thought to be an integral part of chemoresistance, but the relation of these adaptations to chemoresistance is poorly understood. Our aim was to identify the metabolic adaptations that are specifically associated with platinum-resistant (PR) cell lines and its platinum-sensitive (PS) derivatives across multiple OC cell lines.

**Methods** Targeted metabolic analysis evaluating 242 metabolites of the PS A2780, PEO1, and mR182 cell lines was performed along with their respective PR derivatives, C200, PEO4, R182. The group comparison was performed using unpaired t-tests followed by FDR correction. The differentially expressed metabolites were identified using two criteria: FDR ≤ 5% and absolute fold-change ≥ 1.5. The pathway analysis was performed using MetaboAnalyst™ with the metabolites that have unadjusted p-value ≤5%.

**Results** Many significantly impacted pathways were conserved among the PR cell lines. Compared to the PS counterparts, the PR PEO4, C200, and R182 lines had metabolite concentrations with FC > 1.5 in 29, 44, and 28 measured metabolites, respectively. The top pathways impacted were ‘nicotinate and nicotinamide metabolism’, ‘purine metabolism’, and ‘phenylalanine, tyrosine, tryptophan biosynthesis’. A global analysis of PS vs PR was performed. The top five significantly impacted pathways were: Arginine biosynthesis, Pyrimidine and Purine metabolism, Phenylalanine, tyrosine and tryptophan biosynthesis’ and ‘Starch and sucrose metabolism’.

**Abstract EPV002/#308** Figure 3  a) Volcano plot of sensitive cohort vs resistant cohort; b) Heat map of sensitive cohort vs resistant cohort

**Abstract EPV002/#308** Figure 4  Top impacted pathways of combined PR cohort compared to PS cohort

**Conclusions** We identified multiple shared metabolomic pathways among established PR OC cell lines that highlight conserved motifs of PR. These may represent targetable pathways to predict or reverse chemoresistance.

**EPV003/#326** AN INTEGRATED GENOMIC, PROTEOMIC AND IMMUNOPEPTIDOMIC APPROACH TO DISCOVER NOVEL TUMOUR NEOANTIGENS IN AN IMMUNOLOGICALLY COLD OVARIAN CANCER FOR PERSONALISED T-CELL RECEPTOR THERAPY

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**Conclusions** We identified multiple shared metabolomic pathways among established PR OC cell lines that highlight conserved motifs of PR. These may represent targetable pathways to predict or reverse chemoresistance.
Objectives AXL is a receptor tyrosine kinase that is activated by GAS6. Overexpression of AXL is correlated with the glycolytic phenotype in metastatic lung cancer. Cancer cells preferentially convert glucose to lactate via glycolysis which promotes growth and survival. It is unknown whether inhibition of AXL can prevent glycolysis in endometrial cancer causing cell death. The aim of this study was to determine whether AVB-500 can increase sensitivity to paclitaxel through inhibition of glycolysis.

Methods Cell viability was performed with high-grade endometrial, chemoresistant cell lines, ARK1 and PUC1. Cells were treated with paclitaxel (P) and with AVB-500+paclitaxel (AVB-500+P). Intraperitoneal ARK1 or PUC1 tumors were treated with vehicle, AVB-500, P, or AVB+500+P. Cell lysates were analyzed using the Jess system. A Seahorse Analyzer was used for glycolytic rate assays. Stable isotope tracing was used for in vivo metabolite abundance quantification.

Results We found that ARK1 and PUC1 cells had decreased viability when treated with AVB-500+P than when treated with P alone. ARK1 and PUC1 in vivo IP models had significantly fewer tumors and decreased tumor weight when treated with AVB-500+P compared to P alone. Treatment with AVB-500+P was found to decrease basal glycolysis in vitro through decreased AKT activation. Multiple glycolytic metabolites were decreased in the tumors of AVB-500+P compared to treatment with P alone.

Conclusions We demonstrate that the addition AVB-500 to paclitaxel improves endometrial cancer chemosensitivity. We show that this therapeutic combination decreases basal glycolysis through reduced PI3K/AKT signaling. This provides a metabolic mechanism for increasing uterine cancer sensitivity to chemotherapy.

Objectives The molecular processes underpinning distant metastasis in endometrial cancer (EC) are not well understood. We sought to characterize the genomic alterations of primary ECs and matched lung metastases.

Methods Primary ECs, matched lung metastases, and normal tissue from two patients were subjected to whole-exome sequencing. Sequencing data were analyzed using validated bioinformatics tools. Stable isotope tracing was used for glycolytic rate assays. Stable isotope tracing was used for in vivo metabolite abundance quantification.

Results We found that ARK1 and PUC1 cells had decreased viability when treated with AVB-500+P than when treated with P alone. ARK1 and PUC1 in vivo IP models had significantly fewer tumors and decreased tumor weight when treated with AVB-500+P compared to P alone. Treatment with AVB-500+P was found to decrease basal glycolysis in vitro through decreased AKT activation. Multiple glycolytic metabolites were decreased in the tumors of AVB-500+P compared to treatment with P alone.

Conclusions We demonstrate that the addition AVB-500 to paclitaxel improves endometrial cancer chemosensitivity. We show that this therapeutic combination decreases basal glycolysis through reduced PI3K/AKT signaling. This provides a metabolic mechanism for increasing uterine cancer sensitivity to chemotherapy.

Abstracts

EPV006/#578 ROLE OF CHRONIC STRESS ON ANTI-TUMOR T-CELL RESPONSES IN OVARIAN CANCER

1A Aquino-Acevedo*, 2H Knochenhauer, 3M Ortiz-León, 1Y Rivera-López, 1M Bonilla-Claudio, 1R Revis, 2G Armaiz-Pena. 1Ponce Health Sciences University, Department of Basic Sciences (pharmacology), Ponce, Puerto Rico; 2Duke University School of Medicine, Obstetrics and Gynecology, Durham, USA

Objectives A cancer diagnosis increases stress hormones and leads to altered psychological states. Work from our team suggests that chronic stress promotes an increased inflammatory response. Preliminary data show an altered CD4+/CD8+ T-cell ratio and a heterogeneous expression of exhaustion markers in patients with high-grade serous ovarian cancer (HGSOC). Therefore, we hypothesized that chronic stress results in loss of effector T-cell response and increased exhaustion.

Methods We obtained ascites samples from 66 patients with HGSOC and measured cytokine levels using a comprehensive cytokine/chemokine magnetic bead panel. Metanephrine (an epinephrine metabolite) levels from ascites were measured by ELISA. CD8+ T-cells isolated from OC patient ascites were stimulated with epinephrine and flow cytometry was used to measure co-expression of CD38 activation marker and Granzyme B, an essential mediator of CD8+ T-cell killing capacity.

Results Showed a significant increase in inflammatory cytokines in chemo-resistant and recurrent tumors: Eotaxin (p=0.002), IL-6 (p=0.003), and IL-7 (p=0.009). Metanephrine, was positively correlated with pro-tumoral and inflammatory cytokines: SCD40L (p=0.032), FGF-2 (p=0.033) and MIP1a (p=0.03). Ascites-derived CD8+ T-cells treated with epinephrine, showed a decreased co-expression CD38 and Granzyme B (p=0.004). These results suggest a role for stress hormones in T-cell activation suppression.

Conclusions Chemo-resistant and recurrent tumors were associated with increased pro-inflammatory cytokines. Similarly, high metanephrine levels correlated with higher pro-tumoral cytokines. Epinephrine stimulation decreased CD8+ T-cell function in ascites of HGSOC patients. These data suggest a role for stress in immunosuppression and may impact efficacy of therapies that aim to restore T-cell function.