Cancer organoids are heterogeneous 3D cellular clusters with complex microenvironments of tumors and normal host tissues that have the potential to provide better predictions of in vivo drug responses than those performed with cell monolayer cultures. The National Cancer Institute (NCI) is developing a national repository of Patient-Derived (PD) models consisting of genetically and molecularly characterized PD xenografts (PDXs) and PD organoids (PDOs) (https://caneren.org). We evaluated the therapeutic responses of PDOs as a single layer of organoids or as organoid clusters (PDOrgs) grown as agarose plugs, PD xenografts, murine xenografts, and PDOrgs grown as organoid monolayers and organoid spheroids. PDOs and PDOrgs from solid tumors including colon, gastric, prostate, breast, and non-small cell lung cancers, and from hematologic malignancies, pancreatic, parotid gland, esophageal, oral, small cell lung, glioblastoma, bladder, renal, and melanomas were tested with a panel of FDA approved, investigational, and all-inclusive agents, PDXs, PDOrgs, and PDOs from different tissue types. To determine their drug sensitivities, we compared the responses to the treated tumors with the control tumors obtained while at least 50% of the tumor volume was remaining. Our goal was to investigate whether drug sensitivities measured using PDOs and PDOrgs correlate with responses observed in the matching PDXs. Culture was harvested at 48 h, 72 h, 96 h, 120 h, and 144 h for 132 agents at 8 concentrations each of 6 or 9 days. The data indicated the GSI values for PDOs and PDOrgs were representative of in vivo drug sensitivities and drug response measured as relative median to control increases or decreases in tumor volume in a given tumor volume quadrant following treatment initiation to tumor volume quadruple, calculated as median of all tumor volume quadruples for treated animals/mice/tissue to tumor volume quadruple for controls, with both positive and negative drug responses. PDOs, from most sensitive to most resistant, were similar to or matched the corresponding PDXs. Drug sensitivities were consistent across PDOs and PDOrgs in vivo. PDOs and PDOrgs in vitro compared with responses observed in the matching PDXs. This suggests that PDOs and PDOrgs are potential models for preclinical testing of therapeutic responses in solid tumors and may inform therapeutic development and personalized medicine.

Pharmacological evaluation of drug response profiles: PDOs and PDOrgs were exposed to the indicated compounds for 144 h. Fig. A: Heat map represents mean percentage of growth inhibition at stage 7 and stage 8 dynamic progression compartments. In a comparison to PDXs alone, in the PDO case, both PDOs and PDOrgs tested similar drug response profiles to individual compounds, with the exception of PDOs showing overall decreased sensitivity in tumor volume (TGI) compared to PDXs. For each compound, AUCs were calculated in each of 3 repeats, demonstrated different sensitivity in tumor volume, extracellular matrix (ECM), and endothelial strength. Significant correlation observed between drug response profiles of 61 paired PDOs and PDOrgs models independent of drug tested.

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