

# The Mouse Tumor Biology Database: A Public Resource for Cancer Genetics and Pathology of the Mouse<sup>1</sup>

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## Abstract

Developing genetic mouse models for cancer research has been recognized as an “exceptional opportunity” by the National Cancer Institute. The establishment of bioinformatics resources to facilitate access to published and unpublished data on the genetics and pathology of cancer in different strains of the laboratory mouse is critical to developing and using mouse models of human disease. In this article, we review the Mouse Tumor Biology Database (MTB), a public resource for information on cancer genetics, epidemiology, and pathology in genetically defined mice. We outline current content, data acquisition strategies, and query mechanisms for MTB. MTB is accessible on-line at <http://tumor.informatics.jax.org>.

## Introduction

Mice have been used in cancer research for nearly a century (1, 2). Many of the first lines of genetically homogeneous mice were produced in the 1920s for cancer research specifically. For instance, MacDowell and Taylor (3) used a selective inbreeding strategy to establish a strain of mice, C58, that displayed a 90% incidence of leukemia. Today, there are hundreds of inbred strains that carry distinct combinations of alleles in a fixed state and vary greatly in the types of tumors they develop. For instance, AKR/J mice characteristically present with lymphocytic leukemia (4), whereas a related strain, A/J (5), shows a high frequency of lung tumors (6, 7). Inbred mouse strains represent unique genetic resources for the identification of alleles or quantitative trait loci that predispose to oncogenesis. For example, nine colon cancer susceptibility loci, *Sccl* through *Sccl9*, that are distributed throughout the mouse genome have been mapped in crosses between tumor-resistant BALB/cHeA mice and the susceptible strain, STS/A (8, 9). Inbred strains are also the raw material for the generation of genetically engineered mice (transgenics and gene-targeted mutants) that have become indispensable tools for cancer research. They have already added much to our knowledge of the effects of specific genetic anomalies on the cellular processes related to cancer (10).

Knowing about the inherent cancer phenotype of a particular mouse strain is of utmost importance for the development of new mouse models for cancer research. However, finding this information can be difficult because of the dispersed nature of the literature and inconsistencies in the nomenclature used for describing tumors in mice and designating mouse strains. In response to an NCI initiative, MTB<sup>3, 4</sup>

was developed at The Jackson Laboratory as an electronic resource focusing on the genetics, epidemiology, and pathology of cancer in genetically defined strains of mice. The primary objective of MTB is to collect information regarding the effect of genetic background on tumorigenesis in mice. To accomplish this goal, MTB curators integrate published and unpublished data on tumor frequency or incidence, genetics, and pathology for different strains of laboratory mice. MTB is designed to aid researchers in determining the intrinsic cancer-related phenotypes of different mouse strains, reviewing patterns of mutations in specific tumors, and identifying genes that are commonly mutated across a spectrum of cancers in the mouse (11–13).

**Data Acquisition and Curation.** The main data source for MTB is the peer-reviewed scientific literature. The curation staff of the Mouse Genome Database (14)<sup>5</sup> and MTB collaboratively review >350 journals each month. In addition, electronic searches of PubMed at the National Library of Medicine (Bethesda, MD) are performed periodically to identify recent articles describing mouse cancer models. MTB also contains unpublished information obtained from extramural contributors and routine health surveillance studies of The Jackson Laboratory mouse colonies (15).

MTB focuses on providing the most comprehensive coverage possible of tumor pathobiology data associated with inbred strains of mice commonly used in cancer research and recently developed genetic mouse models of cancer. The latter category includes genetically engineered mice, chemically induced mutants (*e.g.*, strains emerging from *N*-ethyl-*N*-nitrosourea mutagenesis projects), and spontaneous mutants. MTB does not contain information on tumor cell lines or preclinical trials using tumor xenograft models, because these types of data are available from other web-based resources (Table 1).

Priority for data entry in MTB is given to the types of cancers that are listed by the NCI as being the most prevalent in the United States population (16). As of December 2001, MTB contained 9429 entries of tumors observed in 2393 strains or cohorts<sup>6</sup> of mice, representing a body of 679 publications (Table 2). Since its initial public release in 1998, use of MTB by the scientific community has increased steadily, reaching a current average of ~450 queries/day. Users of the database include scientists from academic and private research institutions, as well as biotech and pharmaceutical companies.

**Querying the MTB Database.** The major data types in MTB include mouse strains, genes and mutations, tumor types, organs/tissues or cell types of tumor origin, pathology images, and literature

Received 8/20/01; accepted 12/21/01.

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<sup>1</sup> Supported by grant CA89713 and in part by Cancer Core Grant CA34196 from the National Cancer Institute to The Jackson Laboratory.

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<sup>3</sup> The abbreviations used are: MTB, Mouse Tumor Biology Database; NCI, National Cancer Institute; Trp53, transformation related protein 53; p19ARF, alternative-reading-

frame protein; Cdkn2a, cyclin-dependent kinase inhibitor 2A; MMHCC, Mouse Models for Human Cancers Consortium; Apc, adenomatous polyposis coli.

<sup>4</sup> Internet address: <http://tumor.informatics.jax.org>.

<sup>5</sup> Internet address: <http://www.informatics.jax.org>.

<sup>6</sup> MTB distinguishes between males and females of a particular strain or cohort of mice to account for genetic and physiological differences between the sexes. The term cohort refers to populations of mice that were not maintained as breeding strains (*e.g.* F1 siblings of a particular cross), or to individual animals (*e.g.* chimeras, transgenic founders).

Table 1 Web-based resources relevant to mouse models of cancer

Database Name, Provider	Data scope	Reference	URL
MMHCC Phenotype Database, Mouse Models for Human Cancers Consortium, National Cancer Institute	Phenotypic and preclinical data for mouse strains developed by MMHCC, including availability from the MMHCC Repository. Information regarding tumor cell lines, xenograft models, and experimental protocols.		http://emice.nci.nih.gov
Cancer Genome Anatomy Project (CGAP), National Cancer Institute	Data and analysis tools related to genes, gene expression, single nucleotide polymorphisms (SNP), and chromosomal aberrations in mouse and human cancers. Information on cDNA libraries and BAC clones.	25	http://cgap.nci.nih.gov
HistoBank, NIH	Histology images from animal and human tissues. Some data available to registered users only.	26	http://histology.nih.gov/
Mouse Tumor Biology Database, The Jackson Laboratory	Genetics, epidemiology (tumor frequency), and pathology of tumors in genetically defined mice (inbred strains, spontaneous or induced mutants, transgenics).	11–13	http://tumor.informatics.jax.org

citations. Each of the primary data types is represented on the MTB home page by an icon that is linked to a query form (Fig. 1). MTB supports several different query mechanisms, including browsing using controlled vocabularies and customizable query forms.

Researchers who are primarily interested in tumors of a particular organ or tissue can use the “Quick Organ/Tissue Search” option on the MTB home page (Fig. 1). This tool consists of a scrollable list of tissues or cell types for which database entries are available. A database user simply selects the name of the organ/tissue of interest to retrieve database records that match the selected term. Similarly, the “Genetics Search” option can be used to query MTB for tumors associated with mutations in a particular gene of interest. For instance, a search for *Trp53* (p53) will retrieve all of the records of tumors that arose in *Trp53*-mutant mice and records for other mice in which somatic *Trp53* mutations were detected in the tumor tissue.

An overview of the cancer spectrum characteristic of inbred mouse strains can be obtained from a graphical matrix, the Tumor Frequency<sup>7</sup> Grid (Fig. 1). For ease of comparison, strain families are grouped according to their genealogy (5). Color-coded fields indicate the highest reported frequency of spontaneous tumors in a particular organ or tissue. The Tumor Frequency Grid doubles as a query tool; a mouse-click on a colored cell returns a summary table of all of the tumor records pertinent to that particular organ or tissue in the selected strain.

The “Tumor Search” form can be used to perform custom queries. As shown in Fig. 2, the user determines the specificity of the query depending on the number of fields selected from pull-down menus or parameters entered into text fields. This allows database users to cast a broad net (e.g., “show me all records of lymphoblastic leukemias”) or to ask very specific questions (see legend to Fig. 2).

To facilitate database searches, MTB uses standardized nomenclature and controlled vocabularies. The diagnostic terminology comes from standard pathology texts (17–19). Anatomical terms are based on the Mouse Anatomical Dictionary (20) that was developed for the Mouse Gene Expression Database<sup>8</sup> (21). Nomenclature for mouse strains, genes, and germ-line alleles adheres to the guidelines of the International Committee on Standardized Genetic Nomenclature for Mice.<sup>9</sup> MTB also supports the use of nonstandard genetic nomenclature for database queries. As shown in Fig. 2, a user interested in tumors of p19<sup>ARF</sup> knockout mice may type the acronym “ARF” into the Strain Name field of the Strain Search form and select “targeted mutation (knockout)” from the Strain Type list. MTB will retrieve all

<sup>7</sup> Tumor frequency data in MTB represent the percentage of affected animals as reported in a particular study. Tumor incidence is a population-level phenomenon that reflects the inherent tendency of a particular mouse strain to develop a specific type of tumor.

<sup>8</sup> Internet address: <http://www.informatics.jax.org/mgihome/GXD/aboutGXD.shtml>.

<sup>9</sup> Internet address: <http://www.informatics.jax.org/mgihome/nomen>.

Table 2 Number of records in the first release of MTB (October 1998) and the current version

Given are the number of tumor frequency or instance records for the 10 organ systems or tissues in which human tumors most frequently occur, listed in descending order of estimated tumor prevalence (16). MTB is updated weekly.

Organ or tissue of tumor origin	Number of MTB records	
	October 1998	December 2001
Mammary gland	271	1076
Intestine	10	596
Prostate gland	0	104
Uterus	4	120
Lymphohematopoietic system	45	1407
Bladder	0	127
Skin	24	437
Lung	14	1431
Thyroid gland	1	47
Kidney	1	86
other	196	3998
<b>Total</b>	<b>566</b>	<b>9429</b>

of the records pertinent to mice carrying targeted mutations in the *Cdkn2a* locus that affect expression of p19<sup>ARF</sup>.

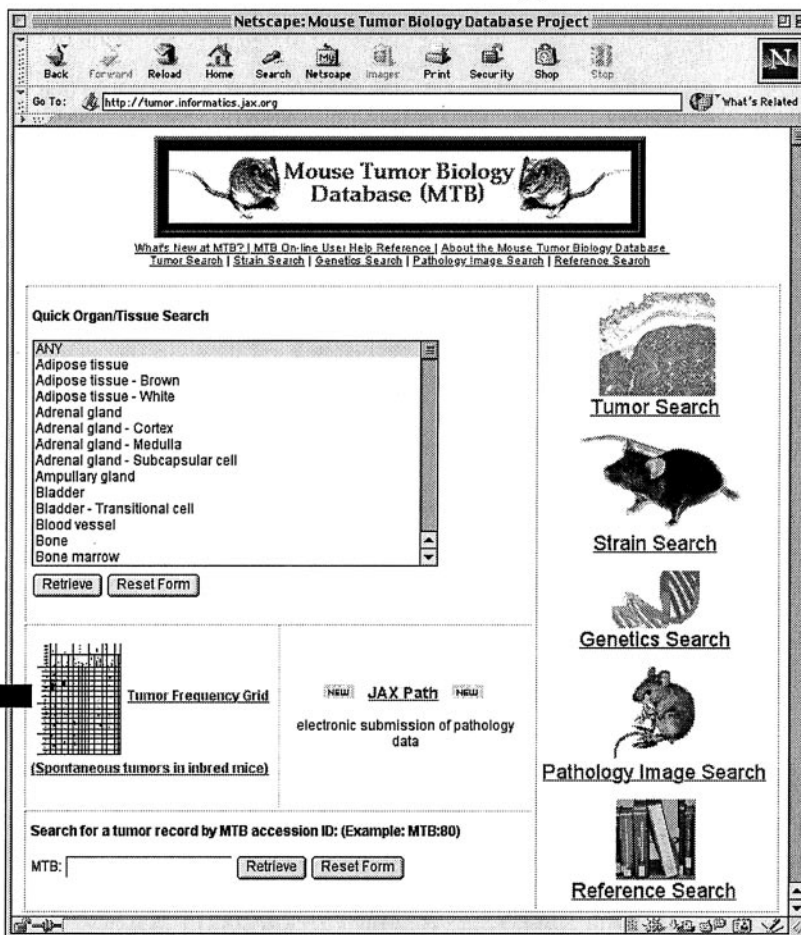
**Data Presentation.** In response to a query by a user, MTB initially returns a tabular summary of all records that match the selected query terms and constraints. The number of records displayed depends on the specificity of the query. The user can then select an individual record from the summary table and retrieve a Detail Information page (Fig. 3).

MTB also contains “negative” data. These include records of tumor-free mice that served as negative controls in a particular study and cases where animals carrying a mutation that is associated with human cancer remained disease-free. For example, loss-of-function mutations in the human *FANCC* gene result in the familial cancer susceptibility disorder, Fanconi anemia, whereas homozygous *Fancc* knockout mice do not develop malignancies (22, 23).

The high degree of data integration allows the user to retrieve a maximum amount of information from one query. Each tumor record is linked to frequency data, information about the genetics of the mouse strain, age of the animals at diagnosis, and a literature citation. Where applicable, MTB reports the experimental regimen (referred to as “treatment”) used to promote or inhibit tumor formation. Tumor pathology data are represented by annotated histology photomicrographs that are associated with detailed captions authored by veterinary pathologists (Fig. 3). MTB currently contains ~100 images of mouse tumors, some of which represent previously unpublished data obtained from The Jackson Laboratory mouse colonies.

Hypertext links connect MTB to other databases providing supplementary information. For instance, gene and allele symbols are hyperlinked to the Mouse Genome Database, which contains gene mapping and expression data, genomic linkage maps, phenotype

### A MTB Home Page



### B Tumor Frequency Grid

	Very High ■	High ■	Moderate ■	Low ■	Very Low ■	Observed ■	Zero 0	Integument		Digestive				Female Reproductive		Male Reproductive							
								Mammary gland	Skin	Lymphohematopoietic	Lung	Esophagus	Fore stomach	Intestine	Salivary gland	Stomach	Oral cavity	Teeth	Tongue	Cervical gland	Ovary	Uterus or Cervix	Vagina
<b>Castle's mice</b>																							
129																							
LP																							
AKR																							
BALB																							
A																							
CBA																							
C3H																							
DBA/1																							
DBA/2																							
I																							
SEA																							
N20																							
N2B																							
N2V																							
<b>C57-related strains</b>																							
C58																							
C57L																							
C57BR																							
C57BL/10																							
C57BL/6																							
C57BLKS																							
MA																							
<b>Swiss mice</b>																							
SVR																							
SJL																							
FVB																							
NOD																							
NON																							
<b>Other inbred strains</b>																							
RIII																							
RIIS																							
BUB																							
CE																							
PL																							
KK																							
<b>Wild-derived strains</b>																							
CZECHII																							
MSM																							

Fig. 1. A, the home page serves as the main entry port to MTB. From here users can launch a broad search of the database by using the "Quick Organ/Tissue Search" option. Icons on the right lead to customizable query forms. B, the Tumor Frequency Grid is a graphical summary and query tool for tumor biology information of standard inbred mouse strains.

descriptions, and links to orthologous genes in other mammals. If a mouse strain is available from The Jackson Laboratory or from the MMHCC,<sup>10</sup> hyperlinks lead to strain and availability information from the JAX Mice<sup>11</sup> database or the MMHCC Repository,<sup>12</sup> respectively. Where appropriate, MTB provides links to tumor type-specific or strain-specific databases, such as the Biology of the Mammary Gland<sup>13</sup> web site at the NIH, and the Transgenic Adenocarcinoma of the Mouse Prostate<sup>14</sup> web site at Baylor College of Medicine (Houston, TX).

**Pathology Data Submission.** Although expert curation of the literature is the primary data acquisition strategy, MTB also invites direct submissions of tumor pathology photomicrographs from the research community. Because most print journals impose restrictions on the acceptable number of figures per article, researchers are often forced to select only a few representative images. Consequently, much valuable pathology data remains unpublished. By providing scientists with the opportunity to contribute supplementary photomicrographs, MTB seeks to fill this gap. To facilitate the data submission process, we have implemented JaxPath, a web-based editorial tool that allows researchers to review their images and edit annotations and captions on-line. JaxPath records are password-protected and are merged into the publicly accessible database only with explicit permission from the submitting inves-

<sup>10</sup> Internet address: <http://emice.nci.nih.gov>.

<sup>11</sup> Internet address: <http://jaxmice.jax.org/index.shtml>.

<sup>12</sup> Internet address: <http://web.ncicrf.gov/researchresources/mmhcc/default.asp>.

<sup>13</sup> Internet address: <http://mammary.nih.gov>.

<sup>14</sup> Internet address: <http://www-tramp-model.cellb.bcm.tmc.edu>.



## A Tumor Search Form

**Mouse Tumor Biology Database (MTB)**

MTB Home | MTB On-line User Help Reference | About the Mouse Tumor Biology Database  
 Tumor Search | Strain Search | Genetics Search | Pathology Image Search | Reference Search

**Tumor Search Form**

Select Maximum Number of Records Displayed per Page:  5  10  20  50  100  
 Sort Query Results By:  Organ of tumor origin  Strain of tumor origin

**Retrieve** To reset the search menus, use your browser's reload command.

**Tumor**

Organ/Tissue of Origin:    
(javascript required)

Tumor Classification:    
(javascript required)  
(If a value is chosen from the first Tumor Classification menu, a value "MUST" be chosen from the second Tumor Classification menu for the database to recognize the search term.)

Treatment:

Agent:

Do you want only those database records that have histopathology images?:  Yes  No

Metastasis:  Metastasizes  Doesn't Metastasize  Ignore this field  
 To The:

**Strain**

Strain Name:

**Tumor Frequency**

Tumor Frequency (%) (enter a number):

**Tumor Genetics**

Allele Type or Genetic Change:

**Retrieve** To reset the search menus, use your browser's reload command.

Fig. 2. Interactive query forms allow users to perform broad or highly specific database searches. *A*, the Tumor Search Form. In this example, the user asks to retrieve records on "prostate gland adenocarcinomas that arose spontaneously in male T-antigen-transgenic mice, with a frequency >40% and that metastasized to the lung." *B*, the Strain Search Form. Depicted is an example of a database query using the nonstandard term, "ARF." Because the current official gene symbol for the locus encoding p19<sup>ARF</sup> is *Cdkn2a*, MTB will return a list of *Cdkn2a* knockout mice.

## B Strain Search Form

**Strain Search Form**

**Retrieve** **Reset Form**

Select Maximum Number of Records Displayed per Page:  5  10  20

Strain Name:

Sex:

Strain Type:

JAX@ Mice Stock Number:

**Retrieve** **Reset Form**

## Tumor Detail Page

**Mouse Tumor Biology Database (MTB)**

[MTB Home](#) | [MTB On-line User Help Reference](#) | [About the Mouse Tumor Biology Database](#) | [Tumor Search](#) | [Strain Search](#) | [Genetics Search](#) | [Pathology/Image Search](#) | [Reference Search](#)

**Tumor Details for MTB:5943**

Organ/Tissue of Origin: **Intestine - Large Intestine**  
 Tumor Classification: **polyp**  
 Organ/Tissue Affected: Intestine - Large Intestine  
 Treatment: None (Spontaneous)

Strain Name: **C57BL/6J.Apc<sup>Min/+</sup>**  
 Sex: **sex not specified**  
 Strain Type: chemically induced mutation  
 Strain Notes: Heterozygous mice - "Min" mutation

Tumor Genetics			
Gene/Locus	Mouse Chrom.	Genotype or Genetic Change	Reference ID
Apc adenomatosis polyposis coli (mouse)	18	Chemically induced / Loss of heterozygosity Apc <sup>Min</sup>	J:40435

**Pathology Image**

Tumor Frequency			
Status (reproductive & infection)	Tumor Frequency (%)	Age at Onset	Notes
		Age at Detection	
reproductive status not specified	observed		Mice were fed a "standard" diet containing 3% total fat and 4% crude fiber. 1.83 tumors/mouse
reproductive status not specified	observed		Mice were fed a "fat" diet containing 10% total fat and 4% crude fiber. 3.78 tumors/mouse
reproductive status not specified	observed		Mice were fed a "high fat" diet containing 15% total fat and 4% crude fiber. 4.12 tumors/mouse
reproductive status not specified	observed		

Pathology			
Status (reproductive & infection)	Age at Necropsy	Description	Notes
reproductive status not specified		Colonic polyp	<a href="#">View all pathology images for this tumor</a>

**Image Caption:** Colonic polyps. Mice die of these benign proliferative lesions throughout the intestines. There is marked proliferation of the crypt epithelium and supporting stroma to produce these polyps that extend into the lumen. As these lesions enlarge they produce a space-occupying tumor that effectively obstructs the bowel resulting in the death of the mouse. Mice do not live long enough to determine if these polyps will progress to malignancy.

**Organism:** mouse  
**Image ID:** 126  
**Source of Image:** Dr. John Sundberg

Other Notes	
Note	Reference ID
No metastases observed.	J:39278

References	
Reference ID	Citation
MTB-001	Dr. John Sundberg, The Jackson Laboratory, (personal communication)
J:39278	Wasan HS, et al. Proc Natl Acad Sci U S A. 1987; 84(7):3308-3313

Citing MTB  
 The Mouse Tumor Database Project has been funded in part by contract 07CSX022A from the National Cancer Institute.  
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 Send questions and comments to User Support.

Fig. 3. Example of a Tumor Detail Page reporting colonic polyps observed in Apc<sup>Min</sup> mutant mice under different feeding conditions. Tumor Detail pages contain information on the host strain, genetic aberrations found in the tumor tissue (in this case, loss of heterozygosity at the Apc locus), pathology, and literature citations. Where appropriate, a camera icon links to annotated photomicrographs.

tigators. Information on the pathology data submission process and sample records can be obtained by following the JaxPath link from the MTB home page (Fig. 1).

**Future Directions.** MTB is the most extensive resource of mouse tumor pathobiology data currently available on the web (24). Maintaining and expanding the database through literature data curation is an integral part of The Jackson Laboratory's Mouse Genome Informatics program. The MTB information content is updated weekly. New tools are being designed for MTB to enhance the representation of quantitative trait loci mapping data, to accommodate large-scale tumor genotype and gene expression profiling data, and to include images produced with *in vivo* tumor imaging technologies that are being adapted to mice. Hyperlinks will connect MTB with the mouse cancer phenotype database being developed by the MMHCC. To ensure database interoperability, MTB will adopt the controlled vocabularies of diagnostic disease terms that are being evaluated by the MMHCC. Finally, MTB welcomes critical comments and suggestions

from the cancer research community to improve data accuracy and user-friendliness.

### Acknowledgments

We thank Dr. Jerrold M. Ward (NCI, Bethesda, MD) for helpful advice. For critical reading of the manuscript we thank Dr. Vivienne I. Rebel (Dana-Farber Cancer Institute, Boston, MA), and Drs. Louise M. McKenzie and Antonio J. Planchart (The Jackson Laboratory, Bar Harbor, ME).

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