IDENTIFICATION OF MOLECULAR TARGETS AND PATHWAYS FOR IMPROVING ENDOMETRIAL CANCER RACIAL DISPARITIES

1Lindsay Borden*, 2Pouya Javadian, 3Amy Kennedy, 4Chao Xu, 5Virginie Spielund, 6Doris Banbrook, 7University of Oklahoma, Gynecologic Oncology, Oklahoma City, USA; 8University of Oklahoma Health Sciences Center, Gynecologic Oncology, Stephenson Cancer Center, Oklahoma City, USA; 9University of Oklahoma, Department of Biostatistics, Oklahoma City, USA

Objectives Identify proteins present at significantly different levels in endometrial cancer specimens across 4 racial groups to direct future therapy.

Methods Proteins extracted from endometrioid endometrial cancer specimens of women who self-identified as Black, American Indian, or White (N=12 each), or Asian (N=10) were measured by Tandem Mass Tag Liquid chromatography-tandem mass spectrometry. Patients were matched for age and body mass index. Significant differences in protein levels were identified by ANOVA after adjustment of the first principal component and evaluated by Ingenuity Pathway Analysis. Drug effects on human Ishikawa endometrial cancer cells were evaluated using an MTT assay.

Results The only patient characteristics significantly different across racial groups were higher rates of diabetes in Blacks and hypertension in Whites. Fifty-eight proteins exhibited significant differences across all groups. The most significant pathways identified to be regulated by proteins significantly different in non-Whites compared to Whites are regulators of protein synthesis. Trametinib and 2-deoxyglucose inhibition of mitogen-activated protein kinase 3 and hexokinase-2, which were significantly upregulated in specimens from Blacks compared to Whites, reduced growth of endometrial cancer cells with half-maximal inhibitory concentrations of 3 uM and 3 mM, respectively, but did not interact synergistically.

Conclusions This study demonstrated significantly different protein expression profiles in endometrioid endometrial cancers across 4 races. These proteins represent candidate biomarkers and drug targets for development of strategies to improve disparate outcomes of endometrial cancer patients.

DNA METHYLATION LANDSCAPE AS A POTENTIAL PLAYER IN ACQUIRED-DRUG RESISTANCE IN OVARIAN CANCER

1,Petronia Silva, 2Kate Glennon, 3Michael Metoudi, 4Bruce Moran, 5Soifa Salta, 6Karen Slattery, 7Antoinette Perry, 8Donal Brennan*. 9Mater Hospital, Gynaecology Oncology, Dublin, Ireland; 10Mater Misericordiae University Hospital, Clinical Research Centre, Dublin, Ireland; 11University of Leicester, Clinical Research Centre, Leicester, UK; 12Trinity College Dublin, Trinity Biomedical Science Institute, Dublin, Ireland; 13Institute of Biomedical Sciences Abel Salazar, Department of Pathology and Molecular Immunology, Porto, Portugal; 14University College Dublin Gynaecological Oncology Group, UCD School of Medicine, Mater Hospital, Dublin, Ireland

Objectives Development of therapeutic resistance is a major cause of mortality in high-grade serous ovarian cancer (HGSOC), thus a better understanding of acquired resistance mechanisms is needed. This study aimed to investigate how epigenomic events might be associated with acquired-drug resistance in HGSOC patients.

Methods Methylation and gene expression differences between primary platinum-sensitive (n=32) and recurrent acquired-resistant samples (n=28) was explored using a HGSOC dataset. High resolution melting was used to validate results using epithelial ovarian cancer cell lines and HGSOC tumours. A CRISPR-Cas9 approach was used to investigate the effects of DNA methylation editing in vitro. Plasma samples from HGSOC patients (n=17) and age-matched healthy controls (n=20) were used to investigate longitudinal methylation dynamics via droplet digital PCR.

Results Comparison of methylation and gene expression analysis identified several genes, known to be involved in diverse immune and chemoresistance-related pathways, that significantly differentiated between paired platinum-sensitive and acquired-resistant HGSOC samples, with three genes displaying the most consistent methylation changes (PDCD1, NFKB, APOBEC3A). A CRISPR-Cas9 approach was used to interrogate the effects of APOBEC3A and NFKB promoter methylation editing on platinum sensitivity, with demethylation of NFKB promoter being associated with increased platinum sensitivity. Hypermethylation of NFKB and APOBEC3A were detected in 46% and 69%, respectively, of plasma samples from women with relapsed HGSOC.

Conclusions Promoter methylation has been identified as potentially involved in HGSOC drug resistance. Further research is warranted to understand the future use of these methylation patterns as prognostic/predictive markers in the OC clinical setting.

EXPLOITING SMARCA2 DEPENDENCY FOR TARGETED THERAPY IN SMARCA4-DEFICIENT OVARIAN CANCERS

1,Melica Brodeur*, 2Higinio Dopeso, 3Hunter Green, 4Koichi Ito, 5Michael Hulse, 6Bruce Moran, 7Trinity College Dublin, School of Medicine, Dublin, Ireland; 8Mater Hospital, Department of Pathology, Dublin, Ireland; 9Mater Misericordiae University Hospital, Clinical Research Centre, Dublin, Ireland; 10University College Dublin, School of Medicine, Dublin, Ireland; 11Memorial Sloan Kettering Cancer Center, New York, USA; 12Trinity College Dublin, School of Medicine, Dublin, Ireland

Objectives Most ovarian cancer (OC) patients recur after frontline treatment and develop chemoresistance, highlighting an unmet need for precision medicine in OC. Half of OCs harbor mSWI/SNF chromatin-remodeling complex alterations including 10% in the SMARCA4 gene. Studies to date have suggested that the catalytic subunits of the mSWI/SNF complex, SMARCA2 and SMARCA4, exhibit paralog dependency and thus present an opportunity for synthetically lethal molecular targeting. The aim of this study is to investigate SMARCA2-dependency in SMARCA4-deficient OCs and to identify synthetic lethal interactions of SMARCA2-protein degradation in these cancers.

Methods Using CRISPR-Cas9 lentiviral-transduction targeting the SMARCA4 gene, we developed novel murine syngeneic/isogenic OC cell lines from well-characterized cell lines ID8 and UPK10, and novel electroporation-based genetically engineered mouse model-derived cell line 3_1. Human isogenic
OC cell lines OAW28 were also derived using the same technique. SMARCA2 protein degrader (proteolysis-targeting chimera) was provided in collaboration with industry. Western blots were performed to define paralog dependency in SMARCA4-deficient cells and to assess adequate SMARCA2-degradation. SMARCA2 protein degrader response was assessed using viability assays.

**Results** SMARCA4-deficient isogenic OC cell lines displays increased SMARCA2 protein expression compared to SMARCA4-wildtype cells, suggesting that paralog dependency exists in OC. Furthermore, near complete SMARCA2-degradation occurs at low nanomolar range after 6-hour incubation. Comparing IC50 values, we show a 5-fold increased sensitivity to the SMARCA2 protein degrader in SMARCA4-deficient OC cell lines compared to control, suggesting a synthetic lethal interaction in these cancers.

**Conclusions** This study identifies SMARCA2 protein degradation as a unique therapeutic vulnerability and potential therapeutic target for SMARCA4-deficient OCs.

**EP006/#812 THE EXPRESSION LEVEL OF OBESITY AND LIPID METABOLISM RELATED GENES CONDITIONS TUMOR BEHAVIOR AND SURVIVAL IN GYNECOLOGICAL CANCERS**

1Mauricio Cuello*, 1Sumie Kato, 1Fernán Gomez, 1Felipe Suárez, 1Cristián Salazar, 2Ignacio Wichmann. 1Pontificia Universidad Católica de Chile, Gynecology, Santiago, Chile; 2Pontificia Universidad Católica de Chile, Obstetrics, Santiago, Chile

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**Objectives** Currently, the carcinogenesis of thirteen neoplasms has been related to obesity. Of the gynecological ones, endometrial and ovarian cancers are associated with it. To date, obesity is defined based on BMI (≥30 kg/m²). However, not all obesity is associated with a metabolic disorder (healthy-metabolic-obesity or HMO). Likewise, there are individuals with normal BMI (<25 kg/m²) who are carriers of metabolic disorders. The objective of this study was to establish whether the abnormal expression of obesity- and lipid metabolism-related genes could determine the biological behavior and survival of the most prevalent gynecological cancers.

**Methods** To do this, we built a 2208 obesity/dyslipidemia/hypercholesterolemia-related gene dataset (ODH) according to phenopedia (PGHKB (v7.7)). We then downloaded TCGA endometrial (UCEC=543-cases), cervical (CESC=304-cases) and ovarian (OVCA=374-cases) cancers RNAseq datasets. NMF-consensus clustering, differential-gene-expression-analyses (DGEA), Gene-set-enrichment (GSEA) and Gene-Ontology (GO) analyses were carried out, and Kaplan-Meier survival curves were built-up. Significantly up- or downregulated genes were defined as those with logFC≥1.5 at non-adjusted p-values ≤0.01.

**Results** Based on ODH-gene expression, we identified UCEC, CESC and OVCA clusters with significantly different overall survival (OS). Regarding UCEC, a cluster allocates the high-copy-number endometrioid-variant as well as the serous type (worse prognosis), in a similar manner as observed with the mesenchymal-variant in high-grade-serous ovarian cancer (see figure 1). Interestingly, the GSEA and GO-analyses show that for worse prognosis histologies exhibit different enrichment patterns regarding antitumor immune response, TGF-beta (EMT)-mediated signaling, lipid metabolism and inflammatory response (all cancer hallmarks).

**Conclusions** These in-silico findings support the role of obesity in conditioning behavior/therapeutic response/prognosis of these gynecologic cancers. (Supported_by_fondecyt_1201083)