NCI's Patient-Derived Models Repository: Generating Models from Racial and Ethnic Minorities

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https://pdmr.cancer.gov
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**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 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),
  - Patient-derived tumor cell cultures and cancer-associated fibroblast cultures (PDCs) developed from primary or metastatic tumors and/or PDXs,

- NCI to provide long-term home for >1000 PDX models and develop matched in vitro and organoid models wherever possible

- Goals:
  - ~50 unique patient models/disease (minimum) with sufficient size of each molecularly-characterized subgroup to power validation and/or efficacy studies
  - Comprehensive pre-competitive molecular characterization of samples and earliest passage PDXs: NCI Cancer Gene Panel, WES, RNAseq, histology, growth curves, and preclinical drug responses
  - All models and associated data made available through a publicly available website
NCI Patient-Derived Models Repository: Multiple Avenues for Discovery

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

3D Culture, 3D Pharmacodynamics
Increasing Drug Concentration

2D and Organoid Cultures

Preclinical Trial Modeling

Live Tumor Imaging
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 publicly available website.
NCI Patient-Derived Models Repository (PDMR) Initial Distribution Types

- Currently have 100 PDX models available for request through the public website.
- Every model has associated patient limited medical history and representative PDX histopathology, whole exome sequence, and RNASeq data 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.
- PDX Pathology Confirmed
- Whole Exome Sequence, RNASeq, and an NCI Cancer Gene Panel Available (4-6 representative PDXs per model)
- Human Pathogen Screening and STR Profile Available
- Confirmed Re-growth from Cryopreserved Fragments
NCI Patient-Derived Models Repository (PDMR) Initial Distribution Types

Disease Distribution Groups

Colorectal Adenocarcinoma

Head & Neck Squamous Cell Carcinoma
- Pharyngeal, Laryngeal, Lip/oral cavity, NOS

Urothelial/Bladder Ca

Melanoma

Pancreatic Adenocarcinoma

Lung Squamous Cell Carcinoma

Adult Soft Tissue Sarcoma
- Ewings, Leiomyosarcoma, Malignant fibrohistiocytoma, Fibrosarcoma, Non-Rhabdosarcoma NOS, Rhabdosarcoma NOS

Renal Ca

Upper GI Ca
- Stomach, Sm. Intest, GIST, Appendiceal
Patient Information and Limited Medical History

CTEP SDC Code: 10003571 - Melanoma

**Diagnosis Subtype:** None Provided

**Date of Diagnosis:** 06/2013

**Age at Diagnosis:** 61

**Limited Medical Information (provided after delinking):**

**Current Therapy**
- **Date Regimen Started:** None Provided
- **Standardized Regimen:** None Provided
- **Best Response:** None Provided
- **Number of Cycles:** None Provided
- **Date of Progression or Off Therapy:** None Provided
- **Comments:** None Provided
- **Reason for Off Therapy:** None Provided

**Prior Therapies and Response**

- **View:** None Provided
- **Date Regimen Started:** None Provided
- **Standardized Regimen:** None Provided
- **Best Response:** None Provided
- **Duration Months:** None Provided
- **Comments:** None Provided

- **Date Regimen Started:** 04/2014
  - **Regimen:** Docetaxel, Vemurafenib
  - **Response:** Disease Progression
  - **Duration Months:** 1
  - **Comments:** All other disease sites responded except left forearm

- **Date Regimen Started:** 09/2013
  - **Regimen:** TYE/C, Ipilimumab
  - **Response:** PR
  - **Duration Months:** 3
  - **Comments:** Left forearm did not respond, all other disease sites responded

**Known Genetic Mutations and V600E-RAF**

**Tumor Markers**

**Additional Medical History**

- Medical history data from first prior therapy

**Social History (provided after delinking):**

- **Ethnicity:** Not Provided
- **Race:** Not Provided
- **Occupation:** None Provided
- **Has Smoked:** Not Provided
- **Ever Cigarettes:** Not Provided
- **Total Pack Years:** Not Provided
- **Tobacco Use History:** None Provided
Pathology and Molecular Characterization of PDX Models
Race/Ethnicity Reporting was an Early Recognized Limitation of the PDMR Models

- During the first two years of patient recruitment, race and ethnicity were not part of the required minimal patient information requirements.
- In addition, from those that were reported there was an obvious gap in racial and ethnic minority patient recruitment.

**Solutions**
- Perform ancestry assessment on all PDX models to provide the research community with additional information on patient inferred genetic ancestry.
- Increase the number of patient specimens and/or PDXs coming into the PDMR from racial and ethnic minorities.

Assessment of patient data from 454 PDX models with confirmed pathology from at least one passage 0 tumor.
Genetic Ancestry Assessment

- Genetic ancestry assessment using the whole exome sequencing that is performed on all of our models.

- SNPweights Reference Panels
  - “Improved ancestry inference using weights from external reference panels” (Chen et al., Bioinformatics, 2013)
  - West African (YRI), European (CEU), East Asian (EA) and Native American (NA) from HapMap 3
  - 364,458 SNPs

- Reporting criteria
  - When available, patient material (“originator”) used for ancestry assessment
  - …Else the average genetic ancestry of all sequenced PDX samples (4-6) is reported
  - If all ancestry assignments are <80%, inferred ancestry reported as “Mixed – All <80%”
# Genetic Ancestry Assessment

<table>
<thead>
<tr>
<th>Gender</th>
<th>Diagnosis</th>
<th>Race</th>
<th>% YRI</th>
<th>% CEU</th>
<th>% EA</th>
<th>% NA</th>
<th>Inferred Ancestry Assignment</th>
<th>Source Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Adenocarcinoma - cervix</td>
<td>Not Provided</td>
<td>1%</td>
<td>1%</td>
<td>98%</td>
<td>0%</td>
<td>East Asian</td>
<td>PDX</td>
</tr>
<tr>
<td>Male</td>
<td>Adenocarcinoma - colon</td>
<td>Not Provided</td>
<td>84%</td>
<td>16%</td>
<td>0%</td>
<td>0%</td>
<td>West African</td>
<td>PDX</td>
</tr>
<tr>
<td>Male</td>
<td>Adenocarcinoma - colon</td>
<td>Not Provided</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>European</td>
<td>PDX</td>
</tr>
<tr>
<td>Female</td>
<td>H &amp; N squamous cell car., NOS</td>
<td>White</td>
<td>5%</td>
<td>95%</td>
<td>0%</td>
<td>0%</td>
<td>European</td>
<td>Originator</td>
</tr>
<tr>
<td>Female</td>
<td>Leiomyosarcoma - uterus</td>
<td>Not Provided</td>
<td>11%</td>
<td>46%</td>
<td>0%</td>
<td>43%</td>
<td>Mixed (All &lt;80%)</td>
<td>PDX</td>
</tr>
<tr>
<td>Male</td>
<td>Melanoma</td>
<td>White</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>European</td>
<td>Originator</td>
</tr>
<tr>
<td>Male</td>
<td>Melanoma</td>
<td>Black or African American</td>
<td>1%</td>
<td>99%</td>
<td>0%</td>
<td>0%</td>
<td>European</td>
<td>PDX</td>
</tr>
<tr>
<td>Male</td>
<td>Non-Rhabdo. soft tissue sarcoma</td>
<td>White</td>
<td>5%</td>
<td>95%</td>
<td>0%</td>
<td>0%</td>
<td>European</td>
<td>Originator</td>
</tr>
<tr>
<td>Male</td>
<td>Pharyngeal squam. cell carcinoma</td>
<td>White</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>European</td>
<td>Originator</td>
</tr>
<tr>
<td>Female</td>
<td>Salivary gland cancer</td>
<td>Not Provided</td>
<td>83%</td>
<td>17%</td>
<td>0%</td>
<td>0%</td>
<td>West African</td>
<td>PDX</td>
</tr>
</tbody>
</table>
Genetic Ancestry Assessment for 151 PDX Models with WES

**Self-reported Race**
- 61% White
- 35% Not Provided
- 3% Multi-Racial (>1 Selection)
- 1% American Indian/Alaska Native
- 1% Asian
- 1% Black or African American
- 1% Native Hawaiian or Other Pacific Islander
- 3% Unknown
- 3% Declined to Answer
- 1% Not Provided

**Inferred Genetic Ancestry (>80%)**
- 88% East Asian (EA)
- 5% European (CEU)
- 3% Native American (NA)
- 3% West African (YRI)
- 1% Mixed (All <80%)
Increasing Racial/Ethnic Minority Representation in PDMR Models

- Minority-Underserved NCORP sites (RFP Awarded, Leidos Biomedical Research – funding in support of the DCTD/NCI)
  - Goal: Enroll patients with cancer from predominantly racial and ethnic minorities to provide research specimens to the PDMR for patient-derived models development
  - Proposed specimen provision includes: Breast (incl. TNBC), Prostate, Pancreatic, Renal, Lung, and Hepatic cancer from patients of Hispanic and African-American descent; Ovarian, Cervical and Endometrial Cancers from patients of African-American descent

- NEW: S17-199 - Acquisition of Biological Samples for the Development of NCI’s Patient-Derived Models (PDM) Repository (LBR RFP funding in support of the DCTD/NCI)
  - Posted to: FedBizOpps and Leidos Biomedical Research website
  - Date Issued: Sept 25, 2017
  - Response Due: October 13, 2017

- PENDING: Minority PDX Development and Trial Centers (M-PDTCs) RFA (U54) to participate as part of the PDXNet
  - Goal to perform large-scale, multicenter preclinical PDX studies
PDMR In Development

- Ancestry SNP Assessment
- Consensus Genomic Variants: list of variants that are 100% represented in WES data
- Germline Whole Exome Sequence
- Designation of Metastatic PDX Models (spontaneous, post-debulking)
- Preclinical Drug Study Results
- Whole Mouse Imaging (e.g., MRI, US)
- In vitro Early-Passage Tumor and Cancer-Associated Fibroblast Cultures
- Models Developed from Rapid Autopsy Procedures:
  - Current focus is on Pancreatic and Prostate Cancer
  - PDX Models from Primary and Metastatic Pancreatic Adenocarcinoma

1°: Pancreas
Met: Liver
Met: Colonic Fat
Met: Myometrium
Met: Colon
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