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Integrating Artificial Intelligence and Functional Precision Oncology for Individualized Cancer Therapies

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Precision oncology seeks to tailor cancer treatments to individual patients. Patient-derived xenograft (PDX) models have emerged as a promising platform for selecting efficacious, personalized therapies and developing new oncology drugs.[2] Here, Certis Oncology presents a workflow for selecting and validating treatments for patients with colorectal cancer (CRC) that integrates orthotopic PDX (O-PDX) models, molecular profiling, machine learning, and *in vivo* pharmacological validation. Of the nine tumor biopsies collected, seven were successfully developed into O-PDX models (78%) with a median time to establishment of 119 days. Five of these models were molecularly profiled for gene expression and were serially passaged to perform orthotopic pharmacology studies to validate test agents selected by CertisAI™. The resulting actual tumor growth inhibition (TGI) was plotted against TGI predicted by CertisAI and yielded a Pearson correlation of 0.79 demonstrating a novel precision oncology platform for determining and validating individualized cancer therapies.

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METHODS

Tumor Implantation and Growth Kinetics

Nine tumor biopsies from eight patients were implanted into female CIEA NOG mice. Up to five mice were used for either a subcutaneous or an orthotopic (liver) initial F1 implantation. Xenograft growth was tracked up to 265 days post-implantation or until xenograft growth reached 1000 mm3.

Molecular Characterization and Predictive AI

Using targeted RNA-seq, we performed molecular profiling of all successful F1 engraftments. Sequencing data was analyzed using Certis' RNA-seq analysis pipeline. To confirm the correct cancer type for selection of the correct prediction model, quantile normalized transcripts per million (TPM) values were used as input into the CertisAI Cancer Type Classifier, which confirmed the original diagnosis of origin. Normalized TPM values from predictive biomarker was used as input, along with each therapy's molecular features, into CertisAI, an ensemble of deep neural network- based machine learning (ML) models to predict personalized therapies for each patient study.

Pharmacological Response of CRC O-PDX Models

Pharmacological studies were conducted using a combination of standard of care therapies and treatment regimens selected through CertisAI. Following orthotopic implantation (caecum), tumor growth was monitored using MRI before (-3 days) and after (5, 14, 21, and 27 days) regimen dosing.

Murine-Scale MRI Tumor Volume Measurements

Animals with orthotopic xenografts were individually imaged using the Aspect Imaging M3™ Compact MRI system. Tumor volumes were quantified from the images using VivoQuant Software (Invicro). The region of interest (ROI), measured in voxels (3-dimensional pixels), was drawn to define the boundaries of cancerous tissue observed in each MRI slice. MRI tumor volume: M-TV (mm3) = Voxel Total Count × H (height in voxels) × W (width in voxels) × D (depth in voxels), where H is the long diameter of the tumor, W is the short diameter of the tumor, and D is the slice thickness.

RESULTS

The work presented here demonstrates a consistent and reproducible functional precision medicine platform for selecting and validating therapeutic options for colorectal cancer patients.

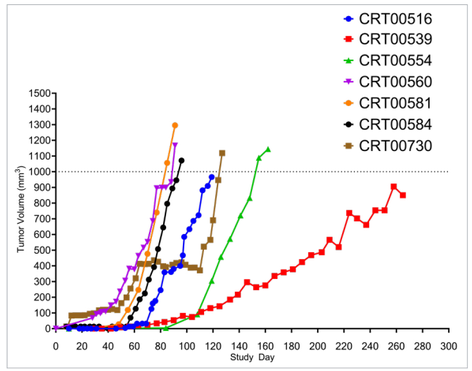

Figure 1. Comparative Initiation F1 Engraftment

Each line shows the tumor growth from an individual mouse, measured either through calipers (Cancer Models CRT00516, CRT00560, CRT00584, and CRT00730) or MRI (CRT00539, CRT00554, and CRT00581). The dotted line (1000 mm3) indicates the target tumor volume for downstream F2 passaging.

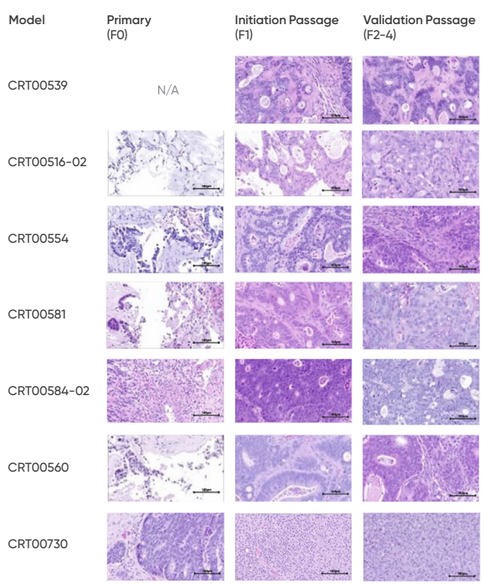

Figure 2. Histological Characterization of Models

Hematoxylin and eoisin (H&E) staining was performed to determine if the engraftment and subsequent passages maintained morphology similar to the original patient biopsy Images of passaged tumors show similar histomorphology to the primary tumors from which they were derived.

Cancer Model	Sex at Birth	Age	Diagnosed CRC Subtype	Stage	Primary Site	Met Sites	Biopsy Site	KRAS	Previous Treatment	Radiation
CRT00516	Female	67	Adenocarcinoma	IV	Colon	Liver	Liver	G12V gained + Ampl	FOLFIRI	Yes
CRT00539	Female	54	Adenocarcinoma	IV	Colon	Liver, Nodes, Peritoneal, Peri-Splenic, Vaginal Cuff	Liver	G12D Gained	FOLFOX, trastuzumab + pertuzumab, trastuzumab emtansine, dendritic cell vaccine, neratinib, immunotherapy, pembrolizimub, FOLFIRI + Avastin, calcium folinate, capecitabine, VEGFR vaccine, Tucatinib + trastuzumab	No
CRT00554	Female	45	Adenocarcinoma	IV	Descending Colon	Pulmonary, Peritoneal	Retroperito-neum	G12C	CAPOX, FOLFIRI + Bevacizumb	Yes
CRT00560	Male	78	Adenocarcinoma	IV	Descending Colon	Liver, Possible Lung	Liver	Ampl	FOLFIRI/FOLFOX + Avastin, Pfizer clin trial, Avastin + Capecitabine	No
CRT00581	Male	80	Adenocarcinoma	IV	Colon	Liver	Liver	G12V, G12D	None	No
CRT00584	Male	58	Sigmoid Adenocarcinoma	IV	Descending Colon	Liver, Possible Lung	Colon	G12V	FOLFOX + Avastin	No
CRT00585							Liver			
CRT00730	Male	74	N/A	IV	Colon	Liver	Liver	WT	Treated; Not Specified	No
CRT00740	Female	35	N/A	IV	Descending Colon	Liver	Liver	"Negative"	Not Specified	No

Figure 3. Study Participant and Tumor Characteristics

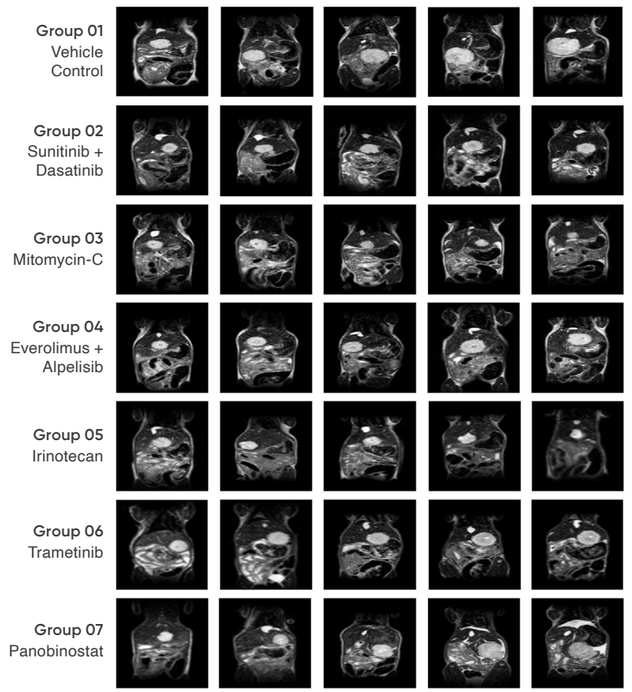

Figure 4. Representative MRI per group for all timepoints (Barney OI Model CRT00516-02).

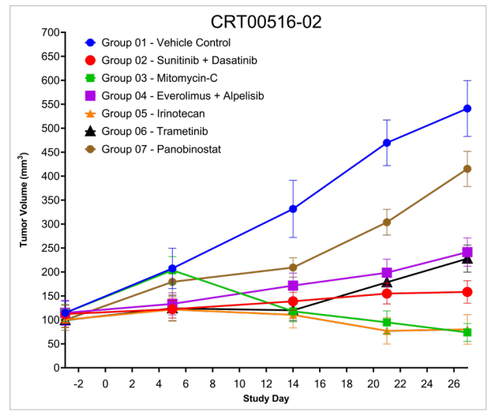

Figure 5. Pharmacology Study Data

Mean group tumor volumes (mm3)± STDEV. Each treatment group consisted of five mice with orthotopic liver engraftments of tumor fragments. (BarneyOI Model CRT00516-02).

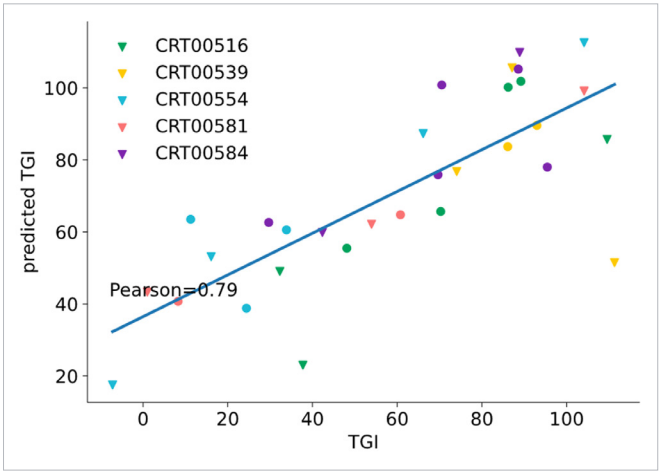

Figure 6. AI Prediction Analysis and Model Validation

Analysis of TGI Correlation to Predicted TGI.
TGI = %Δ Inh = ((MRI mean(C)-MRI mean(C0)) - (MRI mean(T)MRI mean(T0)) / (MRI mean(C)-MRI mean(C0)) * 100
Predicted TGI = (Prediction Zscore * STDEV Experimental Colorectal TGI) + (Experimental Colorectal TGI Mean)

CONCLUSIONS

- O-PDX models have been recognized as reliable models in predicting clinical treatment responses and guiding clinical decisions.[3]
- Our workflow addresses one of the biggest technical challenges to using O-PDX through murine-scale MRI that enables high-resolution, 3D whole-body morphological imaging.
- The current practice of precision oncology that uses biomarker identification (genetic mutations of driver genes) for treatment plan selection, is unsuccessful for many cancers. Here, Certis employs a unique, proprietary set of AI algorithms to predict effective therapies using gene expression.
- In all cases, CertisAI selected efficacious therapies based on the gene expression of individual tumors, demonstrating fair correlation between experimentally derived TGIs and predicted TGIs.
- Data derived from these studies are being used to continuously train and optimize CertisAI to increase its accuracy and predictive capabilities.
- Our precision oncology platform demonstrates a novel approach that integrates AI and functional *in vivo* assays for selecting and validating individualized cancer therapies.

CITATIONS & ACKNOWLEDGEMENTS

*Authors contributed equally

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