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Poster #1

Comprehensive single cell analysis of a patient's primary, recurrent, and xenograft ovarian cancer

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Objectives: Demonstrate a novel precision medicine approach in the diagnosis and treatment of ovarian cancer through comprehensive genomic and histologic analysis of a *BRCA1*+ primary, recurrent, patient-derived xenograft (PDX), and chemo-resistant PDX tumor.

Methods: The patient was consented as part of a prospective precision medicine study in ovarian cancer utilizing single cell sequencing technology. A tumor specimen was taken at the time of primary debulking for single cell RNA sequencing (scRNA-seq, 10x Genomics) and exome sequencing (C1 Fluidigm). Portions were also sent for bulk RNA & DNA sequencing and used to create mouse xenograft avatars. Avatar mice were treated with carboplatin and paclitaxel to generate chemo-resistant PDX tumors which were also single cell sequenced. Tumor was similarly collected and analyzed at the time of the patient's platinum sensitive recurrence. The patient also underwent genetic counselling with subsequent germline medical exome sequencing (covering ~4000 clinically significant loci). Histologic examination of the primary, recurrent, and xenograft tumors was performed by a board-certified pathologist.

Results: scRNA-seq was able to identify 7 distinct subpopulations of stromal and cancer cells, reproducible via multiple clustering algorithms. The patient's known *BRCA1* founder mutation, 187delAG, was identified by both somatic single cell exome sequencing and germline exome analysis. No additional clinically relevant mutations were identified via the extended germline panel. Histologic analysis of the primary, recurrent, and PDX tumors did demonstrate evidence of treatment effect. Analysis of the tumor subpopulations is ongoing to identify cell lineages shared between primary and recurrent samples, with a focus on chemo-resistant/stem-like populations.

Conclusions: We have created a compilation of single cell data on a *BRCA1*+ patient and demonstrated the increased resolution of this method over traditional approaches. Further analysis of cell subgroups may help identify chemo-resistant/stem-like populations present within the primary tumor which increase the risk for recurrence. Identification of these populations may guide novel treatment approaches after front-line therapy to ultimately improve patient outcomes.

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Poster #2

How does microbiome change with chemotherapy? Using an in vivo model of uterine cancer to assess changes in gut microbiome

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Objectives: Recent studies have suggested interactions between microbiome and cancer therapeutics. In addition to direct cytotoxicity, chemo-induced changes in microbiome may play significant role in disease outcomes. Our objective was to evaluate the efficacy of therapeutic agents in a mouse model of human endometrial cancer (EC) and their effect on tumor growth and gut microbiome.

Methods: An EC cell line, HTB-112 (ATCC), was injected subcutaneously into female, athymic mice. After 1week, mice were randomized and treated with one or a combination of 3 chemotherapies, carboplatin (C), paclitaxel (T), and a new investigational agent, Minnelide (M). Mice were treated for 4weeks with either single agent C, T, M, or combination C/T, C/M, T/M, or C/T/M. Mice were euthanized and tumors weighed. Fecal samples were collected prior to establishing tumors and weekly after. Microbial DNA was isolated from fecal samples and processed (Qiagen) for sequencing 16S rRNA gene, variable region 4 (U. of Minnesota, Genomics Center). Diversity between groups was calculated using Bray-Curtis dissimilarity.

Results: Tumors from mice treated with M, or C/M, or T/M were significantly smaller than tumors treated with single agent C or T (both, $p<0.0005$) or with C/T ($p<0.02$). There was no significant difference between single agent M, C/M, or T/M. Triplet therapy C/T/M treated tumors were significantly smaller than all other treatments ($p<0.05$).

Untreated controls with tumor were compared to treatment groups. Both single agent C and T changed beta diversity of fecal microbial composition significantly ($p=0.02$ for both), as did the combination of C/T ($p=0.04$) and tumors were larger. Monotherapy with M or in doublet, C/M or T/M, did not significantly change the microbial beta diversity ($p>0.05$) and tumors were smaller. In taxonomic analyses, M treated tumors were smaller and retained a greater percent of Firmicutes. C or T alone or C/T lost Firmicutes and increased Bacteroides relative abundance (figure attached).

Conclusions: We used a mouse model of EC, with 3 chemotherapies and compared chemotherapeutic efficacy and changes in microbiome. There was a correlation with increasing Bacteroides species abundance and increased tumor size. Interestingly, C treatment showed no significant change in tumor size and correlated with the

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