

NCI's Patient Derived Models Repository (NCI PDMR)

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Overview of Today's Talk

- What is the NCI Patient-Derived Models Repository (PDMR)
 - What are the models and how are they made
 - Data available with the models
 - Requesting institutions and research studies models are requested for

- Advocacy Groups and Individuals Involved with the NCI PDMR

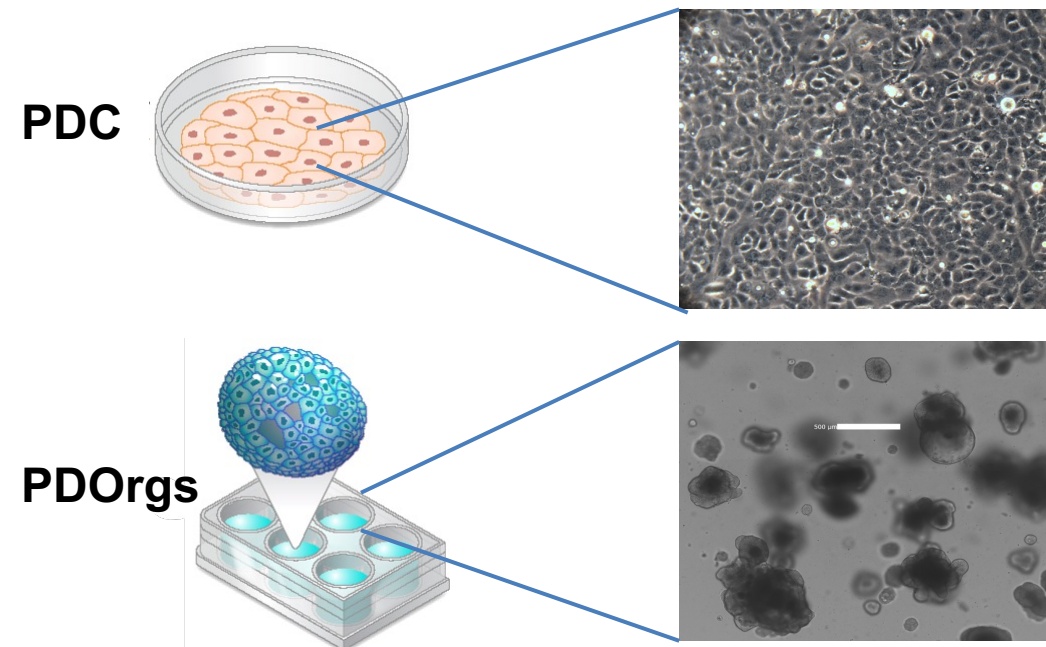
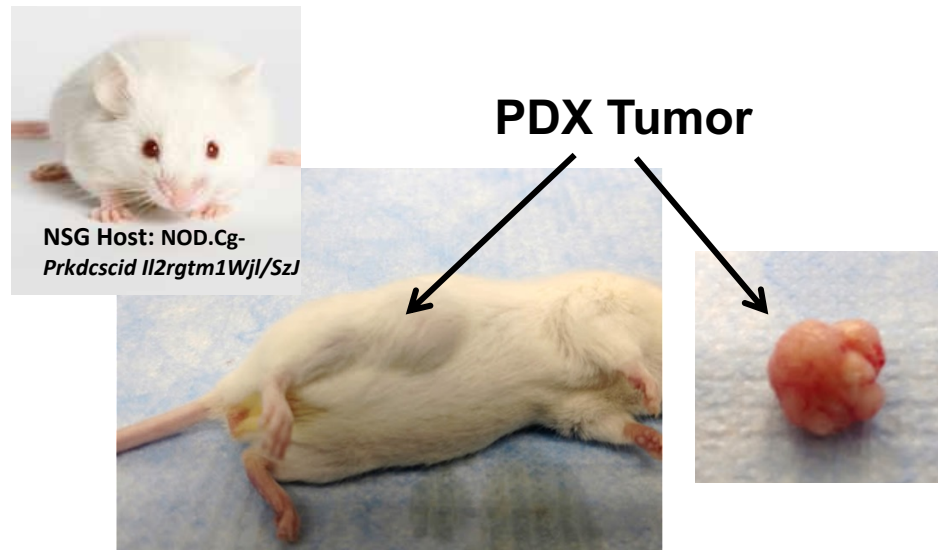
- Ways to Interact with the NCI PDMR



What is the NCI Patient-Derived
Models Repository (PDMR)?

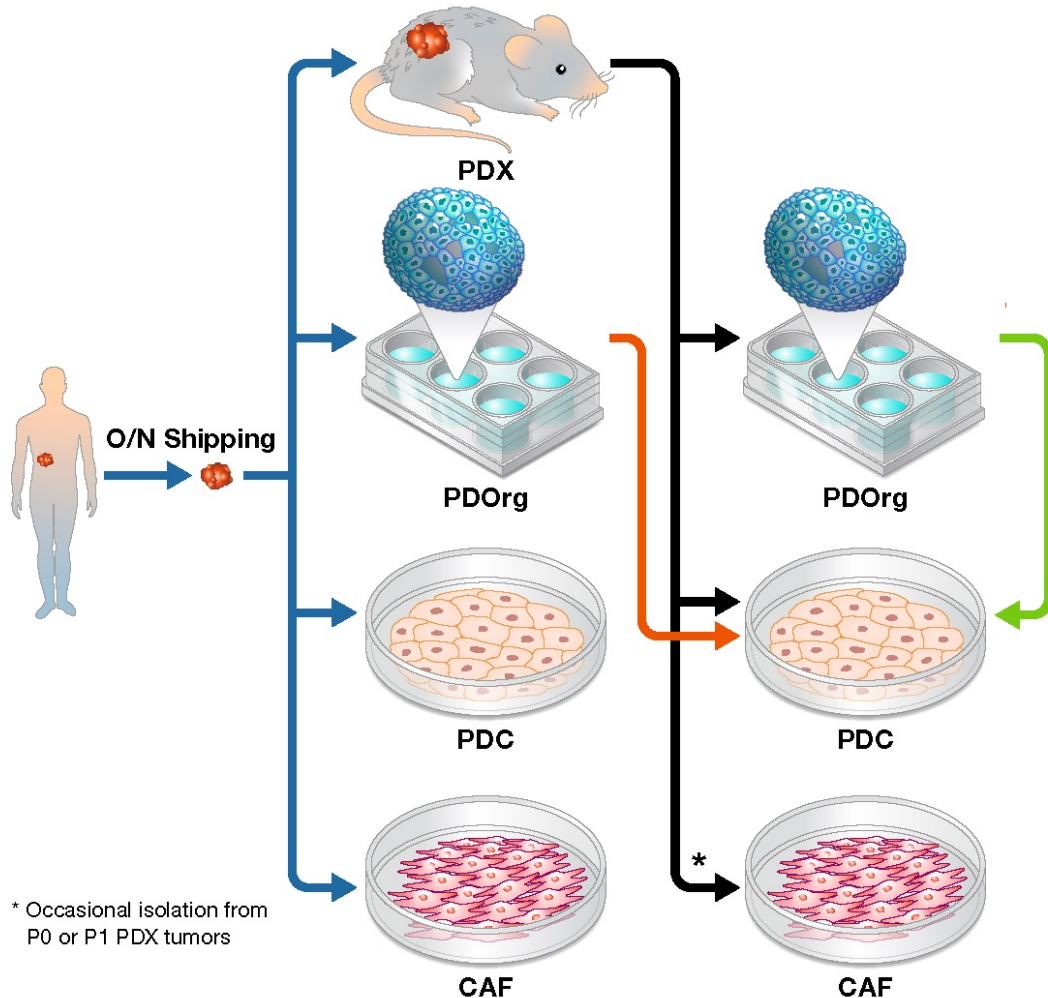
What is the NCI Patient-Derived Models Repository (PDMR)?

- A national repository of Patient-Derived Models (PDMs) that serve as a resource for academic discovery efforts and public-private partnerships for drug discovery. However, we are not a core facility that returns models back to clinicians
- Work with clinics and researchers to provide residual tumor tissue for patient-derived **model development** or **deposit models** developed in other laboratories to the NCI PDMR
- **Develop models of cancer** by implanting patient tumor tissue into host mice to grow patient-derived xenografts (PDXs) or grow the cells in an incubator as an organoid (PDOrg) or cell line (PDC) culture
- **Characterize and Distribute** these models to researchers around the world



NCI's Patient-Derived Models Repository (PDMR)

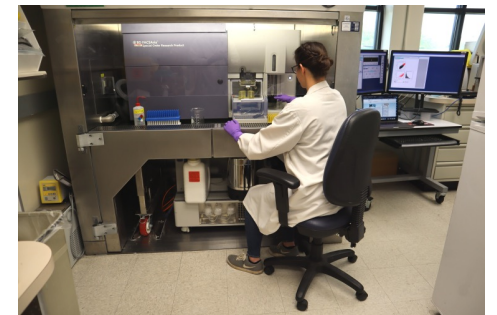
Multiple Attempts to Make a Patient Derived Model



Once a PDX tumor successfully grows in the first host mouse, the tumor can be resected and used for multiple research purposes:

- Implant into additional host mice to make more tumor for future use
- Stored for future distribution to researchers
- Sent for pathology assessment
- Sent for molecular profiling – Next Gen Sequencing
- Implant into host mice to be used for a preclinical drug study

PDOrg and PDC Cultures have a very similar process for expanding the cells and storing, distributing, and preclinical testing



Is a Model Made from Every Piece of Tumor Received?

- Unfortunately, no. Not all tumor cells grow in the laboratory setting
- We calculate each cancer type's "Take Rate" to ensure we focus on receiving more tissue from those cancers with lower take rates
 - Take rate may be dependent of cancer type, cancer stage, current treatment status, or many other variables
 - Many low take-rate histologies have been documented in the literature (e.g., prostate cancer)

Cancer Type (All stages)	# Tumor Samples Received	# Successful PDX Models	"Take Rate"
Colon Adenocarcinoma	193	134	70%
Lung adenocarcinoma	141	18	13%
Lung squamous cell carcinoma	74	34	50%
Pancreatic Adenocarcinoma	114	40	36%
Prostate Cancer	115	4	3%
Ovarian epithelial ca	80	30	38%

Characterizing Models for Researchers

- An important aspect of the NCI PDMR is to ensure models are fully characterized and go through extensive quality control (QC) before they are distributed to the research community.

Deidentified Patient and Model Development Data

* Patient ID 112475

Gender <Unknown> Male Female

Disease Body Location Gynecologic

CTEP SDC Code 10033159 - Ovarian epithelial cancer

Diagnosis Subtype Papillary Serous Cystadenocarcinoma

Date of Diagnosis 04/2009

Age at Diagnosis 67

☺ Limited Medical Information (provided after delinking)

Current Therapy

View	Date Regimen Started	Standardized Regimen	Best Response	Number of Cycles	Date of Progression or Off Therapy	Comments	Reason for Off Therapy
		No Current Therapy	NA	0			

Prior Therapies and Response

View	Date Regimen Started	Standardized Regimen	Best Response	Duration Months	Comments
	05/2009	Carboplatin, Paclitaxel	PR	9	
	06/2010	Bevacizumab, Carboplatin, Paclitaxel	PR	1	
	11/2010	Bevacizumab	Disease Progression	8	
	08/2012	Carboplatin, Gemcitabine	Disease Progression	5	
	08/2012	Paclitaxel	Stable Disease	20	
	07/2013	Bevacizumab, Pemetrexed	Disease Progression	3	

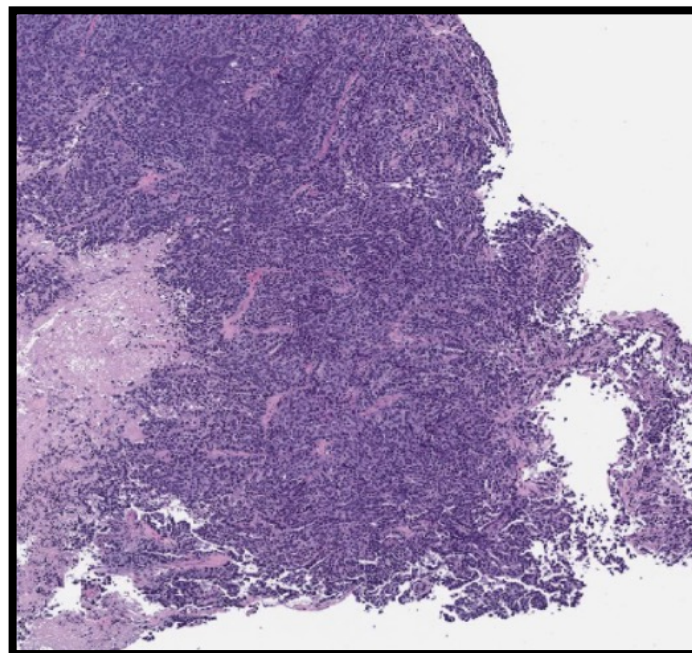
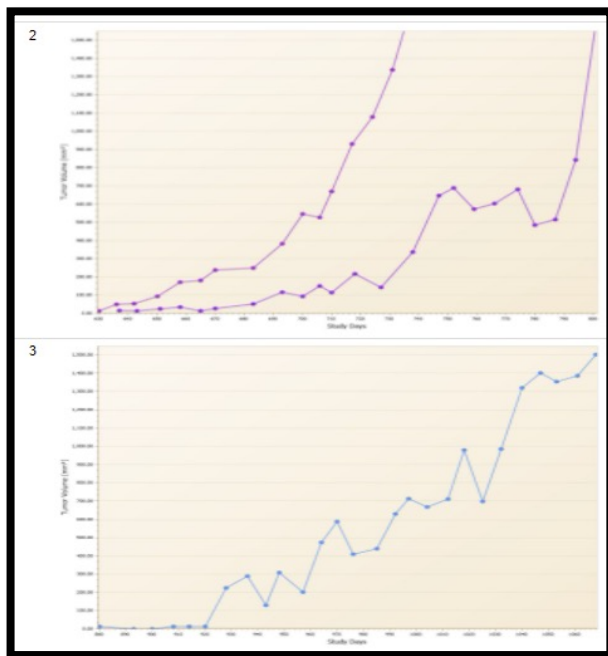
Disease Body Location	Gynecologic	Human Pathogen Testing Summary	Negative
CTEP SDC Code	10033159 - Ovarian epithelial cancer	Specimen Notes	PDX IHC/Path: ER+, PR+ PDX Growth Characteristics: Estradiol not required for growth
Tissue Type	Resection	Able to Viably Passage into Athymic Nude Mice?	Yes
Tissue Collected	Peritoneum	Mouse Strain Used for Engraftment	NSG (NOD.Cg-Prkdc[scid]Il2rg[tm1Wjl]/SzJ)
Provided Tissue Origin	Metastatic Site	Viable Passage Implantation Site	Subcutaneous (flank)
Collection Date	04/2016	MSI Status	MSI-Stable
Age at Sampling	73	Metastatic in NSG?	Not Observed

Characterizing Models for Researchers

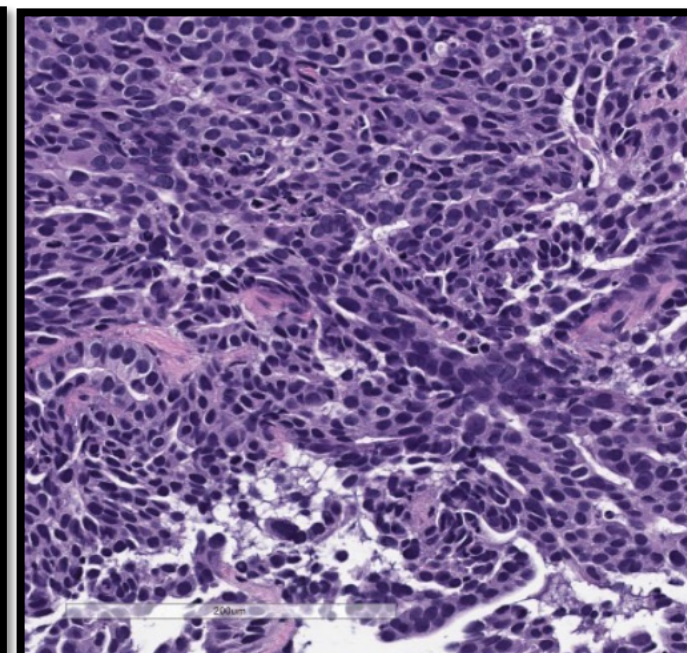
Model Growth Details and Histology Images of Models

<u>Tumor Grade</u>	High grade or poorly differentiated
<u>Tumor Content</u>	40 %
<u>Necrosis</u>	50 %
<u>Stromal</u>	10 %
<u>Inflammatory Cell</u>	1+ (Low)

Pathology Notes
Papillary serous carcinoma of the ovary. The section shows compact ovarian epithelial growth in solid sheets and papillary pattern at periphery. The tumor cells are flat, some of them have bubbly to clear cytoplasm, with high nuclear to cytoplasmic ratio and marked pleomorphism of the nucleus. Occasional multinucleated tumor giant cells are noted. Mitotic figures and necrosis are noted.



Low Magnification



High Magnification

Characterizing Models for Researchers

Sequencing Summary and Files: Whole Exome and RNASeq Analysis Available

OncoKB Gene Panel

View	Hugo Symbol	HGVS Protein Change	Variant Allele Frequency	Total Reads	Variant Class	Oncogenicity	Predicted Functional Effect
	CDKN2A	p.V28_E33del	1.0000	108	In_Frame_Del	Predicted Oncogenic	Unknown
	KRAS	p.G12D	0.4434	221	Missense_Mutation	Oncogenic	Gain-of-function
	BRCA2	p.D1420Y	0.5951	205	Missense_Mutation	Inconclusive	Unknown
	TP53	p.I251Efs*17	0.9483	58	Frame_Shift_Ins	Likely Oncogenic	Likely Loss-of-function

1 - 4

Genomic Analysis

External Genetic Analysis Data

A data file is available if a Download link is displayed:

<input type="checkbox"/> Somatic Mutations Associated with Cancer (*.vcf and *.maf)		
<input checked="" type="checkbox"/> Whole Exome Sequencing (*.vcf)	Download	Ver: 2.0.1.50.0
<input checked="" type="checkbox"/> Whole Exome FASTQ (*.FASTQ.gz; for paired-end sequence, download both files)	Download Read1 FASTQ	Download Read2 FASTQ Ver: 1.2
<input checked="" type="checkbox"/> RNASeq FASTQ (*.FASTQ.gz; for paired-end sequence, download both files)	Download Read1 FASTQ	Download Read2 FASTQ Ver: 1.2
<input checked="" type="checkbox"/> RNASeq Transcripts per Million (TPM; *.RSEM.genes.results and *.RSEM.isoforms.results tab-delimited text file)	Download RSEM (genes)	Download RSEM (isoforms) Ver: 2.0.1.11.0

Who Requests Models from the NCI PDMR

Academic/Non-for Profit (examples)

- Augusta Univ.
- Emory Univ.
- Baylor College of Medicine
- Cleveland Clinic Foundation
- Fred Hutchinson Cancer Research Center
- Georgetown Univ.
- Johns Hopkins Univ.
- Massachusetts General Hospital
- Mayo Clinic
- Mount Sinai/Icahn
- MD Anderson Cancer Center
- Ohio State Univ.
- Oregon Health & Science
- Penn State Univ.
- Thomas Jefferson Univ.
- Univ. Hospital Essen, Germany
- Univ. of California ...
- Univ. of Michigan
- Univ. of Pennsylvania
- Univ. of Rochester
- Univ. of Texas
- Univ. of Utah, Huntsman
- Univ. of Wisconsin

Commercial (examples)

- Bristol Myers Squibb
- GlaxoSmithKline
- HB Therapeutics Inc.
- Ideaya Biosciences
- Melior Discovery Inc.
- Merrimack
- Orphagen Pharmaceuticals
- Poseida Therapeutics
- Thermo Fisher Scientific

Government/Intramural (examples)

- National Cancer Institute, NIH
 - Center for Cancer Research
 - Laboratory of Cellular Oncology
 - Pediatric Oncology Branch
 - Thoracic & GI Oncology Branch
- NCI-Frederick/FNLCR
- National Center for Advancing Translational Sciences (NCATS)
- Argonne National Laboratory (DOE)

Examples of Research Projects

- **Basic Research**
 - Studies focused on understanding the basic biology behind oncogenesis
 - Investigating mechanisms for resistance to therapies
 - Studying mechanisms for metastasis
 - Optimization of cell culture media for patient-derived model growth
- **Biomarker Research and Discovery**
 - Select models with a specific mutation of interest that may predict a response to a targeted agent or combination of agents
 - Identifying or confirm biomarkers that are associated with a specific disease type or whose expression changes in cells after treatment as a possible indication of therapeutic activity
 - Identify protein complexes in specific diseases to provide evidence for rational treatment options
- **Therapeutic Research and Discovery**
 - Test agents or novel combination of agents on models selected to match a future patient population to find translatable strategies that may benefit patients with these mutations
 - Large scale drug screening using PDCs and PDOrgs to identify agents that synergize for drug activity and could be moved forward to a PDX study to support a future early phase clinical trial

Example of Preclinical Studies in PDX Models

Key: Control Arm (no drug), VEGF inhib, EGFR inhib, Combination

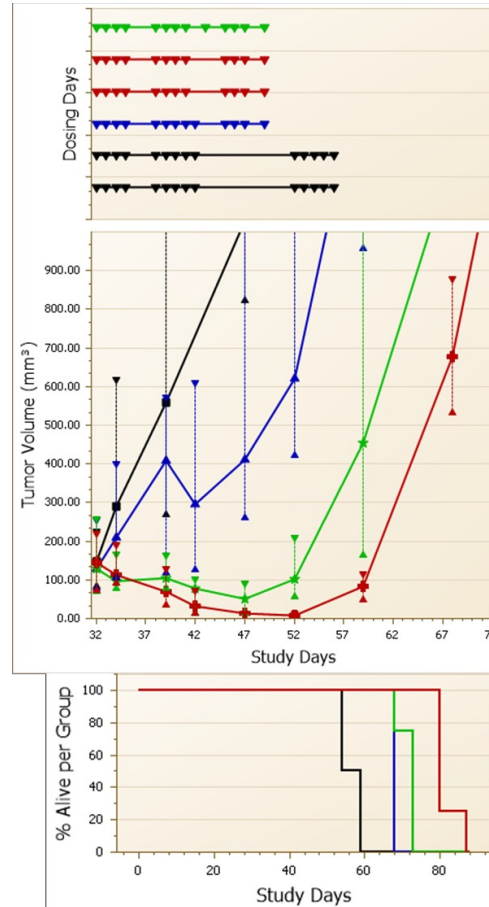
Division of Cancer Treatment & Diagnosis Biological Testing Branch

Goal: Identify novel therapeutic combinations that work better than the individual single agents and move them forward to early phase clinical trials

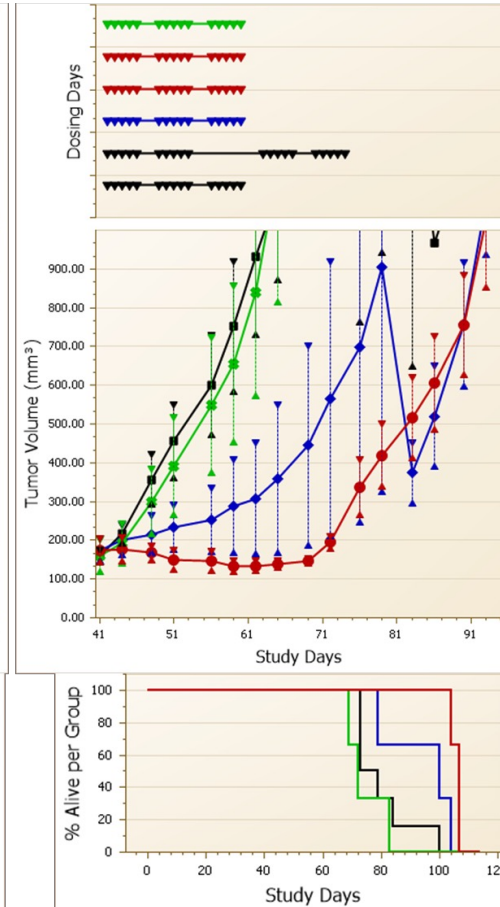
Premise: An ongoing preclinical study using PDMR models of rare cancer to test a wide range of different chemotherapeutic agents

Histologies: Wide range of rare cancers such as soft tissue sarcomas, head and neck cancers, Merkel cell carcinoma, mesothelioma, neuroendocrine cancers

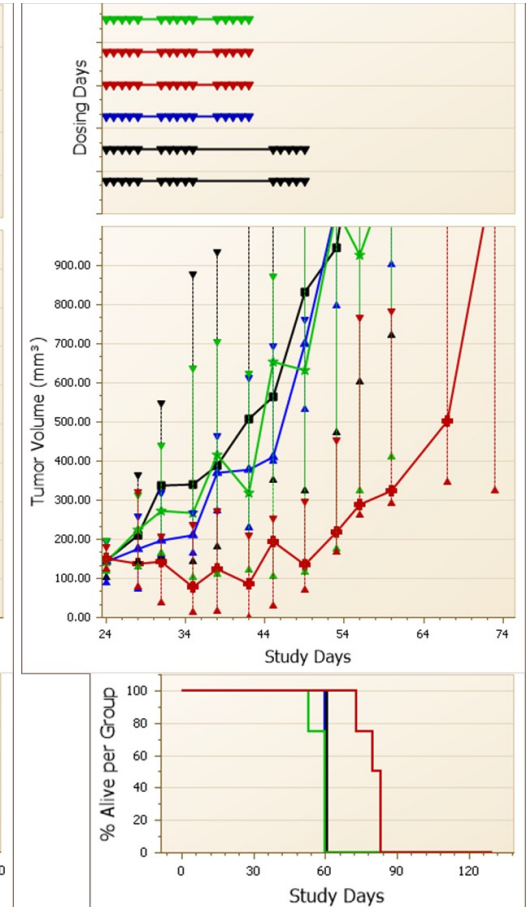
Ba) Penile SCC (epidermoid)



Bb) Synovial Sarcoma



Bc) Neuroendocrine Ca





Advocacy Groups and Individuals Involved with the NCI PDMR

Advocacy Groups/Individuals Involved with the NCI PDMR

- Finding champions within disease to share models to broader stage or provide tumor tissue samples for future model development. Important point: Developing models takes time
- Active Collaborations – Sharing Models
 - Cholangiocarcinoma Foundation: Deposited 10 Cholangiocarcinoma cell lines
 - Dr. Eberhart, John Hopkins University: Deposited a Pediatric Low Grade Glioma cell line
- Active Collaborations – Developing New Models
 - Team of transplant surgeons (UPMC) who work with patients with Pediatric Hepatoblastoma
 - Two Head and Neck surgeons (JHU, OSU) who treat patients with rare sinonasal cancers such as sinonasal NUT carcinoma, esthesioneuroblastoma, glomangiopericytoma, maxillary sinus SCC, ...
- Collaborations in Development
 - Lobular Breast Cancer Alliance: Identifying clinicians to coordinate tissue acquisition with the NCI PDMR
 - Fight CRC: Focus on early onset CRC.

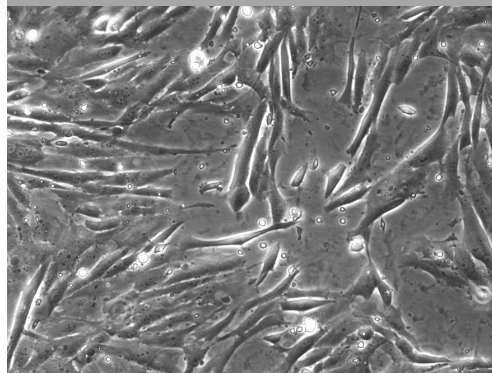
Cholangiocarcinoma Foundation

- Dr. El-Bardeesy (Massachusetts General Hospital) **deposited 10 cell lines** to the NCI PDMR March 2021. Provided confirmation of patient consent for research use of cells and details on the cell line models their lab had developed as part of their work with the Cholangiocarcinoma Foundation
- Process to re-establish models from a depositing laboratory, expand, and fully characterize the models (to match the characterization that is performed on the models developed for the NCI PDMR) can take several years.
- Of the 10 cell lines deposited
 - Three are in the final stages of QC, awaiting full Next Gen sequencing prior to being made public
 - Six are at various mid-level stages of QC including final expansion, testing for their ability to grow in host mice and Next Gen sequencing
 - One line failed to grow

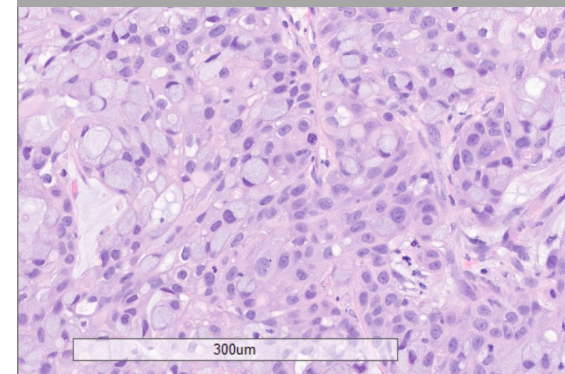
MGH ID: ICC8

PDMR ID: K38593-192-R-J1

Distribution PDC material

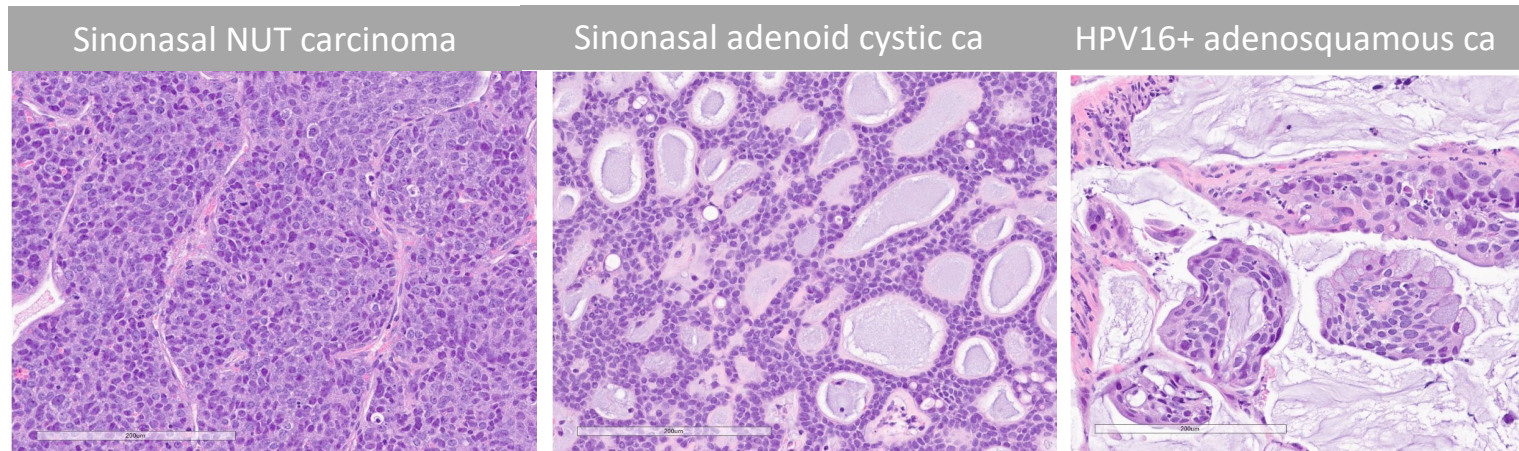


Confirmed Growth in Host Mice



JHU and OSU Sinonasal Surgeons

- Both surgeons also run laboratories with research focused on rare sinonasal cancers and contacted us due to the lack of available models for research
- Main focus is rare sinonasal cancers such as sinonasal NUT carcinoma, esthesioneuroblastoma, glomangiopericytoma, maxillary sinus SCC, and several others
 - Disclaimer: All enrollments are delinked and deidentified so we cannot trace any enrollment back to a specific center. The NCI PDMR works with several clinics who provide tissue from patients with head and neck cancers, including sinonasal cancers.
- The NCI PDMR has several rare sinonasal, salivary, and head and neck cancers. A key to that is identifying champions who can target enrolments for those cancers.





Ways to Interact with the NCI PDMR

Increasing the Numbers and Availability of Patient-Derived Models for Cancer Research

- Connecting Laboratory Scientists who have developed models with the NCI PDMR to make these models available to a broader community through the NCI PDMR (or other NCI-supported mechanism)
- Connecting Clinicians treating patients with cancer to the NCI PDMR to provide residual tissue from medically-indicated procedures for model development
- Important points
 - Champions are needed
 - Model development and QC takes time
 - Well characterized models are incredibly important for research.
 - The NCI PDMR provides deidentified patient history, including treatment history, and molecular characterization of the models available in a publicly accessible database so researchers can select models that best fit their research goals

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PDMR NCI Patient-Derived Models Repository
An NCI Precision Oncology InitiativeSM Resource

<https://pdmr.cancer.gov>

Contributing Clinical Centers

Extramural Participating Sites

Augusta University — Georgia Cancer Center
Baptist Health System/Mid-South Minority/Underserved NCORP
Cancer Research Consortium of West Michigan, NCORP
Cancer Research for the Ozarks, NCORP
Cancer Research of Kansas Consortium, NCORP
Children's Cancer Therapy Development Institute, OR
Christiana Care Health Services NCORP
Columbia University Minority Underserved Site NCORP
Dana-Farber — Harvard Cancer Center, ETCTN LAO
Duke University — Duke Cancer Institute, ETCTN LAO
Fred Hutchinson Cancer Research Center/Univ. of Washington Cancer Consortium
Georgia Cares Minority/Underserved NCORP
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Heartland Cancer Research NCORP
Huntsman Cancer Institute, University of Utah
Indiana University, Simon Cancer Center
JHU Sidney Kimmel Comprehensive Cancer Center, ETCTN LAO
Mayo Clinic Cancer Center, ETCTN LAO
Medical University of South Carolina, Hollings Cancer Center
Michigan Cancer Research Consortium NCORP
Montefiore Minority/Underserved NCORP
Nevada Cancer Research Foundation, NCORP
Northwest, NCORP
Ohio State University, OH
Roswell Park Cancer Institute
Stroger Hospital Cook County Minority/Underserved NCORP
University Health Network — Princess Margaret Phase I Consortium, NCORP
University of Alabama at Birmingham Comprehensive Cancer Center, U54
University of California Davis Comprehensive Cancer Center
University of Colorado Cancer Center
University of Connecticut Health Center — Waterbury Hospital
University of Iowa, Holden Comprehensive Cancer Center
University of Texas MD Anderson Cancer Center, ETCTN LAO
University of Virginia Cancer Center
Vanderbilt-Ingram Cancer Center
Washington University School of Medicine, Siteman Cancer Center
Wisconsin, NCORP
Yale University Cancer Center, ETCTN LAO
Yale University Comprehensive Cancer Center

Rapid Autopsy/ Post-Mortem Participating Sites

City of Hope, Biomedical Research Project
Johns Hopkins Legacy Rapid Autopsy Program
University of Nebraska Medical Center
University of Michigan Comprehensive Cancer Center

NCI Clinics

Developmental Therapeutics Clinic (DTC, DCTD, NCI)
Immune Deficiency - Cellular Therapy Program (CCR, NCI)
Neuro-Oncology Branch (CCR, NCI)
Pediatric Oncology Branch (CCR, NCI)
Surgical Oncology Program (CCR, NCI)
Women's Malignancies Branch (CCR, NCI)
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