MUC16 in Ovarian Cancer: High, Stable Expression Across Histologic Subtypes, Disease Stages, and Platinum-Sensitivity Status Supports Antibody-Drug Conjugate Development

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Objective

The aim of the current study was to assess *MUC16* expression in a large ovarian cancer population, across different histologic subtypes and disease stages

Conclusions

- MUC16 showed tumor-selective protein and mRNA enrichment in ovarian tissue samples, with concordance between *MUC16* mRNA expression and MUC16 protein abundance
- Robust *MUC16* expression was seen across histologic subtypes of ovarian cancer
  - HGSOC, the most common histologic subtype (accounting for ~70% of all ovarian cancer cases),[12] demonstrated high expression across all disease stages
- *MUC16* expression remained high irrespective of platinum-sensitivity status
- CA125 protein abundance was high in all histologic subtypes, including HGSOC, and increased in parallel with advancing disease stage
- These results support MUC16 as a promising ADC target that warrants further investigation in ovarian cancer
  - HWK-016, a next-generation, MUC16-targeted ADC, is currently being evaluated in a phase 1 clinical trial for the treatment of patients with advanced gynecological cancers

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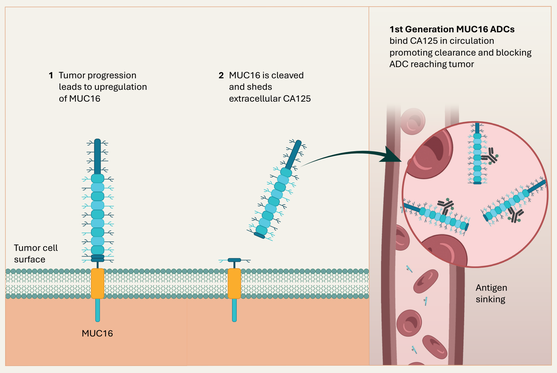
For disclosures of co-authors, please refer to the abstract.

Background

- Mucin 16 (MUC16) is a cell-surface glycoprotein that plays an important role in cancer by promoting tumor cell proliferation, metastasis, and immune evasion[1,2]
- MUC16 is overexpressed in multiple tumor types—including 80% of epithelial ovarian cancers—with limited expression in normal tissue[1–3]
- Early MUC16-directed antibody-drug conjugates (ADCs) comprised antibodies targeted to the extracellular domain of MUC16,[4–6] which is a portion of MUC16 that is proteolytically cleaved and shed into the bloodstream as the well-known serum biomarker cancer antigen 125 (CA125)[1,2]
  - Therefore, the efficacy of these early agents was potentially limited by off-target binding of serum CA125, creating an antigen sink and limiting tumor access (**Figure 1**)[7]

FIGURE 1. CA125 Shedding and Antigen-Sink Effect in MUC16-Positive Cancers



ADC, antibody-drug conjugate; **CA125**, cancer antigen 125; **MUC16**, mucin 16.

- Advances in ADC technology and development of antibodies targeting the MUC16 membrane-bound structure have renewed interest in MUC16 as a therapeutic target[7,8]
  - HWK-016 is an investigational, next-generation ADC that targets membrane-bound MUC16. It comprises a monoclonal antibody conjugated to the novel topoisomerase I inhibitor CPT116 via a stable, cleavable linker that enhances intracellular delivery and limits systemic exposure
- A small study (N=69–94) using data from public proteomic and transcriptomic databases demonstrated significant increases in MUC16 protein and mRNA expression in ovarian tumor tissue versus normal tissue, as well as higher transcript levels in stage 4 ovarian tumor tissue versus stages 1–3[9]
  - However, that study and others utilizing public omics databases are limited by relatively small sample sizes and a lack of histology-specific data[9,10]

Methods

- Data from the Clinical Proteomic Tumor Analysis Consortium database were used to analyze MUC16 protein abundance in tumor tissue versus normal tissue using the Wilcoxon test, and to compare it with *MUC16* mRNA levels using Spearman's correlation
- *MUC16* mRNA expression in tumor tissue versus adjacent normal tissue across multiple tumor types was assessed using publicly available data from TNMplot.com—which incorporates RNA sequencing data from The Cancer Genome Atlas (TCGA), Therapeutically Applicable Research to Generate Effective Treatments (TARGET), and the Genotype-Tissue Expression (GTEx) repositories—with group differences evaluated using the Mann–Whitney U test[11]
- RNA sequencing data from a real-world database (Tempus AI, Inc., Chicago, IL, USA) were used to examine *MUC16* mRNA expression across ovarian cancer histologic subtypes, primary and metastatic tumors, disease stages, and platinum-sensitivity status
  - Gene-expression data were derived from a whole-transcriptome RNA-sequencing panel (Tempus xR) capturing 20,000 genes
  - The gene-expression distributions of other targets of relevance in ovarian cancer were also analyzed
- Serum or plasma CA125 protein (U/mL) was quantified by external laboratories and integrated into the Tempus AI data model
- Median mRNA expression was quantified as $\log_2$(transcripts per million [TPM]+1)
- Platinum-refractory/resistant was defined as occurrence of a disease progression event (progression, recurrence, metastasis, or death) or a progression event proxy (start of a non-platinum or non-maintenance line) within 6 months of starting platinum treatment (refractory) or within 6 months of ending platinum treatment (resistant). Primary platinum-refractory was defined as occurrence of a disease progression event or proxy within 6 months of starting first-line platinum treatment. Platinum-sensitive was defined as no progression event or proxy within 6 months of ending platinum treatment.

Results

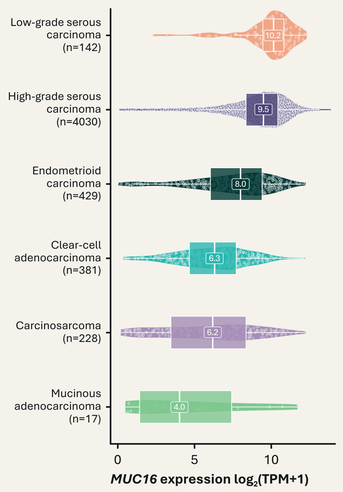
MUC16 PROTEIN ABUNDANCE IS HIGHER IN TUMOR TISSUE VERSUS NORMAL TISSUE AND IS POSITIVELY CORRELATED WITH RNA EXPRESSION; RNA EXPRESSION IS SELECTIVELY ENHANCED IN OVARIAN CANCER

- MUC16 protein abundance in serous ovarian carcinoma tumor samples (n=78) was 1.35-fold greater than in normal adjacent tissue samples (n=17; *P*<0.01) and was positively correlated with *MUC16* mRNA levels (n=71; Spearman's rho [ρ]=0.49, P<0.001) (**Figure 2A**)
- *MUC16* RNA expression was markedly increased in ovarian tumor tissue (n=374) compared with normal ovarian tissue (n=133; *P*<0.001). This differential expression was more pronounced in ovarian cancer compared with other tumor types (**Figure 2B**)

MUC16 IS HIGHLY EXPRESSED ACROSS MOST HISTOLOGIC SUBTYPES OF OVARIAN CANCER

- *MUC16* mRNA expression was analyzed in 5227 ovarian cancer tumor samples, comprising six different histologic subtypes
- The highest median *MUC16* expression ($\log_2$[TPM+1]) was seen in serous histologic subtypes, including 10.2 in low-grade serous ovarian carcinoma (n=142) and 9.5 in high-grade serous ovarian carcinoma (HGSOC; n=4030) (**Figure 3**)
  - Among non-serous subtypes, median *MUC16* expression was 8.0 in endometrioid carcinoma (n=429), 6.3 in clear-cell adenocarcinoma (n=381), and 6.2 in carcinosarcoma (n=228); the lowest expression was seen in mucinous adenocarcinoma (4.0 [n=17])

FIGURE 3. *MUC16* mRNA Expression Across Ovarian Cancer Histologic Subtypes (n=5227)

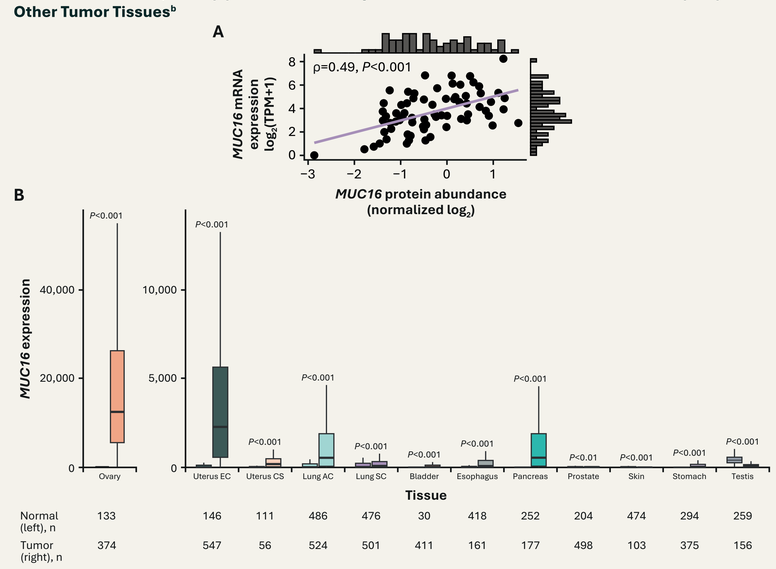


MUC16, mucin 16; **TPM**, transcripts per million.

CA125 PROTEIN ABUNDANCE IS HIGH ACROSS MOST HISTOLOGIC SUBTYPES OF OVARIAN CANCER AND INCREASES WITH ADVANCING DISEASE STAGE

- CA125 data were available for 3549 ovarian cancer tumor samples from six histologic subtypes
- Median CA125 protein abundance was >70 U/mL (2 × upper limit of normal) across most histologic subtypes, including 142.0 U/mL in HGSOC (n=2805), which is the most common ovarian cancer histologic subtype (**Figure 4A**)
- Median serum CA125 protein abundance increased with advancing disease stage, from 44.3 U/mL (n=195) and 66.4 U/mL (n=163) in stage 1 and 2 tumor samples, respectively, to 174.0 U/mL (n=1078) and 170.2 U/mL (n=1152) in stage 3 and 4 tumor samples, respectively (**Figure 4B**)

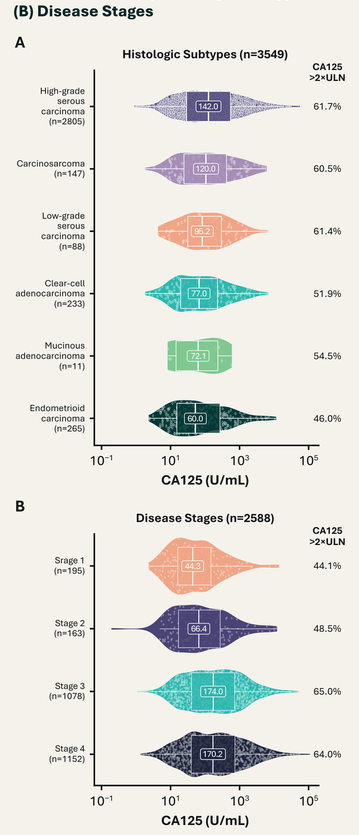
FIGURE 2. MUC16 Protein Abundance (A) Correlated With *MUC16* mRNA Expression in Serous Ovarian Carcinoma;a and (B) *MUC16* mRNA Expression in Normal Tissue Versus Ovarian (Left) and Other Tumor Tissues[b]



Normal (left), n	133		146	111	486	476	30	418	252	204	474	294	259
Tumor (right), n	374		547	56	524	501	411	161	177	498	103	375	156

[a]Data from the Clinical Proteomic Tumor Analysis Consortium. [b]Data from TNMplot.com.[11] ***MUC16***, mucin 16; **ρ**, Spearman's rho.

FIGURE 4. CA125 Abundance Across Ovarian Cancer (A) Histologic Subtypes and (B) Disease Stages

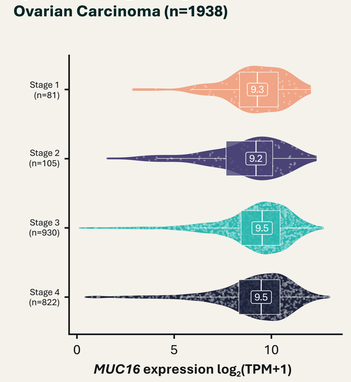


CA125, cancer antigen 125; **ULN**, upper limit of normal.

MUC16 EXPRESSION IS HIGH ACROSS DISEASE STAGES IN HIGH-GRADE SEROUS OVARIAN CARCINOMA

- In HGSOC tumor samples, median *MUC16* expression was similar across primary (n=1116) and metastatic (n=822) tumors (9.5 in both). *MUC16* expression was also similar across disease stages (n=81–930) with no statistically significant difference in expression by disease stage (median, 9.2–9.5 *P*=0.18) (**Figure 5**)

FIGURE 5. *MUC16* mRNA Expression by Disease Stage in High-Grade Serous Ovarian Carcinoma (n=1938)

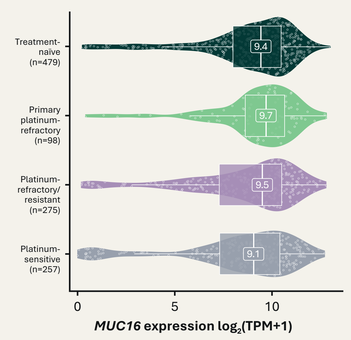


MUC16, mucin 16; **TPM**, transcripts per million.

MUC16 EXPRESSION REMAINS HIGH IRRESPECTIVE OF PLATINUM-SENSITIVITY STATUS

- In ovarian cancer tumor samples with available data on platinum-sensitivity status (n=1109), median *MUC16* expression was similar in platinum-sensitive (9.1 [n=257]) and platinum-refractory/resistant (9.5 [n=275]) tumor samples (**Figure 6**)

FIGURE 6. *MUC16* mRNA Expression Across Platinum-Sensitivity Status in Ovarian Cancer (n=1109)



MUC16, mucin16; **TPM**, transcripts per million.

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