Organoid culture screen for therapies targeting aggressive variant prostate cancer

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Abstract

Background: As inhibition of Androgen Receptor (AR) signaling has become more effective, there is increasing appreciation for aggressive variant prostate cancer (AVPC). These are heterogeneous diseases characterized by alterations in key tumor suppressor genes (*PTEN*, *RB1*, and *TP53*) and exhibiting poor response to standard therapies. New organoid models derived from patient derived xenografts (PDXs) and biopsies accurately represent heterogeneous AVPC and are amenable to medium- and high-throughput studies to identify new therapeutic options for these aggressive cancers.

Methods: 12 organoid models representing a spectrum of AVPC were tested in the robotic screening platform of the National Center for Advancing Translational Science using 108 therapeutic compounds at varying stages of clinical development and with diverse molecular targets. Validation of select compounds was performed in *in vitro* organoid culture and *in vivo* xenograft models.

Results: Nearly 60% of compounds tested showed little activity against any AVPC models. Approximately 2% were highly active against all models tested, suggesting they have little selection and likely have a narrow therapeutic window. Approximately 40% of compounds demonstrated variable activity across models, with IC50 <1 micromolar and >80% maximal inhibition in at least one organoid model. Models with stronger neuroendocrine phenotypes tended to cluster together in patterns of response. *In vitro* validation assays demonstrated reproducibility for individual compounds and models, generally correlating with the original screen. One compound has undergone further evaluation in *in vivo* models. As monotherapy it demonstrated an anti-tumor effect in multiple AVPC models, which was enhanced when given in combination with AR-targeted therapy.

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 identified a compound with significant *in vivo* anti-tumor activity across multiple models and have prioritized additional compounds with significant activity in at least one organoid model of AVPC. 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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