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Mouse models for cancer research – current state and the perspective

Review

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Cancer is one of the leading causes of death worldwide. We still do not understand all the details of carcinogenesis, and effective treatment is lacking for many oncological diseases. Animal models provide an irreplaceable tool to observe the growth and spreading of neoplastic cells in an environment of living organisms, to test the efficacy of cancer treatment, side effects, and toxicity, and to study the tumor microenvironment. Mice are the most often used model organisms because of their easy handling, short reproductive period, multiple strains, and complete DNA sequencing. An ideal model should accurately recapitulate each step of tumor development. Recent techniques have established models that enable the study of different aspects of cancer, but choosing a particular model depends on the application of output data. This article aimed to review induced, transplantable, and engineered mice and highlight their significance for recent and future cancer research.

Key words: in vivo model; mouse; cancer; xenograft

Several species of animals like rabbits, rats, dogs, monkeys, guinea pigs, pigs, zebrafish, *Drosophila*, and *Caenorhabditis* are used in biomedical research. Mice are considered model animals for the study of many human diseases [1], such as obesity [2, 3], Parkinson's disease [4–6], sclerosis multiplex [7, 8], diabetes mellitus [9, 10], depression [11, 12], or cancer [1, 13–16]. Mice are popular because they are mammals of small size, require inexpensive housing, and are easy to handle; they have a rapid onset of the reproductive period, facilitating colony expansion. Their lifespan is relatively long. We know the complete sequence of the mouse genome, which can be easily manipulated. The mouse represents a suitable model organism for growing experimental tumors or simulating the broad spectrum of events that lead to human cancer. They enable understanding of many processes involved in cancer biology at the molecular, cellular, and organ levels [13].

History of using mice as model organisms

The laboratory mouse (*Mus musculus*, house mouse) originated in the Middle East, in today's Pakistan. Man and mouse have coexisted since the end of the last ice age [17]. The breeding of mice with distinct coat colors and behaviors originated in ancient China, Japan, and Europe [18]. The first recorded use of mice as animal models was in ancient Greece. The purpose was to better understand human anatomy, ontogeny, and physiology. Many observations of Alcmaeon of Croton, Aristotle, and Erasistratus were documented and spread to other countries. Hence, animal models soon became a research tool for European and Arab physicians. Small vertebrates have been used in biomedical research since the beginning of the 16th century when biology shifted from descriptive to experimental science. William Harvey (1578–1657) used mice to study reproduction and blood circulation [19], and Robert Hooke (1635–1703) examined the biological consequences of an increase in atmospheric pressure on mice [20]. Gregor Johann Mendel is believed to be the first who worked with mice while writing the Principles of Inheritance (1866) but switched to the peas model after his bishop admonished him because mice were not the optimal tool for the environment of the Augustinian monastery [18]. Also, Théodore Colladon (1792–1862) reported

the findings of his breeding experiments, which matched Mendel's 36 years before the publication of J. G. Mendel's results on the plants [21].

In the 19th and 20th centuries, mice became a favorite pet. Abbie Lathrop started breeding mice and began to sell them to scientists of the nearby technological institute (Harvard University's Bussey Institute of Boston), devoted to the then-new science of genetics. In 1929, Dr. Clarence C. Little founded Jackson Laboratory (JAX), the world's leading supplier of laboratory mice [22].

Today, breeding, model development, and mouse delivery for research are part of the industry sector [18]. In the last century, the rapid development of experimental mouse models occurred, from chemically induced models [23] through cell line-derived xenografts [24] to genetically engineered mice. Figure 1 provides an overview of today's cancer mouse models.

Spontaneous mutation models

Spontaneous mutation models give essential information in the context of tumor development and the molecular mechanisms involved in this process. Large animals, especially companion animals, have a high tendency of incidence of spontaneous cancer, and their response to therapy is very similar to humans [23]. The frequency of spontaneous mutations is very low in mouse colonies (rate of ~$4.5–6.5\times10^{-9}$ per locus). Spontaneous models have been utilized in cancer research during the last decades. Now, they are often substituted by genetically engineered animals [24]. Mice with mutations leading to immunodeficiency are used in cancer research. Strains homozygous for the $Foxn1^{nu}$ mutation exert abnormal hair growth and defective development of the thymic epithelium [25]. Mice bearing $Prkdc^{scid}$ mutation lack functional B- and T-cells [26]. These defects enable the engraftment of tumor xenografts.

Induced mutation models

Induced cancer models are produced by the exposition of the animal to risk factors such as carcinogens, radiation, viruses, or physical stimuli [27]. Carcinogen-induced models of primary cancers can be used to evaluate the therapeutic efficacy of drugs, prove the effect of biological factors, and explore preventive measures for carcinogenicity. Compared to genetically engineered or transplanted models, induced primary malignancies can mimic the cancer progress from the early stage on through initiation, promotion, and progression. Nonetheless, it is not known whether the genomic alterations causing these mouse tumors are comparable to those found in humans [28].

Cancer models can be induced using several carcinogens. Colorectal cancer (CRC) can be induced by azoxymethane and dextran sodium sulfate, methyl nitrosourea, or N-methyl-N-nitro-N-nitrosoguanidine [25, 29]. Diethylnitrosamine is also used for the induction of hepatocellular carcinoma [30], and N-butyl-N-(4-hydroxy butyl)-nitrosamine is used in muscle-invasive bladder cancer research [31]. In breast cancer studies, methyl nitrosourea is used for tumor induction [32].

According to their mechanisms of action, chemical carcinogens can be divided into genotoxic and non-genotoxic, direct and indirect. Genotoxic carcinogens interact with DNA, causing mutations. Non-genotoxic carcinogens modulate the physiological processes of cell growth, division, and epigenetic silencing. A classic example of a genotoxic carcinogen

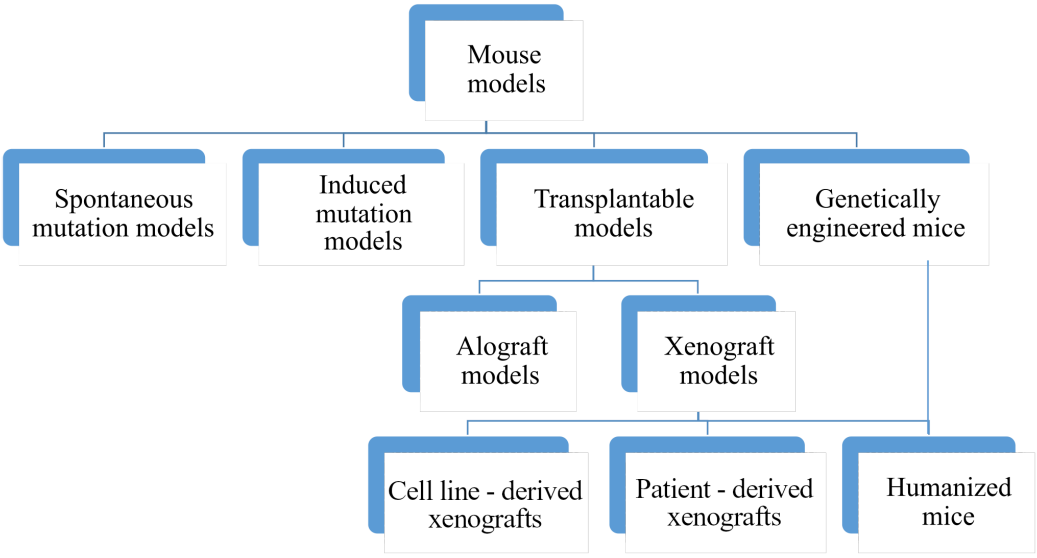

Figure 1. Mouse models used in cancer research.

is dimethylbenz[a]anthracene or the methyl nitrosourea mentioned above [33, 34]. Non-genotoxic sodium phenobarbital is used for the induction of liver tumors [35].

Direct carcinogens do not need to be metabolized to induce cancer, e.g. directly acting N-methyl-N'-nitro-N-nitrosoguanidine is used to induce gastric cancer. In contrast, the indirect agents are applied in their inactive form and must be activated inside the body. To this group belongs, e.g. polycyclic aromatic hydrocarbon-2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, which is applied for induction of experimental mouse breast [36] and colon [37] tumors.

Chemically induced tumors possess multiple advantages, such as easy administration, effective tumor induction, and multifocal lesions simultaneously generated in the target organs. Inducible experimental tumors often have various sizes and degrees of differentiation, but there is a significant analogy to clinical human primary cancers concerning similar morphology, histopathology, and molecular changes [38]. On the other hand, the induction of cancer is a time-consuming process. Tumors occur unpredictably and heterogeneously [27]. Chemically induced mutations show lower heterogeneity than the diversity found within a typical cohort of human patients [30].

Transplantable models

Tumor cells or tissue are administered to the recipient mouse in transplantable models. If the graft is of mouse origin, several options are available: 1) autograft model, when transplanted cells are administered back into the donor; 2) isograft model, when the graft and recipient are genetically identical (twins) or highly inbred strain is used; 3) allograft model, if the recipient is of a different or not of inbreed strain [39]. In these models, immunocompetent mice are used. In the xenograft model, cells/tissues of species different from the recipient are transplanted. It is necessary to use an immunodeficient mouse strain.

The tissues or the cells can be implanted in several ways: heterotopically, orthotopically, or systematically (Figure 2). Heterotopic transplantation is applied outside the place of origin, usually subcutaneously into the flank. It is the most often used method due to ease of administration. In orthotopic administration, the graft is implanted into the equivalent organ from which the cancer cells originated. The orthotopic administration has the most accurate outcomes [40]. It offers a microenvironment specific to a given tumor type. In breast cancer, transplantation into the mammary fat pad is used [41]. The systemic application can be performed intravenously to the tail vein [42, 43] by intracardial injection into the left ventricle to induce lung metastasis [44] or to simulate circulating tumor cells [45]. Intraperitoneal application is used for simulation of the metastatic spread of gastro-intestinal [46] or ovarian cancer [47]. A wide variety of available models allows us to study almost all types of cancer, including metastasis and different stages of tumor progression [48].

Allograft models. Syngeneic models, known as allograft models, are the oldest and most often used in preclinical studies of tumor immunity and testing immunotherapy in a fully functional murine immune system capable of the immune response [49] and the complex tumor microenvironment (TME) [50]. The syngeneic models consist of mouse tumor tissues or cells expanded *in vitro* and implanted into genetically identical mouse strains [51]. Therefore, tumor rejection does not develop. In the syngeneic model, thera-

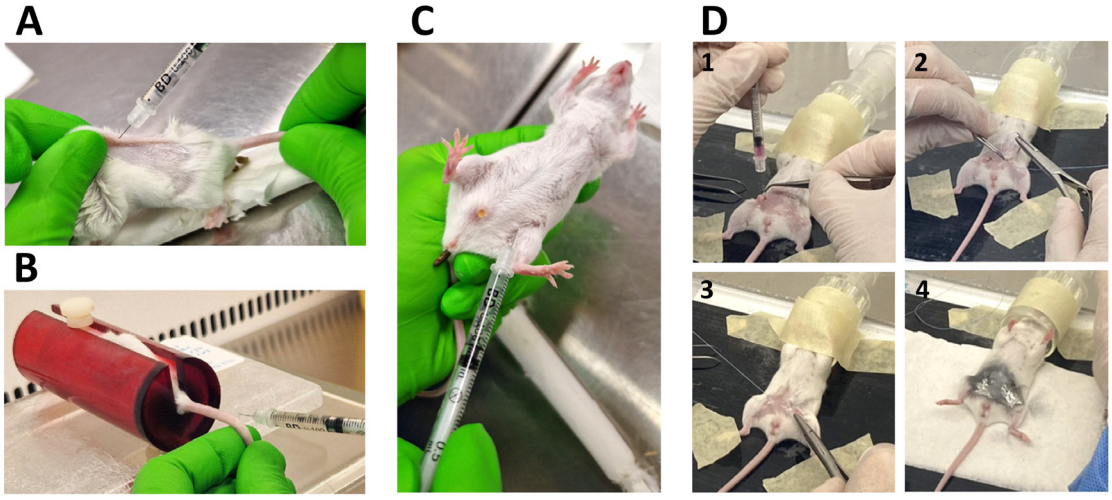

Figure 2. Ways of transplanted cells administration into mouse models: subcutaneous administration into flanks A), intravenous into the tail vein using restrainer B), intraperitoneal into abdominal cavity C) and orthotopic administration into mammary fat pad D). Orthotopic administration is performed under isoflurane anesthesia, starting with a small incision of less than 3 mm, then the mammary fat pad is lifted, and cells are injected (1). The wound is then sutured (2, 3) and covered with a silver spray (4).

peutic effects on tumor growth, metastasis, and immune modulation can be well observed [52].

The number of stabilized tumor cell lines for particular cancer types is restricted, limiting the available models [52]. However, several well-established cell lines are commonly used for breast cancer studies, such as the metastatic cells 4T1 and non-metastatic cells 67NR for BALB/c mice [53–55] and EO771 metastatic breast cancer cell line for C57BL/6 mice [56–58]. When conducting studies that require large group numbers, the syngeneic system is convenient for rapid and reproducible expansion of tumor cell lines before implantation into hosts [59]. Allograft mouse models are summarized in Table 1.

On the other hand, rapid tumor development may alter tumor biology, and the use of established cell lines may skew results due to the selection of features that favor cell proliferation *in vitro* [60]. Considerable selection pressure caused by *in vitro* cultivation and deficiency of cancer stem cells and other progenitor populations reduces tumor heterogeneity and mutational evolution [61]. It is crucial to carefully choose the mice's source to ensure efficient tumor cell engraftment. In the breeding colonies, the minimization of genetic drift must be guaranteed. The use of animals from various sources with various controls of breeding integrity is probably the explanation for the wide range of doses of 4T1 cells for subcutaneous allograft induction, which can be found in publications: 1×10^4 [62], 5×10^4 [63], 2.5×10^5 [64], 1×10^6 cells [65], 2×10^6 cells [66], 4×10^6 cells [67]. We demonstrated that 1×10^4 cells induced growing allografts on mice from one breeder. On the other hand, we observed regression of allografts induced by 1×10^5 4T1 cells in mice from another breeder (unpublished data).

Xenograft models. A xenograft is represented by a transplanted tissue, organ, or cell from a donor of a different species than the recipient (e.g., cells of human origin applied to mice). For this purpose, an immunodeficient strain is needed to avoid xenograft rejection due to an immune reaction. Xenograft models can be induced by established cell lines or patient-derived cells or tissues.

Cell line-derived xenografts. The cell line-derived xenografts (CDX) are prepared by implanting tumor cells in immunodeficient animals. For their technical simplicity and easy administration, they are used to quickly test hypotheses and are suggested to be a bridge between *in vitro* and *in vivo* studies [68]. The CDX models are widely utilized in early-stage drug development [69], in studies focused on drug resistance [69–71], the potential of epigenetic drugs to modulate the sensitivity of cancer cells to therapy [72], the study of mechanisms of tumor growth [73], and tumor-stroma interactions [74].

The CDX are popular due to their low costs, high availability, many cell lines, easy establishment, and short time of tumor development, usually 2–8 weeks [75].

As described above, the cell suspension can be administrated subcutaneously, which is the easiest way, systematically, or orthotopically. A significant advantage for breast cancer research is the easy induction of the orthotopic xenografts in the breast fat pad [72] in comparison with the technically more complicated induction of orthotopic CRC. On the other hand, many breast cancer cell lines are highly dependent on hormones, so sufficient supplements need to be applied via drinking water or pellets [76].

The long-term culture *in vitro* can irreversibly alter the properties of cancer cells, and selection pressure can decrease heterogeneity compared with original tumors [77]. Another drawback that can affect drug efficacy testing, for example, is that most cell lines have been derived from highly aggressive malignant tumors [78]. Frequently used CDX for the most frequent cancer types are stated in Table 2.

Patient-derived xenografts. Compared to CDX, patient-derived xenografts (PDX) represent more relevant models to human cancer biology [79]. They objectively recapitulate key tumor characteristics, including metastatic and invasive potential and genetic changes. In PDX models,

Table 1. Common allograft mouse models.

Cancer type	Cell line	Mouse strain	References
Breast carcinoma (TN)	4T1	BALB/c	[126-128]
Colon carcinoma	CT26.WT	BALB/c	[129, 130]
(N-nitroso-N-methylurethane-induced cell line)			
Prostate carcinoma	Myc-CaP	FVB	[131, 132]
	TRAMP-C2	C57BL/6	[133, 134]
Hepatoma	Hepa1-6	C57BL/6	[135, 136]
Ovarian cancer	ID8	C57BL/6	[137, 138]
Squamous cell carcinoma	SCC7	C3H/He	[139, 140]
Bladder carcinoma	MBT-2	C3H/He	[141, 142]
Pancreatic ductal adenocarcinoma	Panc02	C57BL/6	[131, 143]
	KPC	C57BL/6	[144, 145]
Kidney carcinoma	Renca	BALB/c	[146, 147]
Melanoma	B16-F0, B16-F1, B16-F10	C57BL/6	[148-150]

Abbreviation: TN-triple negative

Table 2. Cell line-derived xenograft mouse models for the 15 most frequent cancer types.

Cancer type	Cell line	Mouse strain	References
Breast carcinoma (TN)	MDA-MB-231	athymic nude	[151]
		NSG	[128]
	MDA-MB-468	athymic nude	[152-154]
Breast carcinoma (ER+)	MCF7	SCID	[155]
Breast carcinoma (HER+)	SK-BR-3	athymic nude	[156, 157]
Breast ductal carcinoma (ER-, HER+, trastuzumab-resistant)	JIMT-1	athymic nude	[158]
		SCID beige	[72]
Non-small cell lung cancer	A549	athymic nude	[159, 160]
	H1299	athymic nude	[161, 162]
	H1975	athymic nude	[163, 164]
Colon carcinoma	SW620	athymic nude	[165]
		NOD/SCID	[166]
	HT-29	athymic nude	[167]
		SCID	[168]
	LS 180	athymic nude	[169, 170]
	SW480	athymic nude	[171, 172]
	HCT 116	athymic nude	[173, 174]
Prostate carcinoma	LNCaP	athymic nude	[175, 176]
	PC-3	athymic nude	[177]
		NSG	[178]
Gastric carcinoma	HGC-27	athymic nude	[179, 180]
Pediatric hepatocellular carcinoma	Hep3B2.1-7	athymic nude	[181]
		NSG	[182]
Liver carcinoma	SK-HEP-1	athymic nude	[136, 183]
Cervix carcinoma	HeLa	athymic nude	[184-186]
	SiHa	athymic nude	[187, 188]
Tongue squamous cell carcinoma	CAL 27	athymic nude	[189]
		NSG	[190]
Esophageal squamous cell carcinoma	KYSE-150	athymic nude	[191]
		SCID beige	[192]
Thyroid carcinoma	8505C	athymic nude	[193, 194]
Bladder carcinoma	T24	athymic nude	[195, 196]
	5637	athymic nude	[197, 198]
B-cells non-Hodgkin's lymphoma	SU-DHL-6	SCID	[199]
		NOD/SCID	[200]
Pancreatic ductal carcinoma	MIA PaCa-2	athymic nude	[201, 202]
	PANC-1	athymic nude	[203]
		SCID	[204]
Renal cell carcinoma	786-O	athymic nude	[205, 206]
	A-498	athymic nude	[207, 208]
Endometrial carcinoma	Ishikawa	athymic nude	[209, 210]
Melanoma	A2058	athymic nude	[211, 212]
	M14	athymic nude	[213]
	A-375	athymic nude	[214, 215]
		SCID beige	[216]

Abbreviations: TN-triple negative; ER+-estrogen receptor positive; HER+-human epidermal growth factor receptor 2 positive

tissue or cells from the donor (human patient) are applied to the mouse recipient. Highly immunodeficient mouse strains like nonobese diabetic/severe combined immunodeficiency (NOD/SCID), NOD scid gamma (NSG), and NOD rag gamma (NRG) mice are preferentially used to minimize xenograft rejection [76]. The engraftment rate is low if athymic mice are utilized for PDX establishment [80].

The PDX models are often used to study the efficiency of anti-tumor drugs [81] and to identify cancer cell characteristics [76] or TME [82].

Tumor specimens are processed to single-cell suspension before transplantation, or small pieces of tissue can be implanted subcutaneously. Our experience with CRC samples shows that non-processed tissues engraft and proliferate better than single-cell suspension (unpublished data).

The efficiency of xenograft engraftment dramatically differs according to the type of tumor origin and strain of immunodeficient mice. For breast cancer, the rate of engrafted fresh patient tissues into NOD/Scid mice is approximately 30% [76]. Engraftment rates can differ according to hormonal sensitivity: estrogen receptor-positive (ER+) 9%, metastatic ER+ 16%, human epidermal growth factor receptor-2 positive (HER2+) 25%, metastatic HER2+ 33%, triple-negative tumor 58%, metastatic triple-negative tumor 85% with using NOD/SCID, NSG, or NRG mice. The start of xenograft growth can take several months. To stabilize xenograft growth, passaging through one or two mice can be performed [76]. It is also necessary to remember that PDX undergoes intense selection pressure [77] caused by replacing human stromal components with different mouse microenvironments [83].

In 2019, the National Cancer Institute launched a repository of PDX and *in vitro* patient-derived cell cultures. The European Molecular Biology Laboratory and the Jackson Laboratory recently launched a platform collecting clinical, genomic, and functional data from patient-derived cancer models [79].

Since patient-derived tissue is engrafted on highly immunodeficient mouse strains, these models do not enable studying the interaction between cancer cells and the immune system [78]. Recently, the induction of PDX in humanized mice (described in detail below) represents a more specific and reliable system [84].

Humanized mice. Humanized mice (HM) are immunodeficient mice engrafted with functional human cells or tissues. They provide a suitable tool for studying tumor development in the context of a human immune system. There are three main classes of humanized mice: A) human gene transgenic model – mice genome is engineered to express a specific human gene; B) humanized organ model – mice carrying a human organ; C) humanized immune system model – immunodeficient mice with the reconstituted human immune system [85]. It is necessary to consider the distinctions between the human and mouse immune systems. Significant differences were identified in T-cell signaling pathways, relative circulating lymphoid and myeloid cell levels, and innate immune mechanisms [86]. Mice with the humanized immune system and engrafted with human xenografts (CDXs or PDXs) represent a valuable preclinical model for the investigation and evaluation of potential therapies and studying molecular pathways and mechanisms of tumor development) [87–89].

Humanized models enable the recapitulation of normal human immune responses, antibody production against injected antigens and allospecific T-cell cytotoxicity [87]. The combination of HM with PDX enables the study of the complex immunobiological properties associated with cancer and provides a more specific assessment of cancer immunotherapies [90].

Several approaches are available for the humanization of mice's immune systems. The first is an intravenous or intraperitoneal injection of human peripheral blood leukocytes, suitable for studying T-cell function *in vivo.* This model is ready to use from the 5th day after humanization, but only for 4–6 weeks due to the development of xenogeneic graft-versus-host disease (GvHD) [91]. In NSG mice humanized by human peripheral blood mononuclear cells (PBMC), GvHD was described after 4–5 weeks. In the NSG-β2m$^{-/-}$ variant deficient in major histocompatibility complex type 1, GvHD was observed by 8 weeks post-engraftment [92]. Another approach is intravenous or intrafemoral application of human CD34^{+} hematopoietic stem cells (HSC). Mice must first be preconditioned with gamma irradiation or injection of busulfan to suppress their bone marrow function for efficient engraftment of administered hematopoietic cells. HSC can be derived from different sources, such as bone marrow, umbilical cord blood, fetal liver, or granulocyte colony-stimulating factor-mobilized peripheral blood. The CD34^{+} cell transplantation results in the presence of human B- and T- lymphocytes, myeloid, and antigen-presenting cells in the peripheral hematopoietic tissues of HM, but only in low levels of granulocytes, platelets, and red blood cells. Application of HSC is more time-consuming (10–12 weeks for cell differentiation) but provides a much more extended period for research (up to 45 weeks from busulfan initiation) [87, 93]. The subsequent infiltration of CD4^{+} and CD8^{+} T-cells in a spleen and tumor xenografts vary by tumor type and depends on the tumor rather than the stem cell donor [94]. The bone marrow/liver/thymus (BLT) model uses transplantation of the human fetal liver and thymus under the kidney capsule and intravenous injection of the autologous fetal liver HSC, which leads to the development of all human hematopoietic cell lineages. BLT model provides a complete and fully functional human immune system due to arranging the microenvironment of the human thymus. On the other hand, T-cells with an affinity for mouse major histocompatibility complex are active, leading to an incidence of xenogeneic GvHD [87, 90, 93].

A study comparing NSG and hu-BLT mice bearing oral or pancreatic cancer showed that hu-BLT mice better reflect the complexity of human cancer. NK cells in hu-BLT mice expanded and exerted functional activation upon activating signals [95].

Humanized NSG mice also represent a valuable model for evaluating the efficacy of anti-PD-1 therapy. In a study by *Rosato et al.*, tumors were induced 24 h after HSC transplantation, which enabled human immune cells to be exposed to tumor antigens during their development. Immune-humanization had no adverse effect on tumor growth. Tumor xenografts were predominantly infiltrated by myeloid cells recapitulating the TME of ER+ breast tumors [96].

Genetically engineered mice

Genetic engineering techniques have recently become an irreplaceable tool for producing mouse cancer models. Genetically engineered mice (GEMs) for cancer research were constructed in the early 1980s by replacing the mouse *myc* gene with the Mouse mammary tumor virus (MMTV) promoter/myc fusion recombinant gene and were termed oncomice. Recently, GEMs have included many mice predisposed to develop particular malignancies spontaneously [97, 98].

Genetic modification leads to the gain or loss of function. The gain of function means incorporating exogenous gene(s) into the mice genome. Animals with a gain-of-function mutation can be transgenic or knock-in, both with inserts in the genome but prepared by different methods (described in more detail below).

The transgenic mouse is generated by the microinjection of foreign DNA or infection with a viral vector containing the gene construct into a zygote or embryonic stem cells. During transgenesis performed in this way, selecting the exact site of transgenic DNA incorporation is impossible, so integration is a random method [99, 100]. Several well-established models were created this way, e.g., MMTV- Polyoma Virus middle T antigen (PyMT) transgenic mice and MMTV-Neu (C-erbB-2) mice – models frequently used to study metastatic breast cancer. They were developed by inserting PyMT or an activated Neu oncogene into the MMTV LTR promoter [101–103].

Knock-in mice are usually generated by inserting a targeting vector into a specific embryonic stem cell genome site via the Cre-loxP recombinase method [99, 100]. Implementing a bacteriophage Cre/loxP recombination system for manipulating mouse genome represents a milestone in developing genetically engineered models [104]. For example, knock-in mice with tissue-specific conditional expression of phosphoinositide-3-kinase (PI3K) catalytic subunit p110α, mutated allele (H1047R) were generated to investigate the initiation development and progression of mammary tumor growth [105]. It was demonstrated on mice with knock-in of steroid receptor coactivator-1 (SRC-1) that the homozygous P1272S single nucleotide polymorphism increases tamoxifen-induced bone protection after ovariectomy, reduces the growth of orthotopic breast tumors but increases metastases to the lungs [106].

The loss of gene function is commonly performed by a knock-out strategy for disrupting or silencing gene(s) of interest. Knocked-out mice are often used to research oncogenes, tumor-suppressor genes, and metabolic genes, and they help understand causes and relationships in cancer development. Knocked-out models also provide a potent tool for assessing targeted therapies [100].

According to the control of gene expression, genetic modifications are classified into constitutive and conditional. Constitutive modifications are present in all cells of animals. They can cause lethality, sterility, and developmental defects that lead to the model's failure. Defects like liver and kidney necrosis, often associated with reduced life span, can be observed [107]. Approximately 30% of gene knock-out mice have no viable descendants [108]. Therefore, spatial and temporal control of genes of interest was developed [99, 109].

Human cancer is caused by the accumulation of somatic mutations arising in a single cell. Therefore, genetically engineered mouse models (GEMMs) with deletion or mutation in entire animal cannot imitate the clonal nature of human cancer. Somatic-engineered mice represent the solution to this issue. Non-germline (somatic) genetically engineered mice carry genetically engineered alleles in somatic cells but not in germline cells. In general, the conditional knock-in GEMs primarily use tissue-specific promoters or termination sequences (STOP cassette) to stop the translation or transcription of insert [110]. In the knock-out and knock-in models, site-specific recombinases, bacterial Cre or yeast FLP enzymes, catalyze the recombination between specific sites to disrupt or insert the target gene [111].

The terms transgenic and genetically engineered mice are often used as synonyms. The National Institutes of Health National Cancer Institute describes the term transgenic as 'whose genome has been altered by the introduction of one or more foreign DNA sequences from another species by artificial means' [112]. The Federation of European Laboratory Animal Science Associations describes the term more specifically in its actualized guidelines for producing and nomenclature of transgenic rodents. Transgenic animals are defined 'by the presence of a stably introduced foreign (*in vitro* recombined) DNA sequence into animal's germline' [113].

To faithfully simulate human cancer, multiple approaches can be combined to create an engineered mouse model. Dual systems employing the MMTV-Flp transgene and the tamoxifen-inducible Cre recombinase were developed to delete or activate target genes in the mammary gland [114].

The essential role of the *E2A* gene, encoding E2A basic helix-loop-helix transcription factors modulating stemness, metastasis, and therapeutic resistance in breast cancer, was demonstrated on PyMT mice harboring a conditional deletion of the E2A [115].

In tumorigenesis, TME plays an essential role. Many GEMs rely on the Cre system, and Cre-loxP recombination cannot be applied in the engineering of stromal cells, which represent a crucial part of TME. Pdx1FlpO knock-in mouse (KPF mouse) expressing FlpO recombinase in pancreatic epithelial cells was established to circumvent this limitation. Combining the KPF mouse with any stroma-specific Cre provides an excellent *in vivo* tool to study mechanisms of crucial tumor-TME interactions [116].

The discovery of the clustered, regularly interspaced short palindromic repeats (CRISPR)-based genome editing approach led to the revolution in preparing non-germline GEMs. It enabled very efficient engineering of mice,

mimicking a broad spectrum of mutations found in human cancer. CRISPR/Cas technology was used to produce female mice that spontaneously developed mammary triple-negative tumors [117] or lobular breast carcinoma [118]. This technology enabled simultaneous knock-in and knock-out mice. Knock-in KRAS and simultaneously conditional p53 and LKB1 knock-out mice with sgRNA cassettes for managing gene expression were produced for observing lung tumor growth [119].

Recently, GEMMs for many types of cancer have become available. Using the transcriptional control of specific promoters, transgenic models can simulate spontaneous tumorigenesis by expressing one or more putative oncogenes [120].

Based on the above-mentioned mammary gland-specific PyMT overexpression, several breast cancer models have been established [102]. Small cell lung cancer (SCLC) is a disease with a poor prognosis, and it represents approximately 15% of lung cancer cases. Almost all tumors exert the loss of RB1 and TP53 tumor suppressor genes, and these mutations also carry SCLS GEMMs [121]. In CRC, many GEMs include *APC* mutation [27]. The increasing incidence and aggressive phenotype of pancreatic ductal adenocarcinoma (PDAC) gave rise to the development of models mirroring the disease. G12D *KRAS* mutation is present in more than one-third of patients suffering from PDAC. Mutated *KRAS* combined with *TP53* mutation was introduced to PDAC mouse models. Examples of GEMMs for the most frequent cancers are mentioned in Table 3.

Engineered mice also represent a valuable tool for immuno-oncology research. A study targeted at the efficacy of anti-PD1 treatment on myeloid tumors demonstrated the impact of Trem2 receptors on the TME via knock-out Trem2 mice [122]. The NINJA (iNversion Inducible Joined neoAntigen) model enables the inducible expression of neoantigens. It was established to overcome the leaky expression of neoantigens in the thymus. NINJA mice bypass central and peripheral tolerance mechanisms and exert cell immune responses to neoantigens expressed in peripheral tissues [123].

In conclusion, GEMMs enable cancer research at different stages and induce experimental tumors within an immunocompetent environment where cell-cell and cell-microenvironment interactions are present. They enable functional validation of the pathways of human tumors and confirm genetic alterations associated with progression and metastasis [109, 124, 125].

Some limitations in extrapolating findings to human malignancies arise from differences between timescales of disease burden and tumor growth in mice (up to 2 years) and humans (years/decades) [124].

In conclusion, future progress in cancer therapy depends on our understanding of the complicated events associated with the development of malignant tumors. Animal models enable the complex study of biological mechanisms

Table 3. Overview of GEMMs for selected types of cancer (according to [217], adapted).

Cancer type	Usual abbr.	Genotype	References
Breast cancer		MMTV-PyMT**	[103]
		MMTV-Erbb2^{V664G}	[218]
		MMTV-Cre;Trp53$^{flox/flox}$	[219]
Lung adenocarcinoma	KP	KrasL$^{SL-G12D/+}$;Trp53$^{flox/flox}$	[220]
Small cell lung cancer*	RP	Rb1$^{flox/flox}$;Trp53$^{flox/flox}$	[221]
	TKO	Rb1$^{flox/flox}$;Trp53$^{flox/flox}$;p130$^{flox/flox}$	[222]
Colorectal cancer	MIN	APC$^{Min/+}$	[223]
	iKAP	Villin-Cre^{ERT2};Tet-Kras^{G12D};Apc$^{flox/flox}$;Trp53$^{flox/flox}$	[224]
	KPC:APC	Apc^{tm1Tno};*Kras^{tm4Tyj}*; Tg(CDX2-cre/ERT2)752Erf	[225]
		Kras$^{LSL-G12V/+}$; Apc$^{flox/flox}$	[226]
Prostate cancer	NPK	Nkx3.1-Cre$^{ERT2/+}$;Pten$^{flox/flox}$;Kras$^{LSL-G12D/+}$	[227]
		Tg(TRAMP)8247Ng	[228]
		Tg(Pbsn-Ar*E231G)7353Ng	[229]
Pancreatic ductal adenocarcioma	KC	Kras^{G12D}, Pdx1 Cre	[230]
	KPC	Kras$^{LSL-G12D/+}$;Trp53$^{R172H/+}$;Pdx1-Cre	[144]
		Kras$^{LSL-G12D/+}$;Cdkn2a$^{flox/flox}$;Pdx1-Cre	[231]
	KPF	Pdx1FlpO^{ki};FSF-Kras$^{G12D/+}$,p53$^{frt/frt}$	[116]
Melanoma		Tyr::Cre^{ERT2};Braf$^{CA(V600E)/+}$;Pten$^{flox/flox}$	[232]
		Tyr::Nras^{Q61K};Ink4a$^{-/-}$	[233]
		Tyr::Cre^{ERT2};Braf$^{CA(V600E)/+}$;Pten$^{flox/flox}$;Ctnnb1$^{loxex3/loxex3}$	[234]
Ovarian cancer		Pax8-Cre;Brca1$^{flox/flox}$; Trp53$^{flox/flox}$;Pten$^{flox/flox}$	[235]
B-cell lymphoma		Tg(Cd79b-TCL1A)BKTeit	[236]

Notes: *for more models, look in [121]; **for more PyMT-based breast cancer models, look in [102]

of neoplastic growth, metastasis, and tumor-stroma interaction. Despite advances in *in vitro* systems and ethical issues, they are irreplaceable in developing new therapeutical strategies. Limitations of particular models represent a challenge to developing more accurate systems.

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