The National Cancer Institute’s Patient-Derived Models Repository (PDMR)

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https://pdmr.cancer.gov
I have the following financial relationships to disclose:

**Employee of:** Leidos Biomedical Research, Inc.

I will not discuss off label use and/or investigational use in my presentation.

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NCI’s Patient-Derived Models Repository (PDMR)

https://pdmr.cancer.gov

- Distribute Early-Passage, Clinically-Annotated, and Molecularly-Characterized Patient-Derived Models at a minimal cost to researchers.
- Provide all related metadata and SOPs through a public website.
NCI Patient-Derived Models Repository (PDMR)

- A national repository of Patient-Derived Models (PDMs) to serve as a resource for academic discovery efforts and public-private partnerships for drug discovery comprised of:
  - Clinically-annotated, Early-passage, Molecularly-characterized Patient-Derived Xenografts (PDXs)
  - Complement existing PDX collections and focus on under-represented model types such as rare cancers and models representing racial and ethnic minorities
  - Patient-derived tumor cell (PDCs) and cancer-associated fibroblast (CAF) cultures developed from tumor material and/or PDXs
  - Patient-derived organoid (PDOrg) models developed from tumor material and/or PDXs

- Goal is to provide long-term home for >1000 PDX models along with matched in vitro and organoid models wherever possible
  - Comprehensive characterization of early-passage models: patient medical information including treatment history and response, WES, RNAseq, histology, growth curves, and preclinical drug responses
  - All models and associated data made available through a publicly available website: https://pdmr.cancer.gov
PDMR Development and QC Process

**QC General**
- Pathology assessed to compare to patient diagnosis and to monitor for EBV-driven human lymphomas, mouse tumors, mouse lymphomas, GvHD...
  - Necropsy of any suspect GvHD, human lymphoma, or metastatic models with indication of disseminated disease
- Confirmation of ability to regrow from Cryopreservation
- Human:Murine DNA Ratio
- Human pathogen testing (hIMPACT panel, IDEXX)
- Rodent pathogen assessment

**Distribution Material**
- Confirmed for every PDX
  - Pathology
  - STR
- Provided for 4-6 representative PDXs
  - H&E images with %tumor, %necrosis, and %stroma
  - WES and RNASeq

**Lineage Information Maintained:**
- Fragment Passaging
- Attempt to Capture Tumor Heterogeneity

**Drug Testing Queue**
- Uses material from various passages

**Passage 0 (P0)**
- NSG host, Subcutaneous implant except
  - Breast Ca: MFP
  - Sarcomas: MFP or Thigh Muscle
  - Prostate: Intra-prostatic

**P1**

**P2**

**P3, P4...**
Passaging stopped once sufficient Distribution and QC Material Obtained
NCI Patient-Derived Models Repository (PDMR)

- Currently have **154 PDX models available** for request (cryo-material) through the public website (pdmr.cancer.gov).
  - Model information also available through PDX Finder at [www.pdxfinder.org](http://www.pdxfinder.org)
- Every model has:
  - Patient medical history including treatment history and response
  - Representative PDX histology images
  - STR Profile
  - Human Pathogen Status
  - WES (FASTQ, vcf) and RNASeq (FASTQ, TPM) from 4-6 representative PDXs
  - Genetic ancestry assessment
- All data are publicly accessible and available for download for metadata analysis and model selection
- Specimens are from patients with both primary and metastatic disease from treatment naïve to heavily pre-treated.
## Recently Released & Upcoming Models

### New Model Includes Rare Cancers

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Currently Available</th>
<th>3-6mo Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCLC</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Merkel Cell Ca</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Small cell ca (extrapulmonary)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Carcinosarcoma of the uterus</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hurthle cell neoplasm (thyroid)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GIST</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pharyngeal SCC</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Ovarian Epithelial Ca</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cervical/Vaginal Ca</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Vulvar Ca</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MPNST</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Nasopharyngeal SCC</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Salivary Gland Ca</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

### Available MSI-High Models

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>PDMR Model#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma - cervix</td>
<td>235635-245-T</td>
</tr>
<tr>
<td>Adenocarcinoma - colon</td>
<td>625472-104-R</td>
</tr>
<tr>
<td>Adenocarcinoma - colon</td>
<td>817829-284-R</td>
</tr>
<tr>
<td>Adenocarcinoma - colon</td>
<td>997537-175-T</td>
</tr>
<tr>
<td>Adenocarcinoma - pancreas</td>
<td>292921-168-R</td>
</tr>
<tr>
<td>Carcinosarcoma of the uterus</td>
<td>327498-153-R</td>
</tr>
<tr>
<td>Endometrioid endomet. Adeno</td>
<td>381249-077-R</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>541946-237-B</td>
</tr>
<tr>
<td>Urothelial/bladder cancer, NOS</td>
<td>558786-286-R</td>
</tr>
<tr>
<td>Vaginal cancer, NOS</td>
<td>283339-068-R</td>
</tr>
</tbody>
</table>
Tumor Heterogeneity by Histomorphology in One Model

**Laryngeal SCC Patient.** Resection of the larynx. Tissue implanted into 5 P0 host NSG mice.  

**Model In development**

P0: Poorly differentiated squamous cell carcinoma with marked pleomorphism including neuroendocrine features.

P0: Well differentiated squamous cell carcinoma with area of keratin pearl formation.

P0: Well to moderately differentiated non-keratinizing squamous cell carcinoma.
Hierarchical Clustering of PDX Models Across Passages

> Pairwise Spearman Correlation

Individual PDXs Cluster by Model and Disease Type

> t-SNE Analysis of RNASeq

Sampling includes RNASeq profiles from Patient material (Originator) and representative PDXs from Passage 0-3
June/July 2018

Finalizing database logic and website content for public release
Will be announced on DCTD website and @NCItreatment Twitter account

- Expect 50-70 PDC [Median passage 20] and >100 CAF [Median passage 15] at launch
- At least 1/3 currently matched to a Public PDX (more in development)
- 6 Matched PDC/CAF cultures (more in development)

- SOPs to be provided on Public website
- All PDCs tested for growth as a xenograft
- All PDCs will have WES and RNASeq available
- CAFs are not transformed. They will have limited number of passages before senescence.
PDMR In Development

- **Germline Sequence for sub-set of models**
- Consensus Genomic Variants: List of variants that are 100% represented in WES data
- Designation of Metastatic PDX Models (spontaneous, post-debulking)
- Whole Mouse Imaging (e.g., MRI, US, CT) via TCIA
- Preclinical Drug Study Results
- Models Developed from Rapid Autopsy Procedures:
  - Current focus is on Pancreatic and Prostate Cancer
  - PDX Models from Primary and Metastatic Locations in the Same Patient

1°: Pancreas  Met: Liver  Met: Colonic Fat  Met: Myometrium  Met: Colon
NCI Patient-Derived Models Repository (PDMR) Posters

April 16: 8AM – 12PM
Session PO.TB01.01 - Advances in the Generation and Analysis of Patient-Derived Xenografts

1038 / 11: Xenograft-associated B cell lymphoproliferative disease as a surrogate model to study Epstein-Barr virus (EBV) driven lymphoma of the elderly
    Tomas Vilimas et al.

1039 / 12: PDX models generated from a patient with metastatic colon adenocarcinoma display both spatial and temporal tumor heterogeneity
    Biswajit Das et al.
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Jordyn Davidson
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Raymond Divelbiss
Kelly Dougherty
Kyle Georgiuses
Marion Gibson
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Kelly Hedger
Sierra Hoffman
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Lisa Riffle

Statistics
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NCI Patient-Derived Models Repository: Multiple Avenues for Discovery

Develop PDX Models and PDC (Tumor & Fibroblast) Lines
DNA, RNA, Protein, WES, RNASEq, Targeted Sequencing

Tumor/Patient Heterogeneity

3D Culture, 3D Pharmacodynamics

2D and Organoid Cultures

Preclinical Trial Modeling

Live Tumor Imaging

Increasing Drug Concentration
Genetic Ancestry Assessment for 255 PDX Models with WES

**Self-Reported Race/Ethnicity**
- 55.6% Not Provided
- 42.2% White
- 0.9% Black or African American
- 0.9% Multi-Racial (>1 Selection)
- 0.4% American Indian/Alaska Native
- 0.4% Native Hawaiian or Other Pacific Islander
- 3 HA

**Inferred Genetic Ancestry (≥80%)**
- 88.9% East Asian (EA)
- 4.9% European (CEU)
- 3.6% Native American (NA)
- 2.7% West African (YRI)
- Mixed (All < 80%)

SNPweights Reference Panels (Chen et al., Bioinformatics, 2013)