Organoid culture screen for combination therapies to target aggressive variant prostate cancer

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Background: There is increasing emergence of aggressive variant prostate cancer (AVPC). AVPCs are heterogeneous diseases, both between and within patients, typically characterized by alterations in the key tumor suppressor genes RB1, TP53, and PTEN. New patient derived xenograft (PDX)-derived and biopsy-derived organoid models accurately represent heterogeneous AVPC. With new technology, these models can be used in a robotic screening platform.

Methods: Twelve PDX- and biopsy-derived organoid models, comprised of five models of NEPC/small cell, five models of adenocarcinoma with loss of key tumor suppressor genes, and two models that maintain mixed lineage, were tested in a robotic high-throughput screening facility using 108 therapeutic compounds. Validation of screen results was performed manually in *in vitro* organoid studies and *in vivo* xenograft studies.

Results: Combining the screen results with manual confirmatory assays, approximately 42% of compounds demonstrated variable activity across models. IC50 < 1 micromolar and maximal inhibition >80% were the most robust markers of activity. Delivery of the compounds to the organoid cultures was the most significant source of variability in the screen. Selected agents were chosen for combination studies, either with enzalutamide or carboplatin, or with another therapeutic compound from the screen. Few compounds showed synergy with either enzalutamide or carboplatin. Instead, the most promising combination is comprised of two test compounds. This combination is prioritized for *in vivo* studies based on marked synergy in organoid models.

Conclusions: Organoid models derived from PDXs or biopsies combine clinical relevance and feasibility in medium- and high-throughput studies. This is especially relevant for aggressive variant prostate cancers, which respond poorly to standard therapies and are not represented well by standard cell line models. We have generated a large dataset of responses to compounds from heterogeneous classes in diverse models of aggressive variant prostate cancer. Moreover, we have identified a combination therapy that demonstrates marked synergy *in vitro* and is prioritized for *in vivo* studies. Future efforts will seek to develop additional therapy combinations that are active against AVPC and identify biomarkers useful for patient selection.

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