Chapter 149
Overview: Specialized Mouse Strains and Study of Gene Expression and Function

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The laboratory mouse has been an invaluable resource for basic and biomedical mammalian research. It is ideally suited for this purpose because of its small size, relatively short generation time, and comparatively low cost. These characteristics, plus the desire to control genetic variability, encouraged the development of a large number of different types of standard and highly specialized inbred mouse strains. In addition, a wide variety of genetically-manipulated mice have recently been produced in which specific genes have been added to, or deleted from, the genome. The ease with which these transgenic and knockout mice can be produced belies the difficulties involved in breeding them for rigorous study, particularly where several generations of mice traceable to the same founder may be required to complete the necessary work.

This overview, and the chapters in this section, provide an introduction to the laboratory mouse and its various forms. Included is a description of the production and use of inbred, mutant, congenic and recombinant inbred strains. In addition, transgenic and knockout mice are discussed with respect to the various ways in which these mice are bred, the implications that the use of different breeding schemes has for subsequent study, and methods that can potentially speed the development of strains with minimal intra-strain genetic variability. For greater detail on genetics and probability in mouse breeding systems see Green [1]; for an update on concepts and applications in mouse genetics see Silver [2]. Tables at the end of this overview and elsewhere in this section list many of the commonly available mouse strains and genetically-manipulated mice; resources for additional information are referenced.

Inbred strains

By convention, mouse strains that were started by crossing two unrelated mice and then inbreeding by brother-sister mating for 20 or more consecutive generations are designated as inbred strains [3, 4]. At 20 generations, the probability that the strain carries residual heterozygosity is 0.014, which means alleles at roughly 1% of the loci are likely to be different and will segregate in the progeny. After an additional 40 generations of incrossing,[1] strains essentially reach 100% homozygosity [5]. Members of an inbred strain are thus genetically identical and can be used to explore the influence of experimental or environmental variability on a given trait while keeping genetic variability constant. Experience has shown that mice in strains inbred for 20 generations are usually sufficiently similar for most studies. In addition, even with highly inbred strains, spontaneous mutations can occur and are either quickly lost or fixed.

Inbred strains are particularly important because they allow the use of a standardized resource by many different laboratories and permit repetition of experiments at different points in time. A wide variety of inbred strains are used in immunology, the most common being A, AKR, BALB/c, CBA, C3H, C57BL, DBA, and SJL and their substrains [6]. For a more comprehensive listing of inbred strains and their characteristics, see [7, 8]. Some of these strains, notably C57BL, have been used in the production of even more highly specialized strains, which are discussed below. A new set of inbred strains, derived from the autoimmune strains NZB and NZW and which exhibit different patterns of disease, may also be of interest [9].

Non-inbred mice

Non-inbred mice are also used in basic research. Examples include: mice that are *random bred* so that the chance that any male or female will be selected for breeding is equal or mice that are *outbred* where matings are set up between genetically unrelated individuals, usually to maximize heterozygosity and hybrid vigor. For a discussion of these and other types of mice and breeding systems, see Green [1, 10] and Klein [11]. Non-inbred mice are used when genetic variability is desired or is considered to be irrelevant.

Mutant strains

Strains known to carry a mutated gene are referred to as mutant strains. Mutant strains commonly arise when a spontaneous or an induced mutation occurs and is fixed by inbreeding. When an inbred mutant strain differs from its progenitor strain at a single locus, the strains are referred to as *coisogenic strains* [12]. The close genetic relationship between coisogenic strains makes them particularly useful for studying the function of a single gene and its interaction with other genes. A listing of H-2 mutant strains is included in the chapter by Melvold (entitled "H-2 Mutations"); and a description of single gene mouse models of immunodeficiency and autoimmune diseases is included in Chapter 150. For additional listings, see [13, 14]; for a discussion of transgenic and knockout mice, see below.

Congenic strains

Congenic strains are inbred strains that are genetically identical except for differences in a limited segment of chromosome [12, 15]. This segment of chromosome contains a marker gene and

[1] An *incross* is a mating between genetically identical individuals, such as members of the same inbred strain, or between individuals that are homozygous for the same allele at a given locus (e.g. A/A x A/A or a/a x a/a).

closely linked[2] genes that have been selectively bred onto a desirable inbred background. Congenic strains were initially produced to study particular alleles on specific genetic backgrounds and to contrast the behavior of a pair of alleles where only they (and closely-linked genes) differ between the test strains. Current methodologies for creating genetically-manipulated mice have now greatly increased the number of congenic strains, since breeding a newly-engineered gene onto an inbred background is one way to develop genetically-homogeneous mice carrying the engineered gene. Congenic strains are usually produced by initially crossing a donor mouse carrying the desired gene (allele) to an inbred recipient strain and then repeatedly backcrossing[3] to the same recipient strain for at least 10 generations. The recipient but not the donor mouse must be from an inbred strain. At each backcross generation, progeny that express the desired gene are selected. Heterozygous progeny from the final backcross are then intercrossed[4] and offspring homozygous for the selected gene are used as founders of the new congenic strain.

With this breeding scheme, donor derived genes that are unlinked[5] to the selected gene are rapidly lost. Half of those that remain are lost at each backcross generation. Thus, the frequency of unlinked donor genes remaining after n backcrosses is $1/2^n$. In contrast, genes linked to the selected gene persist until crossovers separate them. The rate at which linked genes are lost is dependent on their proximity to the selected gene. After 10 backcross generations, the new congenic strain and the recipient strain used for backcrossing are 99.9% identical at unlinked loci and differ at the selected marker locus and at tightly linked loci, usually mapping within about 10 centimorgans on either side of the marker locus.

In practice, congenic strains produced by backcrossing for 10 generations are usually similar enough to the recipient strain for most studies. However, some laboratories opt to continue backcrossing for another 5–10 generations to further reduce the disparity at loci closely linked to the marker locus and at the few remaining unlinked loci. In addition, over time, the new congenic strain and the recipient strain will begin to differ from one another due to fixation of random spontaneous mutations [5]. Therefore, some laboratories also cross the congenic strain to the recipient strain after every 10–20 generations of incrossing and rederive the congenic strain.

Schemes for decreasing the number of backcross generations required to generate congenic strains are currently under development. In essence, these schemes utilize genetic markers spread throughout the genome to select backcross mice for breeding that have the fewest alleles derived from the strain that donates the desired gene. In 1967, Klein and Herzenberg [16] used skin graft survival (from the backcross animal to backcross strain) to reduce the number of backcross generations required to develop a usable immunoglobulin heavy chain gene congenic strain to 5; however, the method was too cumbersome for routine use. In a new approach to this problem, molecular genotyping methods are being developed that should soon make it possible to develop congenic mouse strains quickly and easily [17, 18]. This will be particularly important for moving genetically-engineered genes (transgenic and knockout) onto defined genetic backgrounds (see below).

Table 149.1. Selected H-2 congenic strains*

Congenic Strain	H-2	Recipient Strain	Donor Strain	Producer
BALB.A	a	BALB/cAn	A/J	Lil
B10.A		C57BL/10SnSg	A/WySnSg	Sg
C3H.A		C3H/HeHa	A/HeHa	Ha
A.BY	b	A/WySn	Brachyury	Sn
BALB.B		BALB/cAn	C57BL/10Sn	Lil
C3H.B10		C3H/HeJSf	C57BL/10J	Sf
C3H.SW		C3H/HeDiSn	Swiss	Sn
D1.LP		DBA/1J	LP/J	Sn
B6-H-2^d	d	C57BL/6By	BALB/cBy	By
B10.D2		C57BL/10Sn	DBA/2J	Sn
D1.C		DBA/1J	BALB/cJ	Sn
A.CA	f	A/WySn	Caracul	Sn
B10.M		C57BL/10Sn	Non-inbred	Sn
BALB.K	k	BALB/cAn	C3H/An	Lil
B6.C3H		C57BL/6J	C3H/An	Lil
B6-H-2^k		C57BL/6JBoy	AKR/JBoy	Boy
B10.AKR		C57BL/10J	AKR/J	Lil
B10.BR		C57BL/10Sg	C57BR/c	Sg
B10.K		C57BL/10J	CBA/J	Sf
B10.P	p	C57BL/10Sn	P/J	Sg
B10.G	q	C57BL/10SnSg	Grey lethal	Sg
B10.Q		C57BL/10SnSg	DBA/1J	Sg
C3H.Q		C3H/JSf	STOLI/Lw	Sf
B10.R111 (7INS)	r	C57BL/10Sn	R111/WyJ	Sn
A.SW	s	A/WySn	Swiss	Sn
BALB.S		BALB/cBy	SJL/J	Mrp
B10.S		C57BL/10SnSg	A.SW/Sn	Sg
B10.PL (73NS)	u	C57BL/10SnSg	PL/J	Sn
B10.SM (70NS)	v	C57BL/10Sn	SM/J	Sn

* Adapted from Klein [19] and Shreffler [30]. For complete list of H-2 congenic strains, including H-2 recombinant strains, see [19]. B10 = C57BL/10, B6 = C57BL/6.

Congenic strains have been extremely useful for studying the behavior of different alleles at a single locus or closely linked loci on the same genetic background. They have also been used for testing for close linkage of a particular gene to the gene selected in making the congenic strain. Since some congenic strains may also differ at unlinked loci (even after 10 backcross generations, there is still a 0.1% chance that unlinked genes derived from the mouse providing the selected marker gene are present), putative linkage identified in this way should be confirmed by segregation analysis to formally prove that the two genes in question are closely associated.

A number of different types of congenic strains have been widely used in immunology. These include the H-2 congenic strains listed in Table 149.1 and minor histocompatibility congenic strains described in Chapter 152. Other sets of congenic strains differ for immunoglobulin allotypes or cellular alloantigens (see [19] for listings). For H-2 and immunoglobulin allotype recombinant haplotypes and strains, also see [19]. Several double congenic strains, differing at *H-2* and at a segment of chromosome marked by an unlinked locus, have also been produced [19].

[2] Linked genes are genes on the same chromosome.

[3] A *backcross* is a mating between an individual that is heterozygous at a given locus and an individual that is homozygous for one of the two parental alleles at that locus (e.g., A/a x A/A or A/a x a/a).

[4] An *intercross* is a mating between individuals that are heterozygous for the same two alleles at a given locus (e.g., A/a x A/a).

[5] *Unlinked* genes are genes on different chromosomes.

Table 149.2. Selected recombinant inbred (RI) strains*

RI Strain	Progenitor Strains ♀	Progenitor Strains ♂	Number of Strains	Holder
AXB	A/J	C57BL/6J	41	JAX
BXA	C57BL/6J	A/J		
AKXD	AKR/J	DBA/2J	25	Taylor
AKXL	AKR/J	C57L/J	18	Taylor
BXD	C57BL/6J	DBA/2J	26	Taylor
BXH	C57BL/6J	C3H/HeJ	12	Taylor
CXB	BALB/cBy	DDK	13	JAX
CXDD	BALB/cByJ	DDK	24	Guenet
DDXC	DDK	BALB/cByJ		
CXJ	BALB/cKe	SJL/J	10	JAX
CXS	BALB/cHeA	STS/AHilgers	14	Hilgers
LXPL	C57L/J	PL/J	11	Taylor
NX8	NZB/Icr	C58/J	12	Riblet
NX129	NZB/B1NJ	129/J	10	JAX
NXSM	NZB/B1NJ	SM/J	16	Eicker
OXA	020/A	AKR/FuRdA	14	Hilgers
SMXA	SM/J	A/J	27	Nishimura
SWXJ	SWR/Bm	SJL/Bm	14	Beamer
SWXL	SWR/J	C57L/J	7	JAX
129XB	129/SvPas-*C*	C57BL/6JPas	13	Guenet

* In some cases, DNA only may be available. See Taylor [21] for additional RI strains and for most recent update on loci characterized and strain distribution patterns of alleles. Adapted from Taylor [21] and Silver [2].

Recombinant inbred strains

Recombinant inbred (RI) strains are produced by inbreeding (brother × sister mating) unselected F2 mice derived from crosses between two inbred strains [5, 20, 21]. This breeding scheme results in the initial random assortment and subsequent fixation of genes from the two progenitor strains. When inbreeding is complete, each RI strain is homozygous for either the maternal or paternal progenitor strain allele at any given locus. Since these alleles assort randomly, no two RI strains carry the same set of alleles when all loci are taken into consideration. Consequently, no two RI strains are identical.

Several well characterized sets of RI strains have been developed in which the progenitor origins of alleles at many of the loci have been established. Comparison of expression of alleles at a given, unmapped gene in the RI strains with the pattern of expression of alleles derived from the progenitor strains thus provides a rapid scan for genes likely to segregate together. RI strains have been very useful for conducting genetic linkage analyses, gene mapping, and analysis of complex genetic traits. As with congenic strains, putative linkage should be confirmed by segregation analysis, particularly if the number of RI strains in a given set is limited. A selected list of strain combinations used to generate sets of RI strains is included in Table 149.2. For a more complete listing of RI strains and a listing of strain distribution patterns of alleles, see [21].

In addition to RI strains, recombinant congenic (RC) strains are also available [22]. These strains are produced in the same way as RI strains, except that the F1 is backcrossed twice to one of the progenitor strains before inbreeding. This limits the amount of variation between the RC strains and the progenitor strain used for backcrossing. RC strains have been particularly useful in the analysis of complex quantitative genetic traits. For a listing of RC strains and strain distribution patterns of alleles, see [23].

Transgenic and knockout mice

The production and use of transgenic and knockout mice is discussed in detail in several places in this Handbook, e.g., see the preceding section, "Transgenic, Knockout, and Gene Targeted Mice." Clearly, the ability to tailor-make mutants of choice has added an exciting and important new dimension to basic science. Here, we discuss these mice with regard to the breeding schemes that can be used to propagate them and to decrease genetic variability amongst mice carrying the same genetically-engineered gene. For simplicity, the focus will be on knockout mice.

From a genetic viewpoint, the ideal way to produce a knockout mouse is by manipulation of embryonic stem (ES) cells from an inbred strain followed by crossing to the *same* inbred strain from which the ES cells were derived. F1 mice from this cross that are heterozygous for the manipulated gene can then be intercrossed to produce F2 progeny that are homozygous for the manipulated gene. The F1 and F2 mice are homozygous and identical at all other loci. Provided the knockout is not lethal, the homozygous F2 mice can be incrossed by brother-sister mating thereafter as a typical inbred strain. This production scheme rapidly produces an inbred knockout strain that is coisogenic with the embryonic stem cell donor strain: all progeny within each strain are genetically identical, and the two strains differ only for expression of the manipulated gene.

Producing knockout mice by outcrossing[6] to another inbred strain (not the ES cell donor strain) is an entirely different matter. F1 progeny from this cross are heterozygous at all loci and are genetically distinct from either progenitor strain. In the second generation, usually produced either by intercrossing the F1 mice to produce F2 progeny or by backcrossing the F1 mice to one of the two progenitor strains, all progeny will differ genetically from each other as well as from the progenitor strains. The difference in background genes in mice bred this way can significantly influence the phenotype of the knockout mice. Littermates are not adequate controls because background genes segregate independently. Successive brother-sister matings of F2 mice begins the establishment of one or a series of RI lines, which can take many generations to inbreed sufficiently to remove genetic variability. Even then, no two founder strains produced in this way can be expected to be identical.

Unfortunately, because the 129 strain from which the commonly-used embryonic stem cell is derived does not breed well, most of the knockout mice produced to date were initially outcrossed to another strain and thus do not have a standardized genetic background. The best way to recover in this situation is to produce a congenic strain carrying the knockout gene by crossing existing mice to an inbred strain (ideally, backcrossing to the donor strain for the ES cells or to the strain used in the initial outcross; alternatively, crossing to a commonly used inbred strain such as C57BL) and repeatedly backcrossing the progeny to the same inbred strain. In cases where the manipulated gene is located in a segment of chromosome of the same origin as the backcross strain, the backcross and congenic strains will have a high

[6] An *outcross* is a mating between genetically unrelated individuals or between individuals that carry different alleles at a given locus (e.g., A/A x a/a).

Table 149.3. Selected targeted mutations*

Protein Locus	Phenotype	Initial Report(s)
Abl	Perinatal lethality; multiple developmental defects; lymphopenia	[31–33]
Apolipoprotein E	Hypercholesterolemia and atherosclerosis	[34–36]
B-cell lineage-specific activator protein (BSAP) (*Pax5* gene)	Neonatal lethality; posterior midbrain morphological defects; B-cell development disrupted	[37]
B7 (CD28 ligand)	Decreased co-stimulated response to alloantigen	[38]
Bcl-2	Neonatal lethality; lymphocytopenia; multiple growth defects; tremor; melanin synthesis defect, polycystic kidneys	[39, 40]
Bcl-x	e13 lethal; neuronal and hematopoietic apoptosis	[41]
Bmi-1	Hematopoietic defects; ataxia; seizures; posterior transformation	[42]
Calcium-calmodulin-dependent protein kinase IIα (α-CaMKII)	Deficient hippocampal long-term potentiation and long-term depression; impaired spatial learning; seizure prone; abnormal fear and pain responses	[43, 44]
CD2	No defects observed	[45]
CD4	Decreased helper T-cell activity	[46, 47]
CD8-α (Lyt-2)	Absence of cytotoxic T cells	[48]
CD8-β	Reduced thymic maturation of CD8+ T cells	[49]
CD18 *partial*	Mild granulocytosis; impaired immune responses	[50]
CD23	Defects in IgE regulation and IgE-mediated signalling.	[51–53]
CD28	Decreased T-cell response to lectins; decreased IL-2Rα, IgG1, and IgG2b	[54]
CD40	Defects in thymus-dependent humoral immunity	[55]
CD40 ligand (CD40L)	Defects in thymus-dependent humoral immunity	[56, 57]
CD45 exon 6	Impaired T-cell maturation	[58]
Corticotropin releasing hormone (CRH)	Decreased adrenal corticosterone release in response to stress; offspring of homozygous mother perinatal lethal due to lung dysplasia	[59]
Cyclic AMP-responsive element-binding protein (CREB) α and δ isoforms	Lack late phase of CA1 long-term potentiation; decreased long-term memory; increase in CREM	[60]
Cytochrome b, phagocyte-specific oxidase	Increased susceptibility to pathogens; model for X-linked chronic granulomatous disease	[61]
DNA polymerase β *modification*	Demonstrates feasibility of tissue-specific disruption using *Cre-loxP* system	[62]
E2A	Neonatal lethality; growth retardation; lack B cells	[63, 64]
Fc receptor γ subunit	Pleiotropic effector cell defects	[65]
Fgr	No defects observed	[66]
Fos	Perinatal lethality; osteopetrosis; defects in gametogenesis and hematopoiesis	[67, 68]
Fyn ($p59^{fyn}$)	Signaling defect in thymocytes but not peripheral T cells; impaired long-term potentiation; abnormal olfactory glomeruli and hippocampal morphology; suckling defect	[69–71]
Fyn ($p59^{fynT}$)	Signaling defective in thymocytes but not peripheral T cells	[72]
Granulocyte colony-stimulating factor (G-CSF)	Granulopoietic defects	[73]
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Pulmonary pathology; apparently normal hematopoesis	[74, 75]
Granzyme B	Cytotoxic T-lymphocyte defect	[76]
Growth-associated protein-43 (GAP-43)	Perinatal and neonatal lethality; abnormal path-finding at the optic chiasm	[77]
Hck	Phagocytosis impaired; increased lyn activity	[66]
Hox 11	No spleen	[78]
Hox-A3 (Hox 1.5)	Perinatal lethal; athymic; aparathyroid; throat, heart, arterial, and craniofacial abnormalities	[79]
Ik (Ikaros gene products)	Neonatal lethality; reduced size; lymphocytes and lymphoid progenitors absent.	[80]
Immunoglobulin D	Reduced number of mature B cells	[81, 82]
Immunoglobulin E	No defects observed	[83]
Immunoglobulin E receptor α chain	Resistant to cutaneous and systemic anaphylaxis	[84]
Immunoglobulin κ intron enhancer	No Igκ rearrangement; slight reduction in splenic B cells	[85]
Immunoglobulin κ light chain	Reduced number of B cells	[86, 87]
Immunoglobulin κ replaced with human constant region	B cells produce human-mouse chimeric κ-bearing antibodies	[88]
Immunoglobulin μ membrane exon	Absence of B cells	[89]
Intercellular adhesion molecule-1 (ICAM-1)	Leukocytosis; impaired inflammatory and immune responses	[90, 91]
Interferon α/β receptor	Anti-viral defense impaired.	[92]
Interferon γ	Multiple immune response defects	[93]
Interferon γ receptor	Multiple immune response defects	[94]
Interferon regulatory factor 1 (IRF-1)	Decreased $CD4^-8^+$ T cells; impaired interferon γ response	[95, 96]
Interferon regulatory factor 2 (IRF-2)	Premature lethality; defects in hematopoesis; immunocompromised	[95]
Interleukin-1β-converting enzyme (ICE)	Decreased IL-1 production; resistance to endotoxic shock	[97]
Interleukin-2 (IL-2)	Premature lethality; normal T-cell subset composition, but dysregulated immune system; inflammatory bowel disease	[98]
Interleukin-2 receptor γ chain (IL-2Rγ)	Lymphopenia; absence of NK cells	[99]
Interleukin-4 (IL-4)	$CD4^+$ (Th2)-produced cytokines reduced; serum IgG1 and IgE reduced	[100, 101]
Interleukin-6 (IL-6)	Higher bone turnover rate; no bone loss when ovariectomized; immune defects; reduced IgA producing cells	[102, 103]

Table 149.3. Continued

Protein Locus	Phenotype	Initial Report(s)
Interleukin-7 receptor (IL-7R)	Early lymphocyte expansion severely impaired	[104]
Interleukin-8 receptor (IL-8R)	Lymphadenopathy and splenomegaly; increased B cells and neutrophils	[105]
Interleukin-10 (IL-10)	Reduced growth; anemia; chronic enterocolitis	[106]
Invariant chain (Ii)	MHC class II transport and function defective; reduced $CD4^+$ T cells	[107–109]
J_H-Eμ immunoglobulin heavy chain (joining and enhancer regions)	Suppression of switch recombination at μ gene; absence of B cells	[110]
J_H immunoglobulin joining region	Absence of B cells	[111, 112]
J_H replaced with rearranged V region	Rearranged V transgene expressed in all B cells	[113]
$\lambda 5$	Defective B cell development	[114]
L-Selectin	Defects in lymphocyte homing and leukocyte rolling and migration.	[115]
Lck ($p56^{lck}$)	Thymic atrophy; reduced $CD4^+8^+$ T cells; very few mature T cells; immunocompromised	[116]
Leukemia inhibitory factor (LIF)	Decreased hematopoietic stem cells; deficient neurotransmitter switch *in vitro* but normal sympathetic neurons *in vivo*; blastocysts do not implant in homozygous mother	[117, 118]
Lipoxygenase (5-lipoxygenase)	Resistance to certain inflammatory agents	[119, 120]
LMP-7	Defects in MHC class I expression and antigen presentation	[121]
Major histocompatibility complex class II Aα (MHC II Aα)	Decreased $CD4^+8^-$ T cells; immune defects	[122]
Major histocompatibility complex class II Aβ (MHC II Aβ)	Decreased $CD4^+8^-$ T cells; deficient cell-mediated immunity; some B-cell dysfunctions; inflammatory bowel disease	[123, 124]
Microglobulin (β2-microglobulin)	Decreased $CD4^-8^+$ T cells	[125–127]
NF-IL6	Defects in macrophage bactericidal and tumoricidal activities	[128]
NF-κB p50 subunit	Multifocal defects in immune responses	[129]
Oct-2	Perinatal lethal; decreased IgM+ B cells	[130]
p53	Spontaneous tumors; thymocytes resistant to apoptosis by radiation or etoposide	[131–133]
Perforin	Impaired CTL and NK cell function; unable to clear LCMV infection	[134–136]
Pim-1	Impaired response of early B cells to interleukin-7 and steel factor; impaired response of bone marrow-derived mast cells to interleukin-3	[137]
PU.1	e16–18 lethal; defect in development of lymphoid and myeloid cells	[138]
Recombination activation gene 1 (RAG-1)	Absence of mature B and T lymphocytes	[139, 140]
Recombination activation gene 2 (RAG-2)	Absence of mature B and T lymphocytes	[141]
RelB	Multiorgan inflammation; hematopoietic defects	[142, 143]
Selectin (P-selectin)	Defects in leukocyte behavior; increased neutrophils	[144]
sγ1 class switch region	Shutdown IgM-IgG class switch at that allele	[145]
T-cell factor-1 (TCF-1)	Defect in thymocyte development	[146]
T-cell receptor α (TCRα)	Loss of thymic medullae; devoid of single positive thymocytes; no $\alpha\beta$ T cells; inflammatory bowel disease	[147, 148]
T-cell receptor β (TCRβ)	Reduced % $CD4^+8^+$, and total number of thymocytes; inflammatory bowel disease	[147]
T-cell receptor δ (TCRδ)	Absence of $\gamma\delta$ T cells	[149]
T-cell receptor η (TCRη)	Neonatal lethal; (partial knockout of Oct-1 on opposite strand)	[150]
T-cell receptor η/ϕ (TCRη/ϕ)	Lower birth rate; T cells develop normally; (partial knockout of Oct-1 on opposite strand)	[151]
T-cell receptor ζ (TCRζ)	Decreased $CD4^+8^+$ thymocytes and single positive T cells; low TCR expression	[152–154]
T-cell receptor ζ/η (TCRζ/η)	Decreased $CD4^+8^+$ thymocytes and single positive T cells; low TCR expression	[155]
Tal-1 (SCL)	e9–10 lethal; hematopoietic defect	[156]
Terminal deoxynucleotidyl transferase (TdT)	Decreased TCR diversity	[157]
Transforming growth factor α (TGFα)	Hair follicle and eye defects; allelic with waved-1 (wa-1)	[158, 159]
Transforming growth factor β1 (TGFβ1)	Neonatal lethal; multifocal inflammatory disease	[160, 161]
Transporter associated with antigen processing 1 (TAP1)	MHC class I transport and function defective; lack $CD4^-8^+$	[162]
Tumor necrosis factor receptor 1 (TNF-R-1) (p55)	Resistant to endotoxic shock; susceptible to *Listeria* infection	[163, 164]
Tumor necrosis factor receptor 2 (TNF-R-2) (p75)	Resistance to TNF-induced necrosis and death	[165]
Tumor necrosis factor-β (TNF-β) (lymphotoxin)	No Peyer's patches or lymph nodes; increased IgM^+ B cells	[166]
Vascular cell adhesion molecule-1 (VCAM-1)	e8–10 lethality; chorioalantoic fusion disrupted; surviving adults have elevated mononuclear leukocytes	[167]

* Modified with permission from Brandon E. P., Idzerda R. L., McKnight G. S. Targeting the mouse genome: a compendium of knockouts (Parts I–III). Current Biology 1995, Vol 5 Nos. 5–8. Any information or comments on the table directed to Brandon et al can be submitted through the World Wide Web: go to http://www.cursci.co.uk/BioMedNet/biomedbi.html, and click on General Biology.

likelihood of being coisogenic. The number of backcross generations required to develop the strain can be decreased by application of new molecular techniques currently being developed to speed the establishment of congenic strains (see Congenic strains, above).

Similar concerns exist for the breeding and use of transgenic mice, particularly those produced by genetic manipulation of ova from non-inbred or hybrid mice. Production of congenic strains from knockout and transgenic mice is part of the Jackson Laboratory's Induced Mutant Resource program, which includes over 140 strains that are generally available to the scientific community [24]. A selected list of knockout mice of interest to immunologists is included in Table 149.3. For a more complete listing of knockout mice, see [25], and for a computerized database for transgenic and knockout mice (TBASE), see [26].

In the future, the laboratory mouse will continue to be an indispensable resource, even more so than ever before. Many of the current generation transgenic and knockout mice remain to be fully characterized, and many more will be produced. With new technologies on the horizon (e.g., gene replacement (knock-in mice) [27], targeted gene duplication [28]), additional types of mutants will be generated. These resources have and will continue to facilitate tremendous advances in our understanding of basic biological systems. This, in turn, will allow the development of better regimens for treating and preventing human disease and will improve our overall quality of life [29].

Acknowledgments

The authors gratefully acknowledge critique of this overview and suggestions by Lori Flaherty, Pam Swiatek, and Larry Mobraaten. The assistance of Ellen Shippey and Luba Mintas in the preparation of this manuscript is greatly appreciated. This work was supported in part by NIH grants AI-14349 to Donal B. Murphy and HD-01287 and LM-04836 to Leonore A. Herzenberg.

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