

Drug screening of biopsy-derived multicellular spheroids using microfluidic technology

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Performing drug screening, of physiologically relevant three-dimensional (3D) tumor models, for personalized treatment remains challenging, due to the small amount of tissue available from most biopsies. New microfluidic technologies, enabling greater control over cell positioning and fluid behavior at the micro-scale, allow extensive testing of anticancer agents on human tumor tissue preparations in 3D and offer new solutions for the development of anticancer compounds and personalized medicine. We have developed a microfluidic platform for extensive drug screening of tumor biopsies in a cost-effective manner and validated the system with tumor prostate patient samples. As a typical drug screening assay, up to 22 drug concentration-response curves could be generated from a single biopsy, within a time frame of up to 4 weeks. Biopsy tissue, grown as a heterogeneous co-culture from the primary sample, was prepared as cancer-cell enriched multicellular spheroids, cultured for 3 to 5 days prior to the application of a panel of standard-of-care drugs for prostate cancer. Readouts were obtained via bright-field and epifluorescence microscopy. The microfluidic platform was designed to be operated entirely without the need of external fluid actuation, with the microfluidic network capable of generating long-lasting, stable and repeatable drug concentration gradients across arrays of 240 spheroids. Outcomes were generated as 8-point drug concentration response curves per device, with each drug concentration tested on at least 24 spheroids. In-house developed software was used to analyze bright-field and fluorescent images to provide readouts of spheroid growth and viability, as well as information on drug penetration and drug efficacy over time. Following platform and assay validation using cancer cell lines, proof-of-concept screening was performed on prostate biopsies from 2 different patients. Results showed that biopsy-derived spheroids were more resistant to treatment than LNCaP spheroids, a prostate cancer cell line. For one biopsy, spheroids were sensitive to docetaxel, but resistant to enzalutamide, despite the presence of intact androgen receptors. This preliminary data outlines how this technology could become a useful tool to investigate patient-specific drug resistance and to test novel anticancer agents in a cost-effective manner, based on maximized screening of human tumor tissue in a 3D format.