National Cancer Institute
Patient Derived Models Repository (PDMR)
An NCI Precision Oncology Initiative SM Resource

Presentation to the FNLAC: June 27, 2019

James H. Doroshow, M.D.
Director, Division of Cancer Treatment and Diagnosis
National Cancer Institute, NIH

https://pdmr.cancer.gov

FNLAC Members
• Nilsa C. Ramirez-Milan, M.D., FCAP, Ohio State University College of Medicine
• Kevin Cullen, M.D., Univ. of Maryland
• Lisa Coussens, Ph.D., Oregon Health Sciences University

Extramural Members
• Meenhard Herlyn, D.V.M., D.Sc., Wistar Institute
• Michael Lewis, Ph.D., Baylor College of Medicine
• Peter Houghton, Ph.D., Univ. of Texas San Antonio
Overview

• Overview of Model Development Efforts for the PDMR

• Issues/Challenges Reviewed with the WG

• PDMR Activities for Further Discussion with the WG
NCI’s Patient-Derived Models Repository

- A national repository of Patient-Derived Models (PDMs) to serve as a resource for academic discovery efforts and public-private partnerships for drug discovery
- Clinically-annotated & early-passage models with comprehensive molecular-characterization and quality control metrics
- Complements existing PDM collections and focuses on under-represented model types such as rare cancers and models representing racial and ethnic minorities
- Provides models to the research community at modest cost compared to other distributors
- Provides all related metadata including: de-identified patient clinical history and outcomes, model histology, WES and RNaseq of models, and SOPs through a public website: [https://pdmr.cancer.gov](https://pdmr.cancer.gov)

Tumor biopsies or surgical samples shipped overnight from clinical sites to FNLCR: Multiple patient-derived model types initiated when sufficient material available

PDX  
PDOrg Culture  
PDC/CAF Culture
Multi-laboratory Effort to Develop & Characterize Models

- DCTD (NCI, NIH), James H. Doroshow, MD – leadership, scientific/technical oversight

- PDMR (FNLCR), Yvonne A. Evrard, PhD – scientific/technical oversight, contract management, clinical interface

- Biological Testing Branch (DCTD, NCI, NIH), Melinda Hollingshead, DVM, PhD – scientific/technical oversight, in vivo (PDX development) efforts, in vitro efforts, preclinical efficacy studies

- In Vitro Evaluation Group (FNLCR), Dianne Newton, PhD – cell line and organoid development

- Molecular Characterization Laboratory (FNLCR), P. Mickey Williams, PhD – NextGen Sequencing, bioinformatics
Model Development and Characterization
Patient-Derived Xenografts (PDXs)

233 PDX models publicly available (pdmr.cancer.gov)
- 211 additional models (in queue) going through final QC (final pathology, NGS, STR, regrowth from freeze,...)
- >300 models in Passage 1-4 expansion
- ~400 models in Passage 0

Distribution Material
- Median Passage = 2
  ✓ Range for NCI-generated models: 1-7
- Clinically-annotated, molecularly-characterized
- Specimens from patients with both primary and metastatic disease, ranging from treatment-naïve to heavily pre-treated backgrounds
- Current distribution within the US (pdmr.cancer.gov).
  ✓ Model information also available through PDX Finder at www.pdxfinder.org
Externally Deposited PDX Models

Contributor Sources
- PDXNet Consortium: 179 models
- DCTD Administrative Supplement grantees: 126 models
- Extramural Academic Centers: 27 models

Process
- Required implantation & expansion within mouse isolators to minimize any chance of pathogen contamination
- Implanted in batches by Contributing Center and monitored for growth

Issues
- Limited Isolator Space, one Contributor per Isolator
- Pathogens:
  - One site: Mouse Kidney Parvovirus (MKPV) positive; One site: Achromobacter xylosoxidans positive; and One site had several LDEV+ models from contaminated Matrigel; NOT from PDXnet sites
  - Sites notified of issues
  - 2 models submitted were 100% mouse tumor
# PDX Take-Rate from Tumor Tissue Implantations

<table>
<thead>
<tr>
<th>Body Location</th>
<th>Total Specimens Received</th>
<th>Total Assessable Specimens</th>
<th>%Take-Rate of Assessable Specimens</th>
<th>Histology-Confirmed Tumor</th>
<th>Discontinued</th>
<th>Not Yet Assessable: P0 tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>263</td>
<td>203</td>
<td>14%</td>
<td>28</td>
<td>175</td>
<td>60</td>
</tr>
<tr>
<td>Digestive/ Gastrointestinal</td>
<td>633</td>
<td>559</td>
<td>44%</td>
<td>244</td>
<td>315</td>
<td>74</td>
</tr>
<tr>
<td>Endocrine/ Neuroendocrine</td>
<td>174</td>
<td>154</td>
<td>8%</td>
<td>12</td>
<td>142</td>
<td>20</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>453</td>
<td>392</td>
<td>19%</td>
<td>75</td>
<td>317</td>
<td>61</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>4</td>
<td>4</td>
<td>0%</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>335</td>
<td>243</td>
<td>36%</td>
<td>87</td>
<td>156</td>
<td>92</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>175</td>
<td>162</td>
<td>52%</td>
<td>84</td>
<td>78</td>
<td>13</td>
</tr>
<tr>
<td>Hematologic</td>
<td>8</td>
<td>3</td>
<td>38%</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>370</td>
<td>333</td>
<td>26%</td>
<td>86</td>
<td>247</td>
<td>37</td>
</tr>
<tr>
<td>Neurologic</td>
<td>9</td>
<td>6</td>
<td>0%</td>
<td>0</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory/Thoracic</td>
<td>189</td>
<td>160</td>
<td>32%</td>
<td>51</td>
<td>109</td>
<td>29</td>
</tr>
<tr>
<td>Skin</td>
<td>77</td>
<td>74</td>
<td>58%</td>
<td>43</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Unknown Primary</td>
<td>18</td>
<td>17</td>
<td>18%</td>
<td>3</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>2708</strong></td>
<td><strong>2310</strong></td>
<td><strong>31%</strong></td>
<td><strong>716</strong></td>
<td><strong>1594</strong></td>
<td><strong>398</strong></td>
</tr>
</tbody>
</table>

*All tumor material collected and shipped priority overnight in CO2-independent media for next-day implantation into NSG host mice*
## PDX Take-Rate Assessments by Tumor Source

### Collection Type

<table>
<thead>
<tr>
<th>Collection Type</th>
<th>Total Specimens Received</th>
<th>Total Assessable Specimens</th>
<th>%Take-Rate of Assessable Specimens</th>
<th>Histology-Confirmed Tumor</th>
<th>Discontinued</th>
<th>Not Yet Assessable: P0 tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection (R)</td>
<td>2464</td>
<td>2090</td>
<td>30%</td>
<td>629</td>
<td>1470</td>
<td>373</td>
</tr>
<tr>
<td>Tumor biopsy (T)</td>
<td>230</td>
<td>207</td>
<td>40%</td>
<td>83</td>
<td>122</td>
<td>23</td>
</tr>
<tr>
<td>Malignant Effusion (M)</td>
<td>14</td>
<td>13</td>
<td>33%</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>2708</strong></td>
<td><strong>2310</strong></td>
<td><strong>31%</strong></td>
<td><strong>716</strong></td>
<td><strong>1594</strong></td>
<td><strong>398</strong></td>
</tr>
</tbody>
</table>

### RAPID Autopsy Material

<table>
<thead>
<tr>
<th>RAPID Autopsy Material</th>
<th>Total Specimens</th>
<th>Total Assessable Specimens</th>
<th>%Take-Rate of Assessable Specimens</th>
<th>Passageable Tumor</th>
<th>Discontinued</th>
<th>Not Yet Assessable: P0 tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>5</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Digestive/Gastrointestinal</td>
<td>196</td>
<td>168</td>
<td>23%</td>
<td>39</td>
<td>129</td>
<td>28</td>
</tr>
<tr>
<td>Endocrine/Neuroendocrine</td>
<td>27</td>
<td>21</td>
<td>10%</td>
<td>2</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>34</td>
<td>24</td>
<td>0%</td>
<td>0</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>2</td>
<td>2</td>
<td>0%</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>5</td>
<td>5</td>
<td>20%</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic/Blood</td>
<td>2</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>22</td>
<td>22</td>
<td>0%</td>
<td>0</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory/Thoracic</td>
<td>13</td>
<td>3</td>
<td>0%</td>
<td>0</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Skin</td>
<td>10</td>
<td>10</td>
<td>60%</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>316</strong></td>
<td><strong>255</strong></td>
<td><strong>19%</strong></td>
<td><strong>48</strong></td>
<td><strong>207</strong></td>
<td><strong>61</strong></td>
</tr>
</tbody>
</table>
Understudied Cancer Histologies: PDX Models Available

- Merkel Cell Carcinoma
- Mesothelioma
- Hurthle Cell Neoplasm of the Thyroid
- Malig. Periph. Nerve Sheath Tumor
- Salivary Gland SCC
- Pharyngeal SCC
- Nasopharyngeal SCC
- Laryngeal SCC
- Vaginal Cancer
- Cervical SCC
- Carcinosarcoma of the Uterus

- Synovial Sarcoma
- Liposarcoma
- Leiomyosarcoma – uterine and non-uterine
- Rhabdomyosarcoma
- Osteosarcoma
- Chondrosarcoma
- Malignant fibrous histiocytoma
- Fibrosarcoma – not infantile
- Ewing sarcoma/Peripheral PNET
Inferred Ancestry for PDMR Models

**Inferred Ancestry**
- 336 PDMR models with WES SNP data available

**Self-Reported Race from Patient Enrollments**
- Self-Reported Race above, of these 4% self-reported as Hispanic or Latin American

2 Minority-Based PDXnet sites funded 8 months ago; Minority-Based NCORP sites now enrolling
Patient/PDX-Derived Cancer Cell Lines (PDCs) and Cancer Associated Fibroblast Cultures (CAFs)

**PDCs: 73 Public**
- Adherent & Suspension Cultures
- Requires use of defined media
- Distribution Material
  - Median Passage = 20
  - Range : 12-51

**CAFs: 134 Public**
- Not Transformed - Limited Lifespan
- Requires use of defined media
- Distribution Material
  - Median Passage = 14
  - Range: 9-18
Patient/PDX-Derived Organoids (PDOrg)

- First 46 models now publicly available with another 30 going through QC (NGS, tumorigenicity verification, STR, etc)
- Major developmental effort for new SOPs for H & N, NSCLC, melanoma, cervix Orgs
- Provide all related metadata and SOPs through the PDMR website and public database: pdmr.cancer.gov

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Public</th>
<th>In Queue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other GI Cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head &amp; Neck Cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urothelial/Bladder Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma &amp; Skin Cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic Adenocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Small Cell Lung Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Cell Lung Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult Soft Tissue Sarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecologic Cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo/Neuroendocrine Cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Cancers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Requires use of defined media
- Distribution Material
  - Median Passage = 10
    - Range: 6-30

Goal:
Wherever possible develop a PDX, 2D *in vitro* PDC, and PDOrg culture for comparative preclinical studies
Includes models that are either

1. Publicly Available or
2. Going through final QC for Public release (pathology confirmation of all contributing material, NGS, STR, regrowth from cryopreservation, etc)

<table>
<thead>
<tr>
<th></th>
<th>PDX</th>
<th>PDC</th>
<th>PDOrg</th>
<th>CAF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>441</td>
<td>118</td>
<td>80</td>
<td>160</td>
</tr>
</tbody>
</table>

Matched PDX, PDOrg, PDC, and CAF Models
Glandular architecture is present with nests of glands with areas of back to back gland formation.
Distribution of Models

- Academic, Commercial, and Intramural PIs

<table>
<thead>
<tr>
<th>Material</th>
<th>Number of Vials Distributed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDX Fragments – Viably Cryopreserved</td>
<td>277</td>
</tr>
<tr>
<td>DNA from PDX Fragment (Solution)</td>
<td>3</td>
</tr>
<tr>
<td>RNA from PDX Fragment (Solution)</td>
<td>20</td>
</tr>
<tr>
<td>Fresh-Frozen PDX Fragment for Extraction</td>
<td>257</td>
</tr>
<tr>
<td>In Vitro PDCs – Viably Cryopreserved</td>
<td>101</td>
</tr>
<tr>
<td>In Vitro CAFs – Viably Cryopreserved</td>
<td>10</td>
</tr>
<tr>
<td>PDOrgs – Viably Cryopreserved</td>
<td>20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>688</strong></td>
</tr>
</tbody>
</table>

**USES:**
- Methylome assessment
- Target-specific inhibitors matched to molecular phenotypes
- Small molecule agents
- Angiogenesis
- Proteogenomics
- Radiotherapy
- Small animal imaging studies
- Biomarker assessment matched to molecular phenotypes
- Academic preclinical core services
- Commercial investigational agent validation
Institutions/Companies Receiving PDMR Resources

- Emory University
- Fred Hutchinson Cancer Research Center
- Georgetown University Medical Center
- Huntsman Cancer Institute, Univ Utah †
- Indiana University School of Medicine
- Johns Hopkins University
- MD Anderson Cancer Center * †
- Ohio State University Medical Center †
- Roswell Park Cancer Institute
- Stanford University *
- University of Texas at Dallas
- Thomas Jefferson University
- University of California at Los Angeles *
- University of California – Irvine *
- University of Maryland * †
- University of Michigan * †
- University of Pittsburgh *
- University of Texas - Southwestern Medical Center
- Virginia Commonwealth University * †
- Wake Forest Baptist Comprehensive Cancer Center
- University of Georgia
- Frederick National Laboratory for Cancer Research * †
- Center for Cancer Research, NCI * †

Biotech/Pharma
- Dicerna Pharmaceuticals, Inc †
- Merrimack Pharmaceuticals
- SRI International

* Multiple PI’s have requested material
† The same PI has made >1 request

Continuing to communicate regularly to extramural PI’s to enhance awareness
Working Group Discussion & Input
Issues / Challenges Discussed: Input

• Recent challenges
  ✓ Newly identified Mouse Kidney Parvovirus (MKPV); first described in Fall of 2018 as cause of murine nephropathy.
    --We now have changed all aspects of how externally derived PDX deposits are handled within the Biological Testing Branch (DCTD/NCI).
    --As discussed with WG, all PDMR model recipients notified, as well as PDXnet members; new SOPs posted on PDMR website with details of commercial testing availability for MKPV (now routine at PDMR)
  ✓ PDMR has stopped routinely accepting colon adenocarcinomas for model development (>100 models in hand). Cases with unique histologies or mutational status are reviewed on a case-by-case basis so that something like Lynch Syndrome would still be accepted.

• Advice from WG
  ✓ How to improve knowledge of model availability for the research community?
    --Increase blast emails to DCB grantees as well as DCTD grantees each time a group of new models released
    --Announced on NCI Treatment twitter account
  ✓ Organoids
    --Attempting to make organoids from tumor types that traditionally are not thought to make organoids: Mel’s; Sarcomas
    --Will promote new SOP’s for non-traditional organoid propagation
Issues / Challenges Discussed: Input (2)

• Advice from WG
  ✓ CAFs
    --How do we best use them/market them?
    --Of note: we often develop a CAF line from patient material when no PDX or PDC develops
  ✓ Preclinical Assessment
    --Finding additional metrics for preclinical response; we need to assess multiple ways to get a better picture of response
  ✓ Uses for EBV-transformed DLBCL-like models (Xenograft-associated lymphoproliferative disease; effect of Rituximab)?

• Other Recommendations
  ✓ Expand PDMR with pediatric tumors—ALL samples from Dr. Houghton
  ✓ GBM and other brain tumors from NCI Neuro-oncology program
  ✓ Expand RPPA and other proteomic characterization studies
Other PDMR Activities for Discussion with WG
PDMR-Related Activities

• PDX (patient-derived xenograft) Development and Trial Centers Research Network (PDXNet)—Moonshot effort
  ✓ Perform preclinical studies at PDX centers to accelerate translation to ETCTN trials; PDMR is the Hub

• NCI-DOE Collaboration – Moonshot effort
  ✓ Joint Design of Advanced Computing Solutions for Cancer (JDACS4C)
  ✓ Develop predictive models, both computational and experimental, to improve pre-clinical therapeutic drug screening

• Preclinical Assessment of PDX Models
  ✓ Rare Tumor PDXs: 40 models x 60 novel therapeutic combinations. Goal: to identify new therapies for rare cancers
  ✓ Standard of care: 72 models x 6 single agent SoC. Goal: to determine if PDX models respond similarly to Phase II trials
  ✓ Support for ongoing DCTD efforts for NExT program (preclinical, pharmacodynamics, in vitro screening etc)
  ✓ Genomic assessment of PDX ‘drift’

• Imaging studies (Cancer Imaging Program)
  ✓ Future portal on TCIAA
The NCI expresses its deepest thanks to the patients, families, and clinical teams that make this effort possible.