The Diverse Aspects of Uterine Serous Cancer:

An NCI workshop on the status of and opportunities for advancement of research

Naveena B. Janakiram, PhD*[1], Megan A. Clarke, PhD *[2], Mihoko Kai, PhD*[3], Tiffany A. Wallace, PhD [4], Sandra Russo, MD[5], Toby T. Hecht, PhD [1], Elise C. Kohn, MD^[1], Brandy Heckman-Stoddard, PhD^[5]

[1]Division of Cancer Treatment and Diagnosis, [2]Division of Cancer Epidemiology and Genetics, [3]Division of Cancer Biology, [4]Center for Cancer Health Equity, and [5]Division of Cancer Prevention, National Cancer Institute, Rockville, Maryland 20850

*denotes co-authorship first author positions for equal contribution

^ denotes co-senior authorship for equal contribution

Corresponding Author:

Elise Kohn (kohne@mail.nih.gov)

9609 Medical Center Drive MSC9737

Rockville, Maryland 20850

ABSTRACT

The marked increase in incidence and mortality in endometrial cancer over the last two decades is driven in part by rising rates of higher grade, more aggressive endometrial cancers with mutations in *TP53*, uterine serous cancers and their dedifferentiated component, uterine carcinosarcomas (collectively USC). USC rates have been increasing among all racial and ethnic groups, with higher rates of this aggressive uterine cancer in Black women. The National Cancer Institute (NCI) hosted a workshop in June 2023 to examine the diverse aspects of USC across epidemiology, biology, and molecular genetics, and to advance knowledge from basic to preclinical and translational efforts. Key stakeholders came together including basic scientists, clinical investigators, and patient advocates to identify critical research gaps that, when addressed, would facilitate more comprehensive and rapid progress in understanding and ultimately treating USC across all patients. NCI released a supplemental funding opportunity (NOT-CA-24-044) in Spring 2024 to facilitate rapid translation of these recommendations.

Introduction

On June 22 and 23, 2023, the National Cancer Institute (NCI) held a one-and-a-half-day virtual workshop entitled, "The Diverse Aspects of Uterine Serous Cancer (USC)." The impetus for this event was the keen awareness that the incidence and mortality of endometrial cancer (EC) have been increasing. These increasing trends are particularly apparent for clinically aggressive endometrial cancers commonly defined by mutations in *TP53* and with serous histology, and their dedifferentiated component, uterine carcinosarcomas (UCS; hereafter referred to collectively as USC). While USC accounts for about 10% of all EC cases, it causes a disproportionate 40% of EC deaths.[1, 2] Findings from the Cancer Genome Atlas and subsequent molecular studies have revolutionized our understanding of EC. We recognize the heterogenous molecular features and their associated prognostic and predictive implications, suggesting that EC is a collection of histomolecularly different diseases.[3-8] There is a need to better understand the USC biology (including cellular and molecular characterization of the tumor and the tumor microenvironment), early detection, risk factors, diagnosis, and treatment including preclinical and clinical studies of this type of EC. Furthermore, there are wide disparities in USC incidence, presentation, aggressiveness, and survival, between Black and White women in the United States. The causes of these disparities are understudied, and likely involve a complex interplay of biological (i.e., genetic/molecular factors, tumor characteristics), social (i.e., social determinants of health), and system-level factors.[9-12]

This workshop had two primary objectives. The first was to discuss what is known about USC and to identify important knowledge gaps that, if filled, would advance the field. The second objective was to discuss health disparities seen in this disease and propose opportunities to expand the research in this area. A key goal was to spur interest in USC research, especially among early-stage investigators, since a portfolio analysis of NCI grants focusing on EC revealed a limited number of grant applications and fewer grant awards over the past five years; of these, most did not focus solely on USC. Invited participants, including clinicians, scientists, epidemiologists, pathologists, and advocates, were placed into two working groups: basic science and translational science. These groups met separately over several weeks

before the workshop to discuss the most important short-term and long-term research goals and challenges for the USC field.

The workshop was divided into sessions. The first session laid the groundwork for further discussions focusing on the pathology and diagnostic discrepancies, molecular subgroups including those that might be amenable to immunotherapy, approaches to treatment, and molecular differences in USC that may contribute to disparities. The second session delved into the basic science, early preclinical investigations into the disease, and a discussion of potential risk factors. This was followed by a session exploring the preclinical and translational science knowledge and current opportunities in USC including NCI resources, such as cells, animal models, specimens, and agents, that are available to assist investigators in their studies. For each of these scientific sessions, there was a working group report that was summarized and discussed among the participants. On the second day of the workshop, there were breakout sessions for basic and early preclinical science and for translational science where knowledge gaps and challenges in the field were discussed to identify opportunities and provide recommendations. These included the paucity of clinically relevant animal models, the overall recognition of the significance of the problem, which is often understated, and the need to recruit physician scientists into the field. These sessions were followed by a wrap-up including what directions and resources are needed to make significant strides for the benefit of patients with USC.

Calls to Action (see also Table 1)**:**

- **Focused Scientific Directions:** New and expanded research opportunities are needed to address molecular and cellular heterogeneity of USC, within and between patients. These should include analyses across racial and ethnic, geographic, environmental, metabolic, and genetic diversity to build the most complete picture of this complex disease. Characterization of USC natural history including precursor lesions, such as serous endometrial intraepithelial carcinoma, and causes of disease progression is needed. This will

benefit from development of multidisciplinary teams, recruitment of experienced and new investigators into the field, and enhanced communication and mentoring.

- **Expansion, Enhancement, and Optimized Use of Models, Biospecimens, and Data Resources:** Advancement of scientific directions will be enhanced by development of models ranging from cell lines and organoids to patient-derived xenografts. There is also a critical need for syngeneic animal models to advance studies in the tumor microenvironment, particularly the role of immune cells in their interaction with the tumor. Models to address intra- and inter-tumoral heterogeneity are needed, including those derived from sampling within a patient over time and those derived from patients across different demographic and geographic groups. Greater recognition of existing NCI resources, such as biospecimen access, clinical trial data, and novel drug access for preclinical work will facilitate opportunities (Table 2).
- **Foster Development of the Scientific Community:** Development of multidisciplinary approaches and cross-institutional collaborations can develop enriched teams with broad expertise, ultimately leading to more successful recruitment and retention of scientists and physicians. Cross fertilization with investigators with expertise relevant to USC, and recruitment and mentoring of early career investigators, will help build a critical mass of researchers. Engagement of USC investigators, clinician scientists, and advocates in review and funding operations will enhance understanding of the field and opportunities for investigators and reviewers.
- **Communication Across Stakeholders--Scientists and Clinicians, Consumers and Advocates, Industry:** Progress in overcoming the array of differences in understanding, treating, and ultimately preventing USC requires an open dialog across all interested parties. This also will facilitate interest in and inclusion of a more diverse population of people studying USC, treating USC, and encouraging participation in clinical trials. Incorporation of diversity across all aspects from laboratory models through accrual and analysis of clinical trials, will allow better understanding due to increased representation, thus improving design of next steps and ensuring generalizability, with the goal of promoting health equity.

Leveling the Playing Field

EC develops from cells of the inner lining of the uterus. It is the most common gynecologic malignancy in the U.S. and is estimated to be the fifth leading cause of cancer-related death in women in 2024.[13] EC is rising in incidence and mortality, with an approximately 20-30% increase over the past two decades, respectively[14], with USC contributing disproportionately.[1, 2] The original genome-wide analysis of endometrial cancer revealed molecular genetic alterations and the pathways they control in the development of USC and serous endometrial intraepithelial carcinoma [15]. Those changes, later confirmed and expanded upon by the NCI-sponsored The Cancer Genomic Atlas (TCGA) Program[3] and follow on studies[4-8] have revolutionized how EC is evaluated, identifying four different morpho-molecular EC types: *POLE* mutation, mismatch repair deficient, *TP53* mutant and no specific molecular profile (Figure 1). Over 95% of USC fall into the *TP53* mutant group. USC, and its de-differentiated metaplastic subtype, uterine carcinosarcoma (UCS), are estrogen-independent, more often present with local extension or distant disease, almost uniformly have *TP53* mutations, and even when early stage, have a comparatively poor prognosis.[16-18] This type of USC is disproportionately observed in Black women[1, 19-21], and risk factors for these tumors are not well understood.[22-24]

Incidence and mortality rates of USC and its UCS subtype are more than twice as high among Non-Hispanic Black women compared with other racial and ethnic groups. Survival disparities persist after accounting for USC/UCS (type), and stage and grade at diagnosis.[1, 2, 19] Black women diagnosed with USC have a 5-year overall survival rate of 46% versus 55% in White women. Reasons underlying these disparities are not well-understood but are thought to involve a multitude of factors including tumor genomics and biology, stage at diagnosis, comorbidities, differential access to care, and receipt of guideline concordant treatment.[11, 25-33]

Progress and Unmet Needs: Basic to Preclinical Science

Development of USC Specific Models: Understanding USC and translating that knowledge to patient benefit lags behind research into other types of EC and into gynecologic cancers in

general. Examination of the causes and consequences of its unique genotype and phenotypes requires complex models. Some cell line models are available and recapitulate tumor genomics and behavior in vitro, in organoids, and in patient-derived xenograft models.[34-37] However, to date, no syngeneic models have been generated. Such models are needed to dissect the complex tumor microenvironment and to identify events emanating from precursor lesions. USC models can also be applied to identify potential biomarkers for early detection, effective targeted treatments, immunotherapies, or to test combination strategies and study resistance mechanisms.

Leveraging Knowledge about p53 Biology: p53 dysregulation is recognized generally to be associated with DNA repair abnormalities, altered cell cycle regulation, increased vasculature[38-41], estrogen resistance [42] and altered immune microenvironment.[43-45] There is a need to take the lessons we have learned from high grade serous ovarian cancer and see what can be applied to USC. USC has a high frequency of activation of the AKT pro-survival pathway, predominantly via activating mutations of PI3K family genes.[46, 47] Understanding the initiating event leading to *TP53* mutation and subsequent downstream changes and microenvironment responses may improve targeted therapeutic approaches. For example, HER2 amplification is almost uniquely found in USC and UCS and has both prognostic and predictive value for treatment planning.[48, 49]

Future Directions: Critical directions for study identified by the working group include understanding the precursor event(s) for USC especially the role of the endometrial polyp[50], dissection of the tumor microenvironment and interplay between the vasculature, immune infiltration and tumor, and the degree of tumor heterogeneity as a driver of dynamic change and resistance, all of which require improved and diverse models.

Opportunities and New Directions: Preclinical to Translational research

Applying Molecular Knowledge: One of the greatest needs is to understand the interplay between genotype, genotypic progression, phenotype, and microenvironment, on the progression of USC disease and therapy resistance. The cause and implications of heterogeneity

within a USC tumor, within and between USC populations, and across race and ethnicity are areas for study. The frequency of USC is higher in Black patients and those tumors more commonly have amplification of *ERBB2/*HER2 and/or *CCNE1*, each of which has poor prognostic import.[3, 21, 51, 52] Approximately 35-45% of USC and upwards of 12% of UCS may have HER2 amplification, for which preliminary data has demonstrated added benefit of anti-HER2 treatment.[53, 54] GY026 is an ongoing phase 3 clinical trial in the NCI National Clinical Trials Network (NCTN) testing the benefit of chemotherapy with or without trastuzumab or the combination of trastuzumab/pertuzumab (NCT05256225). The frequency of serous intraepithelial lesions in the endometrium is unknown. Better dissection of the steps occurring in the progressive development and dissemination of USC can lead to opportunities for early detection and prevention, as well as prognostic biomarkers and actionable therapeutic advances. Earlier application of new and developing targeted therapies depends upon knowledge of when events such as HER2 and *CCNE1* amplification occur in the development of USC.

Examining the Immune System: The recognition that deficiency in mismatch repair is associated with a strong, and in some cases, durable, response to immunotherapy has opened an important arena of immunology research in USC. Immunotherapy is thus a hot topic in the "cold" USC tumor. A small percentage, 3-5% of USC may have mismatch repair dysfunction.[5, 6, 55] There is a deficiency of stromal infiltration of CD8+ cells and a profusion of myeloid-derived suppressor cells (MDSCs), which hinders the infiltration of CD8+ cells that all may contribute to immunoresistance.[56-58] An ongoing Cancer Moonshot-funded project is analyzing genomic and molecular characteristics, including the immunologic milieu, of 750 high risk EC cases from people of White and Black women, which will include a large proportion of USC /UCS patients. The observations from this project coupled with other ongoing work in the field will lead to directions on how to manipulate the immunosuppressive USC microenvironment. This underscores the need for immunocompetent syngeneic models for further preclinical research.

Novel Therapeutic Targets and Agents: Antibody-drug conjugates (ADCs), in which the antibody targets a (relatively) unique cell surface molecule to bring into juxtaposition a toxic payload, are

a newer method for targeting and killing cancer cells. High levels of HER2 (35-45%) and TROP2 (~60% 2-3+; [59]) expression in USC make them ready targets for treatment [60]. Evidence suggests benefit of targeting HER2 expression in USC [53, 61-63], and a recent phase 2 trial showed a strong response rate of trastuzumab deruxtecan HER2 2+ and 3+ cases.[64] TROP2 is highly expressed in USC[65] and preliminary studies of sacituzumab govitecan, an anti-TROP2 ADC carrying a toxic camptothecin payloads, suggests potential for this target in USC (2023 abstract/phase 3 trial in development).[66] Preclinical work has shown that targeting TROP2 in USC resulted in both tumor and bystander effects, and antibody dependent cytotoxicity against TROP2+ tumors [59].

Optimizing Resources for USC/UCS Research: Resources available through the NCI to advance research into USC are broad (Table 2). These include tissue biobanks with and without annotated clinical information, access to models with which to capitalize on this knowledge through testing, using newer varied models to enhance our understanding of USC mechanisms of sensitivity and resistance to treatment options. In addition, there are data resources generated and being generated from projects, such as the ongoing Moonshot program.

Conclusion

The increasing incidence and mortality rates of USC (and UCS), combined with racial disparities in USC diagnosis, treatment, and survival, emphasize the importance of this disease as a burgeoning public health problem that warrants increased research. There are major gaps in our understanding of disease natural history and risk factors for USC. These knowledge gaps exist across the entire cancer continuum, and racial disparities span every level of this continuum from etiology to prevention, diagnosis, treatment, and survivorship. Progress can be made with new models, recruitment of investigators into the field, and encouragement of partnerships with industry, advocacy, and within academia.

The NCI has been taking measures to promote collaborative research amongst institutions with the aim of pooling resources, sharing data, accelerating the pace of USC research, and facilitating a smooth transition from preclinical to clinical studies via grant mechanisms such as

SPOREs. Despite the progress made thus far, there is still much to be discovered in this area of research. Work is needed in relation to USC across all areas of the National Cancer Plan. We need to engage every person, expand the workforce, and improve equity by investing in the discovery science that will bring about early detection, better models, and better treatment for better cancer care. The key will be sharing new data as it becomes available to facilitate a bench to bedside and back again approach.

Data Availability: This commentary contains no novel data.

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Figure legend

Figure 1. Major characteristics of the four morphomolecular types of endometrial cancer.
*Abbreviations: CNH/L: copy number high, low; dMMR: deficient mismatch repair; POLEm: deleterious mutation in polymerase ε; GOF/LOF: gain/loss of function mutation; HER2amp: amplified HER2; ER: estrogen receptor; USC/UCS: uterine serous cancer, uterine carcinosarcoma; **clear cell, rare, p53 and ER wt included in NSMP

Table 1. Recommended Action Items.

Scientific Directions	• New and expanded research opportunities • Assessment of molecular and cellular heterogeneity across time and anatomy, and diverse potential contributors • Development of multidisciplinary teams
Models, Biospecimens, and Data Resources	• Cell lines, organoids, PDX from intrapatient and interpatient sampling over time of disease lifecycle • Syngeneic models • Use of existing resources including banked clinical trial biospecimens, clinical trial data, research access to novel agents
Foster Development of the Scientific Community	• Multidisciplinary collaborations to enrich, recruit, and retain investigators • Training and mentorship for recruited senior and early career investigators • Engagement of USC investigators and advocates in review and funding teams
Communication Within and Between Scientific, Consumer, and Advocacy Communities	• Enhance dialog across all stakeholders and engage more consumers, industry partners, and advocates across all levels of scientific discourse • Collect and report demographics of diversity during building of laboratory models through to analysis of clinical trials • Attract interest and inclusion of a broad demographic to clinical trials, biospecimen collection, and research

Table 2: Resources and Links to Websites

Transplantable *in vivo*-derived tumors and *in vitro*-established tumor cell lines from various species.	https://dtp.cancer.gov/repositories/DCTDTumorRepository/
NExT: Advancing Promising Cancer Therapeutics from Bench to Bedside.	https://next.cancer.gov/
NCI Patient-Derived Models Repository (PDMR)	https://pdmr.cancer.gov/
Preclinical Biologics Repository	https://frederick.cancer.gov/resources/repositories/Brb/-
Synthetic Compounds Repository	https://dtp.cancer.gov/organization/dscb/obtaining/default.htm
Natural Products Repository	https://dtp.cancer.gov/organization/npb/introduction.htm
NCTN Biobanks	https://nctnbanks.cancer.gov//
CHTN, The NCI Cooperative Human Tissue Network	https://chtn.cancer.gov/
Specimen resource database	https://www.specimens.cancer.gov/
GTex Biobank	https://gtexportal.org/home/
Cancer Moonshot Biobank	https://www.ncbi.nlm.nih.gov/projects/gap/cgibin/study.cgi?study_id=phs002192.v3.p2
Women's health funding opportunities	https://orwh.od.nih.gov/research/funded-research-and-programs/funding-opportunities-and-notices
USC clinical trials	https://clinicaltrials.gov/search?cond=Uterine%20Serous%20Carcinoma

Figure 1. Major characteristics of the four morphomolecular types of endometrial cancer.

Attribute	*P53*m (CNH*)	NSMP (CNL)**	dMMR	POLEm
% of EC	~20%	~40%	~35%	~5%
Molecular drivers	*p53m* GOF/LOF HER2amp ~1/3	ER↑	dMMR	*POLE*m
TMB/MS status	Low	Low	Moderate - high	ultramutated
Common histology	USC, UCS	Endometrioid, usually grade 1/2	Endometrioid, usually gr 2/3	endometrioid gr3 common
5 yr survival	Worst	Excellent	Variable	Excellent, cure potential
Immune environment	Cold	Cold	Warm/hot	hot

*Abbreviations: CNH/L: copy number high, low; dMMR: deficient mismatch repair; POLEm: deleterious mutation in polymerase ε; GOF/LOF: gain/loss of function mutation; HER2amp: amplified HER2; ER: estrogen receptor; USC/UCS: uterine serous cancer, uterine carcinosarcoma

**clear cell, rare, p53 and ER wt included in NSMP