3D EX VIVO PATIENT TISSUE PLATFORM FOR IMMUNO-Oncology Drug Testing

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Background Many immuno-oncology drugs fail in clinical trials, which is partly due to the lack of in vitro and in vivo models that sufficiently recapitulate the tumor microenvironment (TME). To bridge this gap in translational model systems, a 3D ex vivo patient tissue platform was developed which uses 3D ex vivo tumor cultures, where tumor endogenous cells of the TME are preserved. These TME components can affect tumor drug responses with potentially novel targets for drug development, making them a crucial component to be presented upon drug efficacy evaluations.

Methods Patient tumor tissues, both solid resection and liquid biopsies from metastatic disease, were processed within 24 hours of surgery or fluid drainage. Following minimal processing small tumor clusters and single cells remain, that were manipulated in liquid handling robotics. The material was embedded in a protein-rich hydrogel and exposed to panels of drug treatments in a 384-well format for 5–7 days until samples were fixed. Tissue responses were quantified using a Crown Bioscience proprietary high content image (HCI)-based analysis platform. In addition, histology and FACS were used to characterize primary samples at baseline. Cytokine measurements were performed on the tumor supernatants.

Results Freshly isolated tumor cells from various cancer patients were exposed to tissue relevant treatments, such as standard of care, targeted therapies, and immunomodulatory drugs. Endpoint analysis of fixed and stained material allowed for phenotypic measurement of responses such as tumor cell volume reduction, indicating cell killing, and more in-depth effects including growth arrest, and immune cell proliferation. Differential responses of tumor tissues to various classes of drugs targeting the tumor and/or the TME were demonstrated. In addition, validation of the various TME components for different cancers was confirmed. Using FACS, the presence of tumor cells accompanied by immune-profiling of the TME, including presence of tumor infiltrating lymphocytes, macrophages, and other immune cells was observed. Similarly, biomarker staining using IHC indicated the presence of tumor cells, fibroblasts, and various immune cell types. Cytokine measurement at experimental endpoint aligns with the measured responses of tumor reduction upon certain drug treatments.

Conclusions The 3D ex vivo patient tissue platform offers a rapid, reliable and patient-relevant approach to test preclinical drug candidates (e.g., antibodies, antibody-drug conjugates and small molecules) for different solid tumour types. It has the potential to significantly improve the preclinical evaluation of drugs and support the decision-making process during progression of drug candidates to the clinic.

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A212