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Primary Neoplasms of Bones in Mice: Retrospective Study and Review of Literature

A. M. Kavirayani, J. P. Sundberg, and O. Foreman

The Jackson Laboratory, Bar Harbor, ME

Abstract

To compare and summarize the mechanisms, frequencies of occurrence, and classification schemes of spontaneous, experimental, and genetically engineered, mouse skeletal neoplasms, the literature was reviewed and archived case material at The Jackson Laboratory examined. The frequency of occurrence of spontaneous bone neoplasms was less than 1% for most strains, with the exceptions of osteomas in CF-1 (5.5% and 10% in two studies) and OF-1 outbred strains (35%), and osteosarcomas in NOD/ShiLtJ (11.5%) and NOD derived (7.1%) mice. The frequency was 100% for osteochondromas induced by conditional inactivation of exostoses (multiple) 1 (*Ext1*) in chondrocytes, osteosarcomas induced by tibial intramedullary inoculation of Moloney's murine sarcoma virus, and osteosarcomas induced by conditional inactivation of *Trp53*-with or without inactivation of *Rb1*-in osteoblast precursors. Spontaneous osteogenic neoplasms were more frequent than spontaneous cartilaginous and vascular types. Malignant neoplasms were more frequent than benign ones. The age of occurrence for spontaneous neoplasms ranged from 37 to 720 (Mean 316.35) days for benign, and 35 to 990 (Mean 299.28) days for malignant neoplasms. In genetically engineered mice, the average age of occurrence ranged from 28 to 70 days for benign, and from 35 to 690 days for malignant neoplasms. Histologically, non-osteogenic neoplasms were similar across strains and mutant stocks; osteogenic neoplasms exhibited greater diversity. This comparison and summarization of mouse bone neoplasms provides valuable information for the selection of strains to create, compare, and validate models of bone neoplasms.

Keywords

Bone tumors; chondroma; chondrosarcoma; hemangioma; hemangiosarcoma; laboratory mice; mouse models; ossifying fibroma; osteoma; osteosarcoma

Introduction

Neoplastic lesions of bone are less common in humans, domestic animals, and laboratory mice, compared to neoplasms of other tissues.^{2, 22, 42, 55–57, 68, 86, 89, 95, 96} Malignant neoplasms of bone are generally more common than the benign; and osteosarcoma is the most common skeletal neoplastic lesion in all species including laboratory mice.^{2, 22, 42, 55, 56, 68, 69, 86, 89, 95, 96} Benign tumors of bones that have been reported to occur spontaneously in mice include chondroma, hemangioma, ossifying fibroma, osteoblastoma and osteoma.^{2, 22, 55–57, 59, 61, 79, 80, 99} Spontaneous malignant neoplasms of

Request for reprints information: Anoop M Kavirayani, Veterinary Pathologist, Laboratory Animal Health Services, The Jackson Laboratory, 600 Main Street, Bar Harbor ME 04609, anoop.kavirayani@jax.org.

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bone reported in mice include chondrosarcoma, hemangiosarcoma, and osteosarcoma. 2, 22, 55–57, 60, 79, 80, 99

In this paper the similarities and differences in classification schemes for neoplasms of bone in humans, domestic animals and laboratory mice are addressed. A comparison and summary of spontaneous, genetically engineered, radiation induced and chemically induced neoplasms of bone in various strains of laboratory mice as noted in the literature, and a retrospective evaluation of the frequency of bone neoplasms in various mouse strains submitted for diagnostic necropsy at The Jackson Laboratory are also presented.

Materials and Methods

Reports of spontaneous, experimentally induced, or genetically engineered primary skeletal neoplasms in different inbred, hybrid, genetically engineered, and outbred strains and stocks of mice were reviewed. The mechanisms, frequencies of occurrence, and other features of these neoplasms were summarized. Additional details on the strains of mice, genetic manipulations, and experimental procedures are available in the cited references.

For retrospective evaluation of the frequency of bone neoplasms at The Jackson Laboratory, archived necropsy records and glass slides were reviewed for diagnoses of bone neoplasms in various strains that were submitted to the diagnostic service for necropsy between January 1987 and January 2010. Criteria for submission were clinical assessment of a “sick mouse” or the presence of a grossly visible tumor. Gross necropsy examination was performed on all mice and tissues collected were fixed in Tellyesniczky/Fekete fixative (100 ml 70% ethanol, 5 ml 37–40% formalin, 5 ml glacial acetic acid).⁸⁸ Appropriate tissues were decalcified using 10% formic acid (Formical-2000®, Decal Chemical Corporation, Tallman, NY) or 3% hydrochloric acid (Cal-Ex®, Fisher Scientific, Fairlawn, NJ) for 24 hours. Tissues were paraffin embedded and stained with hematoxylin and eosin (H&E). Diagnoses were reviewed and neoplasms were classified according to criteria described in the *International Classification of Rodent Tumors: The Mouse*.²² Diagnostic designations were also compared with listings on the mouse pathology ontology system (http://eulep.pdn.cam.ac.uk/Pathology_Ontology/index.php; September 2010). Archived and current designations were in agreement for most diagnostic entities. The designation of *osteochondrosarcoma* as used in the archives was not reiterated in the retrospective evaluation. Cartilage or chondroid matrix rich osteosarcomas are currently classified as osteosarcomas of the chondroblastic subtype.^{22, 25} Diagnoses of many differentiated primary skeletal neoplasms rely predominantly on radiographic and histologic features rather than on immunohistochemical studies.²⁸ In this study, as most of the tumors were well differentiated, diagnoses were based on histomorphologic features and immunohistochemistry was not required.

For any strain that had less than 100 total necropsy submissions, the frequency of occurrence was not considered representative. Details of the age of occurrence and frequency of benign and malignant neoplasms sorted by sex are available in supplementary tables 1 and 2 (available at <http://vet.3.sagepub.com/supplemental>).

The Mouse Tumor Biology (MTB; <http://www.informatics.jax.org/>; September 2010)⁵² Mouse Genome (MGD; <http://www.informatics.jax.org/>; September 2010)²¹ and JAX® Mice (<http://www.jaxmice.org/query/>; September 2010) Databases at The Jackson Laboratory were used to verify information on tumor types, tumor frequencies, genes, alleles and mouse strains. Tumor frequencies or comments pertaining to tumor frequencies that reference the Mouse Tumor Biology Database are identified in subscript as (MTB).

Genes with a confirmed involvement in the pathogenesis of bone neoplasms in Genetically Engineered Mouse models and genes known to significantly interact with the aforementioned genes were listed for gene network analysis. For performing the network analysis, each of the genes was assigned a hypothetical fold change score. If the loss or inactivation of a gene resulted in the development of a bone neoplasm in a mouse model, that gene was considered as down regulated and assigned a hypothetical fold-change score of -99 (e.g. tumor suppressor genes). If the transgenic over-expression or dysregulated activation of a gene resulted in the development of a bone neoplasm in a mouse model, that gene was considered as up regulated and assigned a hypothetical fold-change score of +99 (e.g. oncogenes). Ingenuity® IPA Pathway Analysis Software (Redwood City, CA) was used for the gene network analysis. The list of genes is available in supplementary table 3 (available at <http://vet.3.sagepub.com/supplemental>).

Results

COMPARISON OF CLASSIFICATION SCHEMES

The *WHO Classification of Bone Tumors* in humans²⁵ broadly categorizes them under cartilage tumors, osteogenic tumors, giant cell tumors, notochordal tumors, vascular tumors, smooth muscle tumors, lipogenic tumors, neural tumors, miscellaneous tumors, fibrogenic tumors, fibrohistiocytic tumors, primitive neuroectodermal tumors, hematopoietic tumors, miscellaneous lesions and joint lesions. Synovial sarcoma is not included under joint lesions or other categories in this scheme due to its ambiguous histogenesis.²⁵ The *WHO Classification of Bone Tumors* in humans is also used for the mouse pathology ontology (http://eulep.pdn.cam.ac.uk/Pathology_Ontology/index.php), a system for the histopathology of genetically engineered mice in the European mutant mouse pathology database (Pathbase; <http://www.pathbase.net>).

The *Histological Classification of Bone and Joint Tumors of Domestic Animals*⁸⁹ broadly categorizes them as benign tumors, malignant tumors, and tumor-like lesions. Malignant tumors are further sub-categorized as central tumors, peripheral tumors, joint tumors, miscellaneous tumors, and tumors of bone marrow.⁸⁹

The most commonly used scheme for classification of mouse bone tumors is the one detailed in the *International Classification of Rodent Tumors: The Mouse*.²² Tumors of the skeletal system listed in this scheme include osteoma, osteosarcoma, osteofibroma, ossifying fibroma, chondroma, chondrosarcoma, and synovial sarcoma.²² This classification scheme is disparate with extant WHO classifications of bone tumors in humans²⁵ and domestic animals,⁸⁹ as well as with some of the descriptions of bone tumor types observed in laboratory mice.⁵⁵⁻⁶¹ The mouse classification system describes osteofibroma as synonymous with osteoblastoma and ossifying fibroma as synonymous with cementifying fibroma.²² Ossifying fibroma and osteofibroma are not described in the human WHO classification scheme.²⁵ In classifications and descriptions of human bone tumors, osteoblastoma is considered similar to osteoid osteoma^{25, 42, 86, 96} and the designation of ossifying fibroma has been replaced by osteofibrous dysplasia.^{25, 42, 96} The *International Classification of Rodent Tumors: The Mouse* does not consider intra-osseous vascular neoplasms under tumors of the skeletal system.²² In some descriptions of mouse tumors, hemangioma and hemangioendothelioma are considered synonymous⁵⁵ while the latter is considered synonymous with angiosarcoma in descriptions of human tumors.^{42, 96} Classification schemes for tumors of bones and joints are compared and summarized in table 1 and details of these tumors as reported in the literature and observed at The Jackson Laboratory are summarized in tables 2 to 4.

CARTILAGINOUS TUMORS

Osteochondroma—Osteochondromas are benign, cartilage-capped partially ossified tumors that are also known as exostoses. They are typically reminiscent of an epiphyseal plate rotated ninety degrees to the long axis of bone, as they arise from the surface of an endochondral bone adjacent to a physis and are attached to the underlying skeleton by a bony stalk. Histologically, osteochondromas consist of chondrocytes arranged in a manner similar to that in epiphyses.^{42, 86, 89, 95, 96} Spontaneous osteochondromas are the most common benign bone tumor in humans^{42, 86, 96} and are also reported in cats, dogs and horses. They are extremely rare in laboratory mice⁵⁶ and were reported in B6C3F1 mice (0.03% frequency in males).¹⁰⁴ A single osteochondroma was found in a WBB6F1/J-*Kit*^W/*Kit*^{W-v}/J mouse at The Jackson Laboratory.

Chondroma—Chondromas are benign tumors of chondrocytes, consisting mostly of mature hyaline cartilage. They are typically circumscribed, encapsulated, slow growing, expansile, smooth to nodular and usually occur in bones of enchondral origin. They can arise within the medullary cavity, where they are known as enchondromas or on the surface of bone, where they are known as periosteal or juxtacortical chondromas. Histologically, chondromas consist of nodular aggregates of well-differentiated chondrocytes with little to no cellular and nuclear pleomorphism (Figs. 1, 2).^{22, 42, 55–57, 86, 89, 95, 96} Spontaneous chondromas are extremely rare in laboratory mice.^{2, 22, 55–57, 78–80} Chondromas were reported in C57BL/10J (0.1% frequency in females)^{99, 100} and a single case was found in a NOD.129P2(B6)-*B2m*^{tm1Unc}/J mouse (Figs. 1, 2) at The Jackson Laboratory.

Chondromyxoid fibroma—Chondromyxoid fibromas are benign cartilaginous tumors that typically involve the metaphyses of long bones. Histologically, chondromyxoid fibromas are usually lobulated and consist of nodules of poorly formed hyaline cartilage mixed with variable amounts of myxoid matrix delineated by fibrous septae.^{42, 86, 96, 99, 100} Chondromyxoid fibromas are extremely rare in humans,^{42, 86, 96} domestic animals⁸⁹ and mice, and were reported in C57BL/10J mice (0.04% frequency in males).^{99, 100}

Chondrosarcoma—Chondrosarcomas are malignant cartilaginous neoplasms that arise *de novo* in bone or undergo malignant transformation within a pre-existing benign cartilaginous tumor. They are typically expansile, sometimes lobulated, and more commonly involve flat bones than long bones in most species. They have also been reported to arise in locations with extraskeletal cartilage such as the larynx in humans and mice. Chondrosarcomas may arise from the medullary cavity (central chondrosarcoma) or periosteum (peripheral chondrosarcoma), the former being more common. Histologically, chondrosarcomas are often lobulated and consist of different proportions of hyaline or myxoid cartilage composed of chondrocytes that vary in cytologic atypia, mitotic activity, and degree of differentiation (Figs. 3, 4). They primarily produce chondroid and fibrillar matrix, but rarely osteoid. However, occasional chondrosarcomas may contain reactive or metaplastic bone matrix.^{22, 42, 55–57, 86, 89, 95, 96} Chondrosarcoma is the third most common malignancy of bone after myeloma and osteosarcoma in humans,^{42, 86, 96} and is also reported in cats, dogs, and sheep,^{89, 95} but is extremely rare in mice.^{2, 22, 55–57} Spontaneous chondrosarcomas were reported in B6C3F1 (0.13% frequency in females),² C57BL/10J (0.03% frequency in females)^{99, 100} and in ST/Eh (single case) mice,⁹² and observed in a 325 day-old male C57BL/6J mouse (Figs. 3, 4) at The Jackson Laboratory.

OSTEOGENIC TUMORS

Osteoma—Osteomas are rare, benign tumors of osteoblasts composed of mature well-differentiated bone with a predominantly woven arrangement. They are typically solitary, dense, smooth, and preferentially arise from the periosteal surface and merge with

underlying cortical bone. Osteomas most commonly occur in bones of the skull in most species (Fig. 5). Rarely, an osteoma may be seen on the surface of a long bone. Histologically, osteomas are composed of dense coalescing spicules and trabeculae of bone lined by osteoblasts and osteoclasts. Fatty or hematopoietic marrow may be present within the trabeculae (Figs. 6, 7). The inter-trabecular connective tissue is composed of spindle shaped cells and becomes increasingly sparse as the tumor becomes more compact and sclerotic.^{22, 42, 55–57, 61, 86, 89, 95, 96} Spontaneous osteomas are rare in most strains of mice and seem to be more common in females than in males, the difference being attributed partly to a female hormonal influence.^{2, 22, 55–57, 79}

Cases of spontaneous osteoma were documented in AKR,⁶¹ B6C3F1,^{2, 9} C57BL/6N^{Nia}(MTB), CBA/H(MTB), CD-1,^{63, 66, 72} CF-1,^{2, 10, 61} CFW/CarWHanJena(MTB), NMRI^{2, 7} NZO/BI(MTB), Him:OF1,³⁶ and OF-1¹⁰⁸ mice. CF-1, Him:OF1, and OF-1, which are genetically related outbred strains of mice, have the highest documented frequency of osteomas among all mouse strains.^{2, 61} The reported frequency of spontaneous osteomas in CF-1 mice was 5.5% (4.4% in males and 6.5% in females) in one study² and 10% (8.5% in males and 11.5% in females) in another.¹⁰ The combined average age of occurrence for both sexes was 96 weeks in the latter.¹⁰ Spontaneous osteomas are quite rare in other strains, with frequencies ranging from 0.02 to 0.2% in various reports.² In one study, a frequency of 0.13% was observed in female B6C3F1 mice (1 case in 770 mice examined).²

Reports exist of higher frequencies of osteomas with concurrent identification and isolation of retroviral particles.⁶¹ In a study on skeletal lesions of sodium fluoride toxicity in Crl:CD-1 (ICR) outbred mice, the reported frequency was 12.5% in sodium fluoride treated mice (11% in males and 14% in females), and 3.2% in controls (1.1% in males and 5.3% in females) with a suspected retroviral etiology at 55 to 97 weeks of age.⁶⁶ In another study on the carcinogenic potential of cyclosporine A in OF-1 mice, a 26.3% frequency was reported in cyclosporine treated mice (14.7% in males and 38% in females) and 35% in controls (20% in males and 30% in females) at 40 to 78 weeks of age.¹⁰⁸ Type C retroviral particles were identified in tumors from both groups but an etiologic correlation was not conclusively established. In an aging study, Him:OF-1 mice were reported to have a frequency of 51.8% (50.9% in males and 52.7% in females) at 533±98 days of age, and virus-like particles were seen on ultra-structural observation of tumor cells and necrotic tissues.³⁶ Osteomas induced by neonatal administration of Murine polyomavirus were documented in C3H/BiDa mice.¹⁷ At The Jackson Laboratory osteomas were diagnosed in A/J, C57BL/6J (Fig. 5), DBA/2J, B6C3F1/J, C3.SW-H2^b/SnJ, and C57BL6/J-Tg(Amy1Tag)501Kw/J (Figs. 6, 7) mice; one case in each strain, all in females.

Osteosarcoma—Osteosarcomas are malignant mesenchymal neoplasms in which tumor cells typically produce osteoid or bony matrix.^{2, 22, 25, 42, 56, 57, 60, 69, 75, 86, 89, 95, 96, 102} They are typically invasive and frequently metastasize.^{2, 22, 42, 55–57, 60, 75, 86, 89, 95, 96, 102} Osteosarcomas most commonly arise within the medullary cavities of bones, particularly in the metaphyseal regions of long bones and invade the adjacent cortex (Fig. 8). These are referred to as central osteosarcomas. Less commonly, osteosarcomas arise from the periosteum and are called peripheral osteosarcomas. These are of two types, namely periosteal or parosteal (juxtacortical) osteosarcomas. Histologically, osteosarcomas consist of malignant osteoblasts, osteoclasts, or less differentiated mesenchymal cells that often form osteoid matrix (Figs. 9, 10, 11, 12).^{42, 86, 89, 95, 96} Based on histologic and cytologic features, osteosarcomas are often subtyped as osteoblastic, osteoclastic, fibroblastic, chondroblastic, telangiectatic/vascular, mixed, or anaplastic.^{22, 86, 89} With the exception of myeloma and lymphoma in humans, osteosarcoma is the most common primary bone tumor in most species.^{2, 22, 42, 55, 57, 86, 89, 95, 96, 102} Rarely, osteosarcomas arise in extraskeletal soft tissues independent of adjacent bones.²⁴

Osteosarcomas are the most commonly reported bone tumors in laboratory mice, ^{2, 22, 55, 57, 68, 69} but the average frequency of spontaneous osteosarcomas in most strains of mice is relatively low_(MTB). ^{2, 56} There have been single case reports of osteosarcoma in a 5 month-old AKR/J male, ¹ 300 day-old AKR/MS, ⁷⁰ 5 week-old C57BL/6J male, ¹⁴ 224 day-old C57BL/6J female_(MTB), ⁷⁵⁷ day-old C57BL/6J-*Ptpn6^{mev}/Ptpn6^{mev}* female, ⁴⁵ and 17 month-old C3Hf/Sed;CB17-*Prkdc^{scid}/Prkdc^{scid}* female, ³⁹ mouse. A relatively higher frequency of spontaneous osteosarcomas was reported in NOD/ShiLtJ and NOD derived mice at The Jackson Laboratory in a recent study. ⁵⁰ Spontaneous osteosarcomas were also observed in C3Hf/He (0.4% to 1% frequency in females) _(MTB), C57BL/6NNia (1.1% frequency) _(MTB), RF/Un (0.7% frequency) _(MTB), and SWR/J (0.6% frequency) _(MTB) mice. The age of occurrence of osteosarcomas as reported in various mouse strains varied from 35 days (5 weeks) in a C57BL/6J male ¹⁴ to 31 months (more than 900 days) in C57BL/1crf mice. ²⁶

Virally induced osteosarcomas were periodically reported and most notable among them are the ones induced by retroviruses (Finkel Biskis Jenkins (FBJ) murine osteosarcoma virus and Moloney murine sarcoma virus) ^{23, 73, 77, 105} and Murine polyomavirus. ^{17, 97} Periosteal chondro-osseous tumors resembling human parosteal osteosarcomas were induced in NIH Swiss mice by neonatal intraperitoneal inoculation of FBJ virus. ¹⁰⁵ Osteosarcomas with and without metastases in CzechII/EiJ and C3H/BiDa mice respectively were induced by neonatal intraperitoneal inoculation of the RA strain of Murine polyomavirus. ⁹⁷ Osteosarcomas in cranial bones are a relatively frequent observation in many SV40 Large T antigen transgenic mice regardless of the promoter suggesting a direct effect (Sundberg, unpub obser).

Osteosarcomas induced by intraperitoneal administration of bone seeking radionuclides ²²⁴Ra, ²²³Ra, and ²²⁷Th were reported in C3H/HeI.102, (BALB/c x CBA) F2, (C3Hx101) F1, and NMRI mice, ⁶⁴ and by external irradiation with ⁹⁰Sr-⁹⁰Y beta rays in ICR mice. ⁷¹ In other studies, administration of radiostrontium (⁹⁰Sr) was reported to cause osteosarcomas and skeletal hemangiosarcomas in CBA and C3H mice. ^{2, 4, 57}

Strains of mice varied widely with respect to metastases of osteosarcomas and metastases were infrequent or non-existent in some. Metastases of spontaneous osteosarcomas were noted in BALB/c, ²⁷ C3Hf/Sed;CB17-*Prkdc^{scid}/Prkdc^{scid}*, ³⁹ C57BL/6J, ¹⁴ C57BL/10J, ¹⁰⁰ C57BL/1crf, ²⁶ CF-1, ¹⁰ NZB/Bl, ²⁹ and RF/Un_(MTB) mice. Metastases were quite infrequent in NOD/ShiLtJ and NOD-derived mice, ⁵⁰ and absent in AKR ¹ and B6C3F1 ⁹ mice. Among virally induced osteosarcomas, metastases were prominent in BALB/c and CD-1 mice inoculated with Moloney Murine Sarcoma Virus ⁷³ and CzechII/EiJ and CZC3F1 mice inoculated with Murine polyoma virus. ⁹⁷ Metastases were not evident in CBA/J mice inoculated with the FBJ virus. ⁷⁷

At The Jackson Laboratory osteosarcomas were diagnosed in 129Sv/J, A/J, AKR/J (Figs. 9, 10), B6;129P2-*Nos2^{tm1Lau}/J*, B6129SF2/J, B6C3F1/J, BALB/cJ, BALB/cByJ, BKS.Cg-*Dock7^mLepr^{db}/++/J*, C3D2F1/J, C3H/HeJ, C3.Smn.CB17-*Prkdc^{scid}/J*, C57BL/6J, CAF1/J, CBA/J, CBXNO-7, CWDAKRF1/J, CXJ-8/SlkJ, NOD/ShiLtJ (Figs. 11, 12) and NOD-derived (Fig. 8), NOR/LtJ, and WBB6F1/J-*Kit^W/Kit^{W-v}/J*, mice. The age at necropsy varied from 49 days in a NOD.CB17-*Prkdc^{scid}/J* female to 537 days in a NOD.Cg-*Prkdc^{scid}Il2rg^{tm1Wjl}/SzJ* female. Osteosarcomas were also found in mice transgenic for the Simian Virus 40 Tumor antigen (SV40 Tag) ^{40, 51, 65, 106} and in mice bearing targeted mutations of *Trp53* (*Trp53^{tm1TyJ}*), ⁴⁴ in agreement with previous reports in the literature.

VASCULAR TUMORS

Hemangioma—Hemangiomas are benign vascular tumors composed of blood-filled, endothelium-lined spaces. They are typically soft tissue tumors, but can rarely arise as primary bone tumors, occurring more frequently in the axial skeleton than elsewhere in humans.^{42, 96} Histologically, hemangiomas consist of a partially circumscribed network of vascular spaces usually lined by a single layer of well differentiated endothelial cells embedded in a fibrous stroma. Intra-osseous hemangiomas are extremely infrequent in laboratory mice^{2, 55} as well as dogs and cats.^{89, 95} They were reported in BALB/c mice (0.95% frequency).⁵⁵ An intra-osseous hemangioma was observed in an HRS/J +/+ mouse at The Jackson Laboratory.

Hemangiosarcoma—Hemangiosarcomas (hemangioendothelial sarcomas) are malignant vascular tumors composed of endothelium-lined vascular channels supported by various proportions of stroma.^{30, 42, 89, 95, 96} They are typically soft tissue tumors but can rarely arise as primary bone tumors.^{30, 42, 89, 95, 96} Histologically, hemangiosarcomas consist of malignant endothelial cells that differ in their degree of differentiation and cytologic atypia and form vascular channels and solid sheets embedded in a fibrovascular stroma (Figs. 13, 14).^{30, 42, 89, 96} Intra-osseous hemangiosarcomas are extremely infrequent in laboratory mice and domestic animals.^{2, 55, 56, 89} The primary differential diagnosis for an intra-osseous hemangiosarcoma is a telangiectatic osteosarcoma in which osteoblasts rather than neoplastic endothelial cells line the blood-filled spaces.^{42, 89, 95, 96} A spontaneous intra-osseous hemangiosarcoma (angiosarcoma) was reported in an NZB mouse.⁴¹ Hemangiosarcomas of bone were found in CD-1, DBA/2J, HRS/J, FVB/NJ-*Trp53^{tm1TyJ}*/J, B6;129-*Ox^{tm1Wsy}*/J, B6.CAST-*Gpi-1^a*/EiJ and NOD.Cg-*Prkdc^{scid}Il2r^{tm1Wjl}/SzJ* (Figs. 13, 14) mice at The Jackson Laboratory.

MISCELLANEOUS TUMORS AND LESIONS

Ossifying Fibroma, Osteofibroma, and Osteofibrous Dysplasia—Ossifying fibromas are rare fibro-osseous tumors that usually involve the mandible and maxilla in most species. They are typically solitary, slow growing, expansile, sharply demarcated, and distort the normal contour of the affected bone. They are morphologically similar to a fibroma, but contain metaplastic bone. Histologically, ossifying fibromas are well demarcated from surrounding tissue by bone and consist of spindle shaped fibroblasts. The fibroblasts appear to transform into osteoblasts forming irregular spicules of woven bone. In general, ossifying fibromas are of relatively low cellularity with a higher proportion of fibrous stroma than bone. Lamellar bone is extremely rare in an ossifying fibroma but may be formed where woven bone trabeculae are resorbed and replaced.^{2, 22, 57, 58, 89, 95}

A few authors consider ossifying fibromas as synonymous with osteofibroma or fibrous osteoma⁸⁹ while some others describe them as synonymous with cementifying fibroma when teeth are involved.^{22, 57, 58} The latter authors describe osteofibromas as being distinct from ossifying fibromas and more similar to osteoblastomas. Such osteofibromas are typified as benign, expansile, non-invasive bone forming tumors with a predilection for the vertebral column. Histologically, osteofibromas are characterized by mature trabecular bone within a densely cellular spindle cell stroma.^{22, 57, 59} Human tumors previously described as ossifying fibroma are currently designated as osteofibrous dysplasia.^{25, 42, 96} Osteofibrous dysplasia is characterized by a hypocellular spindle cell proliferation with the production of immature woven bone.⁴² Spontaneous ossifying fibromas (incidence not available) were reported in CD-1, CF-1 and NMRI mice.^{2, 57} A single case was diagnosed in a NONcNZO10/LtJ mouse (Figs. 15, 16) at The Jackson Laboratory. The latter lesion had some microscopic features resembling those described in osteofibrous dysplasia of humans.^{42, 96}

EXPERIMENTAL AND GENETICALLY ENGINEERED MOUSE MODELS

Numerous genetically engineered mouse (GEM) models have contributed to the elucidation of genetic mechanisms involved in skeletal tumors.⁴⁹ Selected models and their characteristics are summarized below.

Exostoses (multiple) 1 and 2 (*Ext1*, *Ext2*)—The genes exostoses (multiple) 1 (*EXT1*) and exostoses (multiple) 2 (*EXT2*) encode proteins that function in the biosynthesis of heparan sulfate on the cell surface and in the extracellular matrix.^{46, 86, 91} Germline loss-of-function mutations in *EXT1* and *EXT2* were associated with cartilaginous tumors and multiple hereditary exostoses in humans.^{42, 46, 86, 91} Mice with conditional inactivation of *Ext1* (*Ext1^{neofl}*) and *Ext1^{efl}*) in chondrocytes were shown to develop osteochondromas by 6 to 10 weeks of age.⁴⁶ Mice with a targeted mutation of *Ext2* (*Ext2^{tm1Werb}*) were shown to develop foci of chondrocyte hypertrophy by 2 weeks of age that progress to osteochondromas.⁹¹ Both are regarded as models of human multiple hereditary exostoses and are among the few currently available genetically engineered mouse models of benign bone tumors.

GLI-Kruppel family member oncogene (*Gli2*)—Enchondromas were shown to develop with high frequency in mice with transgenic over-expression of the GLI-Kruppel family member oncogene (*Gli2*) in chondrocytes and expression of a mutant form of the human parathyroid hormone/parathyroid hormone related protein receptor (*R150CPTHRI*) in growth plates, both regulated by the Collagen 2a1 (*Col2a1*) promoter.³⁷ Chondrosarcomas were found to develop on account of transgenic overexpression of the *Gli2* gene in chondrocytes under regulation of the *Col2a1* promoter in heterozygous *Trp53^{tm1TyJ}* mice.³⁵ In the enchondroma model, chondrocyte proliferation mediated by Indian hedgehog (*Ihh*) signaling is thought to be the mechanism of tumorigenesis.³⁷ In the chondrosarcoma model, overexpression of *Gli2* and deficiency of *Trp53* additively down regulate Insulin like growth factor binding protein 3 (*Igf3*), which in turn inhibits chondrocyte apoptosis to facilitate proliferation and transformation.³⁵

Nuclear factor of activated T-cells, cytoplasmic calcineurin dependent-2 gene (*Nfatc2*)—Mice with targeted mutations in the *Nfatc2* gene (*Nfatc2^{tm1Glm}*) were shown to develop cartilaginous proliferations resembling chondrosarcoma. In these mice chondrosarcomas developed predominantly in the shoulder, knee, hip and ankle joints. In this model, by an unclear mechanism, *Nfatc2* functions as a repressor of chondrocyte differentiation and proliferation and its loss facilitates excessive proliferation of chondrocytes.⁸⁴

Osteosarcoma associated genes—The molecular mechanisms and genetic pathways implicated in osteosarcomagenesis include aberrations involving transformation related protein 53 (*Trp53*),^{6, 15, 18, 19} retinoblastoma 1 (*Rb1*),^{6, 15, 43, 49, 101, 107} myelocytomatosis oncogene (*Myc*),⁴⁹ Finkel Biskis Jenkins osteosarcoma oncogene (*Fos*),^{16, 31, 87, 103} hypermethylated in cancer 1 (*Hic1*),^{11, 12} GLI-Kruppel family member (*Gli1*),⁴⁹ fibroblast growth factor receptor 2 (*Fgfr2*),⁴⁹ runt related transcription factor 2 (*Runx*),⁴⁹ osterix or the Sp7 transcription factor 7 (*Osx* or *Sp7*),⁴⁹ neurofibromatosis 2 (*Nf2*),⁶⁷ bone morphogenetic proteins (BMPs) and their receptors.⁴⁹ Genetically engineered mouse models that have contributed to understanding these mechanisms include mice with targeted mutations or conditional inactivation of BCL-2 associated x protein (*Bax^{tm1SjK}*) and cyclin-dependent kinase inhibitor 2A (*Cdkn2a^{tm1Cjs}*),²⁰ *Hic1* (*Hic1^{tm1Sbb}*),^{11, 12} *Nf2* (*Nf2^{tm1TyJ}*),⁶⁷ *Trp53* (*Trp53^{tm1Brd}* / *Trp53^{tm1TyJ}* / *Trp53^{tm1Brn}*),^{18, 19, 33, 44, 48, 54} *Trp53* (*Trp53^{tm1TyJ}*) and *Nf2* (*Nf2^{tm1TyJ}*),⁶⁷ *Trp53* (*Trp53^{tm1TyJ}*) and *Rb1* (*Rb1^{tm1TyJ}*),¹⁰⁷ *Trp53* (*Trp53^{tm1TyJ}*) and cyclin dependent kinase inhibitor 2C (*Cdkn2c^{tm1Yxi}*);¹⁵ and mice with

transgenic expression of *c-fos* (under the human metallothionein promoter or H2-K^b class I MHC promoter)^{31, 49, 87, 103} or the Simian Virus 40 Tumor antigen.^{6, 40, 51, 65, 106}

Mice with mutations of *Trp53* in tandem with mutations of *Rb1* specifically in osteoblast precursors are among the most successful models of osteosarcoma.^{6, 101} In one study mice with conditional alleles of *Trp53* (*Trp53^{tm1Brn}*) and *Rb1* (*Rb1^{tm3TyJ}*) developed tumors that ranged in histology from fibroblastic with little osteoid or mineral, to osteoblastic with abundant osteoid and mineral. Such tumors occurred most commonly in the lower jaw and upper jaw, followed by the hip and ribs, and less frequently in the dorsal cranium, forelimb and sternum.¹⁰¹ In another study employing concurrent loss of *Trp53^{tm1TyJ}* and *Rb1^{tm1TyJ}* tumors arose in the femur, nasal bones, vertebral column and skull.⁶ Between both studies, the average age of tumor occurrence varied from 125 days in *Trp53* and *Rb1* double null mice to 338 days in mice heterozygous for *Trp53* (*Trp53*^{+/-}, *Rb1*^{+/+}). Transformation of an Osterix (*Osx1*) expressing preosteoblast cell due to concurrent loss of *Trp53* and *Rb1* is implicated in the pathogenesis of osteosarcoma in these models.^{6, 101}

Mice that bear the tumor antigen gene from Simian Virus 40 (SV40 Tag) in their genome were also shown to develop osteosarcomas^{5, 40, 51, 65, 106} and lesions resembling synovial chondromatosis.⁹⁸ The lesions of chondromatosis reportedly involved the articular cartilages of the legs and feet in these mice.⁹⁸ In SV40 Tag induced osteosarcomas, sequestration and inactivation of the P53 and RB1 proteins by the SV40 Tumor Antigen (usually large T antigen) resulted in tumorigenesis in a promoter independent manner. Tumors arose predominantly in the axial skeleton with variable involvement of the skull, vertebral column, sternum, ribs, shoulder and pelvic girdle, and less frequent involvement of the humerus and femur.^{5, 40, 51, 65, 106}

Human synovial sarcomas are marked by a signature translocation-mediated fusion of the Synovial Sarcoma Translocation, Chromosome 18 (*SYT*) gene on chromosome 18q11 to the Sarcoma, Synovial, X breakpoint (*SSX1*, *SSX2*, or *SSX4*) gene on Chromosome Xp11.³² The recently reported transgenic mouse model of synovial sarcoma based on conditional expression of the human *SYT*-*SSX* fusion gene is a unique genetically engineered model of synovial sarcoma,³² an extremely rare spontaneous tumor in laboratory mice.^{22, 55} In these mice, tumors were induced by conditional expression of the human *SYT*-*SSX* fusion gene in myoblast precursors expressing the myogenic regulatory factor *Myf5*.³² Tumors occurred between 3 to 5 months of age in the skeletal muscle in intercostal areas and near joints of the limbs. These tumors recapitulated the histological, immunohistochemical, and transcriptional profiles of human synovial sarcoma. This study implicates *Myf5*-specific myoblast lineage cells in the histogenesis of synovial sarcoma.³² Reports also exist of synovial sarcomas induced by interscapular injections of cannabinoids in BALB/c and C57BL/6 mice. In this model, cannabinoids are thought to initiate tumorigenesis and sex steroids are thought to facilitate progression. A clear mechanistic correlate is yet to be elucidated.⁹³

GENE NETWORK ANALYSIS

A list of candidate genes was created from genes with a confirmed involvement in the pathogenesis of neoplasms of bone and additional genes known to significantly influence the former. Hypothetical fold change scores were assigned to each of the listed genes and gene network analysis was performed to deduce network interactions between these genes.

Results of the analysis (supplementary table ST4 and supplementary Figs. S1-S4, available at <http://vet.sagepub.com/supplemental>) suggested that transformation related protein 53 (*Trp53*), retinoblastoma 1 (*Rb1*), neurofibromatosis 2 (*Nf2*), Werner syndrome homolog, human (*Wrm*), nuclear factor of activated T-cells, cytoplasmic calcineurin dependent-2

(*Nfatc2*), and hypermethylated in cancer 1 (*Hic1*) could be most significant among those genes whose loss or inhibition led to the development of bone neoplasms in mouse models. Results of the analysis also suggested that bone morphogenic protein receptor type 2 (*Bmpr2*), cadherin 11 (*Cdh11*), collagen type 2 alpha 1 subunit (*Col2a1*), catenin beta 1 (*Ctnnb1*), fibroblast growth factor receptor 2 (*Fgfr2*), Finkel Biskis Jenkins osteosarcoma oncogene (*Fos*), GLI-Kruppel family member GLI1 (*Gli1*) and GLI-Kruppel family member GLI2 (*Gli2*) could be most significant among those genes whose over-expression or activation led to the development of bone neoplasms in mouse models. In addition to the aforementioned genes, the analysis also suggested that constitutive photomorphogenic homolog subunit 3, *Arabidopsis thaliana* (*Cops3*), endothelin 1 (*Edn1*), twist homolog 1, *Drosophila* (*Twist1*), sequestosome 1 (*Sqstm1*), RecQ protein-like 4 (*Recql4*), and insulin like growth factor binding protein (*Igfbp3*) could be most significant among the network of genes involved in the pathogenesis of bone neoplasms.

Discussion

Spontaneous bone tumors were infrequent in most strains of mice with the exceptions of osteosarcomas in NZBR/BI, NOD, and NOD-derived mice, and osteomas in CF-1 and OF-1 mice. The most popular inbred strains of mice currently available through The Jackson Laboratory are 129S1/SvImJ, 129X1/SvJ, A/J, AKR/J, BALB/cByJ, BALB/cJ, C3H/HeJ, C57BL/6J, C57BL/6NJ, C57BL/10J, CBA/J, DBA/1J, DBA/2J, FVB/NJ, NOD/ShiLtJ and SJL/J (JAX® Mice; <http://www.jaxmice.org/>; September 2010). Among these 129S1/SvImJ, C57BL/10J, DBA/1J, FVB/NJ, and SJL/J mice had no documented bone neoplasms in the diagnostic necropsy archives. This is noteworthy even though, the colony sizes of these strains have varied through the years, many of the submitted mice were 8 months or younger, and focus of the diagnostic necropsy program was evaluation of sick mice rather than a systematic study of cancer with equal numbers of age and sex matched mice. Systematic aging studies¹⁰⁹ have been designed to better address such questions. In those mice with documented neoplasms, spontaneous osteogenic neoplasms occurred more frequently than cartilaginous, vascular, and hematopoietic ones, with osteoma being the most common benign bone tumor and osteosarcoma, the most common malignancy of bone. Spontaneous cartilaginous neoplasms were the least frequent tumors of bone in mice, in direct contrast to chondrogenic neoplasms being the second most common bone tumor type, after hematolymphoid malignancies in humans. In this context it is worth noting that chondrogenic tumors were produced by targeted mutations of *Nfatc2* in mice,⁸⁴ but no correlative mutations of *NFAT1* were identified in a set of human chondrosarcomas and enchondromas.³ This disparity needs further investigation.

Another noteworthy aspect is that strains of mice with spontaneous neoplasms of bone varied in their propensity to develop metastases. Metastases were infrequent or non-existent in many studies. At The Jackson Laboratory, the age at necropsy of mice with spontaneous or genetically engineered malignant neoplasms of bone ranged from 41 to 537 (Mean 215.55) days and 35 to 990 (Mean 393.17) days in the literature and metastases were relatively rare. Most of the metastases that occurred were of osteosarcomas and lung was the favored site. In some of these cases with relatively younger ages of occurrence, mice not living long enough to develop metastases could be a contributory factor. A more important determinant of strain specific differences in metastasis is their inherent diversity with respect to genes that influence cell-cell and cell-matrix adhesion and cell migration. In a recently published study, the difference between C3H/BiDa and CzechII/Ei mice in metastasis of Murine polyoma virus induced osteosarcomas was attributed to variability in the levels of the metalloproteinase MMP-2 and the transcription factor NFAT.⁹⁷ CZC3F1 mice in this study exhibited metastases suggesting dominance of the metastatic phenotype.⁹⁷ In studies on spontaneous osteosarcomas, metastases were evident in “black” strains of mice such as

C57BL/1crf, ²⁶ C57BL/6J ¹⁴ and C57BL/10J, ¹⁰⁰ and absent in B6C3F1 mice. ⁹ Such an apparent contrast between two different F1 hybrid strains of mice involving the C3H strain warrants further investigation of bone tumor metastases in inbred and hybrid strains.

Conspicuous disparities exist between classification systems for human, veterinary, and mouse bone and joint tumors. Unified systems of classification and characterization for human, veterinary, mouse and genetically engineered bone tumors that reconcile differences in designation for similar entities would enhance comparative studies of tumors of the skeleton across species. The Mouse Pathology Ontology (Pathbase; http://eulep.pdn.cam.ac.uk/Pathology_Ontology/index.php) developed by a consortium of veterinary and physician pathologists, has reconciled these differences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Cranium; NOD.129P2(B6)-*B2m^{tm1Unc}*/J mouse. There is a chondroma (Ch) arising from the squamosal bone. Note the circumscribed, non-invasive nature of the well-differentiated cartilaginous neoplasm. Hematoxylin and Eosin.

Figure 2.
Cranium; NOD.129P2(B6)-*B2m^{tm1Unc}*/J mouse.
Higher magnification of the chondroma in figure 1 illustrates an orderly proliferation of well differentiated chondrocytes (Ch) with a paucity of mitotic figures. Hematoxylin and Eosin.

Figure 3.
Hip joint, C57BL/6J mouse. There is a chondrosarcoma (Ch) arising from the coxofemoral articulation. Note the infiltrative nature of the well differentiated cartilaginous neoplasm. Hematoxylin and Eosin.

Figure 4. Hip joint, C57BL/6J mouse. Higher magnification of the chondrosarcoma in figure 3 illustrates proliferating chondrocytes (Ch) within a hyaline matrix. There is a mitotic figure (arrowhead). Hematoxylin and Eosin.

Figure 5. Head; C57BL/6J mouse. There is a circumscribed bony neoplasm (osteoma) arising from the cranium.

Figure 6. Cranium; C57BL/6J mouse. There is an osteoma (Os) arising from the cranium. Note the non-invasive proliferation of well differentiated mature bone. Hematoxylin and Eosin.

Figure 7. Cranium; C57BL/6J mouse. Higher magnification of the osteoma in figure 6 illustrates a benign proliferation of well-differentiated mature bone (Mb) with elements of bone marrow (arrowhead). Hematoxylin and Eosin.

Figure 8.
Body; NOD.NON-*Thy*^{1a}/J mouse. There is an infiltrative bony neoplasm (osteosarcoma) involving skeletal and soft tissues of the left forelimb.

Figure 9. Cranium, AKR/J mouse. There is an osteosarcoma (Os) arising from the maxilla. Note the disorderly proliferation of less-differentiated bone and the absence of bone marrow within the neoplasm. Hematoxylin and Eosin.

Figure 10. Cranium, AKR/J mouse. Higher magnification of the osteosarcoma (Os) in figure 9 illustrates haphazardly arranged spindloid cells in an eosinophilic matrix. Note the focus of mineralized osteoid (arrowhead). Hematoxylin and Eosin.

Figure 11. Right hind limb, NOD/ShiLtJ mouse. There is an osteosarcoma (Os) arising from the os coxa. Note the highly cellular and disorderly proliferation of osteoblasts. Hematoxylin and Eosin.

Figure 12. Right hind limb, NOD/ShiLtJ mouse. Higher magnification of the osteosarcoma in figure 11 illustrates osteoid (arrowhead) embedded within sheets of polygonal to ovoid neoplastic osteoblasts. Hematoxylin and Eosin.

Figure 13. Left hind limb, NOD.Cg-*Prkdc*^{scid}*Il2rg*^{tm1Wjl}/SzJ mouse. There is a hemangiosarcoma (He) arising within the femur. Note the cavernous blood filled spaces that obliterate medullary architecture. Hematoxylin and Eosin.

Figure 14. Left hind limb, NOD.129P2(B6)-*B2m^{tm1Unc}/J* mouse. Higher magnification of the hemangiosarcoma in figure 13 illustrates haphazardly oriented vascular channels (arrowhead) lined by neoplastic endothelial cells (En). Hematoxylin and Eosin.

Figure 15. Right hind limb; NONcNZO10/LtJ mouse. There is an ossifying fibroma (Of) surrounding the metatarsal bone. Note the expansile neoplasm consisting of a modestly cellular fibrous portion and mature osseous elements mostly towards the periphery. Hematoxylin and Eosin.

Figure 16. Right hind limb; NONcNZO10/LtJ mouse. Higher magnification of the ossifying fibroma in figure 15 illustrates trabecular bone (Tb) embedded in a fibrous stroma (Fs). Hematoxylin and Eosin.

Table 1

Classification schemes for bone tumors

WHO – HUMAN BEINGS ²⁵	WHO – DOMESTIC ANIMALS ⁸⁹	INTERNATIONAL CLASSIFICATION OF RODENT TUMORS ²²	CORRESPONDING SPONTANEOUS TUMORS IN MICE ^{2, 55, 56, 57, 68, 69}	CORRESPONDING GENETICALLY ENGINEERED MOUSE MODELS	COMMENTS
CARTILAGINOUS TUMORS					
Osteochondroma	Osteochondroma	NCDE	Osteochondroma	Conditional inactivation of <i>Ext1</i> ^{ex2neo1} or <i>Ext1</i> ^{ex2fl} in chondrocytes ⁴⁶ Targeted mutation of <i>Ext2</i> ⁹¹	Models for multiple hereditary exostoses or multiple osteochondromas ^{46, 91}
NA	Osteochondromatosis (feline)	NA	NA	NA	
Chondroma	Chondroma	Chondroma	Chondroma	See below	
- Enchondroma	NCDE	NCDE	NCDE	Transgenic overexpression of <i>Gli2</i> in chondrocytes ³⁵ Transgenic expression of mutant human <i>PTH/PTHrP</i> type I receptor (<i>R150C.PTHrP</i>) in growth plates ³⁷	
- Periosteal chondroma	NCDE	NCDE	NCDE	NCLM	
- Multiple chondromatosis	NCDE	NCDE	NCDE	NCLM	
Chondroblastoma	NCDE	NCDE	NCDE	NCLM	
Chondromyxoid fibroma	NCDE	NCDE	Chondromyxoid fibroma	NCLM	
Chondrosarcoma	Chondrosarcoma	Chondrosarcoma	Chondrosarcoma	Transgenic overexpression of <i>Gli2</i> in combination with inactivation of <i>Trp53</i> (<i>Trp53</i> ^{+/-}) in chondrocytes ³⁵ Targeted mutation of <i>Nf1atp2</i> (<i>Nf1atp</i>) ⁸⁴	
- Central, primary and secondary	- Central chondrosarcoma	NCDE	NCLS	NCLS	
- Peripheral	- Periosteal chondrosarcoma	NCDE	NCLS	NCLS	
- Dedifferentiated	NCDE	NCDE	NCLS	NCLS	
- Mesenchymal	NCDE	NCDE	NCLS	NCLS	
- Clear Cell	NCDE	NCDE	NCLS	NCLS	
OSTEOGENIC TUMORS					
Osteoid osteoma	Osteoma	Osteoma	Osteoma	NCLM	
Osteoblastoma	NCDE	Osteoblastoma / Osteofibroma	NCDE	NCLM	

WHO – HUMAN BEINGS ²⁵	WHO – DOMESTIC ANIMALS ⁸⁹	INTERNATIONAL CLASSIFICATION OF RODENT TUMORS ²²	CORRESPONDING SPONTANEOUS TUMORS IN LABORATORY MICE ^{2,55,56,57,68,69}	CORRESPONDING GENETICALLY ENGINEERED MOUSE MODELS	COMMENTS
NCDE	NCDE	Listed synonymously with osteoblastoma	Osteofibroma	NCLM	
Osteosarcoma	Osteosarcoma	Osteosarcoma	Osteosarcoma	Transgenic expression of <i>H2-cfosLTR</i> ^{16,31,87} Targeted mutation of <i>Trp53</i> ^{18,19,33,44} Conditional inactivation of <i>Trp53</i> and <i>Rb1</i> ^{6,101} Targeted mutation of <i>Cdkn2a</i> ²⁰ Targeted mutation of <i>Bax</i> and <i>Cdkn2a</i> ²⁰ Targeted mutation of <i>Nf2</i> ⁶⁷ Targeted mutation of <i>Nf2</i> and <i>Trp53</i> ⁶⁷ Transgenic expression of Simian Virus-40 (SV40) T antigen ^{5,40,51,65,106}	Various subtypes of osteosarcoma are infrequently described in genetically engineered mouse models of osteosarcoma
NCDE	- Poorly differentiated	NCDE	Poorly differentiated		
- Conventional	NCDE	NCDE	NCDE		
NCDE	NCDE	- Eburnating	NCDE		
- - Chondroblastic	- Chondroblastic	- Chondroblastic	Chondroblastic		
- - Fibroblastic	- Fibroblastic	- Fibroblastic	Fibroblastic		
- - Osteoblastic	- Osteoblastic	- Osteoblastic	Osteoblastic		
NCDE	NCDE	- Osteoclastic	NCDE		
NCDE	NCDE	- Vascular	Vascular		
NCDE	NCDE	- Anaplastic	Anaplastic		
NCDE	NCDE	- Mixed	Mixed		
NCDE	NCDE	NCDE	Sclerosing		
- Telangiectatic	- Telangiectatic	NCDE	Telangiectatic		
NCDE	- Giant cell type	NCDE	NCDE		
- Small cell	NCDE	NCDE	NCDE		
- Low grade central	NCDE	NCDE	NCDE		
- Secondary	NCDE	NCDE	NCDE		
- Parosteal	Parosteal	NCDE	NCDE		
- Periosteal	Periosteal	NCDE	Periosteal		
- High grade surface	NCDE	NCDE	NCDE		
NCDE	Multilobular tumor of bone	NCDE	NCDE	NCLM	
FIBROGENIC TUMORS					

WHO – HUMAN BEINGS ²⁵	WHO – DOMESTIC ANIMALS ⁸⁹	INTERNATIONAL CLASSIFICATION OF RODENT TUMORS ²²	CORRESPONDING SPONTANEOUS TUMORS IN LABORATORY MICE ^{2,55,56,57,68,69}	CORRESPONDING GENETICALLY ENGINEERED MOUSE MODELS	COMMENTS
Desmoplastic fibroma	NCDE	NCDE	NCDL	NCLM	
Fibrosarcoma	Fibrosarcoma	NCDE	NCDL	NCLM	
NCDE	- Periosteal fibrosarcoma	NCDE	NCDL	NCLM	
NCDE	Maxillary fibrosarcoma (dogs)	NCDE	NCDL	NCLM	
FIBROHISTIOCYTIC TUMORS					
Benign fibrous histiocytoma	NCDE	NCDE	NCDL	NCLM	
Malignant fibrous histiocytoma	NCDE	NCDE	NCDL	NCLM	
EWING SARCOMA / PRIMITIVE NEUROECTODERMAL TUMOR					
Ewing Sarcoma	NCDE	NCDE	NCDL	Transgenic expression of <i>EWS-FLI1</i> (Poorly differentiated sarcoma) ⁵³	
HEMATOPOIETIC TUMORS					
Plasma cell myeloma	Myeloma	NCDE	Myeloma	Transgenic expression of <i>Xbp-1</i> - <i>Tg(Eμ-Xbp-1)</i> ⁸ Transgenic expression of mutant <i>Myc</i> (<i>Vk*MyC</i>) ¹³	
Malignant lymphoma, NOS	Malignant lymphoma	NCDE	Malignant lymphoma	Transgenic overexpression of <i>Myc</i> ⁴⁷ Transgenic expression of mutant <i>Myc</i> (<i>Vk*MyC</i>) ¹³	
NCDE	NCDE	NCDE	Mastocytoma	NCLM	
GIANT CELL TUMOR					
Giant cell tumour	Giant cell tumor of bone	NCDE	NCDL	NCLM	
Malignancy in giant cell tumour	NCDE	NCDE	NCDL	NCLM	
NOTOCHORDAL TUMORS					
Chordoma	NCDE	NCDE	Chordoma	NCLM	
VASCULAR TUMORS					
Haemangioma	Haemangioma	NCDE	Haemangioma Hemangioendothelioma	NCLM	Specific models of intra- osseous hemangioma are uncommon
Angiosarcoma	Haemangiosarcoma	NCDE	Haemangiosarcoma Angiosarcoma	NCLM	Specific models of intra- osseous

WHO – HUMAN BEINGS ²⁵	WHO – DOMESTIC ANIMALS ⁸⁹	INTERNATIONAL CLASSIFICATION OF RODENT TUMORS ²²	CORRESPONDING SPONTANEOUS TUMORS IN LABORATORY MICE ^{2, 55, 56, 57, 68, 69}	CORRESPONDING GENETICALLY ENGINEERED MOUSE MODELS	COMMENTS
					hemangiosarcoma are uncommon
SMOOTH MUSCLE TUMORS					
Leiomyoma	NCDE	NCDE	NCDL	NCLM	
Leiomyosarcoma	NCDE	NCDE	NCDL	NCLM	
LIPOGENIC TUMOURS					
Lipoma	NCDE	NCDE	NCDL	NCLM	
Liposarcoma	Liposarcoma	NCDE	NCDL	NCLM	
NEURAL TUMORS					
Neurilemmoma	NCDE	NCDE	NCDL	NCLM	
MISCELLANEOUS TUMORS					
Adamantinoma	NCDE	NCDE	NCDL	NCLM	Adamantinoma is listed synonymously with ameloblastoma under tumors of teeth in the mouse classification system ²²
Metastatic malignancy	NCDE	NCDE	NCDL	NCLM	
NCDE	Malignant mesenchymoma	NCDE	NCDL	NCLM	
NCDE	Others	NCDE	NCDL	NCLM	
MISCELLANEOUS LESIONS					
Aneurysmal bone cyst	NCDE	NCDE	Aneurysmal bone cyst	NCLM	
Simple cyst	NCDE	NCDE	Bone cyst	NCLM	
NCDE	Solitary bone cyst	NCDE	NCDL	NCLM	
NCDE	Juxtacortical bone cyst	NCDE	NCDL	NCLM	
NCDE	Epidermoid cyst of the phalanx	NCDE	NCDL	NCLM	
NCDE	Myositis ossificans	NCDE	NCDL	NCLM	Myositis ossificans is considered under non-neoplastic diseases of bones ⁴² and tumors of soft tissue ²⁴ in human beings.

WHO – HUMAN BEINGS ²⁵	WHO – DOMESTIC ANIMALS ⁸⁹	INTERNATIONAL CLASSIFICATION OF RODENT TUMORS ²²	CORRESPONDING SPONTANEOUS TUMORS IN LABORATORY MICE ^{2, 55, 56, 57, 68, 69}	CORRESPONDING GENETICALLY ENGINEERED MOUSE MODELS	COMMENTS
Fibrous dysplasia	Fibrous dysplasia	NCDE	NCDL	NCLM	
NCDE	Myxoma of the jaw	NCDE	NCDL	NCLM	
Osteofibrous dysplasia	Ossifying fibroma	Ossifying fibroma / Cementifying fibroma	Ossifying fibroma	NCLM	Osteofibrous dysplasia is currently used for conditions previously described as ossifying fibroma ⁹⁶
Langerhans cell histiocytosis	NCDE	NCDE	NCDL	Multisystem histiocytosis ⁹⁰	
Erdheim-Chester disease	NCDE	NCDE	NCDL	NCLM	
Chest wall hamartoma	NCDE	NCDE	NCDL	NCLM	
JOINT LESIONS					
Synovial chondromatosis	NCDE	NCDE	NCDL	Disruption of hedgehog signaling in <i>Gli3</i> mutants ³⁸ Transgenic expression of Simian Virus-40 (SV40) Tumor antigen ⁹⁸	
NCDE	Synovial Sarcoma	Synovial Sarcoma	Synovial sarcoma	Conditional expression of human <i>SYT-SSX</i> in <i>Myf5</i> expressing myoblasts ³²	
NCDE	Villonodular synovitis	NCDE	NCDL	NCLM	

NA – Not applicable to the species

NCDE – No corresponding designation or entry in this classification scheme

NCDL – Not commonly diagnosed or listed as a primary tumor of bone or joint

NCLM – No commonly listed genetically engineered mouse model with primary involvement of bone or joint

NCLS – Not commonly listed as a subtype

Table 2

Benign bone tumors in various strains of mice as reported in the literature

MOUSE STRAIN	MECHANISM	AGE AT NECROPSY ^a	TUMOR FREQUENCY		
			Both sexes	Males	Females
CARTILAGINOUS TUMORS - CHONDROMA					
C57BL/10J ^{99, 100}	Spontaneous	18 to 24 m	0.05% (2 of 3968)	0	0.1% (2 of 1984)
Strain not specified (Tg(<i>Gli2</i> ; <i>Col2a1</i>)) ³⁵	Transgenic overexpression of <i>Gli2</i> in chondrocytes	NA	NA	NA	NA
Strain not specified (Tg(<i>Gli2</i> ; <i>Col2a1</i> ; <i>PTHrI</i>)) ³⁷	Transgenic expression of mutant human PTHrP type I receptor (<i>R150CPTHrI</i>) in growth plates	From 8 w	NA	NA	NA
CARTILAGINOUS TUMORS – CHONDROMYXOID FIBROMA					
C57BL/10J ^{99, 100}	Spontaneous	24 m	0.02% (1 of 3968)	0.04% (1 of 1984)	0
CARTILAGINOUS TUMORS - OSTEOCHONDROMA					
B6C3F1 ¹⁰⁴	Spontaneous	NA	0.02% (1 of 5065)	0.03% (1 of 2543)	0
B6;129- <i>Ext1</i> ^{tm1Kjns} ⁴⁶	Conditional inactivation of <i>Ext1</i> ^{tm1Kjns} or <i>Ext1</i> ^{tm2fl} in chondrocytes	6 to 10 w	100% ⁿ	NA	NA
C57BL/6- <i>Ext2</i> ^{tm1Web} ⁹¹	Targeted mutation of <i>Ext2</i>	NA	28% (7 of 25)	NA	NA
OSTEOGENIC TUMORS - OSTEOMA					
B6C3F1 ²	Spontaneous	NA	0.06% (1 of 1540)	0	0.13% (1 of 770)
CD1 ⁶³	Spontaneous	NA	0.17% (3 of 1781)	0.11% (1 of 891)	0.22% (2 of 890)
CrI:CD-1(ICR) ⁶⁶	Suspected to be retroviral (control mice)	55 to 97 w	3.2% (6 of 190)	1.1% (1 of 95)	5.3% (5 of 95)
	Suspected to be retroviral (Sodium Fluoride treated mice)	55 to 97 w	12.5% (34 of 272)	11% (15 of 136)	14% (19 of 136)
CF1 ²	Spontaneous	NA	5.5% (142 of 2600)	4.4% (57 of 1300)	6.5% (85 of 1300)
CF1 ¹⁰	Spontaneous	96 w (average)	10% (67 of 668)	8.5% (28 of 328)	11.5% (39 of 340)
CF1 ¹⁰	Spontaneous (mice were treated with DDT or urethane)	NA	14.4% (479 of 3319)	11.7% (208 of 1763)	17.4% (271 of 1556)
Han:NMRI ³⁶	Spontaneous	19 m	0.1% (1 of 900)	0	0.1% (1 of 900)
Him:OF1 ³⁶	Suspected to be viral (etiology not convincingly established)	533 ± 98 d	51.8% (116 of 224)	50.9% (57 of 112)	52.7% (59 of 112)
NMRI ^{2, 7}	Spontaneous	NA	0.16% (1 of 614)	0.16% (1 of 614)	0

MOUSE STRAIN	MECHANISM	AGE AT NECROPSY ^a	TUMOR FREQUENCY		
			Both sexes	Males	Females
CARTILAGINOUS TUMORS - CHONDROMA					
OF-1 ¹⁰⁸	Spontaneous (type C retroviral particles were observed in the tumors)	40 to 78 w	35% (35 of 100)	20% (10 of 50)	30% (15 of 50)
	Spontaneous (mice were treated with Cyclosporine A and type C retroviral particles were observed in the tumors)	40 to 78 w	26.3% (79 of 300)	14.7% (22 of 150)	38% (57 of 150)
VASCULAR TUMORS - HEMANGIOMA					
BALB/c ⁵⁵	Spontaneous	NA	0.95% (2 of 210)	NA	NA
MISCELLANEOUS TUMORS – OSSIFYING FIBROMA					
CD1 ²	Spontaneous	NA	NA	NA	NA
CF1 ²	Spontaneous	NA	NA	NA	NA
NMRI ²	Spontaneous	NA	NA	NA	NA

^a Age of incidence in days (d), weeks (w) or months (m) as indicated in the original reference.

ⁿ Numbers of tumor bearing mice and mice examined by necropsy are not available from the reference.

Table 3

Malignant bone tumors in various strains of mice as reported in the literature

MOUSE STRAIN	TUMORIGENESIS (GENOTYPE IF APPLICABLE)	AGE AT NECROPSY _a	TUMOR FREQUENCY		
			Both sexes	Males	Females
CARTILAGINOUS TUMORS - CHONDROSARCOMA					
B6C3F1 ²	Spontaneous	110 w	NA	NA	0.13% (1) ⁿ¹
ST/Eh ⁹²	Spontaneous	NA	NA	NA	NA
C.129- <i>Nf1atc2</i> ^{2ml} /Glm ⁸⁴	<i>Nf1atc2</i> (<i>Nf1atp</i>)	6 m	NA	100% <i>n2</i>	33% <i>n2</i>
Strain not specified (<i>Tg</i> (<i>Gli2</i> ; <i>Col1A1</i> - <i>Trp53</i> ^{tm1Tyj}) ³⁵	Transgenic overexpression of <i>Gli2</i> combined with inactivation of <i>Trp53</i> (<i>Trp53</i> ^{+/-}) in chondrocytes)	NA	NA	NA	NA
OSTEOGENIC TUMORS – OSTEOSARCOMA - SPONTANEOUS					
AKR/J ¹	Spontaneous	5 m	Single case	NA	NA
AKR/Ms ⁷⁰	Spontaneous (Type C retroviral particles were identified in the tumors)	300 d	NA	Single case	NA
B6CF1 ²⁷	Spontaneous	NA	1 <i>n1</i>	0	1 <i>n1</i>
B6C3F1 ²	Spontaneous	NA	0.52% (8 of 1540)	0.26% (2 of 770)	0.53% (6 of 770)
B6C3F1 ¹⁰⁴	Spontaneous	NA	0.98% (5 of 5065)	0.03% (1 of 2543)	0.15% (4 of 2522)
B6C3F1 ⁹	Spontaneous	NA	0.25% (1 of 400)	0.5% (1 of 200)	0
BALB/cCr ⁶²	Spontaneous	NA	0.03% (1 of 2928)	NA	NA
BALB/cCr ⁷⁴	Spontaneous	NA	0.05% (1 of 2065)	NA	NA
BALB/c ²⁷	Spontaneous	541 ± 297 d	0.08% (2 of 2376)	NA	0.08% (2 of 2376)
BALB/c ²⁷	Spontaneous (mice were treated with 2-acetylaminofluorene)	581 ± 149 d	0.06% (14 of 21,816)	NA	0.06% (14 of 21,816)
C3Hf/Sed/CB17- <i>Prkdc</i> ^{scid} ³⁹	Spontaneous	17 m	NA	NA	Single case
C57BL/6J ¹⁴	Spontaneous	5 w	NA	Single case	NA
C57BL/6J- <i>Ptpn6</i> ^{quev} ⁴⁵	Spontaneous	757 d	NA	NA	Single case
C57BL/6Jcrf ²⁶	Spontaneous	12 to 31 m	0.16% (7 of 4381)	0	0.41% (7 of 1707)
CD-1 ⁶³	Spontaneous	NA	0.22% (4 of 1781)	0.22% (2 of 891)	0.22% (2 of 890)
CD-1 HaM/ICR ⁷²	Spontaneous	4 to 20 m	0.6% (6 of 1000)	NA	NA

MOUSE STRAIN	TUMORIGENESIS (GENOTYPE IF APPLICABLE)	AGE AT NECROPSY _a	TUMOR FREQUENCY		
			Both sexes	Males	Females
CARTILAGINOUS TUMORS - CHONDROSARCOMA					
CF-1 ²	Spontaneous	NA	0.12% (3 of 3600)	0.15% (2 of 1300)	0.8% (1 of 1300)
CF-1 ¹⁰	Spontaneous (a subset of mice were treated with DDT or urethane)	49 to 130 w	0.37% (15 of 3987)	0.24% (5 of 2091)	0.53% (10 of 1896)
Han:NMRI ^{2,85}	Spontaneous	11 to 33 m	1.1% (10 of 900)	NA	1.1% (10 of 900)
NMRI ^{2,7}	Spontaneous	NA	0.41% (5 of 1205)	0.33% (2 of 614)	0.51% (3 of 591)
NMRI/Nhg ²	Spontaneous	NA	NA	NA	0.75% (15 of 2002)
NOD/ShiLJ ⁵⁰	Spontaneous	66 to 247 d (129.6 d)	10.8% (39 of 361)	8.9% (14 of 158)	12.3% (25 of 202)
NOD.SCID substrains ⁵⁰	Spontaneous	49 to 537 d (161.2 d)	3.9% (16 of 407)	3.1% (4 of 129)	5.5% (12 of 218)
NZBR/BI ²⁹	Spontaneous	340 to 593 d	3.67% (4 of 109)	6.98% (3 of 43)	1.5% (1 of 66)
NZBR/BI ²⁹	Spontaneous (mice were treated with Paraffin)	270 to 391 d	6.12% (3 of 49)	6.12% (3 of 49)	NA
Swiss Webster (CFW) ⁷⁶	Spontaneous	NA	1.5% (1 of 66)	0	2.6% (1 of 38)
SWR/J ⁸¹	Spontaneous	22 m	0.14% (1 of 671)	0	0.25% (1 of 402)
OSTEOGENIC TUMORS – OSTEOSARCOMA – HORMONALLY INDUCED					
BALB/c ³⁴	Dietary administration of diethylstilbestrol	NA	1 nl	0	1 nl
B6CF1 ³⁴	Dietary administration of diethylstilbestrol	NA	2 nl	1 nl	1 nl
B6CF2 ³⁴	Dietary administration of diethylstilbestrol	NA	2 nl	1 nl	1 nl
C3H/HeJ ³⁴	Dietary administration of 17βestradiol or diethylstilbestrol (mice had a high titer of Mouse Mammary Tumor Virus)	NA	3 nl	0	3 nl
C3HeB/FeJ ³⁴	Dietary administration of diethylstilbestrol (mice had a low titer of Mouse Mammary Tumor Virus)	NA	3 nl	0	3 nl
C3H/HeN ³⁴	Dietary administration of diethylstilbestrol (mice had a high titer of Mouse Mammary Tumor Virus)	NA	2 nl	0	2 nl
C57BL/6J ³⁴	Dietary administration of diethylstilbestrol	NA	9 nl	4 nl	5 nl
OSTEOGENIC TUMORS – OSTEOSARCOMA – RADIATION INDUCED					

MOUSE STRAIN	TUMORIGENESIS (GENOTYPE IF APPLICABLE)	AGE AT NECROPSY _a	TUMOR FREQUENCY		
			Both sexes	Males	Females
CARTILAGINOUS TUMORS - CHONDROSARCOMA					
C3101F1 ⁶⁴	Induced by administration of radionuclides (²²⁴ Ra or ²²⁷ Th); type A and/or type C retroviral particles were isolated from tumors	8 to 20 m	26 <i>n</i> l	7 <i>n</i> l	19 <i>n</i> l
CBA/H ⁴	Administration of the bone seeking radionuclide Strontium-90	NA	NA	NA	NA
Cr:CD-1(ICR) ⁷¹	External irradiation of the back with ⁹⁰ Sr- ⁹⁰ Y β-rays	NA	23 <i>n</i> l	NA	NA
NMRI ⁶⁴	Induced by administration of radionuclides (²²³ Ra, ²²⁴ Ra, or ²²⁷ Th); type A and/or type C retroviral particles were isolated from tumors	11 to 27 m	26 <i>n</i> l	1 <i>n</i> l	25 <i>n</i> l
OSTEOGENIC TUMORS – OSTEOSARCOMA – VIRALLY INDUCED					
BALB/cCh ⁷³	Induced by intramedullary inoculation of Moloney’s murine sarcoma virus into the proximal tibial metaphysis	NA	100% (66 of 66)	NA	100% (66 of 66)
C3H/BiDa ⁹⁷	Intraperitoneal inoculation of Mouse polyomavirus in neonates	188 d	17% (18 of 106)	NA	NA
CzechII/EiJ ⁹⁷	Intraperitoneal inoculation of Mouse Polyoma Virus in neonates	190 d	86.8% (33 of 38)	NA	NA
C3CZF1 ⁹⁷	Intraperitoneal inoculation of Mouse Polyoma Virus in neonates	NA	75% (12 of 16)	NA	NA
CF1/Anl ²³	Spontaneous retroviral (FBJ virus)	260 d	NA	Single case	NA
N:NIH(s) (NIH Swiss) ¹⁰⁵	Intraperitoneal inoculation of FBJ virus in neonates	26 to 145 dØ	55.17% (80 of 145)	NA	NA
OSTEOGENIC TUMORS – OSTEOSARCOMA – GENETICALLY ENGINEERED					
B6;CBA:Hm:OF-1-Tg(<i>H2-c-fosLTR</i>) ³¹	Transgenic expression of <i>c-fos</i> under the <i>H-2kb class I MHC</i> promoter	6 m (heterozygotes) 10 to 12 w (homozygotes)	NA	NA	NA
OSTEOGENIC TUMORS – OSTEOSARCOMA – GENETICALLY ENGINEERED – SV40 Tag					
B6.129S- <i>B2m</i> ^{tm1Jae} ;B6-Tg(Amy1TAg)501Knnw/J ⁶⁵	SV40 T antigen	300 to 795 d	70.8% (51 of 72)	NA	NA
B6.129S2- <i>CD4</i> ^{tm1Knnw} ;B6-Tg(Amy1TAg)501Knnw/J ⁶⁵	SV40 T antigen	165 to 585 d	63.3% (93 of 147)	NA	NA
BDF1-Tg(<i>hsp70SV40Tag</i>) ¹⁰⁶	SV40 T-antigen	31 w (homozygous) 46 w (hemizygous)	9 <i>n</i> l	7 <i>n</i> l	2 <i>n</i> l

MOUSE STRAIN	TUMORIGENESIS (GENOTYPE IF APPLICABLE)	AGE AT NECROPSY _a	TUMOR FREQUENCY		
			Both sexes	Males	Females
CARTILAGINOUS TUMORS - CHONDROSARCOMA					
C57BL/6J-Tg(Amy1TAg)501Kw/J ⁵¹	SV40 T antigen	15 m	66.7% (20 of 30)	NA	NA
C57BL/6J-Tg(Amy1TAg)501Kw/J ⁶⁵	SV40 T antigen	240 to 570 d	69.1% (112 of 162)	NA	NA
C57BL/6J-Tg(WAPTag)3Kw/J ⁴⁰	SV40 T antigen	6 months	98.5% (67 of 68)	100% (37 of 37)	96.8% (30 of 31)
Strain not specified (Tg(mPl-SV40Tag)) ⁵	SV40 T antigen fused to the mouse Protamine gene	NA	4 nI	NA	NA
OSTEOGENIC TUMORS – OSTEOSARCOMA – GENETICALLY ENGINEERED – Nf2					
129S2-Nf2 ^{tm1Tyj} ⁶⁷	Targeted mutation of Nf2 (Nf2+/-)	18.7 m (females) and 23 m (males)	76% (28 of 37)	67% (12 of 18)	84% (16 of 19)
(C57BL/6 × 129S2-Nf2 ^{tm1Tyj}) F1 ⁶⁷	Targeted mutation of Nf2 (Nf2+/-)	NA	63% (62 of 99)	56% (38 of 68)	77% (24 of 31)
(C57BL/6 × 129S2-Nf2 ^{tm1Tyj}) F2 ⁶⁷	Targeted mutation of Nf2 (Nf2+/-)	NA	51% (23 of 45)	60% (9 of 15)	47% (14 of 30)
OSTEOGENIC TUMORS – OSTEOSARCOMA – GENETICALLY ENGINEERED – Trp53					
B6.129S1-Trp53 ^{tm1Brd} ¹⁸	Targeted germline mutation of Trp53 (Trp53-/-)	16 w	2.85% (1 of 35)	1 nI	NA
B6.129S1-Trp53 ^{tm1Brd} ¹⁸	Targeted germline mutation of Trp53 (chimera)	60 w	1 nI	1 nI	NA
129S2-Trp53 ^{tm1Brd} ³³	Targeted germline mutation of Trp53 (Trp53-/-)	NA (5 weeks for tumors in general)	6.89% (2 of 29)	NA	NA
B6.129S1-Trp53 ^{tm1Brd} ³³	Targeted germline mutation of Trp53 (Trp53-/-)	NA	3.33% (2 of 60)	NA	NA
B6.129S2-Trp53 ^{tm1Tyj} ⁴⁴	Targeted germline mutation of Trp53 (Trp53-/-)	NA	NA	NA	NA
B6.129S2-Trp53 ^{tm1Tyj} ⁴⁴	Targeted germline mutation of Trp53 (Trp53+/-)	NA	NA	NA	NA
129S2-Nf2 ^{tm1Tyj} ⁶⁷ and (C57BL/6 × 129S2-Nf2 ^{tm1Tyj} Trp53 ^{tm1Tyj}) F1 ⁶⁷	Targeted mutations of Nf2 and Trp53 in cis - both on Chromosome 11 (Nf2+/-Trp53+/-)	NA	77% n2	NA	NA
Mixed C57BL/6, 129 FVB/N background - (Rb ^{tm1Tyj} Trp53 ^{tm1Tyj} Ox ^{1GFPcre}) ¹⁰¹	Osteoblast restricted deletion of Trp53 and / or Rb	See below for number of tumors and penetrance by genotype			
	Trp53+/-, Rb+/+	338 d	8.33% (1 of 11)	0	8.33% (1 of 11)
	Trp53-/-, Rb+/+	292.8 ± 21.8 d	100% (5 of 5)	60% (3 of 5)	40% (2 of 5)
	Trp53+/-, Rb+/-	-	0	0	0
	Trp53+/-, Rb-/-	-	0	0	0

MOUSE STRAIN	TUMORIGENESIS (GENOTYPE IF APPLICABLE)	AGE AT NECROPSY _a	TUMOR FREQUENCY		
			Both sexes	Males	Females
CARTILAGINOUS TUMORS - CHONDROSARCOMA					
Mixed C57BL/6, 129 FVB/N background - (<i>Rb</i> ^{tm1Ty} <i>Trp53</i> ^{tm1Ty} <i>Ox1</i> ^{IGFPCre}) ⁶	<i>Trp53</i> ^{+/-} , <i>Rb</i> ^{+/-}	198.3 ± 22 d	30% (13) <i>nI</i>	8 <i>nI</i>	5 <i>nI</i>
	<i>Trp53</i> ^{+/-} , <i>Rb</i> ^{-/-}	177 ± 14.4 d	77.8% (13) <i>nI</i>	6 <i>nI</i>	7 <i>nI</i>
	<i>Trp53</i> ^{-/-} , <i>Rb</i> ^{+/-}	158.4 ± 10.2 d	100% (27 of 27)	19 <i>nI</i>	8 <i>nI</i>
	<i>Trp53</i> ^{-/-} , <i>Rb</i> ^{-/-}	127.9 ± 3.4 d	100% (24 of 24)	15 <i>nI</i>	9 <i>nI</i>
	Conditional inactivation of <i>Trp53</i> and / or <i>Rb</i> in osteoblast precursor cells		See below for tumor frequency by genotype		
	<i>Trp53</i> ^{-/-}	281 ± 55 d	100% (25 of 25)	NA	NA
	<i>Rb</i> ^{+/-} , <i>Trp53</i> ^{+/-}	299 ± 84 d	100% (16 of 16)	NA	NA
	<i>Rb</i> ^{-/-} , <i>Trp53</i> ^{+/-}	251 ± 87 d	94.4% (17 of 18)	NA	NA
	<i>Rb</i> ^{+/-} , <i>Trp53</i> ^{-/-}	207 ± 33 d	100% (21 of 21)	NA	NA
	<i>Rb</i> ^{-/-} , <i>Trp53</i> ^{-/-}	147 ± 31 d	65.12% (28 of 43)	NA	NA
VASCULAR TUMORS - HEMANGIOSARCOMA					
B6C3F1 ²	Spontaneous	NA	11 <i>nI</i>	0.78% (6) <i>nI</i>	0.65% (5) <i>nI</i>
NZB ⁴¹	Spontaneous	12 m	NA	Single case	NA
C3H/HeH ⁴	Administration of the bone seeking radionuclide Strontium-90	NA	NA	NA	NA
CBA/H ⁴	Administration of the bone seeking radionuclide Strontium-90	NA	NA	NA	NA
HEMATOPOIETIC TUMORS – MULTIPLE MYELOMA					
C57BL/KaLwRij ⁸⁴	Spontaneous	> 2y	0.5% <i>n</i> 2	NA	NA
C57BL/6J-Tg(<i>Eμ-Xbp-1</i>) ⁷	Overexpression of <i>Xbp-1</i>	14 to 24 m	26% (8 of 35)	NA	NA
C57BL/6J-Tg(<i>Vk*Myc</i>) ¹³	Mutant <i>Myc</i> transgene (<i>Vk*Myc</i>)	NA	NA	NA	NA
TUMORS OF UNCERTAIN HISTOGENESIS – SYNOVIAL SARCOMA					
B6;129X1-Tg(<i>SYT-SSX</i>) ³²	Conditional expression of human <i>SYT-SSX</i> fusion transgene in <i>Myf5</i> expressing myoblasts	3 to 5 m	100% (18/18)	NA	NA

^a Age of incidence in days (d), weeks (w) or months (m) as indicated in the original reference.

*n*1 Number of mice examined by necropsy is not available from the reference.

ⁿ² Numbers of tumor bearing mice and mice examined by necropsy are not available from the reference.
 ⊗ Induction time - time to appearance of the neoplasm after inoculation with the virus (at 1 to 2 days of age)

Table 4

Benign and malignant bone tumors in strains of mice from The Jackson Laboratory diagnostic necropsy archives

STRAIN	Chondroma		Osteochondroma		Chondrosarcoma		Osteoma		Ossifying fibroma		Osteosarcoma		Hemangioma		Hemangiosarcoma	
	F	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A
OUTBRED STOCK																
CD-1															1.81% (1/55)	230
INBRED STRAINS																
129S1/SvImJ																
129X1/SvJ											0.91% (1/109)	188				
A/J							0.13% (1/752)	168			0.13% (1/752)	111				
AKR/J											0.77% (4/513)	137.75				
BALB/cByJ										0.1% (1/991)	166					
BALB/cJ										0.1% (2/1892)	225.5					
C3H/HeJ										0.13% (1/1344)	200					
C57BL/6J				0.04% (1/2326)	325	0.04% (1/2326)	47			0.09% (2/2326)	251.5					
C57BL/6NJ																
C57BL/10J																
CBA/J										0.15% (1/669)	191					
DBA/1J																
DBA/2J						0.19% (1/538)	247							0.19% (1/538)	57	
FVB/NJ																
NOD/ShiLtJ										11.5% (43/375)	133					

NOR/LdJ										6.66% (1/15)	235								
SJL/J																			
TALLYHO/JngJ																			
HYBRID STRAINS																			
B6129SF2/J											25% (1/4)	263							
B6C3F1/J							0.74% (1/134)	338			0.74% (1/135)	348							
B6CBAF1/J																			
B6D2F1/J																			
B6SJLF1/J																			
C3D2F1/J											4.5% (1/22)	199							
CAF1/J											0.44% (1/224)	298							
CB6F1/J																			
CWDAKRF1/J											100% (2/2)	281.5							
NZBWF1/J																			
RECOMBINANT INBRED STRAINS																			
CX1-8/SalkJ											100% (1/1)	148							
CBXNO-7											100% (2/2)	194.5							
RECOMBINANT CONGENIC STRAINS																			
NONcNZO10/LdJ											25% (1/4)	186							
SPONTANEOUS MUTANT STRAINS																			
BKS.Cg-Dock7 tm +/- Lepr ^{db} /J											0.52% (1/189)	191							
HRS/J													0.22% (1/441)	175			0.22% (1/441)	175	

WBB6F1/J- <i>Ki1^W/Ki1^{W-vj}/J</i>			16.7% (1/6)	44						16.7% (1/6)	295						
SPONTANEOUS AND TARGETED SCID MUTANT STRAINS																	
C3SnSmn.CB17- <i>Prkdc^{scid}/J</i>										0.64% (1/157)	177						
NOD.CB17- <i>Prkdc^{scid}/J</i>										5.7% (11/194)	150.8						
NOD.Cg- <i>Prkdc^{scid}/129g^{em1W}/SzJ</i>										3.2% (5/157)	188				0.6% (1/157)		268
CONGENIC MUTANT STRAINS																	
B6.CAST- <i>Gpi-1^u/EiJ</i>															25% (1/4)		236
C3.SW- <i>H2^b/SnJ</i>							9.09% (1/11)	103									
GEM STRAINS - <i>Trp53</i> MUTANTS																	
129- <i>Trp53^{tm1Tyj}/J</i>										4.34% (1/23)	51						
B6.129S2- <i>Trp53^{tm1Tyj}/J</i>										2.53% (6/237)	105						
BALB/cJ- <i>Trp53^{tm1Tyj}/J</i>										5.9% (1/17)	70						
C.129S2(B6)- <i>Trp53^{tm1Tyj}/J</i>										6.67% (1/15)	70						
C3H/HeOul- <i>Trp53^{tm1Tyj}/J</i>										11.11% (1/9)	358						
C57BL/6J- <i>Trp53^{tm1Tyj}/J</i>										2.5% (1/40)	87						
FVB/NJ- <i>Trp53^{tm1Tyj}/J</i>															14.28% (1/7)		87
GEM STRAINS – SV40 Tag TRANSGENIC																	
B6.129S6- <i>CD4^{tm1Knn}/J</i> ;B6-Tg(Amy1TAg)501Knn/J										50% (2/4)	285.5						
C57BL/6J-Tg(Amy1TAg)335Knn/J										100% (1/1)	358						
C57BL/6J-Tg(Amy1TAg)501Knn/J							100% (1/1)	342		100% (1/1)	463						
C57BL/6J-Tg(SV)419Bri/J										33.33% (1/3)	308						
C57BL/6J-Tg(WAPTA)3Knn/J										92.3% (12/13)	169						
GEM STRAINS - OTHER																	
B6;129- <i>Ox1^{tm1Woy}/J</i>															100% (1/1)		498
B6;129P2- <i>Nos2^{tm1Lm}/J</i>										8.3% (1/12)	174						
NOD.129P2(B6)- <i>B2m^{tm1Unc}/J</i>	16.7% (1/6)	37															

F – Frequency of tumors (Number of cases by number of necropsies)

A – Average age of observation of tumor (average age at necropsy) in days

Tumor frequencies and average ages for males and females separately are available in supplementary tables ST1 and ST2.

No bone tumors were found in the diagnostic archives for the inbred and hybrid strains highlighted in gray.

The frequencies were considered non-representative for strains with less than 100 total necropsies (highlighted in gray).

Hashed columns indicate that there were no documented cases of that tumor type for that strain in the necropsy archives.