**Applicant's Name:** Anna Yemelyanova, M.D.

**Applicant's Division:** GYN Pathology

**"P16 Expression in Uterine Adenocarcinomas: Diffuse P16 Expression Distinguishes Uterine Serous Carcinomas from Uterine Endometrioid Carcinomas of Endometrial Origin but not HPV-Related Endocervical Adenocarcinomas"**

Anna Yemelyanova, Hongxiu Ji, Brigitte M. Ronnett
Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD

**Background:** Uterine serous carcinomas (USC) typically have a characteristic morphology (papillary architecture, high-grade nuclei) and immunoprofile (diffuse strong p53 expression, loss of hormone receptor expression) that distinguish them from most uterine endometrioid carcinomas of endometrial origin (UEC). However, pure glandular variants of USC can simulate FIGO grade 2 UEC and some USCs lack p53 expression and retain hormone receptor expression, making classification difficult. P16 expression patterns distinguish UECs (patchy) from HPV-related endocervical adenocarcinomas (ECC) (diffuse) but utility for distinction of USCs from UECs and ECCs has not been evaluated.

**Design:** Immunohistochemical expression of p16 was evaluated in 15 typical uterine serous carcinomas and compared to expression in 43 typical uterine endometrioid carcinomas of endometrial origin (21 FIGO grade 1, 17 FIGO grade 2, 5 FIGO grade 3) and 14 HPV-positive HPV-related endocervical adenocarcinomas. All tumors were from hysterectomy specimens.

**Results:** All uterine serous carcinomas demonstrated diffuse moderate to strong p16 expression, with percentage of positive tumor cells ranging from 90-100% (mean/median, 96%/100%). In contrast, uterine endometrioid carcinomas of endometrial origin exhibited less diffuse and less intense expression, with percent of positive tumor cells ranging from 5-90% (mean/median 36%/30%; staining intensity ranging from weak to strong). All HPV-related endocervical adenocarcinomas exhibited diffuse moderate to strong p16 expression, with percentage of positive tumor cells ranging from 90-100% (mean/median, 96%/100%)

**Conclusions:** Uterine serous carcinomas are characterized by diffuse moderate to strong p16 expression, which is distinct from the patchy pattern of expression seen in uterine endometrioid carcinomas of endometrial origin. P16 can serve as an additional diagnostic marker of Uterine serous carcinomas which can be added to an immunohistochemical panel including p53, Ki-67, ER, and PR for distinction of USCs from UECs, particularly glandular variants of USC (which can be misclassified as FIGO grade 2 UEC), those lacking p53 expression (due to p53 mutations leading to lack of immunoreactive p53 protein), and those retaining hormone receptor expression. The diffuse p16 expression pattern shared by uterine serous carcinomas and HPV-related endocervical adenocarcinomas, coupled with frequent lack of hormone receptor expression in both tumor types, could lead to misclassification of the same problematic subsets of uterine serous carcinomas as HPV-related endocervical adenocarcinomas.