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## Identifying Mouse Models for Skin Cancer using the Mouse Tumor Biology Database

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### Abstract

In recent years the scientific community has generated an ever-increasing amount of data from a growing number of animal models of human cancers. Much of these data come from genetically engineered mouse models. Identifying appropriate models for skin cancer and related relevant genetic data sets from an expanding pool of widely disseminated data can be a daunting task. The Mouse Tumor Biology Database (MTB) provides an electronic archive, search, and analysis system that can be used to identify dermatological mouse models of cancer, retrieve model-specific data, and analyze these data. In this report we detail MTB's contents and capabilities, together with instructions on how to use MTB to search for skin-related tumor models and associated data.

### Keywords

animal model; skin cancer; tumor; mouse; pathology; database; images

### Background

The explosion in the amount and complexity of data generated by molecular biology and genomics technologies has made traditional approaches to the identification and analysis of relevant data difficult. Large-scale data generating projects, such as the human genome sequencing project (1), the ENCODE project (2), and Genome Wide Association Studies (GWAS) (3) exemplify this problem. Virtually all fields of biological study face this data deluge, including dermatology.

Human disease model systems have assumed an important role in the production of phenotypic and genetic dermatology related information. The laboratory mouse has been and continues to be the most commonly used and important model system used in studying human skin. However, while important, the utility of mouse models is limited by the complexity of the disease and the inbred nature of the mouse genetics (4, 5). Mouse models

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are widely used because mice are easily maintained, have a fully sequenced and annotated genome, can be studied at all life stages even before disease onset, and have an extensive array of molecular and genetic tools available to manipulate their pathophysiology (6–8). Mouse models are particularly advantageous when studying human diseases due to their similar physiology, and numerous established inbred, congenic, consomic, and recombinant inbred strains. Additionally, patient-derived xenograft (PDX) models based on human tumor grafts grown in mouse hosts are becoming more important in translational research (9).

Identifying and accessing skin-related mouse model data from the published literature and sifting through the strains, mutations, nomenclature, and pathological descriptions generated from these models to enable new discoveries and facilitate experimental designs is no longer feasible for an individual working manually on this corpus.

## Questions Addressed

The ability to locate very specific dermatology data related to particular genetic and biological details such as tissue type, related genes, and tumor type is very important in designing future experiments and interpreting current publications. As an example of this, recent dermatology publications use mouse models designed to investigate tumor metastases and lesion staging in transgenic mice and human xenograft models (10–12). How can MTB assist scientists in identifying potentially useful and highly specific mouse models of dermatological tumors and access and analyze the diverse amount of data associated with these models?

## Experimental Design

MTB has been publicly available since 1998 (13–15). MTB was constructed with the goal of making available a central electronic resource for the collection, integration, and analysis of the diverse data derived from mouse cancer models and to support development of new models. MTB incorporates information on the frequency/incidence, latency, and tissue of origin of mouse tumors and metastases. Detailed pathology reports, and associated images are also available. In addition, MTB includes data on the genetics of the background strain and somatic mutations in the tumors including Spectral Karyotyping (SKY), Comparative Genome Hybridization (CGH), Quantitative Trait Loci (QTL) associated with cancers, and indexes gene expression array data for mouse tumors from the Gene Expression Omnibus (GEO) and the Array Express (16–19). All data are attributed to the original source. MTB enables integrated searches of data from diverse sources through application of multiple controlled vocabularies and standardized nomenclature.

MTB has also developed web forms to access data from the Patent Derived Xenograft (PDX) resource at The Jackson Laboratory (20). This program establishes models of human tumors utilizing the NOD.Cg-Prkdc<sup>scid</sup>Il2rg<sup>tm1Wjl</sup>/SzJ mice as the host for human tumors (NSG, JR#5557, The Jackson Laboratory). The PDX resource includes comprehensive genomic characterization of engrafted tumors with links to de-identified patient clinical data. The PDX resource currently contains over 320 models from 28 different tissues and 66 tumor types including nine skin tumor (melanoma and squamous cell carcinoma) models.

Going forward, MTB plans to improve access to translational and pre-clinical data as well as mouse model credentialing data and mouse-human comparative genomics.

## Results

MTB provides a mechanism for researchers to search for dermatology related data in a very detailed manner. For example, to search for data about mouse melanoma models involving *Nras* that have metastases, users would select the “Advanced Search Form” listed on the left side of the MTB home page. On this form melanoma would be selected from the pull-down list of tumor types and skin-melanocyte as organ of origin. *Nras* would be entered in the “Gene or Allele” textbox and the “Restrict search to metastatic tumors only.” box would be checked. This search returns 8 “Tumor Instances” (Fig. 1) and shows relevant data for all the search results. The “Summary” links on the right open a detailed summary of the selected tumor and associated metastases with links to References, Pathology Records, and any additional notes. Fig. S1 shows a Pathology Record of an unpublished image of a novel mouse melanoma submitted to MTB by SS Dadras (21).

The “Patient Derived Xenograft Search Form” allows researchers to query MTB for PDX models. The search form can be queried by PDX model identifier, primary cancer site, Gene variant, or Gene expression. For example selecting “skin” for primary cancer site returns 8 results: 6 melanomas, 1 squamous cell carcinoma, and an unspecified cancer type. The results also indicate tumor site, patient gender, and age as well as if any additional data, histology, genomics, etc., as shown in Fig. 2. Fig. S2 shows a PDX model details page with histology and tumor growth data.

## Conclusions

MTB provides the most comprehensive source of mouse tumor data available, the highest quality of data curation, and search forms that allow data queries from many different scientific perspectives. MTB also serves as a repository for data from the dermatopathology community; for example, including images from the Jackson Aging Center, Pathbase (22, 23), and information on antibodies used to study mouse cancer models. MTB enables researchers to present their tumor data to the scientific community in a way that will place these data in the wider context of genetic and molecular data and assists researchers in identifying appropriate mouse models for their research. Finally, MTB provides community access to key pathology data connected to tumor diagnoses and outcomes that are otherwise unavailable for scientific analysis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Begley D.A. acquired the data, and wrote the paper.

Krupke D.M. designed the database, acquired the data, and critically revised the paper.

Neuhauser S.B. wrote the software for the database.

Richardson J.E. designed the software for the database.

Schofield P.N. submitted data, and reviewed the paper.

Bult C.J. designed the database, critically revised the paper.

Eppig J.T. designed the database, critically revised the paper.

Sundberg J.P. submitted data, and wrote the paper.

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**Advanced Search Form**

**Sort By:**  Tumor Classification  Organ of tumor origin  Strain name  Strain Type  Treatment Type

**Max number of items returned:**  25  100  500  No Limit

**Strain / Genetics**

**Strain Name:**  
Contains

**Strain Type:**  

- ANY
- chemically induced mutation
- chimeric
- congenic
- conplastic
- consomic
- consomic - partial
- embryo transfer

**Gene or Allele:**

**Tumor**

**Organ/Tissue of Origin:**  

- Skin - Hair follicle
- Skin - Hair follicle - Basal cell
- Skin - Head
- Skin - Inguinal region
- Skin - Melanocyte
- Skin gland
- Skin gland - Apocrine sweat gland
- Skin gland - Perianal gland

**Tumor Classification:**  

- mastocytoma - malignant
- medulloblastoma
- medulloepithelioma
- melanocytoma
- melanoma
- melanoma - amelanotic
- melanoma - benign
- melanoma - malignant

**Treatment Type:**

**Metastasis:**  
 Restrict search to metastatic tumors only

**Pathology Images:**  
 Restrict search to entries with pathology images

**Advanced Search Results**

**Search Summary**  
**Genetic Name:** Nras  
**Organ/Tissue of Origin:** Skin - Melanocyte  
**Tumor Classification:** melanoma  
**Restrict search to metastatic tumors only.**  
**Sort By:** Tumor Classification  
**Display Limit:** 25


8 unique tumor instances representing 49 tumor frequency records returned.

Tumor Name	Organ Affected	Treatment Type Agents	Strain Name Strain Types	Tumor Frequency Range				Metastasizes To	Images	Tumor Summary
				F	M	Mixed	Un.			
Skin - Melanocyte melanoma	Skin - Melanocyte	None (spontaneous)	<a href="#">B6:CBA/2-Cdkn2a<sup>tm1Bdp</sup>Tg(Tyr- NRAS*O61K)1Bee</a> <i>transgenic targeted mutation (knockout)</i>	Observed	Observed			Liver Liver Lung Lymph node - Cervical Lymph node - Cervical Lymph node - Cervical Lymph node - Cervical Lymph node - Inguinal Lymph node - Inguinal Lymph node - Sacral		<a href="#">Summary</a>
Skin - Melanocyte melanoma	Skin - Melanocyte	None (spontaneous)	<a href="#">B6:CBA/2-Cdkn2a<sup>tm1Bdp/+</sup>Tg(Tyr- NRAS*O61K)1Bee</a> <i>transgenic targeted mutation (knockout)</i>	observed	observed			Liver Liver Lung Lymph node - Axillary Lymph node - Brachial Lymph node - Inguinal		<a href="#">Summary</a>
Skin - Melanocyte melanoma	Skin - Abdomen	None (spontaneous)	<a href="#">B6:CBA/2-Cdkn2a<sup>tm1Bdp/+</sup>Tg(Tyr- NRAS*O61K)1Bee</a> <i>transgenic targeted mutation (knockout)</i>	observed				Lung Lymph node - Axillary		<a href="#">Summary</a>

**Figure 1.** Example of a search for metastatic melanoma involving *Nras* in skin melanocytes. This illustrates the ability of the “Advanced Search Form” to design very detailed queries.

?
**Patient Derived Xenograft Search Form**
Request more information on the JAX PDX program.

Patient Derived Xenograft (PDX) models for cancer research are created by the implantation of human cells and tumor tissue into immune compromised mouse hosts. PDX models provide a platform for in vivo cancer biology studies and pre-clinical cancer drug efficacy testing. The current state of the art mouse host is the "NOD-SCID-Gamma2" (NSG) mouse. NSG mice lack mature T and B cells, have no functional natural killer cells, and are deficient in both innate immunity and cytokine signaling.



Search
Reset

**Search by PDX model identifier**

**Model ID**

**Search by primary cancer site**

**Primary Site**

Pancreas  
Prostate gland  
Rectum  
Retropitoneum  
Salivary gland  
SKIN  
Stomach  
Uterus

**Limit results to models** with drug response data,  with tumor growth graphs.

**Search by diagnosis**

**Diagnosis**

ANY  
Adenocarcinoma  
Adenocarcinoma: Adenocarcinoma  
Adenocarcinoma: Anal adenocarcinoma  
Adenocarcinoma: Colon adenocarcinoma  
Adenocarcinoma: Endometrial adenocarcinoma  
Adenocarcinoma: Mucinous adenocarcinoma  
Adenocarcinoma: Pancreatic adenocarcinoma

**Search by gene variants (in engrafted tumors)**

**Gene**

ANY  
ABL1  
AKT1  
ALK  
APC  
ATM  
BRCA1  
C11orf65

Show Variants No variants for selected gene.

**Display a chart of gene expression across PDX models for a gene**

**Gene**

A1CF  
ABL1  
ACVR1B  
ADAR  
ADARB1  
AFF2  
AICDA  
AKT1

**Search by gene amplification and deletion**

**Gene**

A1CF  
ABL1  
ACVR1B  
ADAR  
ADARB1  
AFF2  
AICDA  
AKT1

Search
Reset

Check boxes can be used to select models to request details on availability.

Search Again

?
**Patient Derived Xenograft Search Results**
Request more information on the JAX PDX program.

Search Summary  
Primary Site: Skin  
Diagnosis: Any  
Gene: Any  
Variants: Any

# matching PDX Model(s)

Model ID	Previous ID	Medical Record No.	Primary Site	Diagnosis	Tumor Site	Tumor Type	Sex	Age	Additional data	
<input type="checkbox"/>	3563281	SK12882F	0009	Skin	Melanoma	Lung	Not Specified	Male	86	Histology/Tumor Growth
<input type="checkbox"/>	3563282	SK12882F	0008	Skin	Melanoma	Lung	Not Specified	Male	78	Histology/Tumor Growth
<input type="checkbox"/>	3563283	SK12882F	0005	Skin	Melanoma	Lung	Not Specified	Male	59	Tumor Growth Rate
<input type="checkbox"/>	3563288	SK12882F	139802	Skin	Melanoma	Ovary	Not Specified	Female	unspecified	Tumor Growth Rate
<input type="checkbox"/>	3563292	SK12882F	1062_3	Skin	Melanoma	Bone	Not Specified	Female	59	
<input type="checkbox"/>	3563295	LD0071F	SK-0071	Skin	Unspecified cancer type	Lung	Not Specified	Female	37	
<input type="checkbox"/>	3563298	SK181A1F	PC181-A-1	Skin	Melanoma	Skin	Not Specified	Male	60	
<input type="checkbox"/>	3563298	T801140F	13-11204	Skin	Carcinoma, Squamous cell carcinoma	Skin	Not Specified	Male	unspecified	

**Figure 2.** Example of a Search for PDX Data. The “Patient Derived Xenograft Search Form” is displayed with “Skin” selected as “Primary Tumor Site”. The inset shows the results of this search.