Patient-Derived Models of Rare Cancers in the National Cancer Institute's Patient-Derived Models Repository (PDMR)

CR Timme[1*], SY Alcoser[3], D Breen[1], J Carter[1], TC Chang[2], AP Chen[4], L Chen[2], K Cooley[1], B Das[2], E Delaney[1], MA Eugeni[3], MM Gottholm-Ahalt[3], T Grinnage-Pulley[3], J Hull[1], C Karlovich[2], K Klarmann[3], S. Jiwani[2], C Mallow[1], C McGlynn[1], J Mills[1], M Morris[1], M Mullendore[1], D Newton[1], T Shearer[1], J Stottlemyer[1], S Uzelac[1], T Vilimas[2], T Walsh[1], PM Williams[2], YA Evrard[1], MG Hollingshead[3], JH Doroshow[4]

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

*Contact Cindy R Timme: Cindy.Timme@nih.gov

Frederick National Laboratory for Cancer Research

leidos Biomedical Research, Inc.

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Overview

There is an unmet need for preclinical models of rare cancers and rare disease sub-types. The National Cancer Institute's Patient-Derived Models Repository (NCI PDMR; https://pdmr.cancer.gov) is developing early-passage, clinically-annotated patient-derived tumor xenografts (PDXs), in vitro tumor cell cultures (PDCs), cancer associated fibroblasts (CAFs), and patient-derived organoids (PDOrg) from adult and pediatric patients with rare cancers. To date, NCI has created and molecularly characterized over 150 such models (see tables). As part of the quality control process, rare cancer models are reviewed and their histopathologic and molecular characteristics compared to that reported in the clinical setting. A pipeline to identify fusion proteins in these rare cancers such as the Ewing sarcoma EWSR1-FLI1 fusion and NAB2-STAT6 fusions in solitary fibrous tumors (SFT) has been implemented. Four malignant peripheral nerve sheath tumor (MPNST) PDX models are available for researchers; these models were developed from patients diagnosed between the ages of 37-68. At the time of model development, two patients were treatment-naïve and two had prior radiotherapy. Two of the MPNST PDX models have NF1 oncogenic mutations, three have deep deletions in CDKN2A/B, and three have a mutation in either EED or SUZ12 consistent with the reported molecular characteristics of patients with MPNST. Also of clinical relevance, of two mesothelioma models available, one carries an NF2 driver mutation and the other BAP1 and LATS2 and a PDX model for Hürthle cell carcinoma has wide-spread loss of heterozygosity (LOH ~80%). Models for other rare cancers are being expanded for molecular characterization and distribution including four cholangiocarcinoma PDXs.

References

1 American Cancer Society's Cancer Facts and Figures 2020

2 NIH/NCI https://rarediseases.info.nih.gov/diseases/diseases-by-category/1/rare-cancers

3 SWOG DART study: S1609, "DART: DUAL ANTI-CTLA-4 AND ANTI-PD-1 BLOCKADE IN RARE TUMORS" Study Chairs: Drs. S.P. Patel, Y.K. Chae, and R. Kurzrock.

Rare Cancer PDX Models in the PDMR

Musculoskeletal

Diagnosis	No. of Models
Alveolar soft part sarcoma	1
Chondrosarcoma	1
Ewing sarcoma/Peripheral PNET	3
Fibrosarcoma - not infantile	7
Leiomyosarcoma - not uterine	3
Leiomyosarcoma - uterus	4
Liposarcoma	3
Malig. periph. nerve sheath tum. (MPNST)	4
Malignant fibrous histiocytoma	9
Non-Rhabdo. soft tissue sarcoma	16
Osteosarcoma	3
Rhabdomyosarcoma, NOS	2
Soft tissue neoplasm, NOS	3
Synovial sarcoma	4

Head and Neck

Diagnosis	No. of Models
H & N squamous cell car., NOS	9
Laryngeal squamous cell carcinoma	5
Lip/oral cavity squam. cell car.	22
Pharyngeal squam. cell carcinoma	13
Salivary gland cancer	6

Endocrine/Neuroendocrine

Diagnosis	No. of Models
Hürthle cell neoplasm (thyroid)	1
Merkel cell tumor	4
Neuroendocrine cancer, NOS	3
Small cell car. (extrapulmonary)	3

Gynecological

Diagnosis	No. of Models
Adenocarcinoma - cervix	1
Carcinosarcoma of the uterus	7
Ovarian cancer, NOS	2
Ovarian epithelial cancer	5
Squamous cervical cancer	4
Uterine cancer, NOS	2
Vaginal cancer, NOS	2
Vulvar cancer, NOS	0

Miscellaneous

Diagnosis	No. of Models
Mesothelioma	2

Digestive/Gastrointestinal

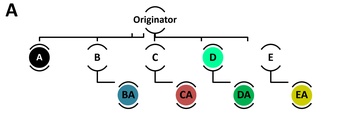
Diagnosis	No. of Models
Adenocarcinoma - GEJ	1
Adenocarcinoma - small intest.	3
Adenocarcinoma - stomach	2
Gastric cancer, NOS	1
Gastrointestinal stromal tumor	1
Squamous cell carcinoma - anus	4

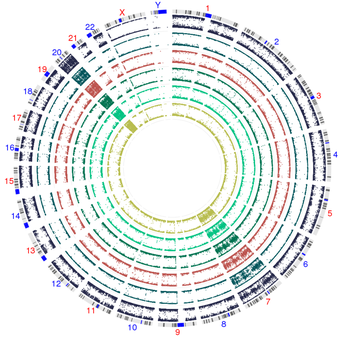
In Development (Not Yet Public)

Diagnosis	No. of Models
Adrenocortical carcinoma	3
Alveolar rhabdomyosarcoma	2
Cervical cancer, NOS	1
Cholangiocarcinoma	10
Liver/hepatobiliary cancer	1
Neuroblastoma	1
Papillary thyroid carcinoma	2
Penile squamous car.(epidermoid)	1
Carcinoid tumor	1

The above rare tumor models are available for investigators through the PDMR. PDX models in development will be ready for distribution within 6-8 months. **Bold** text indicates rare cancers highlighted in this poster.

Hürthle Cell Carcinoma





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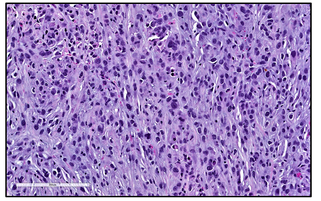

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Mutations:

DNMT3A p.H355Rfs*49

NF1 p.R1534*

NF2 p.Q362*

(A) Circos Plot of Variant Allele Frequency (VAF) of highly conserved genome-wide heterozygous single nucleotide polymorphisms (SNPs) among 6 PDX samples (representative of passage 0 and 1 PDX tumors across 5 lineages) showing global loss of heterozygosity (LOH). **(B)** H&E image (200µm scale bar) of a passage 3 PDX tumor, and **(C)** List of observed likely oncogenic mutations as annotated by OncoKB for Tumor Model 248138.

Hürthle Cell Carcinoma is a rare subtype (3-4%) of thyroid cancer and few PDX models have been developed. The PDMR has one Hürthle Cell Carcinoma model available that recapitulates previously reported molecular features of this rare cancer including widespread loss of heterozygosity (LOH) except in chromosomes 7 and 20 and mutations in *DNMT3A*, *NF1*, and *NF2*.

Genomic Landscape

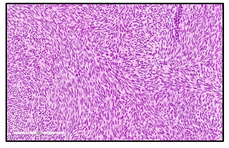
Mutations are reported here for select PDX models of rare cancer that recapitulate the varied genomic landscape in the clinical setting and possibly represent distinct subtypes.

Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

Model	NF1	CDKN2A/B	TP53	EED	SUZ12
467112	p.Y235Pfs*6	Deep Deletion	--	--	P257Qfs*31
589616	--	--	p.P153Afs*2	p.X287_splice	--
632484	--	Deep Deletion	p.L344P	--	--
719797†	p.M242Nfs*3	Deep Deletion	--	--	E314*

† 2D/3D tumor culture available/in development

The PDMR currently has 4 MPNST PDX models, each containing a distinct combination of mutations/alterations in *NF1*, *CDKN2A/B*, *TP53*, *EED*, and/or *SUZ12*.



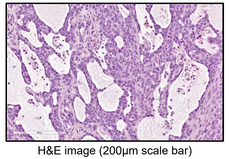
H&E image (200µm scale bar) of a MPNST PDX tumor

Mesothelioma

Model	BAP1	CDKN2A/B	NF2	LATS1	LATS2
933738	Deep Deletion	Deep Deletion	p.Y153*		
941425†	p.K205*	Deep Deletion		p.K182Lfs*19	p.K257Gfs*99

† 2D/3D tumor culture available/in development

The PDMR currently has 2 mesothelioma PDX models, each with distinct *BAP1* and *CDKN2A/B* alterations and accompanied by either *NF2* or *LATS1/2* mutation(s).



H&E image (200µm scale bar) of a Mesothelioma PDX tumor

Genomic Landscape

Fusion Detection

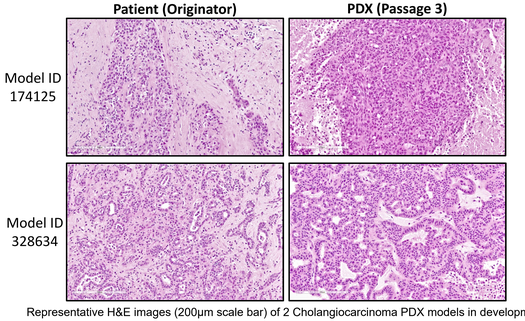
Fusion	Diagnosis	No. of Models
EWSR1-FLI1	Ewing Sarcoma	2
CIC-DUX4	Ewing Sarcoma	1
SS18-SSX1	Synovial Sarcoma	3
NAB2-STAT6	Solitary Fibrous Tumor	1
FGFR3-TACC3	Pharyngeal SCC	1
EIF3E-RSPO2	Stomach Cancer	1

The PDMR is developing a fusion caller pipeline to assist in identifying known gene fusions to confirm histology/diagnosis of rare cancer subtypes using RNASeq data.

To date, six gene fusions have been identified within the PDMR PDX rare cancer collection.

Cholangiocarcinoma

Six PDX models for cholangiocarcinoma have been developed by the NCI and are in the final steps of whole-exome sequencing and RNASeq to be performed before being made public. In addition, external laboratories have deposited an additional four PDX models for distribution by the PDMR.



Representative H&E images (200µm scale bar) of 2 Cholangiocarcinoma PDX models in development

Summary

- The PDMR has targeted collection of tissue from rare cancers and rare disease subtypes to develop patient-derived, early passage PDX models for preclinical studies.
- All available models in the PDMR are clinically-annotated and have representative genomic (Whole Exome Sequencing, Gene Expression, and Annotated Gene Mutation) data freely accessible to the research community.
- Where possible, matched in vitro organoids, tumor cell cultures, and cancer-associated fibroblasts are available or being developed.
- Please visit us at **https://pdmr.cancer.gov/** where you can find a link to our database of available models and information on how to request them.
- Email us at **NCI_PDM_Repository@mail.nih.gov**

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