

## PROFILING OVARIAN CANCER TUMOR AND MICROENVIRONMENT WITH DISEASE PROGRESSION FOR THE DESIGN OF IMMUNOTHERAPY STRATEGIES

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**Background** Ovarian cancer (OC) is a deadly disease with a high mortality rate due to its propensity for late detection and frequent recurrence. Following initial treatment, typically a combination of surgery and chemotherapy administration, patients often experience a disease remission but will likely experience a relapse. Once the disease has reached this recurrent state, therapies have limited efficacy. Identification of novel therapeutic targets and improved understanding of the molecular and cellular characteristics of the OC tumor microenvironment (TME) are urgently needed to advance treatment options for this devastating disease.

**Methods** Here, we conducted a comprehensive analysis of tumor cells and the TME in 26 primary OC patient samples, including 16 chemo-naïve patients and 10 recurrent patients. Profiling antigens on tumor cells allowed for the identification of potential targets for the development of cell-based therapies, and profiling the TME in OC patients yielded insights into the differences between OC patients over the course of disease progression. In addition, we developed multiple cell-based immunotherapies to target OCs identified by various tumor antigens, including chimeric antigen receptor (CAR)-engineered T cell-based therapy, and allogeneic HSC-engineered invariant natural killer T (iNKT) cell-based therapy.<sup>1 2</sup>

**Results** Our results demonstrated that our HSC-engineered iNKT(HSC-iNKT) cells exhibited robust antitumor efficacy in all patient-derived tumor cells tested, irrespective of the expression levels of tumor antigens and CSC markers, supporting the potential utility of HSC-iNKT cell therapy as a viable treatment option for OC, particularly in the setting of recurrent disease. In addition, the HSC-iNKT cells successfully targeted TAMs/MDSCs in our patient TME in a CD1d-dependent mechanism, while sparing healthy T cells, B cells, and NK cells, indicating their capacity to alter OC TME.

**Conclusions** Overall, our study provides a detailed characterization of the tumor cell and TME profiles among primary OC patients and suggests the potential for developing cell-based therapies for the treatment of OC, particularly for recurrent disease.

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**Ethics Approval** This study was approved by the UCLA Office of the Human Research Protection Program, IRB #10-000727 and IRB #20-001659.

**Consent** Primary OC patient samples were collected from consented patients through an IRB-approved protocol (IRB #10-000727) and processed.

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