DEVELOPMENT OF EX VIVO 3D TUMOR MODELS TO AID IN IMMUNO-ONCOLOGY DRUG DISCOVERY EFFORTS


Background Improved efficiency of pre-clinical drug development translation to clinical use ensures that new therapeutics are available to patients faster. Co-development of drug and biomarker tests, such as PD-1/PD-L1 targeting agents with PD-L1 expression, have been advantageous for patient stratification. Unfortunately, they are poor proxies for drug response. Animal models and genomics have traditionally been used to aid in predicting clinical success. However, with the Modernization Act 2.0, in vitro model development has received more attention. Here we have further modified our current platform of ex vivo models for immuno-oncology. They may be used to serve as decision tools for drug developers by identifying the right patients for a potential therapeutic validating that a drug candidate displays the right effect in a proposed tumor model. As a case study, we evaluated the efficacy of atezolizumab compared with chemotherapy and combinations in patient samples approved, withdrawn, or not FDA-approved for specific treatment paradigms.

Methods Spheroids were generated from dissociated patient-derived xenograft (PDX) tumors or patient-derived organoids. Non-small cell lung cancer (NSCLC) (certain types approved for first-line atezolizumab), advanced urothelial carcinoma (no longer FDA-approved for atezolizumab), and high-grade glioma (no FDA-approved immunotherapies) were selected for this study. Dosing optimization was conducted in the presence or absence of T-cells. Single agent atezolizumab efficacy was compared to platinum/gemcitabine combination or a triple combination of all three agents for NSCLC and urothelial carcinoma models. Tumor cell killing was assessed via flow cytometry. Microtumors were generated to test T-cell infiltration across all solid tumor indications to relate chemokines to phenotype.

Results Ex vivo models maintained primary tissue characteristics. Tumor marker expression ranged across and within tumor types. The presence of T-cells impacted cytotoxicity to chemotherapy. Cisplatin demonstrated more favorable response when T-cells were present compared to other chemotherapies. Less tumor cell cytotoxicity was detected in urothelial carcinoma models compared to NSCLC models. The presence of chemokines was correlated with model susceptibility to T-cell infiltration in microtumors. Differences in T-cell infiltration were detected across tumor types and drug treatments, with NSCLC models being the most susceptible to atezolizumab efficacy.

Conclusions Our preclinical ex vivo 3D models can be tailored to evaluate different drug classes for modulating an immune response across multiple tumor types. PDX and organoid samples can be utilized to verify that drug response is achieved in both a cancer-type specific manner as well as in a patient specific manner.

REFERENCES