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

An NCI Precision Oncology Initiative℠ Resource

Y A Evrard[1], MM Gottholm-Ahalt[2], SY Alcoser[2], UT Anidi[1], K Arthur[1], M Baldwin[1], LL Blumenauer[2], C Bonomi[1], S Borgel[1], E Bradtke[1], C Camalier[4], J Carter[1], T Chase[1], A Chen[3], DW Coakley[1], NE Craig[1], B Das[4], V Datta[4], C Davis[1], MR DeFreytas[1], MA Crespo-Eugeni[2], R Divelbiss[1], K Dougherty[1], P Fliss[4], T Forbes[4], M Gibson[1], P Jacobs[3], F Jimenez[1], A Jordon[1], J Kalen[1], C Karangwa[1], C Karlovich[4], S Kummar[5], J Lih[4], S McDermott[4], A Millione[1], M Morris[1], JE Moyer[1], M Mullendore[1], D Newton[1], K Plater[1], M Radzyminski[1], Larry Rubinstein[3], H Si[4], J Smith[1], MB Smith[1], A Stephens[1], , LH Stockwin[1], H Stotler[1], J Stottlemyer[1], J Tatum[3], D Trail[1], MJ Troncatti[1], A Wade[1], A Walke[1], W Walsh[4], J Welker[1], J Yingling[1], PM Williams[4], MG Hollingshead[2], JH Doroshow[3]

[1]Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc., Frederick, MD 21702; [2]Biological Testing Branch, Developmental Therapeutics Program, National Cancer Institute at Frederick, Frederick, MD 21702; [3]Division of Cancer Treatment and Diagnosis, National Cancer Institute, NIH, Bethesda, MD 20892; [4]Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc., Frederick, MD 21702, [5]Stanford School of Medicine, Stanford, CA 94305

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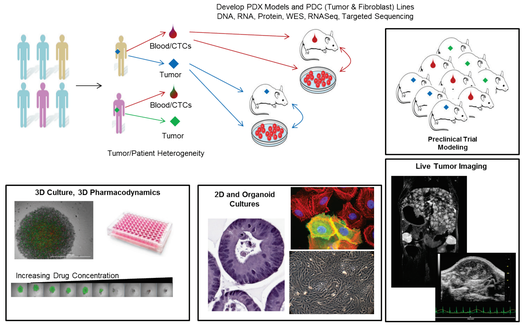
Funded by NCI Contract No. HHSN261200800001E

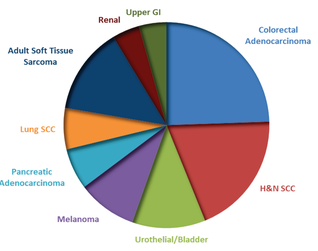
Introduction

The National Cancer Institute (NCI) is developing a Patient-Derived Models Repository (PDMR) comprised of quality-controlled early-passage clinically-annotated patient-derived xenografts (PDXs) and in vitro patient-derived cell cultures (PDCs), including tumor cell and cancer-associated fibroblast cell cultures, to serve as a resource for public-private partnerships and for academic drug discovery efforts. These PDMs will be clinically-annotated with molecular information (whole exome sequence, RNASeq) available in a publicly accessible database and will be available to the extramural community for research use. The PDMR was established by NCI at the Frederick National Laboratory for Cancer Research (FNLCR) in direct response to discussions with academia and industry; the oncology community's highest priority need is better preclinical models that more faithfully reflect the patient's tumor and are associated with the patient's treatment history. NCI has focused on collecting specimens from patients with cancer that are under-represented in many other PDX collections such as head and neck, pancreatic, bladder, ovarian and small cell lung cancers, melanomas and sarcomas. In addition, NCI is increasing its focus on creating PDXs from minority/underserved populations and will soon be expanding to include pediatric cancers. The PDMR generates the majority of its PDXs by subcutaneous implantation; however certain histologies have better take-rates in either orthotopic or alternate implant sites. All SOPs and quality-control standards developed by the PDMR as well as those shared by collaborators will be posted to the public web site that houses the PDMR database.

The overall goal of NCI is to create a long-term home for at least 1000 models such that sufficient biological and clinical diversity is represented to allow researchers to ask questions such as: what is the impact of tumor heterogeneity on target qualification or clinical response; do PDXs more faithfully represent the human tumor for pharmacodynamic assay and predictive marker development; or can an adequately powered preclinical PDX clinical trial lead to better evaluation of therapies for future clinical use.

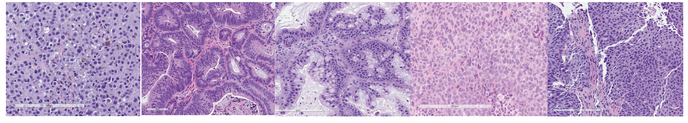


The PDMR primarily generates PDX models by subcutaneous implantation of tumor fragments into NOD.*Cg-Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ (NSG) mice. Alternate implant locations are used for specific cases where the take-rate is improved; for instance sarcoma tissue implantation in the mammary fat pad increased the take rate from <5% to 35%. All animal studies were conducted in an AAALACi-accredited facility under an approved IACUC protocol. Each model goes through multiple quality control steps including histological review by a board-certified pathologist, assessment of variant concordance across PDX tumors within the same model, STR profiling, and human and murine pathogen assessment. All models have patient-associated limited medical history, race/ethnicity, any provided patient pathology findings associated with them.



Disease Distribution Groups
Colorectal Adenocarcinoma
Head & Neck Squamous Cell Carcinoma • Pharyngeal, Laryngeal, Lip/oral cavity, NOS
Urothelial/Bladder
Melanoma
Pancreatic Adenocarcinoma
Lung Squamous Cell Carcinoma
Adult Soft Tissue Sarcoma • Ewings, Leiomyosarcoma, Malignant fibro. histiocytoma, Fibrosarcoma, Non-Rhabdosarcoma NOS, Rhabdosarcoma NOS
Renal
Upper GI • Stomach, Sm. Intest, GIST, Appendiceal

Release of the first 100 PDMR models: Coming soon https://pdmr.cancer.gov

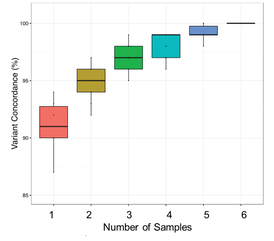


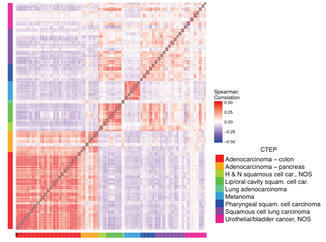
Melanoma | Colon Adenocarcinoma | Pancreatic Adenocarcinoma | PNET | Lung Squamous Cell Carcinoma

Body Location	Total Received	Total Assessable Specimens	%Take-Rate of Assessable Specimens	Passageable Tumor*	Discontinued†	*Not Yet Assessable: P0 tumors*
Breast	94	58	12%	7	51	36
Digestive/ Gastrointestinal	246	177	61%	108	69	69
Endocrine/ Neuroendocrine	83	52	13%	7	45	31
Genitourinary	267	186	30%	56	130	81
Germ Cell	4	3	0%	0	3	1
Gynecologic	139	73	56%	41	32	66
Head and Neck	133	118	64%	76	42	15
Hematologic/Blood	4	2	50%	1	1	2
Musculoskeletal	246	173	35%	61	112	73
Neurologic	20	19	84%	16	3	1
Respiratory/Thoracic	98	67	51%	34	33	31
Skin	53	44	66%	29	15	9
Unknown Primary	11	9	33%	3	6	2
Totals	1398	**981**	**45%**	**439**	**542**	417

PDX Take-Rate from Tumor Tissue Implantations. *Passageable tumors include any PDX where a palpable tumor has been passaged to at least P1 as well as Distributable PDXs. One or more of QC steps for PDX confirmation are pending for earlier passages. †Discontinued Models include any model that: (1) Did not successfully grow palpable tumor in P0 (monitored 300 days), (2) Passaged tumor failed to grow in subsequent passages, (3) Mouse found dead/tumor not passageable, (4) Palpable tumors were 100% murine content, (5) Tumors in all lineages were determined to be XALD.

Molecular Characterization





(A) Variant concordance data to show that whole exome sequencing of 4 samples in a model represents more than 95% concordance with sequencing 6 samples in the same model. Variant concordance rate = number of common variants/number of total variants in comparison. (B) Heatmap of pairwise correlation of 408 samples representing 97 unique models across 9 disease types. Samples from within the same model have higher correlation than others and samples belonging to same disease type are correlated with each other.

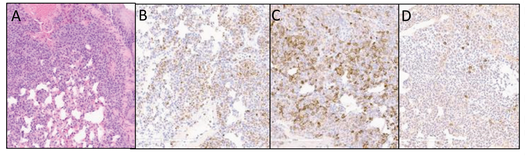
All PDX models in the PDMR will have whole exome sequence (FASTQ, vcf), RNASeq (FASTQ, RSEM TPM and isoforms), and variant results from an NCI Cancer Gene Panel associated with a minimum of 4 individual PDXs. The NCI Cancer Gene Panel Assay is an amplicon-based NextGen sequencing (NGS) assay for 62 genes (oncogene hotspot regions and the majority of protein coding-regions for tumor suppressor genes) implicated in cancer; all non-synonymous variants present in these 62 genes are reported. Given the nature of PDX tumors, even with a rigorous pipeline (detailed on website) there will be murine content in the sequences and investigators should be aware of this when doing metadata analysis of the public sequence files.

Future Directions

The PDMR will continue to add models to the public database as QC is finalized on each model. In addition, several data types are being added to the analysis pipeline for inclusion in the public database, including:

- Consensus Genomic Variants: list of variants that are 100% represented in PDX whole exome sequencing data
- Germline Whole Exome Sequence
- Ancestry SNP Assessment
- Whole Mouse Imaging (e.g., MRI, US)
- Designation of Metastatic PDX Models
- Preclinical Drug Study Results
- In vitro Early-Passage Tumor and Cancer-Associated Fibroblast Cultures

Xenograft-Associated Lymphoproliferative Disorders (XALD)



XALD in a lung section. (A) Lymphoid cell infiltration in lungs of a mouse bearing an EBV-driven XALD tumor. Immunohistochemistry of the lung section demonstrating a human mitochondria + (B), CD45+ (C), and focally positive anti-EBV-LMP1 (D) infiltrate.

Patient Diagnosis	CK	CD45	EBV	HuMit	CD20	CD19	CD3	CD4	CD8	CD279	CD274	CD56
RCC, clear cell adenocarcinoma	-	+	+	+	+	2+ (80% +)	5-10%+	-	<5% +	2+ (30%+)	4+	-
Adenocarcinoma - stomach	-	+	+	+	+	2+ (80%+)	15%+	-	15% +	2+ (60%+)	4+	-
Adenocarcinoma - rectum	-	+	+	+	+	2+ (40%+)	50%+	5%+	40% +	3+ (40%+)	4+	-
Papillary thyroid carcinoma	-	+	+	+	+	3+ (80%+)	20%+	-	20% +	3+ (60%+)	4+	1%+
Embryonal rhabdomyosarcoma	-	+	+	+	+	3+ (90%+)	50%+	-	50% +	3+ (90%+)	4+	-
Adenocarcinoma - colon	-	+	+	+	+	2+ (40%+)	5%+	-	-	2+ (10%+)	4+	5%+

Immuno-profiling of 6 xenograft-associated lymphoproliferative disorder (XALD) in NSG mice. Following implantation of patient tumor material and PDX passage, several models form EBV-driven lymphomas in NSG mice. Analysis of a sub-set of ten models at passage 0 indicate the majority of XALDs are diffuse large B-cell-type lymphomas

The PDMR uses the term XALD to group several lymphoproliferative disorders that are encountered in during PDX generation including GvHD, EBV-driven human lymphoma, mouse lymphomas, 'multiple histology XALD' where there is a mix of XALD and the patient tumor. The IHC characterization below focuses on human lymphoma XALDs. Briefly, this is characterized by the proliferation of the patient's atypical lymphocytes at the site of implant or as a disseminated disease. This is most commonly seen with models generated from circulating tumor cells due to the high PBMC content; however, it is also observed with tumor tissue implants. These tumors are highly cellular, mitotically active, and composed of monomorphic or polymorphic blue cells at the site of implant. Cellular features are primarily centroblast-type however, immunoblastic features have also been noted