Pancreatic Cancer Organoids from the Human Cancer Models Initiative Biobank Reflect Disease Genotypes, Capture Patient Heterogeneity, and are Amenable to Therapeutic Screening

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States (~3% of all cancer cases) and has one of the lowest 5-year relative survival rates.

There is a lack of clinically representative, easily available, validated, in vitro pancreatic cancer models that reflect the genomic and phenotypic diversity of the disease.

The Human Cancer Models Initiative (HCMI) is an international collaborative effort devoted to the development and distribution of approximately 1,000 novel human primary tissue–derived tumor models supported with clinical and molecular annotation.

ATCC® has made 300+ of these next-generation cancer models, including human PCOs, available to the research community through our catalog.

Here, we describe a subset of the pancreatic model cohort, highlight their clinical characteristics, characterize their genotype, and investigate their response to a 10-compound panel of chemotherapeutics that include taxanes, platinum drugs, KRAS-targeting inhibitors, and PARP inhibitors.

Human Cancer Models Initiative (HCMI)

HCMI is an international consortium of laboratories with the shared goal of creating next-generation in vitro cancer models that better represent the diversity and complexity of human cancers than seen in current cell line collections. These models are annotated with detailed clinical, patient demographics, and treatment histories covering a wide range of genomic data (e.g., WGS, WES). These novel models are manufactured and distributed by ATCC®. Over 300 models are currently available, including > 30 cancer organoids, from 23 different primary tissue sites. Over 50 PCOs are currently available, a subset of which are described in Table 1.

Methods

Organoid culture: PCOs were secured from ATCC® and subdivided under standard aseptic conditions (GAMmedium supplemented with 0.5 mg/mL ECM). Compounds for the drug screening panel were KRpep-2d, MRTX-1133, nab-paclitaxel, cisplatin, and PARP inhibitors.

Drug response: Viability studies were performed between passages 2 and 3. Organoids were grown in suspension in 4% FBS-supplemented medium for 72 hours prior to seeding to allow single celling and cell fragments to reform organoids prior to assay and drug exposure. Viability was determined using the CellTiter-Glo® 3D Viability Assay (Promega, Madison, WI, USA) according to the manufacturer’s instructions. Each compound was tested at a single concentration across 6 wells in quadruplicate.

Figure 1: Summary of workflow.

Figure 2: Oncoplot of selected somatic pancreatic cancer relevant mutations in patient-derived organoid models (n=46).

Table 1: Clinical characteristics of established human PCOs (n=46) from the HCMI biobank.

<table>
<thead>
<tr>
<th>Organoid</th>
<th>Tumor Type</th>
<th>Primary Site</th>
<th>Tumor Stage</th>
<th>Age</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDM-26™</td>
<td>Pancreatic Adeno. ductal type</td>
<td>Primary Pancreatic head</td>
<td>Male</td>
<td>72</td>
<td>--</td>
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<tr>
<td>PDM-288™</td>
<td>Pancreatic Adeno. (NOS)</td>
<td>Primary Pancreatic body</td>
<td>Female</td>
<td>64</td>
<td>Stage IIB</td>
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<tr>
<td>PDM-203™</td>
<td>Pancreatic Adeno. ductal type</td>
<td>Primary Pancreatic head</td>
<td>Male</td>
<td>54</td>
<td>--</td>
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<tr>
<td>PDM-138™</td>
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<td>Primary Pancreatic head</td>
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<td>Stage III</td>
</tr>
<tr>
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<td>Primary Pancreatic body</td>
<td>Male</td>
<td>66</td>
<td>Stage IIB</td>
</tr>
</tbody>
</table>

Figure 3: Heterogeneity of morphology across PCOs (n=4).

Summary and Conclusions

The HCMI biobank contains organoids from a diverse collection of patients and disease indications, including from pancreatic cancer.

PCOs from the HCMI have canonical mutations in key genes (KRAS, TP53, SMAD4, and CDKN2A) seen in patient populations and existing large cancer datasets such as the TCGA.

We used PCOs to validate a viability screening assay with a panel of 10 anti-cancer drugs.

PCOs exhibited variable drug toxicity that may be part in consequence of genotype.

Learn more at www.atcc.org/hcmi & www.atcc.org/organoids

Acknowledgements and References

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Table 2: 2’-D factor scores from drug response assays. Columns represent drug exposure from 168h (highest) to 0h (lowest).

Figure 4: Toxicity induced by 10 anti-cancer drugs. Toxicity induced by the IC50 values at 168h were compared across all 10 drugs.

Figure 5: Toxicity induced by 10 anti-cancer drugs. Toxicity induced by the IC50 values at 168h were compared across all 10 drugs.

Figure 6: Toxicity induced by 10 anti-cancer drugs. Toxicity induced by the IC50 values at 168h were compared across all 10 drugs.

Figure 7: Toxicity induced by 10 anti-cancer drugs. Toxicity induced by the IC50 values at 168h were compared across all 10 drugs.