High and Stable *MUC16* Expression in Endometrial Cancer Highlights Potential for Targeted Antibody-Drug Conjugate Development

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Objective

The aim of this study was to assess *MUC16* expression across endometrial cancer histologic subtypes and disease stages using a large dataset of real-world tumor samples

Conclusions

- MUC16 protein expression was higher in endometrial tumor tissue versus normal tissue and showed robust concordance with *MUC16* mRNA expression, underscoring its reliability as a cross-modal biomarker
- *MUC16* expression was high in the most common histologic subtypes of endometrial cancer—serous adenocarcinoma and endometrioid adenocarcinoma
- In endometrial serous adenocarcinoma, *MUC16* expression was uniformly high irrespective of disease stage
  - Furthermore, *MUC16* showed the highest expression of the known ADC targets in development, including *PTK7, SLC34A2* (NaPi2b), *ERBB2* (HER2), *TACSTD2* (TROP2), *FOLR1* (FRα), and *VTCN1* (B7-H4)
- These results support MUC16 as a promising therapeutic target for further clinical investigation in endometrial cancer
  - HWK-016, a next-generation, MUC16-directed ADC, is currently being evaluated in a phase 1 clinical trial in 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 facilitates tumor cell proliferation, metastasis, and evasion of the immune response to cancer[1,2]
- *MUC16* expression is upregulated in several tumor types, including endometrial cancer—in which *MUC16* upregulation is associated with poor prognostic features such as increased risk of high-grade tumors and lymph node metastasis[1–3]
- First-generation MUC16 antibody-drug conjugates (ADCs) were composed of antibodies targeted to the extracellular portion of MUC16,[4–6] which is proteolytically cleaved to produce the well-known serum biomarker cancer antigen 125 (CA125)[1,2]
- Advancements such as the development of antibodies specific for the membrane-bound portion of MUC16,[7] along with improved linker-payload design in ADCs,[8] have reignited interest in MUC16 as a therapeutic target
  - HWK-016 is an investigational, next-generation ADC that targets membrane-bound MUC16. It comprises a monoclonal antibody conjugated to a novel topoisomerase I inhibitor via a stable, cleavable linker that enhances intracellular delivery and limits systemic exposure

Methods

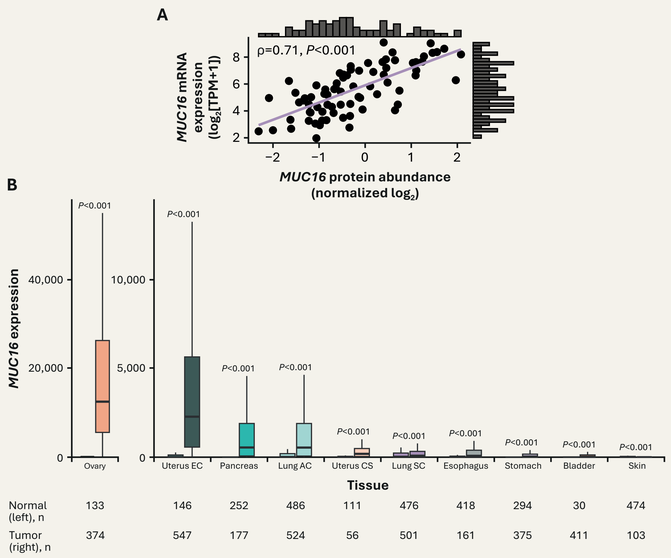
- MUC16 protein expression in tumor tissue versus normal tissue was assessed using Clinical Proteomic Tumor Analysis Consortium (CPTAC) data. Differences were analyzed using the Wilcoxon test
  - Concordance between MUC16 protein abundance and *MUC16* mRNA expression was assessed via Spearman's correlation
- *MUC16* mRNA expression in tumor tissue versus normal tissue across various cancer types was examined using publicly available datasets from TNMplot.com—which integrates RNA sequencing data from The Cancer Genome Atlas (TCGA), Therapeutically Applicable Research to Generate Effective Treatments (TARGET), and the Genotype-Tissue Expression (GTEx) repositories—and group differences were assessed using the Mann–Whitney U test[9]
- RNA sequencing data from a real-world database (Tempus AI, Inc., Chicago, IL, USA) were used to evaluate *MUC16* expression across endometrial cancer histologic subtypes, disease stages, and primary versus metastatic tumors
  - 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 endometrial cancer were also analyzed
- Median mRNA expression was reported as $\log_2$(transcripts per million [TPM]+1)

Results

MUC16 PROTEIN ABUNDANCE IS HIGHER IN TUMOR TISSUE VERSUS NORMAL TISSUE AND IS CONCORDANT WITH *MUC16* RNA EXPRESSION

- In uterine corpus endometrial carcinoma, MUC16 protein levels were 1.21-fold higher in tumor samples (n=86) than in normal adjacent tissue (n=43; *P*<0.1), and they showed a strong positive correlation with *MUC16* mRNA expression (n=77; Spearman's rho [ρ]=0.71; *P*<0.001) (**Figure 1A**)
- *MUC16* RNA expression was markedly increased in tumor tissue compared with normal tissue in several tumor types, including ovarian, endometrial, and pancreatic cancers, and lung adenocarcinoma (all *P*<0.001) (**Figure 1B**)

FIGURE 1. (A) MUC16 Protein Abundance Concordance with *MUC16* mRNA Expression in Uterine Corpus Endometrial Carcinoma;[a] and (B) *MUC16* mRNA Expression in Normal Tissue Versus Tumor Tissue Across Tumor Types[b]



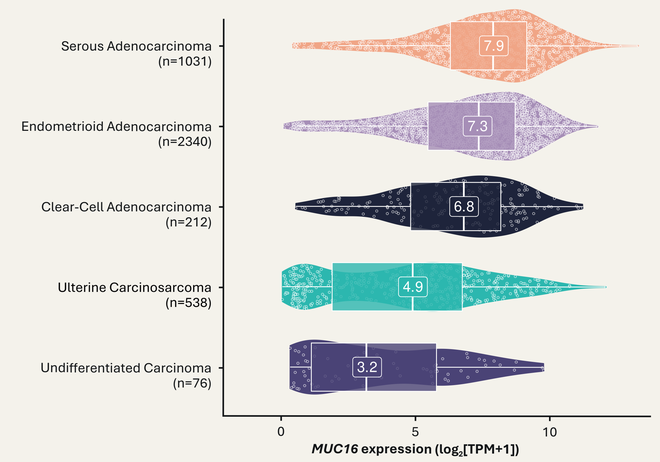
Normal (left), n	133	146	252	486	111	476	418	294	30	474
Tumor (right), n	374	547	177	524	56	501	161	375	411	103

[a]Data from the Clinical Proteomic Tumor Analysis Consortium. [b]Data from TNMplot.com.[9] **AC**, adenocarcinoma; **CS**, carcinosarcoma; **EC**, endometrial cancer; ***MUC16***, mucin 16; **ρ**, Spearman's rho; **SC**, squamous cell carcinoma; **TPM**, transcripts per million.

MUC16 EXPRESSION VARIES ACROSS HISTOLOGIC SUBTYPES OF ENDOMETRIAL CANCER AND IS HIGHEST IN SEROUS ADENOCARCINOMA

- *MUC16* mRNA expression was analyzed in 4205 endometrial tumor samples across five histologic subtypes; 1943 (46.2%) of these were from metastatic tumors
- Median *MUC16* expression ($\log_2$[TPM+1]) varied by histologic subtype. The highest expression (median, 7.9) was observed in serous adenocarcinoma (n=1031), followed by endometrioid adenocarcinoma (median, 7.3 [n=2340]) (**Figure 2**)
  - Expression was lowest (median, 3.2) in undifferentiated carcinoma, though the sample size was small (n=76)

FIGURE 2. *MUC16* mRNA Expression Across Endometrial Cancer Histologic Subtypes (n=4205)

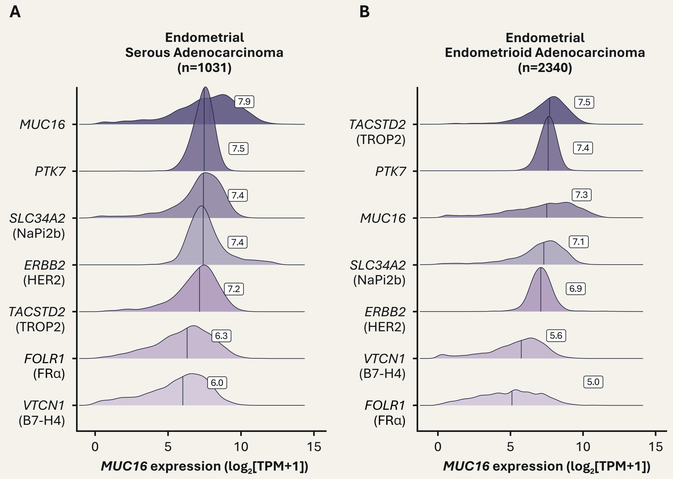


MUC16, mucin 16; **TPM**, transcripts per million.

MUC16 RNA EXPRESSION IS HIGHER THAN THAT OF SEVERAL KEY TUMOR MARKERS IN ENDOMETRIAL CANCER

- *MUC16* was the most highly expressed gene in serous adenocarcinoma tumor samples, with 1.4–3.7-fold higher expression than that of other therapeutic targets in late-stage development for endometrial cancer, including protein tyrosine kinase 7 (*PTK7* [1.4-fold]), *SLC34A2* (sodium-dependent phosphate transport protein 2B [NaPi2b]; 1.4-fold), *ERBB2* (human epidermal growth factor receptor 2 [HER2]; 1.4-fold), *TACSTD2* (trophoblast cell-surface antigen 2 [TROP2]; 1.6-fold), *FOLR1* (folate receptor alpha [FRα]; 3-fold), and *VTCN1* (B7-H4; 3.7-fold) (**Figure 3A**)
- In endometrioid adenocarcinoma tumor samples, *MUC16* was the third most highly expressed gene relative to other key tumor markers, with 1.1–5.1-fold higher expression than *SLC34A2* (NaPi2b; 1.1-fold), *ERBB2* (HER2; 1.3-fold), *VTCN1* (B7-H4; 3.3-fold), and *FOLR1* (FRα; 5.1-fold) (**Figure 3B**)

FIGURE 3. *MUC16* mRNA Expression Relative to That of Other Therapeutic Targets in Endometrial (A) Serous Adenocarcinoma and (B) Endometrioid Adenocarcinoma

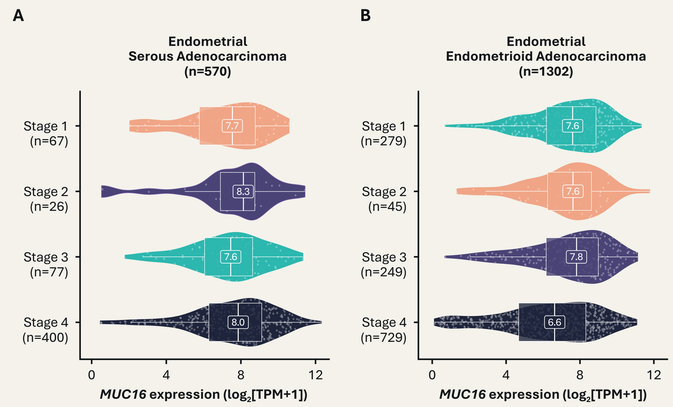


FRα, folate receptor alpha; **HER2**, human epidermal growth factor receptor 2; ***MUC16***, mucin 16; **NaPi2b**, sodium-dependent phosphate transport protein 2B; ***PTK7***, protein tyrosine kinase 7; **TPM**, transcripts per million; **TROP2**, trophoblast cell-surface antigen 2.

MUC16 EXPRESSION IS HIGH ACROSS DISEASE STAGES IN ENDOMETRIAL SEROUS ADENOCARCINOMA

- Of the 570 serous adenocarcinoma tumor samples, 170 (29.7%) were primary and 400 (69.9%) were metastatic. High median *MUC16* expression was maintained in primary versus metastatic tumors (7.7 vs 8.0, respectively; *P*=0.13)
- High median *MUC16* expression was similar across disease stages (n=26–400), with no statistically significant differences (median, 7.6–8.3) (**Figure 4A**)
  - However, sample sizes were small for stage 1–3 tumors (n=26–77)
- Of the 1302 endometrioid adenocarcinoma tumor samples, 573 (43.9%) were primary and 729 (55.9%) were metastatic. High median *MUC16* expression was maintained in primary versus metastatic tumors (7.7 vs 6.6, respectively; *P*<0.001)
- Median *MUC16* expression was significantly higher in tumor stages 1–3 (n=45–279) versus stage 4 (n=729; 7.6–7.8 vs 6.6, *P*<0.001) (**Figure 4B**)

FIGURE 4. *MUC16* mRNA Expression by Disease Stage in Endometrial (A) Serous Adenocarcinoma and (B) Endometrioid Adenocarcinoma



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

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