of information into meaningful biomedical insights remains a major challenge. I will highlight our recent work to develop an AI-driven chatbot that enables frictionless bioinformatics analysis of big cancer genomics data, moving us toward a data-value–driven ecosystem.

LEVERAGING TWO IMAGE-BASED TECHNOLOGIES TO UNRAVEL THE OBESITY PARADOX AND IDENTIFY NOVEL PROGNOSTIC FACTORS IN EPITHELIAL OVARIAN CANCER

Rikki Cannioto[1*] Gyorgy Paragh[2], Scott I. Abrams[3], Kirsten Moysich[1], Kunle Odunsi[4], Joseph Hanson[5], Hans Minderman[5], Orla Maguire[5]

[1]Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY

[2]Department of Dermatology, Roswell Park Comprehensive Cancer Center, Buffalo, NY

[3]Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY

[4]Medicine and Biological Sciences Division, University of Chicago Medicine Comprehensive Cancer Center, Hyde Park, Chicago, IL

[5]Flow & Immune Analysis Shared Resource, Roswell Park Comprehensive Cancer Center, Buffalo, NY

A fundamental conundrum regarding our understanding of how obesity impacts anti-tumor immunity and cancer outcomes currently exists. Preclinical evidence from a variety of animal models suggests obesity disrupts host homeostasis and promotes tumor progression, in part, through metabolic and immunologic dysregulation. Yet, epidemiological evidence for several cancer types suggests obesity is linked with improved survival or improved immunotherapy outcomes (an obesity paradox or an obesity-immunotherapy paradox). In epithelial ovarian cancer (EOC), the association of BMI-defined obesity and CT-assessed body composition at diagnosis with survival remains poorly understood, with three recent meta-analyses suggesting there is either no association of excess adiposity with EOC mortality or there is an obesity paradox. Importantly, there are currently no standard metrics for defining 'obesity' or interpreting risk based on CT-assessed body composition. Moreover, most EOC patients do not experience an effective response to immunotherapy and comprehensive multiplexed immunofluorescent characterization of the tumor immune microenvironment (TIME) remains rather preliminary. Thus, optimal patterns of immune infiltration for improved EOC survival outcomes have not been well-established in the extant literature and there is limited data to suggest that body composition is associated with anti-tumor immunity in patients diagnosed with EOC or other cancers. To address these fundamental gaps in knowledge, we initiated the Body Composition and Epithelial Ovarian Cancer Survival Study (BComES) to disentangle the obesity-paradox in EOC using CT-based body composition assessment. We quantified four independent tissue depots and defined associations of each depot with EOC outcomes using several epidemiological and biostatistical approaches including machine learning. This work shows that when appropriately considering muscle mass, there is no evidence of an obesity paradox and excess adiposity is consistently associated with poor survival in EOC. Building off this work, we next initiated several pilot studies to determine whether optimal versus risk body composition phenotypes were associated with circulating metabolomic and immune biomarkers and immune cell abundance in the TIME. Most recently, our pilot work using the cutting-edge PhenoCycler Fusion platform and a 15-plex immunofluorescence panel to interrogate 50 whole tumor sections suggests that body composition at diagnosis is associated with immune cell abundance in the EOC TIME. Today's talk will summarize this body of work which has uncovered and externally validated a novel Body Composition Index and a previously unknown macrophage which are both independent predictors of EOC survival.

DEVELOPING AUTOLOGOUS HUMANIZED ENDOMETRIAL CANCER PDX TO MODEL PATIENT IMMUNE RESPONSES

Mara P. Steinkamp

The clinical success of immunotherapies combined with chemotherapy for the treatment of endometrial cancer opens up new avenues of therapeutic exploration. To optimize immunotherapies, there is a need for preclinical animal models that better represent a patient's immune response. As part of the multi-institutional collaboration Route 66 Endometrial Cancer SPORE, our team has developed innovative patient-derived models with autologous immune components from both mismatch repair deficient and proficient endometrial cancer cases.

Tumor tissue collected during surgery is used to generate patient-derived 3D organoids (PDOs) and xenografts (PDXs). Matched blood samples provide erythroid progenitors, which are reprogrammed into induced pluripotent stem cells (iPSCs). These iPSC clones are then differentiated into hematopoietic stem and progenitor cells (HSPCs) using a complex differentiation program based on embryonic development. The resulting HSPCs can be further differentiated into various immune cells for co-culture with PDOs or engrafted into immunocompromised mice bearing matched PDX tumors.

In the first year of this project, we have collected 12 matched sets of blood and tumor samples and established iPSC lines as well as PDO and PDX models of endometrial cancer. Co-culture of PDOs with iPSC-derived macrophages has revealed distinct tumor-immune interactions. Notably, organoid viability and treatment response differ when cultured with autologous vs allogeneic macrophages. Both autologous and allogeneic pro-tumor macrophages enhance organoid viability, but autologous anti-tumor macrophages appear to be less cytotoxic than allogeneic macrophages, highlighting the importance of autologous systems for evaluating therapeutic efficacy.

To extend these findings *in vivo*, iPSC-derived HSPCs and T cell progenitors have been engrafted into the NBSGW-HLA-A2/HHD strain of immunocompromised mice. These mice express the human HLA-A2* 2:01 to support human T cell maturation. Early results from intrahepatic neonatal engraftment has show promising human immune cell reconstitution, with human CD45+ cells detectable in peripheral blood. Implantation of matched PDX into these humanized mice establishes a renewable and reproducible autologous platform for testing immunotherapy regimens in a clinically relevant context.

We are currently testing the response of the anti-PD1 antibody, dostarlimab alone and in combination with chemotherapy in these models. Future studies in these models will examine immunotherapy resistance and tumor recurrence. Our autologous humanized models represent a significant step toward personalized immunotherapy testing in endometrial cancer.

PEG CELL IS A CANDIDATE CELL-OF-ORIGIN FOR HIGH-GRADE SEROUS OVARIAN CANCER

Nagarajan Kannan, Ph.D., M.S.

High-grade serous ovarian cancer (HGSOC) is the most common and lethal ovarian cancer, yet its cellular origins remain incompletely defined. To address this, we established a living organoid biobank of human fallopian tube tissue with more than 200 donors and generated the largest integrated molecular atlas of the fallopian tube epithelium to date. Using optimized culture protocols and multi-omic profiling, including single-cell RNA sequencing, chromatin accessibility (ATAC) analysis, proteomics, and secretomics, we defined epithelial cell states and their regulatory networks, including a rare multipotent epithelial subpopulation (cluster-5) with hybrid epithelial–mesenchymal features. Cluster-5 cells localized to basal epithelium and displayed transcriptional and proteomic similarity to mesenchyme-like HGSOC, suggesting they represent a potential cell-of-origin. Importantly, their identity is preserved in organoid models, enabling mechanistic interrogation and translational applications. This new resource establishes a foundation for understanding epithelial hierarchy and cancer susceptibility and provides a platform for the development of early detection and prevention strategies in HGSOC.

OVARIAN PRECANCEROUS ATLAS CONSORTIUM

Ie-Ming Shih[1], Ronny Drapkin[2]

[1]Johns Hopkins University, [2]University of Pennsylvania

Studying precancerous lesions is essential for improving early detection and prevention, particularly in aggressive cancers such as ovarian high-grade serous carcinoma (HGSC). JHU-PENN Ovarian SPORE proposes the Ovarian Precancerous Atlas Consortium (OPAC) and invites investigators from the Gyn SPORE community to participate. The updated paradigm regarding the origin of HGSC suggests that many HGSCs are derived from the fallopian tubes through a sequential tumor progression, starting from a p53 signature, followed by serous tubal intraepithelial lesion, serous tubal intraepithelial carcinoma (STIC), and ultimately HGSC, which later spreads to ovarian tissues and disseminates. Despite the biological and clinical significance of each of those precursor lesions yet to be elucidated, molecular and morphological correlative studies demonstrate unique features associated with individual precancerous lesions. Chromosomal instability, aneuploidy patterns, activation of specific cancer signaling pathways, and stromal/immune microenvironment contribute to tumor progression to HGSC. The knowledge gained thus far is transforming various aspects of ovarian cancer research and gynecological practice. Opportunistic salpingectomy prevents HGSC in average-risk women, and molecular analyses in routine liquid-based cervical Pap tests hold promise to detect STIC- and HGSC-related tissue biomarkers. The purpose of the proposed collaborative SPORE-OPAC study is to expand the pre-existing STIC repository at JHU/PENN, collect follow-up data, and establish a test for standardization in the diagnostic, early detection, risk stratification, and prevention of this devastating ovarian cancer.

Session 3: Tumor Biology, Early Detection, and Prevention

Moderators – Jamie Bakkum-Gamez, M.D. and Doris Benbrook, Ph.D.

Kimberly Levinson, M.D., M.P.H.

Johns Hopkins University

2:30 – 2:50 pm

“Therapeutic HPV vaccination in patients with HPV16-positive low-grade cervical dysplasia”

Doris M. Benbrook, Ph.D.

University of Oklahoma HSC (Route 66)

2:50 – 3:10 pm

“Targeting endometrial cancer vulnerabilities”

Siddhartha Yadav, M.B.B.S., M.D.

Mayo Clinic

3:10 – 3:30 pm

“Genomics of hereditary breast and ovarian cancer in the South Asian population”

Nadine Hempel, Ph.D.

University of Pittsburgh

3:30 – 3:50 pm

“Cancer metastasis”

ADVANCING HPV THERAPEUTIC VACCINATION

Kimberly Levinson[1], Rebecca Arend[2], Teresa Boitano[2], Warner Huh[2], TC Wu[1], Richard Roden[1]

[1]Johns Hopkins University, [2]University of Alabama

Over 5% of all cancers globally are caused by human papillomavirus. High risk human papillomavirus genotypes (hrHPV) are a necessary cause of 99% of all cervical cancer cases and drive a subset of other anogenital cancers. The most oncogenic genotypes, HPV16/18, cause approximately 70% of cervical cancer and 90% of other HPV-related anogenital cancers. While most hrHPV infections are asymptomatic and cleared, if infection persists, hrHPV-related precancers and cancers can develop. While the licensed HPV prophylactic vaccines target up to 7 hrHPV types, including types 16 and 18, they are only effective for the *prevention* of *new* HPV infections. Thus, further research is needed to address already-established infections, as nearly half of persistent (i.e., ≥ 6 months) HPV16 infections and a quarter of HPV18 infections progress to CIN2/3. Our group has developed two therapeutic DNA vaccines, pNGVL4aCRTE6E7L2 and pBI-11, that specifically target HPV16 and HPV16/18 respectively. Our group has employed several strategies to increase the immunogenicity of DNA vaccines and has begun enrolling in patients in clinical trials to evaluate these strategies. Here, Dr. Levinson will present an update on the current ongoing clinical trials and next steps towards advancing therapeutic HPV vaccination and elimination of established HPV infections.

TARGETING ENDOMETRIAL CANCER VULNERABILITIES.

Doris Mangiaracina Benbrook, PhD, Multi-PI, Route 66 Endometrial Cancer SPORE
Stephenson Cancer Center, University of Oklahoma, Health Sciences Campus

Background

The goal of our research team is to develop drugs for prevention and treatment of cancers without causing harmful side effects. We identified a compound called SHetA2 that kills cancer cells without harming healthy cells and found that it binds three heat shock 70 kDa proteins (HSP70s), mortalin, hsc70 and Grp78 encoded by the *HSPA* genes *HSPA9*, *HSPA8* and *HSPA5*. These proteins are over-expressed in cancer. The Cancer Genome Atlas (TCGA) data revealed that endometrial cancer has the highest frequencies of *HSPA9*, *HSPA8* and *HSPA5* mutations compared to all other cancers studied. HSP70s utilize ATP hydrolysis to fold newly synthesized and misfolded proteins and support their functions. Elevation of HSP70s in stressful conditions and cancer supports cell survival. Therefore, mortalin, hsc70 and Grp78 represent candidate vulnerabilities of endometrial cancer for development of experimental therapeutics.

Approach

The Route 66 Endometrial Cancer SPORE Project 1 Aim 1 is to identify mutation profiles associated with SHetA2 response and mechanism. In this study, we evaluated non-cancer cultures, as well as cell lines and ascites-derived spheroid cultures from multiple endometrial cancer types, histologies and p53 statuses for their sensitivities to SHetA2 in metabolic, molecular and cellular assays.

Results

SHetA2 differed from other HSP70 inhibitors by binding to the substrate binding domain instead of the ATPase binding domain of mortalin and prevented mortalin import into mitochondria and removal of its mitochondria localization sequence. Its disruption of mortalin/client protein complexes inhibited glycolysis down-stream of known SHetA2 sensitivity biomarkers in ovarian cancer ascites specimens, mitochondrial metabolism and fatty acid synthesis. SHetA2-induced mitochondrial damage caused release of cytochrome c and truncated AIF leading to apoptosis. Its interference with hsc70 sequestration of truncated AIF in the cytoplasm increased DNA damage and cell death. Excessive mitochondria-selective autophagy (mitophagy) also contributed to the mechanism of cell death. Non-cancerous cells resisted SHetA2 cytotoxicity in association with increased mitochondrial fusion and low-level autophagy. There was no association between the potency or efficacy of SHetA2 in 6 ascites-derived spheroid cultures from patients with endometrial cancer based on histology (endometrioid, serous, adenosarcoma) or *TP53* mutation status (wild type versus missense mutant).

Conclusions and Future Plans

HSP70 proteins in endometrial cancer cells represent a vulnerability that can be targeted with SHetA2 to cause cell death, while non-cancer cells exhibit resistance through natural cell survival pathway activities that are defective in cancer cells. Future research will include identifying and validating mutations and specific biomarkers in the ascites specimens and patient-derived xenografts that predict SHetA2 sensitivity and that can be used to screen for patients most likely to benefit from planned clinical trials with SHetA2-based therapies.

GENOMICS OF HEREDITARY BREAST AND OVARIAN CANCER IN THE SOUTH ASIAN POPULATION

Siddhartha Yadav, MD

Abstract

There is limited understanding of the differences in frequency of germline pathogenic variants in breast or ovarian cancer predisposition genes by race/ethnicity and its implications on cancer risk. Women of South Asian ancestry is a rapidly expanding population in the United States, but despite the size of this community, there remains a lack of comprehensive data regarding epidemiology of breast or ovarian cancer and the contribution of germline genetic factors to cancer riks.

The South Asian Regional Alliance for Hereditary Cancers (SARAH) was established to foster collaboration among leading institutions in India, Pakistan, Bangladesh, Nepal, and global partners to understand genetic predisposition to breast and ovarian cancer in the South Asian population. This consortium aims to generate robust, population-based estimates of hereditary cancer risk, establish the feasibility of large-scale germline sequencing efforts, and ultimately inform clinical guidelines tailored to South Asian populations. Preliminary work has demonstrated both the promise and challenges of multinational collaboration in this space, highlighting the importance of harmonized data collection, logistical coordination, and sustained follow-up. Building on these early efforts, the project is entering a critical phase with large-scale sequencing and case-control analyses underway. These initiatives will lay the groundwork for future studies, including expanded sequencing, outcome analyses, and the development of specific recommendations for genetic testing and risk-reducing interventions in this patient population.

Dr. Siddhartha Yadav will present early insights from this collaborative initiative, discuss the evolving landscape of hereditary breast and ovarian cancer research, and outline future directions aimed at reducing the global burden of hereditary cancers.

STRESS ADAPTATIONS DURING TRANSCOELOMIC METASTASIS

Nadine Hempel, PhD

Associate Professor of Medicine, Division of Malignant Hematology & Medical Oncology, University of Pittsburgh

Since the progression to metastatic disease represents the most lethal stage of ovarian cancer, our lab has focused on identifying novel tumor cell stress adaptations necessary for metastasis that may be unique to transcoelomic spread and can be harnessed for novel therapeutic interventions. We have established that high-grade serous ovarian cancer cells rapidly rewire their mitochondrial antioxidant status and consequential redox signaling during metastasis. Following on from our studies demonstrating the necessity for mitochondrial superoxide dismutase (SOD2) in regulating mitochondrial redox changes during metastatic progression, we recently turned our attention to the role of hydrogen peroxide (H_2O_2) as a novel signaling molecule in ovarian cancer. Manipulating mitochondrial sources of oxidants by genetic and pharmacologic means, we identified HER2 signaling as a novel target of mitochondrial redox signaling in cell culture models of anchorage-independence using an unbiased RNA sequencing screen. In validating these findings, we found that sublethal mitochondria-produced H_2O_2 was necessary for AKT signaling, the increase in HER2 protein expression observed in response to anchorage-independence, and the interaction of HER2 with EGFR. Moreover, pharmacologic inhibition of HER2 redox regulation using mitoQ synergized with Trastuzumab. Mechanistically, we find that cells cultured in anchorage-independent conditions displayed significant differences in cysteine oxidation compared to attached cells, as assessed by proteomics. This included disulfide-forming cysteines in critical functional regions of the extracellular domains of HER2 and EGRF. Of clinical importance, our data show for the first time that HER2 expression is susceptible to upregulation at the protein level in a mitochondrial redox-dependent manner in HGSOC and sets the stage to assess the heterogeneity in HER2 expression across tumor sites, including malignant ascites. This has the potential to delineate additional therapeutic windows for HER2 targeting, thus broadening the patient pool that could benefit from HER2-targeted therapies.

Special Session

Patient Advocates

Katie Keyser & Diana Lasswell

OU Health | Stephenson Cancer Center
The UNIVERSITY of OKLAHOMA

Session 4: Early-Stage Investigators

Moderators – Nadine Hempel, Ph.D. and Kimberly Levinson, M.D., M.P.H.

4:20 – 4:30 pm	Rajani Rai, Ph.D., CEP, University of Oklahoma (Route 66)
4:30 – 4:40 pm	Vishal Chandra, Ph.D., CEP, University of Oklahoma (Route 66)
4:40 – 4:50 pm	Bethany Hannafon, Ph.D., Pilot Project University of Oklahoma (Route 66)

TARGETING CHEMORESISTANCE IN OVARIAN CANCER

Dhanamjai Penta, Vishal Chandra, Lauren E Dockery, Rajani Rai

[1]Gynecologic Oncology Section, Obstetrics and Gynecology Department, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA.

Email Address: rajani-rai@ouhsc.edu

Abstract

Introduction: Ovarian cancer (OvCa) is a highly aggressive malignancy characterized by frequent relapse and metastasis, both of which contribute to its high mortality rate. Although most patients initially respond to platinum-based chemotherapy, up to 80% eventually develop resistance, rendering OvCa largely incurable. Therefore, there is urgent need to identify new therapeutic targets and develop strategies to overcome chemoresistance. This study investigates molecular drivers of cisplatin resistance and evaluates the repurposing potential of the anthelmintic drug mebendazole (MBZ) for OvCa treatment.

Methods: Transcriptomic alterations associated with chemoresistance were assessed in OVCAR8 wild-type (WT) and cisplatin-resistant (CPR) OvCa spheroids using RNA sequencing. Differentially expressed selected genes were validated by qRT-PCR, and western blotting. The clinical relevance of identified genes was determined by analyzing publicly available datasets (GSE133859 and TCGA-OV) and through immunofluorescence staining on tissue microarrays (TMA) from primary and recurrent OvCa patient samples. Functional roles were further examined using genetic manipulations. MBZ efficacy against OvCa was evaluated using 2D and 3D viability, migration, and invasion assays in OVCAR8 WT/CPR cell lines and patient-derived ascites cultures. Preclinical efficacy was tested in both orthotopic and patient-derived xenograft (PDX) models.

Results: Transcriptomic profiling revealed ITGB4 overexpression and SERPINB2 downregulation in CPR spheroids, findings that were consistent with GEO, TCGA-OV datasets as well as TMA analysis of patient samples. High ITGB4 expression in platinum-resistant OvCa patients was significantly associated with worse overall and progression-free survival. CRISPR-mediated ITGB4 knockout resensitized OVCAR8 CPR cells to cisplatin and reduced their invasion and migration capacities. In contrast, SERPINB2 expression suppressed invasion. MBZ treatment downregulated ITGB4, upregulated SERPINB2, and inhibited TGF-β/SMAD signaling. Functionally, MBZ reduced spheroid growth, invasion, and migration in vitro, enhanced cisplatin sensitivity in OVCAR8 CPR cells, and suppressed tumor progression in orthotopic and PDX models without causing systemic toxicity.

Conclusion: These findings demonstrate that ITGB4 overexpression promotes invasion and chemoresistance, while SERPINB2 exerts tumor-suppressive effects. MBZ overcomes cisplatin resistance by regulating ITGB4 and SERPINB2 expression, inhibiting EMT-related signaling pathways, and reducing tumor growth in preclinical models. MBZ represents a promising repurposed therapeutic candidate for chemoresistant ovarian cancer and warrants further clinical evaluation.

Acknowledgment of Funding: The work is supported by COBRE P20GM135009, SCC CT Pilot Grant, PHF-Seed and PHF CTGA Grant Program

SEMAGLUTIDE ENHANCES PROGESTERONE RESPONSE IN ENDOMETRIAL CANCER THROUGH AKT/FOXO1 PATHWAY ACTIVATION

Nuzhat Bano[a], Rajani Rai[a], Vishal Chandra[a],

[a]Gynecologic Oncology Section, Stephenson Cancer Center, Obstetrics and Gynecology Department, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

Background:
Endometrial cancer (EC) is among the most common gynecologic malignancies, with rising incidence linked to obesity and insulin resistance. Although combining progesterone (P4) treatment with activation of the glucagon-like peptide-1 receptor (GLP1R) via agonists such as semaglutide has shown promise in preclinical and clinical studies, the molecular mechanisms underlying their combined effects remain poorly understood.

Methods:
We analyzed The Cancer Genome Atlas (TCGA) data using UALCAN and GEPIA to examine GLP1R expression in EC versus normal tissue and its relationship with tumor stage and patient body mass index (BMI). GLP1R mRNA and protein levels were confirmed in multiple EC cell lines. A high-fat diet (HFD)–induced mouse xenograft model was established to mimic obesity-associated EC. Mice were treated with semaglutide (SEMA), P4, or their combination. Tumors were evaluated for growth, weight, and proliferation (Cyclin D1, Ki-67) as well as cell cycle arrest marker (p21) using immunohistochemistry and RNA sequencing. In vitro, ECC1 and Ishikawa cell lines (both wild-type and P4-resistant) were used to assess cell growth, colony formation, apoptotic markers (caspase-3/7), and signaling pathway alterations. Pharmacologic inhibitors—a FOXO1 inhibitor (AS1842856) and an AKT inhibitor (LY294002)—were used to evaluate dependence on the AKT/FOXO1 pathway.

Results:
GLP1R expression was significantly higher in endometrial tumors than in normal tissue and increased with tumor stage and higher patient BMI. In EC cell lines, GLP1R was elevated at both mRNA and protein levels. In the HFD xenograft model, combined SEMA + P4 treatment led to greater reductions in tumor growth and weight than either agent alone. Combination therapy reduced Cyclin D1 and Ki-67 expression and increased p21. RNA sequencing of tumor tissues showed suppression of oncogenic pathways and activation of FOXO1 signaling. In vitro, the SEMA + P4 combination exhibited strong synergy in inhibiting growth, restored P4 sensitivity in resistant cell lines, and reduced colony formation. Mechanistically, SEMA + P4 treatment decreased the pAKT/AKT and p-FOXO1/FOXO1 ratios, promoted nuclear FOXO1 accumulation, and triggered apoptosis, as indicated by increased caspase-3/7 activity. Pretreatment with the FOXO1 inhibitor AS1842856 in EC cell lines abolished the sensitizing effect of the SEMA + P4 combination, significantly reducing P4 responsiveness. Notably, blocking the PI3K/AKT pathway with LY294002 also inhibited the effect of SEMA + P4, indicating that their anti-tumor activity is dependent on the AKT/FOXO1 pathway.

Conclusions:
GLP1R represents a promising therapeutic target in obesity-driven endometrial cancer. Co-treatment with a GLP1R agonist (semaglutide) and progesterone produces synergistic anti-tumor effects by inhibiting AKT signaling and activating FOXO1, restoring P4 sensitivity even in resistant cells. This combination may serve as a novel treatment strategy for EC, particularly in the context of obesity and insulin resistance.

Acknowledgments:
This work was supported by the Career Enhancement Program (CEP) of the Route 66 Endometrial Cancer SPORE and the Mary Kay Ash Foundation (MKAF) Grant. We sincerely thank these programs for their support in advancing our research.

TARGETING TUMOR–IMMUNE INTERACTIONS WITH OKN-007 IN ENDOMETRIAL CANCER

Nicole Minalt[1]; Sugantha Priya Elayapillai[1,4]; Cole Hladik[1,2]; Saeede Soleimanian[3]; Samrita Dogra[1,4]; Dinesh Thotala[3,4], and Bethany N. Hannafon[1,2,4]

[1]Department of Obstetrics and Gynecology, [2]Department of Cell Biology, [3]Department of Radiation Oncology, and [4]Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background/Objective: Recurrent, advanced-stage endometrial cancer (EC) remains a major clinical challenge due to limited therapeutic options and poor patient outcomes. OKN-007, a novel nitrone currently in Phase I clinical trials for malignant glioma, exhibits pleiotropic properties, including antioxidant, anti-inflammatory, anti-angiogenic, and neuroprotective effects, and has demonstrated potent anti-tumor activity in multiple preclinical cancer models, including EC. Our previous studies revealed that OKN-007 significantly downregulates indoleamine 2,3-dioxygenase 1 (IDO1) expression and modulates both upstream and downstream IDO1-associated pathways. As IDO1 is a critical regulator of immunometabolism and is associated with poor prognosis in EC, this study aimed to elucidate the mechanisms by which OKN-007 regulates IDO1 signaling and to determine whether OKN-007 enhances anti-tumor immunity and responsiveness to immune checkpoint blockade (ICB) through modulation of tumor–immune interactions.

Methods: To define the functional role of IDO1, we employed gain- and loss-of-function in vitro EC models. To assess the effect of OKN-007 on immune-mediated tumor clearance, we developed a real-time, three-dimensional assay for immune-mediated EC cell killing. To evaluate OKN-007 activity in a physiologically relevant setting, we established and validated an immunocompetent Mouse Endometrial Cancer Pten-deleted Kras-activated (MECPK) orthotopic model and characterized its immune microenvironment using multiparameter flow cytometry to assess lymphoid and myeloid subsets and immune checkpoint marker expression in peripheral blood mononuclear cells (PBMCs).

Results: IDO1 knockout doubled the IC50 of OKN-007, suggesting partial dependency on IDO1-mediated signaling. OKN-007 demonstrated single-agent anti-tumor efficacy in high-grade EC cell lines, with variable combinatorial activity when paired with ICB, dependent on cell line context. In vivo, tumor-bearing mice exhibited a significant reduction in $CD8^+$ T cell populations ($p = 0.03$) and NK cells. Furthermore, the upregulation of exhaustion markers, including PD-1, LAG-3, and TIM-3, was observed on $CD4^+$, $CD8^+$, and NK cells, with TIM-3 showing the most pronounced increase in serum levels.

Conclusions: These findings support OKN-007 as a promising therapeutic candidate for high-grade EC, either as a monotherapy or in combination with ICB. Immune alterations observed following OKN-007 treatment were consistent with immune exhaustion within the EC tumor microenvironment, highlighting tumor-associated immune evasion. To our knowledge, this represents the first characterization of the immune landscape in an immunocompetent syngeneic orthotopic model of EC, establishing a novel platform for the evaluation of immunotherapies and identification of candidate targets in gynecologic and other solid tumors. Future studies will extend these investigations to mismatch repair-deficient (dMMR) EC cell lines and the development of advanced dMMR syngeneic models to further define the therapeutic potential of OKN-007, both alone and in combination with ICB, for the treatment of advanced EC.

Day 2

Friday, October 17, 2025

OU Health | Stephenson Cancer Center
The UNIVERSITY of OKLAHOMA

Session 5: Combination Therapies and Immunotherapy

Moderators – Kimberly Leslie, M.D. and Scott H. Kaufmann, M.D., Ph.D.

Matthew Powell, M.D.

Washington University (Route 66)

9:00 – 9:20 am

“NRG Combination Immunotherapy Trials”

Arun Kanakkanthara, Ph.D.

Mayo Clinic

9:20 – 9:40 am

“PARPi/ALKi combinations for ovarian cancer”

Rugang Zhang, Ph.D.

MD Anderson Cancer Center

9:40 – 10:10 am

“Leveraging epigenetic vulnerabilities to overcome PARP inhibitor resistance induced by acidic tumor microenvironment”

Marion Curtis, Ph.D.

Mayo Clinic

10:10 – 10:30 am

“Cryptic antigens (PMID: 39970218, Science Advances 2025)”

NRG COMBINATION IMMUNOTHERAPY TRIALS

Matthew Powell, MD

Outcomes for patients with advanced stage and recurrent endometrial cancer has been poor with worsening incidence and death rates. NRG oncology has investigated the role of the PDL-1 inhibitor pembrolizumab for these patients (NRG-GY018: Endometrial cancer). This Phase 3 study evaluated adding the immunotherapy drug pembrolizumab to standard chemotherapy (paclitaxel-carboplatin) for patients with advanced or recurrent endometrial cancer. The combination of pembrolizumab plus chemotherapy significantly improved progression-free survival compared to chemotherapy with a placebo, regardless of the patient's mismatch repair (MMR) status. NRG-GY025: Is an ongoing randomized Phase 2 trial compares dual-agent immunotherapy to a single-agent approach in patients with recurrent endometrial cancer that has a deficient mismatch repair (dMMR) system. This study is testing whether the combination of nivolumab (anti-PD1) and low-dose ipilimumab (anti-CTLA4) is more effective than nivolumab alone. NRG-GY035 is about to be activated and will be building on the success of GY018 and findings from GOG-86P investigating the addition of bevacizumab to standard chemotherapy with or without pembrolizumab for patient with TP53 mutated high grade endometrial cancer. We will review the key findings from these trials and the rationale for NRG-GY035.

PARPI/ALKI COMBINATIONS FOR OVARIAN CANCER

Arun Kanakkanthara, Ph.D. Mayo Clinic

Abstract

PARP inhibitors (PARPis) are an important therapy for high-grade serous ovarian cancer (HGSOC). However, PARPi resistance frequently emerges, necessitating new approaches to improve HGSOC responses. Here we showed that the FDA-approved ALK inhibitor brigatinib enhances PARPi activity in HGSOC cells by disrupting an adaptive survival mechanism orchestrated by FRA1 in response to PARPi. Notably, this effect of brigatinib occurred through an ALK-independent pathway, wherein brigatinib induced a dual blockade of FAK and EPHA2 tyrosine kinases, leading to the suppression of AKT and ERK signaling accompanied by disruption of a phosphorylation event crucial for FRA1 protein stability. Moreover, in HGSOC patient-derived xenograft (PDX) models, brigatinib and PARPi combination therapy induced tumor regression and improved overall survival compared to PARPi alone, 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, particularly the subset characterized by high FAK and EPHA2.

LEVERAGING EPIGENETIC VULNERABILITIES TO OVERCOME PARP INHIBITOR RESISTANCE INDUCED BY ACIDIC TUMOR MICROENVIRONMENT

Rugang Zhang

The University of Texas MD Anderson Cancer Center

Resistance to PARP inhibitor (PARPi) remains a major clinical obstacle in epithelial ovarian carcinoma (EOC), ultimately limiting therapeutic efficacy and contributing to patient mortality. Here, we demonstrate that the acidic tumor microenvironment contributes to the observed resistance. Through three independent CRISPR-Cas9 screens based on an epigenetic-focused library, we identified p300 as a druggable target for overcoming PARPi resistance induced by physiologically acidic pH. Mechanistically, we uncovered an ERK1/2–p300–PARP1 signaling axis activated under low pH, which alleviates PARPi-induced PARP1 trapping by directly acetylating PARP1 and thereby contributes to resistance. Notably, two novel p300 inhibitors, IACS-16559 and TT125-802, restore sensitivity to PARPis (e.g., Olaparib and Saruparib) in multiple preclinical EOC mouse models. Together, our findings establish p300 as a promising therapeutic target for overcoming pH-driven PARPi resistance in EOC.

CRACKING THE CODE: IDENTIFYING IMMUNOGENIC TARGETS IN HIGH-GRADE SEROUS OVARIAN CANCER

Marion Cutis, Ph.D.

Despite advances in immunotherapy, high-grade serous ovarian cancer (OC) remains largely refractory to current treatments. The diversity of antigens expressed in OC has not been fully elucidated, limiting targeted approaches. Using immunopeptidomic profiling of HLA-A02:01$^+$ OC cell lines and metastatic patient samples, we sought to identify a broader range of actionable antigens. Among canonical tumor-associated peptides, we found epitopes from TTLL8, POTEE, and PKMYT1—proteins with minimal expression in normal tissues but elevated in OC. TTLL8, in particular, correlated with poor prognosis and elicited robust CD8$^+$ T cell responses, underscoring its immunogenic potential. In a separate study, we detected 311 cryptic (noncanonical) peptides derived from noncoding genomic regions across five metastatic OC tumor samples. Although representing <1% of total peptides, these cryptic antigens dominated the immunogenic landscape, with nearly 70% inducing autologous CD8$^+$ T cell activation, as measured by 4-1BB and IFN-γ expression. Together, these findings expand the antigenic repertoire of OC and support the development of new immunotherapies targeting both canonical and cryptic tumor antigens.

Investigators Transitioning to Endometrial Cancer Research

Moderators – Kimberly Leslie, M.D. and Scott H. Kaufmann, M.D., Ph.D.

10:30 – 10:40 pm Deirdre Hill, M.P.H., Ph.D., University of New Mexico

10:40 – 10:50 pm Xiang Xue, Ph.D. University of New Mexico (Route 66)

Assessing Endometrial Cancer Etiology by Histologic Subgroups

Hill DA, Muller C, Leslie KK, Route 66 Endometrial Cancer SPORE.

Background: Endometrial cancer incidence has increased substantially in the past two decades, with the increases occurring primarily in tumors of nonendometrioid histology, which have a poor prognosis. Evidence regarding the origin(s) of the increase is sparse. We sought to determine whether women who had particular molecular signatures of endogenous and exogenous exposures had an increased risk of nonendometrioid histology, particularly serous tumors.

Methods: We investigated single-base substitution signatures in exome sequencing data from The Cancer Genome Atlas (TCGA). Standard algorithms for mutational signature assessment were applied. Signatures were evaluated on a continuous scale, and also using a high/low cutpoint determined by maximally selected rank statistics. Relative risks (RR) and 95% confidence intervals (CI) were computed for 49 signatures, comparing risk for serous in relation to endometrioid histology. Disease-specific survival (DSS) was also evaluated in Cox proportional hazard models, with calculation of hazard ratios (HR) and 95% CI. The proportional hazards assumption was verified by Schoenfeld residuals. All analyses were adjusted for age at cancer diagnosis, and DSS analyses were also adjusted for stage.

Results: Included were n=414 women with endometrioid and n= 134 with serous nonendometrioid tumors. High Mismatch Repair defective (dMMR) (SBS6 and SBS15) and Polymerase Epsilon mutation (POLE) (SBS10a; SBS10b) signatures were less common in serous than endometrioid tumors, as expected from the literature (**dMMR**: SBS6 RR 0.21;95% CI 0.12-0.39; SBS15 0.22;95% CI 0.12-0.40;SBS26 0.21;95% CI 0.12-0.40); SBS15 RR 0.22;95% CI 0.12-0.40 and **POLE** SBS10a RR 0.23;95% CI 0.10-0.54 and SBS10b 0.33; 95% CI 0.19-0.58). A signature related to **tobacco use** (SBS4) was also less common in serous tumors (RR 0.32;95% CI 0.15-0.71). Risk of serous tumors was elevated among women with a signature of **aflatoxin** (SBS24) (RR 2.01;95% CI 1.51-2.70). Women with high **dMMR** (SBS6: HR 0.06;95%CI 0.01-0.47; SBS15 HR 0.23;95%CI 0.08-0.64; SBS26: HR 0.42;95% CI 0.21-0.84)) or high **POLE** (SBS10a HR 0.06;95% CI 0.01-0.46; SBS10b HR 0.13; 0.03-0.54) signatures had a reduced risk of endometrial cancer mortality. Risk of mortality was 1.63x in those with a high **aflatoxin** signature (95% CI 0.95-2.81) vs those with a lower signature.

Discussion: A higher risk of serous tumors in association with a signature of Aflatoxin, an established carcinogen and contaminant of peanuts and other nuts, corn, dried fruits (particularly figs), and cocoa beans, is a novel finding. Aflatoxin induces mutations through binding to tp53, thus is consistent with some of the known biology of serous disease. The reduced dMMR and POLE signature risk in relation to both serous tumors and DSS are also in agreement with other findings. Our results open up new prospects for exploration of serous tumor etiology.

Curcumin Analogues Trigger HMOX-1-Mediated Ferroptosis to Halt Endometrial Cancer Growth

Xiangxiang Wu[1], Jamie L. Padilla[1], Lane E. Smith[1], Lavanya Goodla[2], Kimberly Leslie[1], #, Xiang Xue[2],#

[1]Division of Molecular Medicine, Department of Internal Medicine,
[2]Department of Biochemistry and Molecular Biology, University of New Mexico, Albuquerque, NM 87131
#Correspondence: kkleslie@salud.unm.edu or xxue@salud.unm.edu

Abstract

Background and Purpose

Endometrial cancer poses major treatment challenges, particularly in advanced stages where therapeutic options are limited. Ferroptosis, an iron-dependent form of cell death, has emerged as a promising approach for cancer suppression and overcoming drug resistance. Unlike apoptosis (a common target of drug resistance), ferroptosis may be effective in resistant cells. Curcumin, a natural ferroptosis inducer, exhibits anticancer activity but suffers from poor bioavailability. In contrast, bioavailable curcumin analogues, such as AKT-100 and HO-3867, show potent anticancer effects at low micromolar to nanomolar concentrations in endometrial tumors harboring mutant p53 by restoring wild-type p53 function. This study examines the effects of these analogues on ferroptosis-related gene expression, focusing on heme oxygenase-1 (HMOX-1), and their therapeutic potential in endometrial cancer.

Methods

RNA sequencing was performed to evaluate ferroptosis-related gene expression changes following treatment with HO-3867 and its next-generation analogue, AKT-100, across multiple endometrial cancer cell lines, including KLE and Hec50. Real-time qPCR and immunoblotting were used to confirm HMOX-1 expression at RNA and protein levels after 24 hours of drug exposure. FerroOrange and DCFH-DA staining assessed intracellular iron and ROS levels, respectively. CyQUANT cell proliferation assays measured cytotoxicity of the analogues and the effects of HMOX-1 inhibition (Zinc protoporphyrin, ZnPP) or ferroptosis inhibition (Liproxstatin-1).

Results

HO-3867 and AKT-100 significantly upregulated HMOX-1 expression in KLE and Hec50 cells, confirmed by qPCR and immunoblotting. FerroOrange and DCFH-DA staining revealed significantly increased iron and ROS levels after 24 hours of AKT-100 treatment. CyQUANT assays showed that inhibition of HMOX-1 with ZnPP or ferroptosis inhibition with Liproxstatin-1 partially reversed the cytotoxic effects of HO-3867 and AKT-100, supporting an HMOX-1–mediated ferroptosis mechanism. Notably, AKT-100 exhibited potent cytotoxicity with nanomolar IC_{50} values, underscoring its therapeutic promise.

Conclusions

Curcumin analogues AKT-100 and HO-3867 induce HMOX-1–mediated ferroptosis and effectively suppress endometrial cancer cell growth. These findings highlight the therapeutic potential of curcumin analogues in overcoming drug resistance in endometrial cancer. Further in vivo studies are warranted to define the role of HMOX-1 in endometrial cancer progression using both genetic and pharmacological approaches.

Keywords: Curcumin analogues, Ferroptosis, Endometrial cancer, Heme oxygenase-1

Poster Session

Abstracts

OU Health | Stephenson Cancer Center
The UNIVERSITY of OKLAHOMA

Poster Session

(Listed A-Z by Presenter's First Name)

Poster Number	First Name	Last Name	Institution	Title of Abstract
1	Andrea	O'Riordan	Washington University in Saint Louis School of Medicine	Escaping the O-Loop: Endometrial Cancer Risk in Reproductive-Age Bariatric Surgery Patients
2	Hua-Ying *Abstract omitted per request*	Fan	University of New Mexico Comprehensive Cancer Center	Auranofin as a Novel Notch Pathway Inhibitor to Enhance Platinum-Based Therapy in Endometrial Cancer
3	Jason	Weber	Washington University in St. Louis	ADAR1 and DHX9 Represent a Therapeutic Opportunity in p53-mutated Endometrial Cancer
4	Katie *No abstract available*	Keyser	The University of Oklahoma Health Campus	The Road Map of a Patient Advocate's Cancer Journey
5	Tu-Yung	Chang	Johns Hopkins University	Integrated Spatial Analysis of Ovarian Precancerous Lesions
6	Yan	Yin	Washington University School of Medicine	Deciphering the Role of SALL1 in Endometrial Cancer

ESCAPING THE O-LOOP: ENDOMETRIAL CANCER RISK IN REPRODUCTIVE-AGE BARIATRIC SURGERY PATIENTS

Andrea O'Riordan, Jayme Sparkman ANP-BC, Danny Mou MD MPH, Andrea Hagemann MD MSCI

Rates of endometrial cancer among premenopausal women are rising as obesity increases. However, many OBGYN providers don't feel equipped to discuss weight with obese patients. In contrast, bariatric surgery patients are seen explicitly for weight management and represent a population at high risk for endometrial atypical hyperplasia and cancer. We collaborated with a bariatric surgery clinic at WashU to assess access to OBGYN care, anovulatory cycles, and red flag symptoms for endometrial cancer. Between March and July 2025, 141 women completed the questionnaire; 95 (67%) were reproductive age (18-45). Of these, 22 (23%) had no OBGYN. Though 45 (47%) reported regular cycles, 78 (82%) reported at least one abnormal menstrual symptom (i.e. heavy bleeding (34%), spotting (26%), irregular cycles (20%)). 9 (9%) had already had a hysterectomy, and 6 (6%) reported amenorrhea. These findings suggest that many bariatric patients lack gynecologic care but have abnormal cycles, highlighting an opportunity for interdisciplinary collaboration to improve early detection and prevention.

ADAR1 AND DHX9 REPRESENT A THERAPEUTIC OPPORTUNITY IN P53-MUTATED ENDOMETRIAL CANCER

Jason Weber

Endometrial cancer (EC) is the fourth most common cancer among women in the United States, with an estimated 66,000 new cases in 2023. Unlike most cancers, endometrial cancer incidence and mortality are on the rise, with a 1.7% increase annually in mortality since 2007. While most patients have low-grade and early-stage disease, patients with advanced, high-grade tumors will generally progress within one year and die within five years of diagnosis. Prior studies have shown that distinct molecular subtypes of endometrial cancer defined by ***Pro***active ***Mo***lecular R***is***k Classifier for ***E***ndometrial Cancer (ProMisE) respond differentially to specific therapies and have distinct prognoses. The four subtypes include: mismatch repair deficient (MMR-D), polymerase epsilon (*POLE)* exonuclease domain mutated, p53 abnormal (p53 abn), and p53 wildtype/non-specific molecular profile (p53wt/NSMP). We have discovered a novel interferon (IFN) pathway present at elevated levels in p53 abn endometrial cancers. Previous work by my lab has shown that this pathway is largely controlled by the ADAR1 and DHX9 oncogenes. We provide evidence that ADAR1 and DHX9 expression is correlated with worse overall survival in endometrial type II serous cancer. We hypothesized that increased expression of ADAR1 and DHX9 in p53 abn endometrial cancers represents a novel vulnerability that can be exploited with innovative therapeutic approaches to improve overall survival.

We compared the basic characteristics of one p53 wild type and six p53 abn cell lines. DHX9 and ADAR1 expression were consistently higher in the p53 abn cell lines. Knockdown of DHX9 or ADAR1 resulted in cell death in several of the cell lines to varying degrees. Treatment of the five cell lines with a maximal dose of ATX968, the DHX9 selective inhibitor resulted in cell death in all five lines to varying effect. However, a dose curve with ATX968 in two of the cell lines suggested that there are IC50 differences between cell lines. We also showed a clear interaction between ADAR1 and DHX9 in each of the cell lines, suggesting that the complex may play an important role in the function of the proteins in regulating proliferation and survival in EC.

INTEGRATED SPATIAL ANALYSIS OF OVARIAN PRECANCEROUS LESIONS

Tu-Yung Chang

Abstract

Studying precancerous lesions is essential for improving early detection and prevention, particularly in aggressive cancers such as ovarian carcinoma. Here, we conducted integrated and spatial analyses of transcriptomes, aneuploidy, and clinic-pathological features in 166 ovarian precancerous lesions. Four pre-cancerous subtypes were identified transcriptomically: proliferative, immunoreactive, dormant, and mixed. These subtypes varied in their frequency of germline-*BRCA1/2* mutations, aneuploidy, *CCNE1/MYC* amplification, proliferative activity, immune-regulatory gene expression, and histological features. Notably, the immunoreactive subtype upregulated immune-regulatory genes, exhibited chronic inflammation, and was enriched in cases with germline-*BRCA1/2* mutations, deletions of chromosomes 17 (harboring *TP53* and *BRCA1*) and 13 (harboring *BRCA2*), leading to a double "two-hit" involving *TP53* and *BRCA1/2*. Tumor invasion was associated with the activation of interferon response pathways, epithelial-mesenchymal transition, and extracellular matrix remodeling. In summary, our results elucidate the earliest molecular landscape of ovarian precancerous lesions, serving as the foundation for future risk stratification to identify aggressive pre-cancerous lesions.

DECIPHERING THE ROLE OF SALL1 IN ENDOMETRIAL CANCER

Yan Yin[1], Vivian Robles-Pinos[1], Eliana Wolf[1], Emily So[1], Meade E. Haller[1], Michael Rauchman[2,3], David Y. Chen[1] and Liang Ma[1]

[1]Division of Dermatology and [2]Division of Nephrology, Department of Medicine, Washington University School of Medicine, St. Louis, MO, 63110

[3]VA Saint Louis Health Care System, St. Louis, MO, 63106, USA

Introduction

Endometrial cancer (EC) is a common gynecologic malignancy with rising incidence and limited treatment options for patients with poor prognosis. Genetic and epigenetic alterations contribute to disease heterogeneity, yet novel therapeutic targets remain needed. SALL1, a member of the Spalt-like transcription factor family, has emerged as a candidate regulator of EC biology. We aimed to determine the role of SALL1 in EC progression and evaluate its potential as a therapeutic target.

Methods

We analyzed patient datasets to assess associations between SALL1 mutations and survival. In vitro studies using human EC cell lines employed siRNA-mediated knockdown of SALL1 to examine effects on proliferation, apoptosis, and migration. In vivo, SALL1 function was evaluated in xenograft and genetic mouse models of EC. A SALL1-HiBit reporter EC cell line was generated to facilitate high-throughput screening of compounds that alter SALL1 stability.

Results

Deleterious SALL1 mutations correlated with improved survival in EC patients. siRNA-mediated knockdown of SALL1 in EC cell lines resulted in growth inhibition, impaired migration, and increased apoptosis. In mouse models, reduced SALL1 expression suppressed EC development. Moreover, establishment of a SALL1-HiBit reporter system enabled compound screening and identified agents that destabilize SALL1, thereby inhibiting EC cell growth.

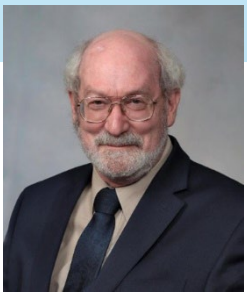
Conclusions

Our findings identify SALL1 as a critical regulator of EC progression. Genetic or pharmacologic reduction of SALL1 impairs tumor growth and survival, highlighting SALL1 as a promising therapeutic target. These studies provide both mechanistic insight and a preclinical platform for drug discovery in endometrial cancer.

Special thanks to the following:

Chair – Naveena Basa Janakiram, Ph.D.

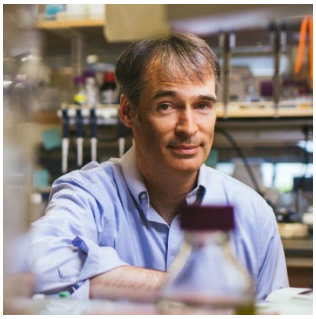
Special Talk Introduction – Scott H. Kaufmann, M.D., Ph.D.



Session 2 Moderators:

Anil Sood, M.D., Ph.D.

Ronald J. Buckanovich, M.D., Ph.D.



Working Group 1 Moderators:

Kirsten Moysich, Ph.D.

Ronald J. Buckanovich, M.D., Ph.D.

Session 3 Moderators:

Jamie Bakkum-Gamez, M.D.

Doris Benbrook, Ph.D.

Special Session Introductions:

Doris Benbrook, Ph.D.

Session 4 Moderators:

Nadine Hempel, Ph.D.

Kimberly Levinson, M.D., M.P.H.

Session 5 & Investigators Transitioning to Endometrial Cancer Research Moderators:

Kimberly Leslie, M.D.

Scott H. Kaufmann, M.D., Ph.D.

Working Group 2 Moderators:

Andrea Hagemann, M.D.

Danuta Kozbor, Ph.D.

Thank you for coming!

---

*Please fill out this SHORT **10 question** feedback form to help us make improvements.*

---

https://qualtrics.ou.edu/jfe/form/SV_6Ke66jpNmV0Sa90