FNLCR Resources to Support Extramural Research

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FNLCR Advisory Committee

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Research Resources for Extramural Investigators at FNLCR

- **Biopharmaceutical Development Program**
- **Patient Derived Models Repository**

Mission: "*Our goal is the rapid translation of innovative scientific discoveries into therapeutic products that hold the real hope for preventing and curing cancer and other diseases.*"

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DCTD established the BDP in 1993 to:

- Provide specialized technical expertise and services to develop biotechnology products
- Conduct feasibility testing and develop new manufacturing processes and analytical test methods to support clinical use
- Manufacture GMP-grade biopharmaceuticals for early stage clinical trials
- Provide USFDA and international regulatory documentation and support
- Transfer technology to commercial entities
- Educate the extramural community by providing standardized documents and training

Profile of BDP Projects

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Common hurdles:

- Intended for orphan indications, unmet medical needs, limited markets
- Involve novel, high-risk/high-reward technology; many types of biologicals
- May have regulatory uncertainty (e.g. first-in-class products)
- Allow project originators to retain Intellectual Property rights
- Process development, manufacturing, fill/finish, QC, QA, regulatory

Sources of projects:

- NCI Experimental Therapeutics program (NExT) for extramural community
- NCI CCR: Intramural projects
- NIH Institutes such as NIAID and NCATS
- Other federal agencies such as DoD under Economy in Government Act
- Collaborative Research and Development Agreements (CRADAs) between NCI and private industry

Upstream: Fermenters and Bioreactors

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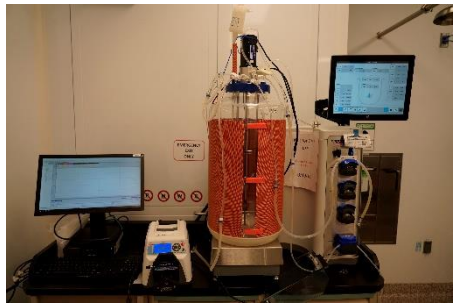
Eukaryotic and Prokaryotic Production Systems



A variety of different-sized fermenters and bioreactors are used for process development and GMP production

150-L and 500-L fermenters can produce up to 500 grams of raw product

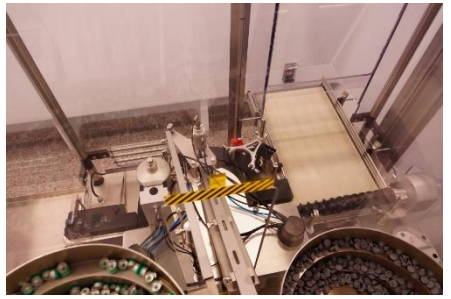
1000-L bioreactor for cell suspension; yields of up to 300 grams of raw product

Downstream: Purification and Fill/Finish

Purification is usually via column chromatography:

Chromatography Skid with Product and Buffers (bags) and Column

Final product is filled by hand (small lots) or by machine:



A semi-automatic vial filling machine

Recently Expanded Capabilities: Autologous Cell Therapy Manufacturing

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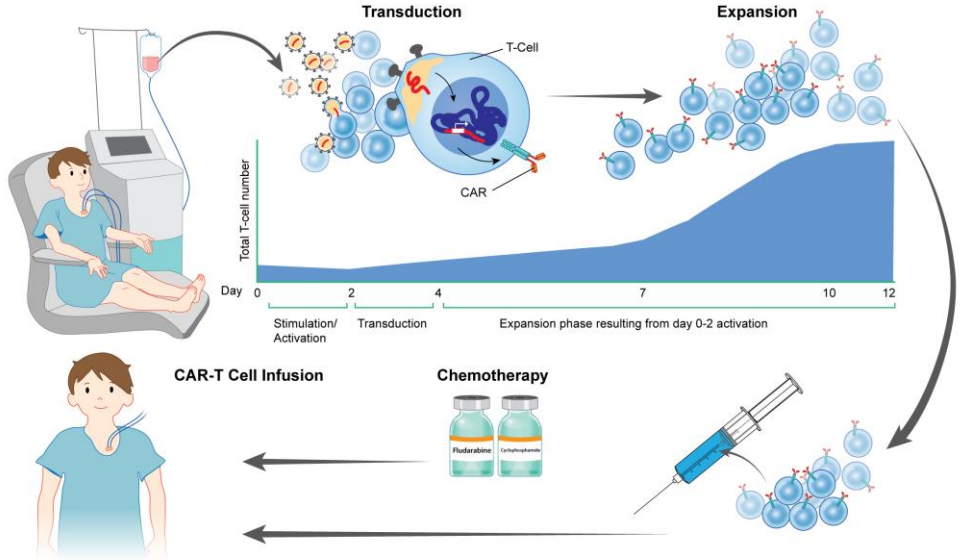
Autologous products require raw material (apheresis) and product chain logistics: cryopreservation, scheduling manufacturing, chain of custody.



Clinical Trial	Sponsor
Phase 1/2 Study of Anti-CD33 Chimeric Antigen Receptor Expressing T-Cells (CD33CART) in Children and Young Adults with Relapsed/Refractory AML	Pediatric Blood & Marrow Transplant Consortium (PBMTC)
GD2-CAR PERSIST: Production and Engineering of GD2-Targeted, Receptor Modified T Cells for Sarcoma and Neuroblastoma to Increase Systemic Tumor Exposure	NCI/CTEP Pediatric Cancer Immunotherapy Trials Network (PED-CITN)

BDP Has Developed Many Types of Products

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- **Monoclonal Antibodies – 26**
- **Recombinant Proteins/Natural Products – 5**
- **Immunotoxins – 4**
- **Immunomodulators - 17**
- **Oncolytic Viruses - 10**
  - AdV Type 5
  - HSV
  - Measles Virus
  - Poliovirus
  - Vaccinia
- **Virus Vectors - 4**
  - AAV Types 2 and 9
  - Lentivirus
  - Retrovirus (in development)
- **Cell Therapy Products - 2**
- **Vaccines: Cancer – 16**
  Infectious disease - 9
  - Peptide
  - Oligonucleotide
  - Viral – VEE, EBV, MVA
  - Recombinant protein
  - Plasmid
  - Adsorbed
  - Cellular

Productivity Summary for Life of Program:

> 250 product lots released for clinical use

> 130 distinct products manufactured

> 60 products have been or are in human clinical trials

> 14 products are being readied for licensure

2 products are licensed and commercially available

Currently, 21 products under active IND

Ch14.18 Monoclonal Antibody

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- **ch14.18 is a monoclonal antibody that targets the GD2 receptor on the surface of neuroblastoma cells.**
- **The NCI Children's Oncology Group (COG) performed a clinical trial led by Dr. Alice Yu at UCSD in children with high-risk neuroblastoma. The trial showed improved progression-free survival (58%->73%) when ch14.18 together with cytokines IL-2 and GM-CSF were added to the standard treatment regimen.**
  - Yu, A.L., A.L. Gilman, M.F. Ozkaynak, et al. (2010). Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 363:1324-1334.
- **The BDP developed the manufacturing process for ch14.18 and manufactured the national supply for clinical trials in the USA, Canada, Australia, and New Zealand.**
- **The product, Unituxin (dinutuximab), is now available commercially.**

Products in Commercial Development

<u>Ad-delta24/RGD (DNX-2401)</u> - Genetically modified adenovirus for treatment of Rb pathway-defective cancers

- The BDP developed the manufacturing and analytical processes to generate clinical supplies for the Phase 1 study at MD Anderson
- Granted FDA Fast-track and Orphan Drug status in 2014; currently in Phase 2 clinical development
- Licensed to DNAtrix in 2014

<u>Tet-CMV (PepVax)</u> – Peptide vaccine to prevent CMV recurrence in HCT patients

- The BDP contracted peptide synthesis, and developed stable formulation and analytic assays supporting clinical trials for Phase 1 and 2
- Licensed to Helocyte (formerly DiaVax) in 2016

<u>Ch11-1F4 (CAEL-101)</u> – Monoclonal antibody targeting amyloid fibrils for imaging and immune-mediated clearance of Primary Amyloidosis

- The BDP Developed manufacturing process, assays, clinical supplies for Phase 1 imaging trial and Phase 1 therapeutic trial
- Orphan drug designation in April 2017
- Phase 2 trial in progress 2020; Licensed as imaging/therapeutic agent to Caelum 2017

Supporting Other Institutes: NCATS, NIAID, NIDDK, and DOD

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- **RLIP76: Radical ion transporter protein for Acute Radiation Syndrome (NCATS, co-sponsored by NIAID)**
  - ✓ BDP process development improved the final product purity from ~40% to >95%
- **AGIL-AADC: AAV-based gene therapy for the treatment of Rare Disease Aromatic L-amino acid Decarboxylase (AADC) deficiency (NCATS)**
  - ✓ BDP expanded capabilities to include Adeno-associated Virus vectors
- **GP-350- and gH/gL/gp42-Ferritin nanoparticles; Vaccine for Epstein Barr Virus (NIAID, Co-sponsored by NCI)**
  - ✓ BDP developed production and purification process for multi-component vaccine
- **Transmission-blocking Malaria Vaccine and Conjugated Carrier Protein EPA (NIAID)**
  - ✓ BDP expanded capabilities to include *Picchia*-based production
- **IL-2Fc and mutIL15-Fc for treatment of Type I diabetes (NIDDK)**
- **Multiple DOD projects**

Providing Expertise and Resources: Documents and Training

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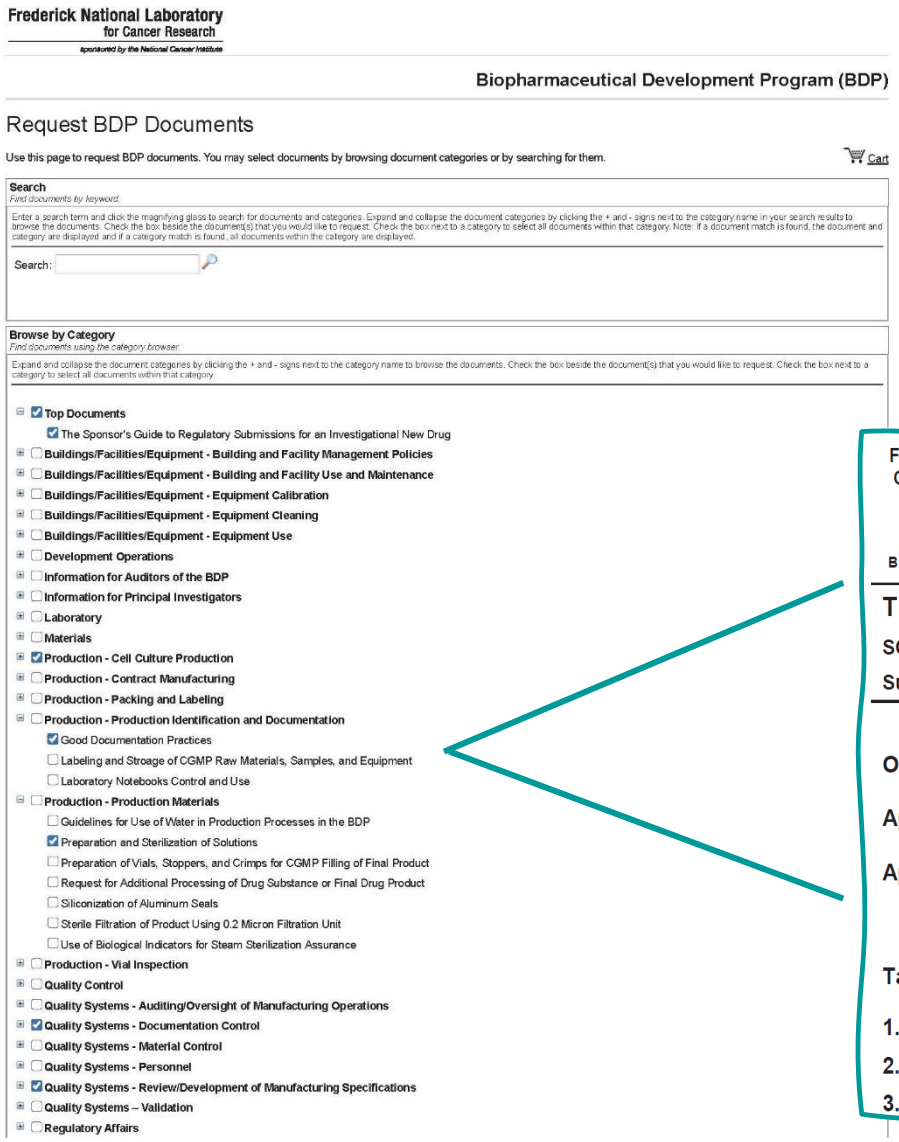
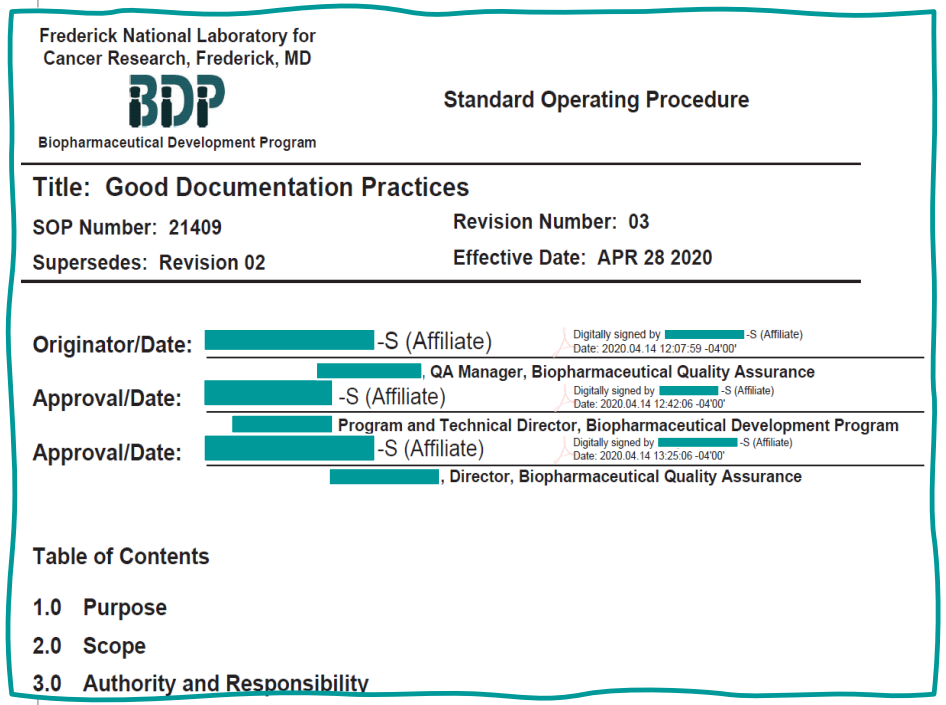
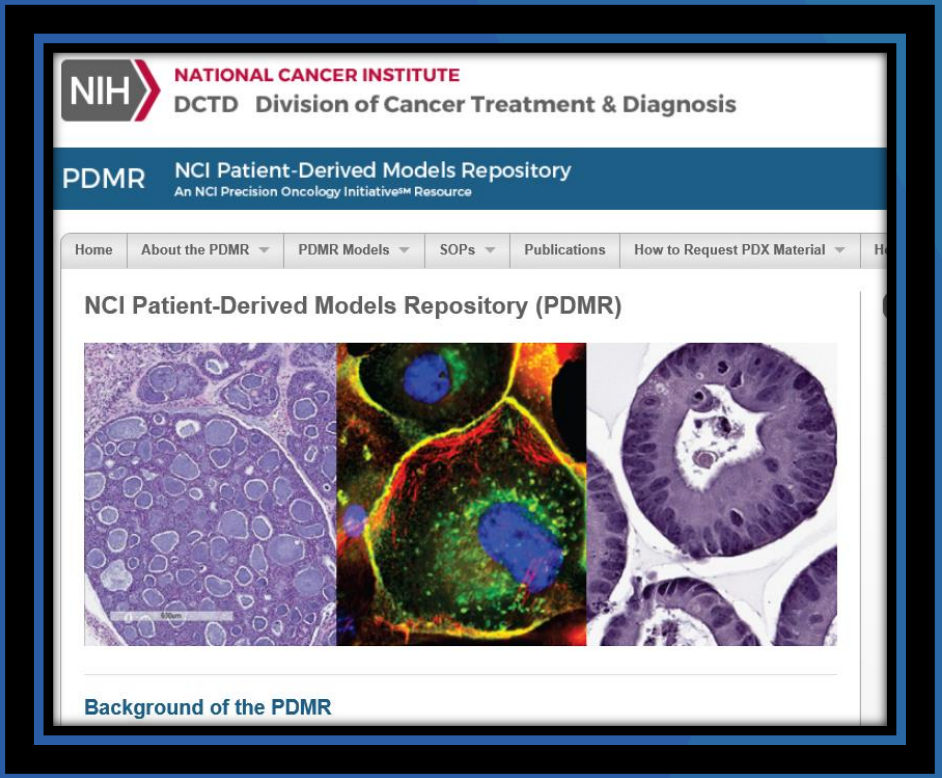


BDP Website:

http://ncifrederick.cancer.gov/Programs/Science/BDP

>300 SOPs, manufacturing and testing, quality system, and training documents





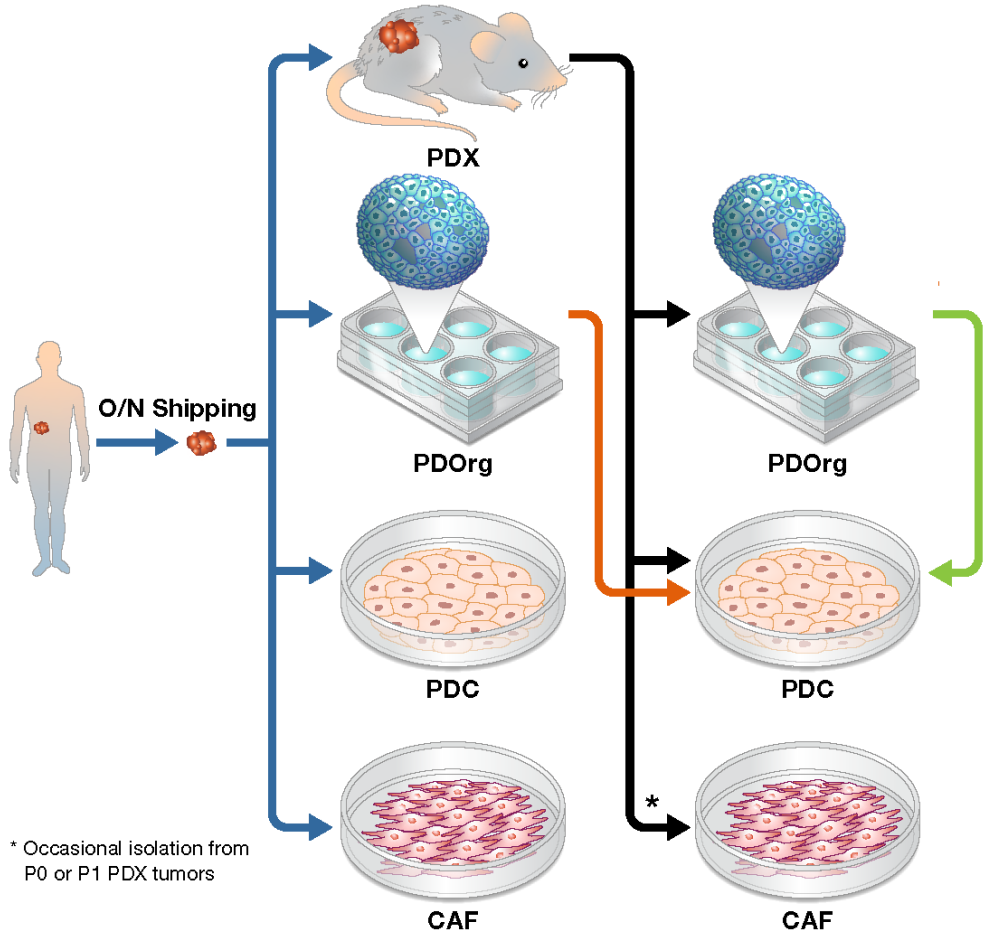
The National Cancer Institute Patient Derived Models Repository (PDMR)

An NCI Precision Oncology Initiative^{SM} Resource

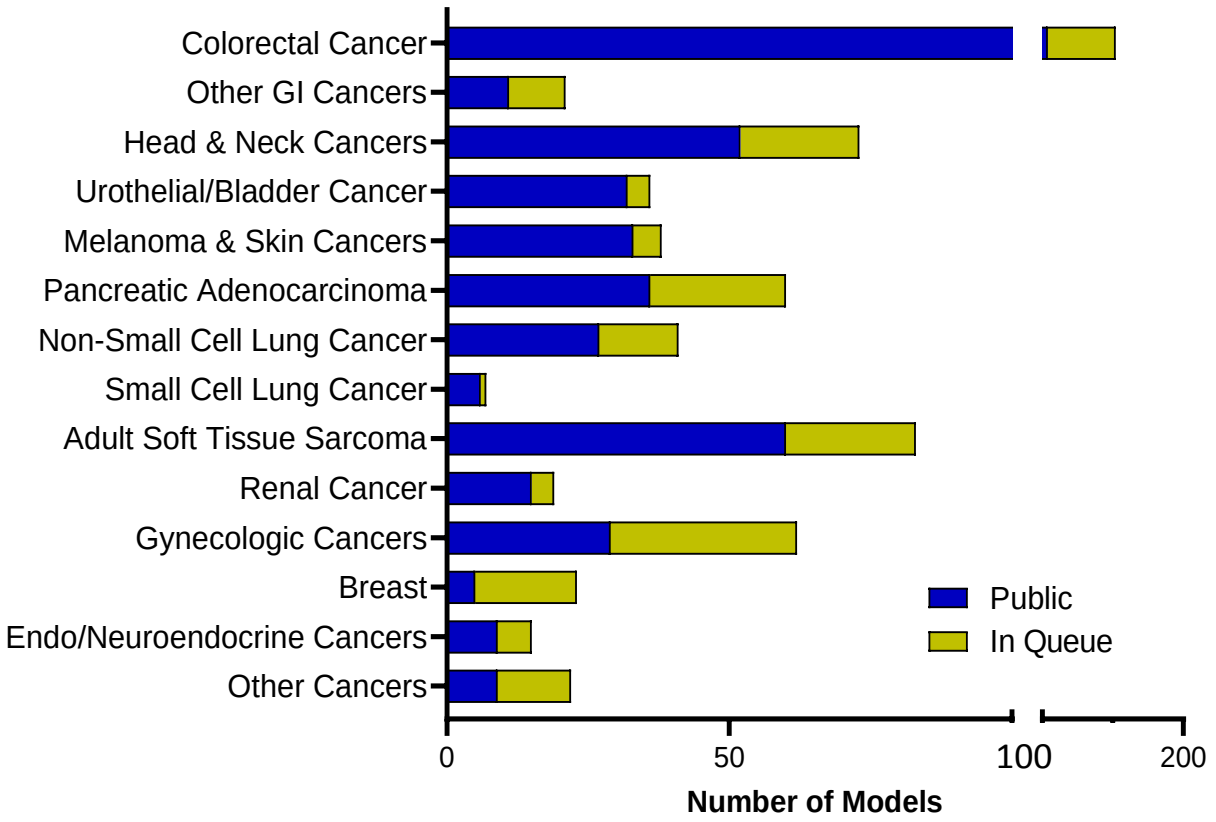
https://pdmr.cancer.gov

NCI's 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
- Clinically-annotated & early-passage models with comprehensive molecular-characterization and quality control metrics
- Complement existing PDM collections and focus on under-represented model types such as rare cancers and models representing racial and ethnic minorities
- Provide models to the research community at a modest cost compared to other distributors
- Provide all related metadata including: deidentified patient clinical history and outcomes, model histology, WES and RNASeq of models, and SOPs through a public website: https://pdmr.cancer.gov



Patient-Derived Xenograft (PDX) Models Available Across Solid Tumor Histologies



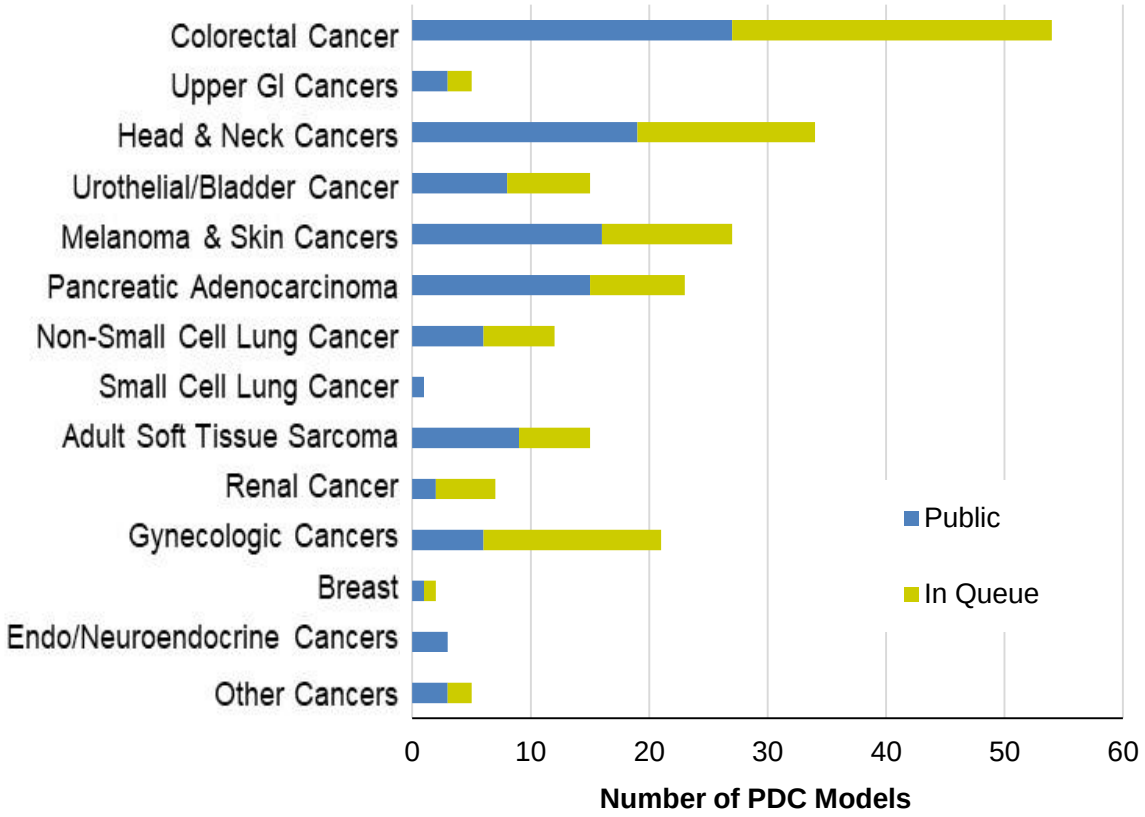
- 429 Public models. 223 additional models in Final QC (going through pathology, NGS, STR, regrowth from freeze); Median Passage =2
- Clinically-annotated, early-passage, molecularly-characterized patient-derived models
- Complement existing PDX collections and focus on under-represented model types such as rare cancers and models representing racial and ethnic minorities
- Provide all related metadata and SOPs through a public website
- Current distribution within the US (pdmr.cancer.gov).
  - ✓ Model information also available through PDX Finder at www.pdxfinder.org
- Specimens are from patients with both primary and metastatic disease from treatment naïve to heavily pre-treated

Rare Cancer Histologies Available

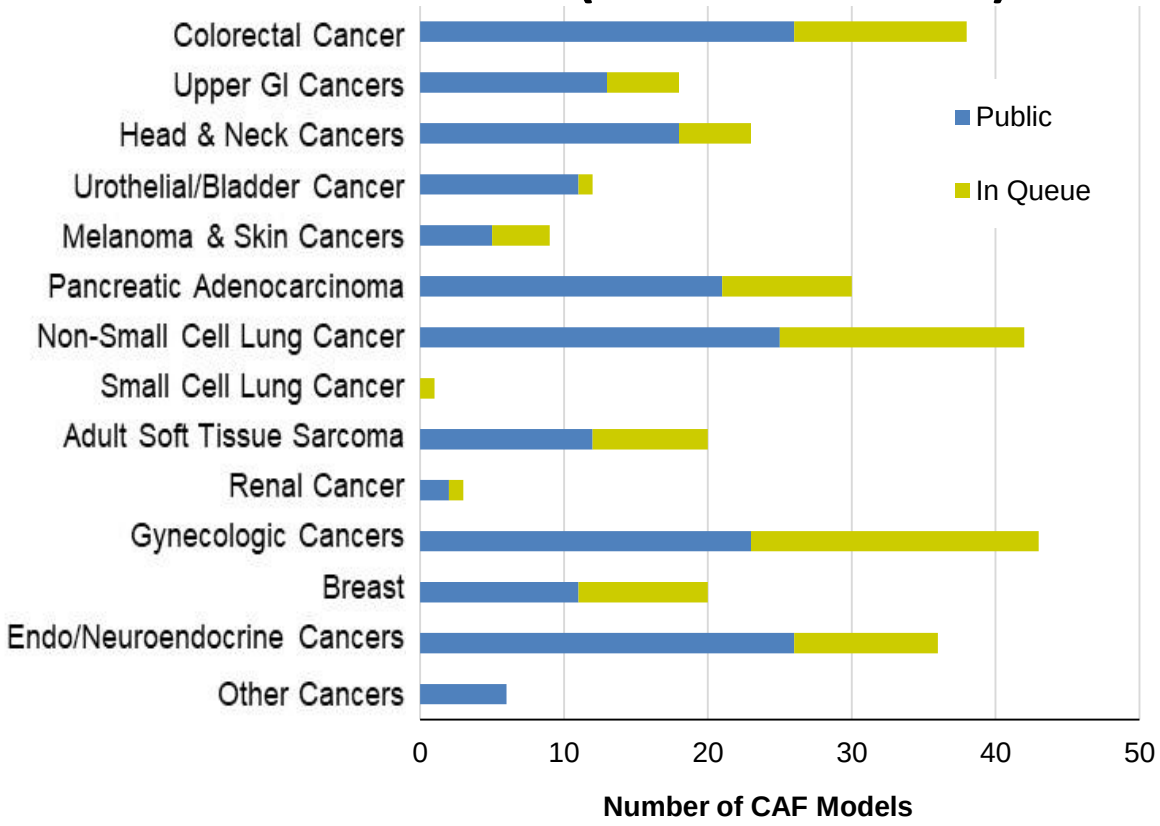
- Merkel Cell Carcinoma
- Mesothelioma
- Hurthle Cell Neoplasm of the Thyroid
- Malig. Periph. Nerve Sheath Tumor
- Salivary Gland SCC
- Pharyngeal SCC
- Nasopharyngeal SCC
- Laryngeal SCC
- Carcinosarcoma of the Uterus
- Vaginal Cancer
- Cervical SCC
- Synovial Sarcoma
- Liposarcoma
- Leiomyosarcoma – uterine and non-uterine
- Rhabdomyosarcoma
- Osteosarcoma
- Chondrosarcoma
- Malignant fibrous histiocytoma
- Fibrosarcoma – not infantile
- Ewing sarcoma/Peripheral PNET

Patient-Derived Cancer Cell Lines (PDCs) and Cancer Associated Fibroblast Cultures (CAFs)

119 Public PDCs (105 In Final QC)



200 Public CAFs (103 In Final QC)

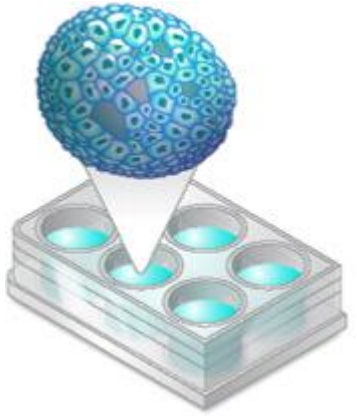


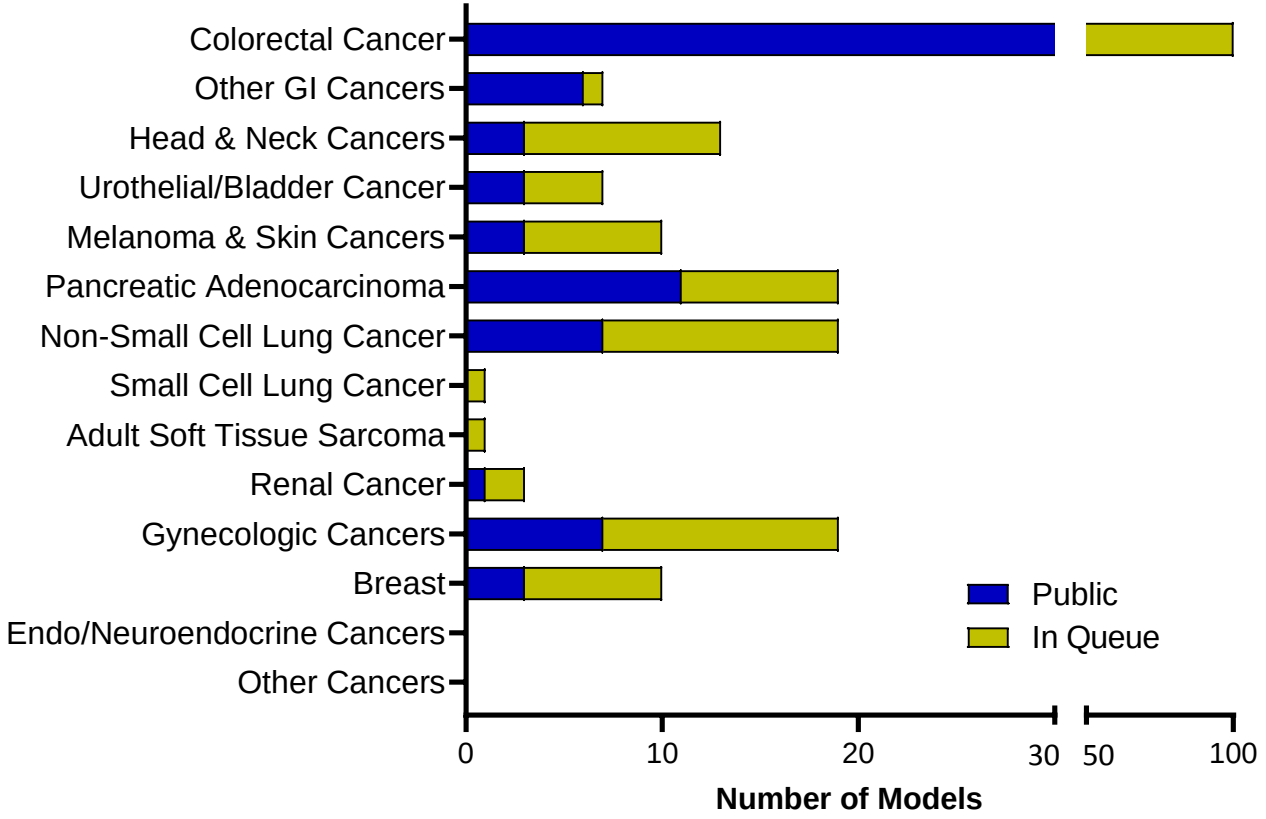
- **Adherent & Suspension Cultures**
- **Requires use of defined media**

21	**Median Passage**	**14**
12	**Min Passage**	**9**
51	**Max Passage**	**34**

- **Not Transformed**
- **Limited Lifespan**
- **Requires use of defined media**

Patient-Derived Organoids (PDOrg)





Requires use of defined media

- 88 Public models, 123 in Final QC
- Goal: Wherever possible develop a PDX, 2D *in vitro* PDC, and PDOrg culture for comparative preclinical studies
- Provide all related metadata and SOPs through the PDMR website and public database: pdmr.cancer.gov

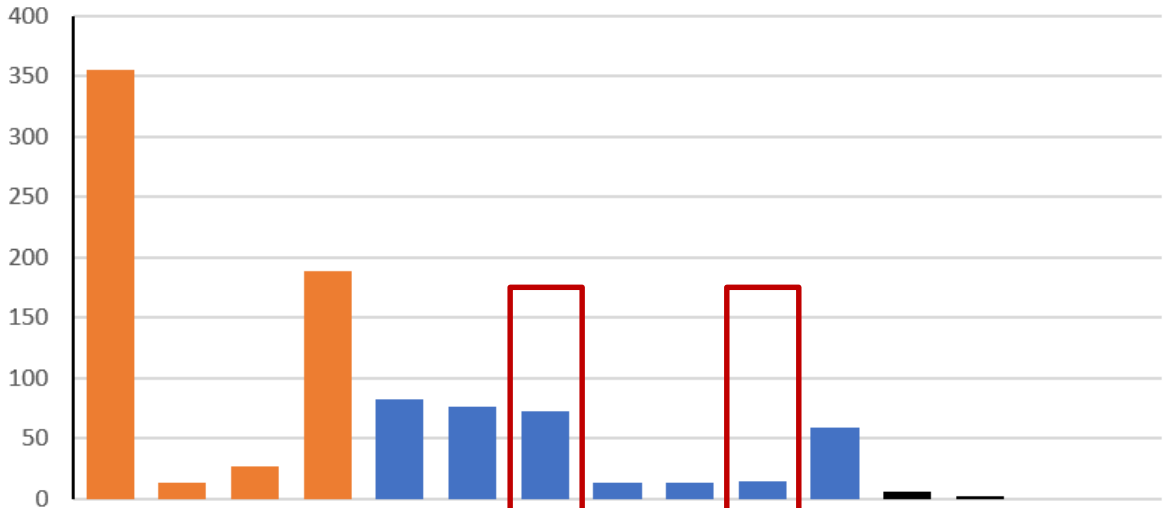
Median Passage	**11**
Min Passage	**4**
Max Passage	**39**

Matched PDX, PDOrg, PDC, and CAF Models

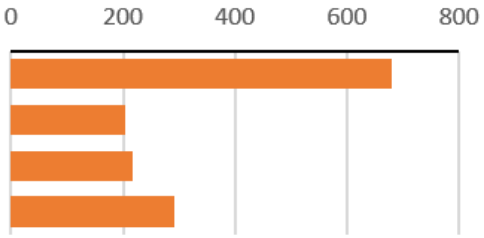
Includes models that are either

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

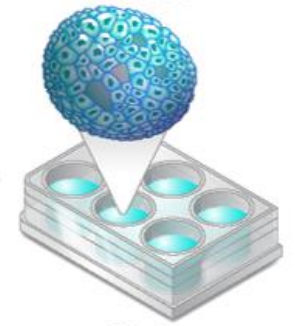
87 models with PDX, PDOrg, & PDC for mid/high-throughput translational screening



Total Individual	Total Intersect	356	13	27	189	82	76	72	13	13	15	59	6	2	0	0
680	PDX	■				■	■	■	■	■	■	■				
203	PDOrg		■			■		■	■		■		■	■	■	
217	PDC			■			■	■		■	■		■	■		■
291	CAF				■				■	■	■	■		■	■	■



PDX



PDOrg

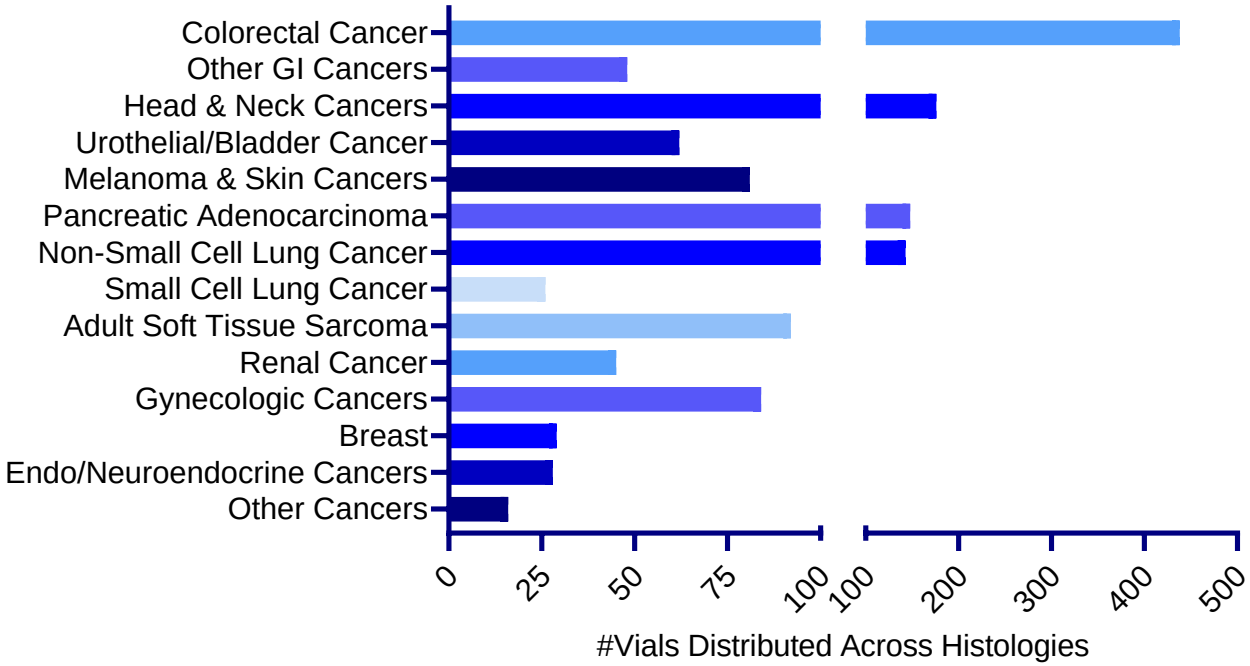
PDC

CAF

Distribution of Models to the Public

Academic, Commercial, and Intramural

Material	Number of Vials Distributed
PDX Fragments – Viably Cryopreserved	555
DNA from PDX Fragment (Solution)	13
RNA from PDX Fragment (Solution)	28
Fresh-Frozen PDX Fragment for Extraction	457
In Vitro PDCs – Viably Cryopreserved	252
In Vitro CAFs – Viably Cryopreserved	22
PDOrgs – Viably Cryopreserved	89
TOTAL	1416



USES:

- ✓ Academic preclinical core services
- ✓ Commercial investigational agent validation
- ✓ Target-specific inhibitors matched to molecular phenotypes
- ✓ Small molecule agents
- ✓ Methylome assessment
- ✓ Tumor microenvironment
- ✓ Small animal imaging studies
- ✓ Biomarker assessment matched to molecular phenotypes
- ✓ Angiogenesis
- ✓ Proteogenomics
- ✓ Radio-therapy

Institutions/Companies Receiving PDMR Resources

Academic/Non-for Profit

Augusta University *
Brown University
Cleveland Clinic
Dartmouth College
Emory University
Georgetown University
Harvard University (Boston Children's Hospital)
Harvard University (Massachusetts General Hospital) *
Houston Methodist Research Institute (Weill-Cornell Medicine)
Indiana University
Johns Hopkins University * †
MD Anderson Cancer Center * †
Mount Sinai (Icahn School of Medicine)
Ohio State University * †
Roswell Park Cancer Institute
Saint Louis University
San Diego State University
Stanford University *
The Wistar Institute
Thomas Jefferson University †
University of California, Irvine *
University of California, San Francisco
University of California, Los Angeles * †
University of California, Davis
University of Georgia
University of Maryland †
University of Miami
University of Michigan * †
University of Pittsburgh *
University of South Alabama
University of Southern California (Keck Medicine)
University of Tennessee
University of Texas, Dallas
University of Texas, Southwestern
University of Washington (Fred Hutchinson Cancer Research Center) * †
University of Wisconsin, Madison (Morgridge Institute)
Virginia Commonwealth University *
Wake Forest University *
Washington University

Center for Cancer Research, NCI * †
Division of Cancer Epidemiology and Genetics, NCI
Division of Cancer Treatment and Diagnosis, NCI * †
Frederick National Laboratory for Cancer Research * †
National Center for Advancing Translational Sciences (NCATS), NIH

Biotech/Pharma

AstraZeneca
Chimera Bioengineering
Dicerna Pharmaceuticals, Inc
GlaxoSmithKline
Kenjockety Biotechnology
Merrimack Pharmaceuticals *
Orphagen 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

Ongoing Efforts

- Proteomic and Phospho-proteomic analysis of PDMR, CPTAC
- Planning PDX Tissue MicroArray (TMA) Panels
- HLA-Typing of all PDX models
- Collaboration with Tempus, Inc.
  - ✓ Exchange Organoid models and test with same drugs other site has experience to compare reproducibility of preclinical response across sites
- Performing preclinical studies with matched PDMR PDXs and Organoid to assess consistency of response in models from the same patient

Questions?