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Poster Abstract Form

Large-scale pharmacotranscriptomics maps genotype- and cell-state-specific drug responses in pancreatic cancer

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Drug response in pancreatic ductal adenocarcinoma (PDAC) is shaped by genotype and cellular state, yet how these contexts influence treatment-induced transcriptional responses remains poorly understood. Large-scale pharmacotranscriptomic profiling offers an opportunity to map these relationships and uncover context-specific vulnerabilities.

We present a previously unpublished pharmacotranscriptomic resource: 200 genetically engineered mouse-derived PDAC cell lines spanning 17 genotypes, three oncogenic drivers (Kras, Braf, Pik3ca), and four morphological states. Screening 95 anticancer agents generated approximately 19,000 matched pre- and post-treatment transcriptomes linked to drug response. We built a DMSO-anchored per-drug differential expression framework, coupled to gene set enrichment and connectivity mapping, to quantify drug-induced shifts across molecular contexts.

Baseline transcriptomes separated oncogenic drivers (PERMANOVA $R^2 = 0.14$, $P < 0.001$) and epithelial from mesenchymal states ($R^2 = 0.23$, $P < 0.001$), recapitulating features of human PDAC. Epithelial models were enriched for fatty-acid metabolism, whereas mesenchymal models showed increased EMT, angiogenesis and myogenesis (GSVA rank-biserial $r = 0.70$ - 0.89 , $FDR < 0.001$). MAPK- and protease-targeting agents induced among the strongest transcriptional shifts ($r = 0.65$, $P = 0.004$). Panobinostat showed preferential activity in mesenchymal models ($\Delta AUC = -0.34$, $P < 0.001$), and decitabine in Pik3ca-driven models ($\Delta AUC = -0.15$, $P < 0.001$). Connectivity mapping of perturbation-derived pathway signatures grouped drugs that shared morphology- and driver-specific sensitivity, linking induced transcriptional programmes to context-specific vulnerability. Profiling drug action rather than drug efficacy alone, this resource resolves the programmes underlying context-specific response. Integration with human cell-line and patient datasets will identify conserved vulnerabilities and prioritise subtype-matched therapies.