

EX VIVO PROFILING OF PD-1 BLOCKADE USING AN ORGANOTYPIC TISSUE SLICE MODEL IN SOLID TUMORS

Lina Ding*, Kristin Sullivan, Chensheng Zhou, Jimena Trillo-Tinoco, Anne Lewin, Catherine King, David Nelson, Benjamin Chen, Michaela Bowden. *Bristol Myers Squibb, Cambridge, MA, USA*

Background Tumor explant models provide a powerful ex vivo tool to evaluate complex biological mechanisms in a controlled environment. Ex vivo models retain much of the original tumor biology, heterogeneity, and tumor microenvironment, and therefore provide a useful preclinical platform and functional approach to assess drug responses rapidly and directly.

Methods To explore mechanisms of resistance to cancer immunotherapy, we established an organotypic tissue slice Air-Liquid Interface (ALI) ex vivo system utilizing surgical tumor specimens from patients to assess the impact of the clinically utilized anti-PD-1 antibody nivolumab (OPDIVO). In the present study, we built a real-world patient cohort comprised of six tumor types: non-small cell lung cancer, melanoma, pancreatic ductal adenocarcinoma, breast cancer, prostate cancer, and colorectal cancer. We assessed tissue morphology, histology, PD-L1 IHC (CPS and TPS), CD8 T cell topology, proliferation in the tumor and stromal compartments, and secretome profiling.

Results Our tumor slice model highly recapitulated features of the original tumor, including tumor architecture, immune phenotypes, and the prognostic markers. To identify responses to aPD-1 treatment, we compared baseline values for the cultured tumor slices with values at different timepoints post treatment. Secretome profiling of tissue explant supernatants using a panel of 94 analytes, revealed alterations to cytokines produced in the tumor microenvironment in response to aPD-1 treatment. We found that soluble expression patterns were associated with T-cell patterns (inflamed, excluded and desert) and PD-L1 score (CPS and TPS) in tumor tissues. These cytokines mediate critical functions across the immune cell cycle. Ongoing efforts to characterize T cell activation, exhaustion, tumor intrinsic responses and microenvironment composition using Imaging Mass Cytometry will be presented.

Conclusions In this study, we demonstrated the feasibility of using fresh, surgically resected human tumors to test aPD-1 responses in an ex vivo system. Further, this model system has the potential to drive discovery and translational efforts by evaluating mechanisms of resistance to cancer immunotherapy and evaluate new single agent or combination therapies in the ex vivo setting.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.292>