REVIEW

Molecular basis of mouse developmental mutants

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Throughout this century, the characterization of phenotypic variants of the mouse has played an invaluable role in the establishment of mammalian genetics and in furthering our understanding of embryology and the cellular mechanisms underlying mammalian development. Until very recently, molecular characterization of these mutants was hampered by the size and complexity of the mouse genome and by the difficulties in translating complex developmental phenotypes into feasible cloning strategies. With recent advances in recombinant DNA technology and improvements in genetic and physical mapping methodologies, the molecular definition of this large collection of mutants is now possible.

Two broad genetic strategies have been taken to understand mammalian development at the molecular level (Table 1). Genes that may play critical roles in murine development have been identified by (1) cloning murine homologs of genes essential for normal development in other organisms (for reviews, see Holland and Hogan 1988; Kessel and Gruss 1990), (2) identifying genes involved in cellular proliferation and tumorigenesis (for reviews, see Adamson 1987; Mercola and Stiles 1988; Boettiger 1989), and (3) screening techniques based on differential expression patterns in the embryo (Allen et al. 1988; Kothary et al. 1988; Gossler et al. 1989). The roles played by such genes in mammals have been largely inferred from the biochemical properties of their protein products, their expression patterns in the developing embryo, and by extrapolation from the available genetic evidence of their homologs in other experimental systems, particularly *Drosophila melanogaster*. Direct genetic analysis of the function of such genes in mammalian development is now possible by generating gain or loss of function of mutations through the random or targeted insertion of exogenous DNA into the mouse germ line (for reviews, see Jaenisch 1988; Capecchi 1989; Rossant and Joyner 1989; Westphal and Gruss 1989).

A second and complementary approach is provided by the molecular analysis of existing mouse mutants (Table 1). Many of the 1300 or so genetic loci currently mapped in the mouse were identified originally on the basis of a mutant developmental phenotype (Lyon and Searle

1989). This collection of "classic" mutants has been recently augmented by the use of highly efficient chemical mutagens (for review, see Rinchik 1991) and by the production of insertional mutations by transgenic techniques. The rapid increase in the number of cloned genes, coupled with improved genetic and physical mapping techniques (Taylor 1978; Avner et al. 1988; Schlessinger 1990; Copeland and Jenkins 1991), has made the molecular definition of such mutant mouse strains an attainable goal.

Table 1. *Molecular genetic analysis of mammalian development*

A. Genotype → phenotype

1. Homologs of genes implicated in other developmental systems
2. Genes involved in cellular proliferation and tumorigenesis
3. Screens based on differential gene expression in the embryo
4. Generation of novel germ-line mutations in cloned genes
 - i. Gain-of-function/dominant-negative transgenes
 - ii. Gene targeting
 - iii. Cell ablation
 - iv. Antisense RNA

B. Phenotype → genotype

1. Spontaneous mutations
2. Radiation-induced mutagenesis
3. Chemical-induced mutagenesis
4. Transgene insertional mutagenesis
5. Molecular definition of mutant phenotypes
 - i. Association with previously cloned genes
 - ii. Physical mapping starting with closely linked marker

Two overlapping strategies are offered toward the further understanding of the molecular basis of development in the mouse. The first (genotype → phenotype) involves the isolation of potential development genes using a variety of criteria, followed by analysis of the phenotypic consequences of mutations in such genes by use of germ-line manipulation techniques. The second (phenotype → genotype) involves the utilization of existing, or generation of novel, mutant mouse strains that can then be defined either by association with a previously cloned gene or by physical mapping procedures (for examples, see text).

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In this review we consider some recent examples that serve to illustrate how molecular analyses of existing mouse mutant stocks are providing insights into the developmental functions of a variety of growth factors, receptors, and putative or known transcription factors. This work is also revealing the domains and residues critical for in vivo functions of these protein families, providing models for the types of mutations that may be usefully employed in the generation of gain- or loss-of-function mutations in the mouse germ line. In addition, novel protein families essential for normal development are being identified on the basis of the phenotypic consequences of their mutation.

Direct association of cloned genes with mutant loci

The rapid increase in cloning and mapping of genes in both man and mouse is resulting in increasingly detailed genetic and physical linkage maps, providing cloned markers close to specific mutant loci. In some cases, a connection can be made between the phenotypic properties of the mutant locus and the known biochemical properties and/or expression pattern of a closely linked gene, providing a basis for further investigation of the relationship between the mutant locus and a candidate gene. A relatively large number of mutant loci have been successfully identified in this way (Table 2).

Table 2. Mouse mutant loci for which candidate genes have been identified

Locus (name)	Mutated gene	Cell types or stage of development affected	Reference
<i>Direct association with cloned genes</i>			
<i>b</i> (brown)	tyrosinase-related protein 1	melanocytes	Jackson et al. (1990); Zbarsky et al. (1990)
<i>c</i> (albino)	tyrosinase	melanocytes	Kwon et al. (1987)
<i>dw</i> (Snell's dwarf)	<i>pit-1</i>	anterior pituitary	Camper et al. (1990); Li et al. (1990)
<i>jp</i> (jumpy)	myelin proteolipid protein	axons in CNS	Dautigny et al. (1987)
<i>mdx</i> (X-linked muscular dystrophy)	dystrophin	muscle fibers	Hoffman et al. (1987); Sicinski et al. (1987)
<i>op</i> (osteopetrosis)	CSF-1	osteoclasts, macrophages	Yoshida et al. (1990)
<i>Ph</i> (Patch)	platelet-derived growth factor receptor α -subunit	melanoblasts, hematopoietic cells, recessive embryonic lethal	Stephenson et al. (1990)
<i>rd</i> (retinal degeneration)	cGMP phosphodiesterase	rod cells in retina	Bowes et al. (1990)
<i>shi</i> (shiverer)	myelin basic protein	axons in CNS and PNS	Readhead et al. (1987)
<i>Sl</i> (Steel)	Kit ligand	hematopoietic cells, germ cells, melanoblasts	Copeland et al. (1990); Huang et al. (1990); Zsebo et al. (1990b)
<i>spf</i> (sparse fur)	ornithine transcarbamylase	skin, hair, liver, colon, intestine	Veres et al. (1987)
<i>un</i> (undulated)	<i>Pax-1</i>	vertebral sclerotome	Balling et al. (1988)
<i>W</i> (Dominant white spotting)	<i>c-kit</i>	hematopoietic cells, germ cells, melanoblasts	Chabot et al. (1988); Geissler et al. (1988)
<i>Insertional mutagenesis</i>			
<i>d</i> (dilute)	novel myosin heavy chain	melanocytes, neurological	Mercer et al. (1991)
<i>ld</i> (limb deformity)	novel (formins)	limb bones, kidney development	Woychik et al. (1985, 1990)
<i>Mov-13</i> , (Moloney leukemia virus-13)	α -1 procollagen I	late gestation lethal	Schnieke et al. (1983)
<i>Mov-34</i> (Moloney leukemia virus-34)	novel (Mov34)	postimplantation lethal	Soriano et al. (1987); Gridley et al. (1990)
<i>Mpv17</i>	novel (Mpv17)	adult kidney function	Weiher et al. (1990)
<i>Physical mapping</i>			
<i>T</i> (Brachyury)	novel (pme75)	mesoderm formation, notochord development	Herrmann et al. (1990)
<i>Tdy</i> (Testis determining-Y)	novel (Sry)	testis determination	Gubbay et al. (1990)

Murine developmental loci for which mutated genes have been identified are shown. Molecular analyses of many other transgene insertional mutants have been initiated, but the gene products of such loci remain to be identified. Some are known to be allelic with previously identified loci, including *downless* (*dl*) (Shawlot et al. 1989), *dystonia musculorum* (*dt*) (Kothary et al. 1988), *Purkinje cell degeneration* (*pcd*) (Krulowski et al. 1989), *extra toes* (*Xt*) (Pohl et al. 1990), *hotfoot* (*ho*) (Gordon et al. 1990), *pygmy* (*pg*) (Xiang et al. 1990), and *microphthalmia* (*mi*) (J. Krakowsky and J. Lingrel, pers. comm.; H. Arnheiter, Y. Hara, L. Forrester, and A. Bernstein, unpubl.). Others, such as *MyK103* (Wilkie and Palmiter 1987), *sympatric spermatids* (*sys*) (MacGregor et al. 1990), and *H β 58* (Radice et al. 1991) represent novel developmental loci. An additional *Sl* allele has also been generated by transgene insertional mutagenesis (Keller et al. 1990).

Mutations at the *Dominant-white spotting* (*W*) locus (Little 1915) on chromosome 5, or the *Steel* (*Sl*) locus (Sarvella and Russell 1956) on chromosome 10, result in similar phenotypes that can include severe macrocytic anemia, sterility, and coat color abnormalities. Transplantation, tissue chimera, and in vitro coculture assays have established that the cellular bases of *W* and *Sl* mutations are distinct: *W* mutations act intrinsically within stem cells of hematopoietic and melanogenic lineages, whereas the *Sl* defect acts within the microenvironment of such cells (Russell 1979; Silvers 1979).

Insight into the molecular basis of the *W* and *Sl* mutations was obtained with the finding that the receptor tyrosine kinase *c-kit* mapped to human chromosome 4 (Yarden et al. 1987) in a region syntenic with mouse chromosome 5, where the *W* locus is located. Together with the known biology of *W* mutants, this made *c-kit* a highly attractive candidate gene for the *W* locus. This possibility was confirmed by showing extremely tight genetic linkage between *W* and *c-kit* in interspecific crosses (Chabot et al. 1988; Geissler et al. 1988), and mutations affecting *c-kit* structure, expression, and/or function in all 11 independent *W* alleles analyzed to date (Chabot et al. 1988; Geissler et al. 1988; Dubreuil et al. 1990; Nocka et al. 1990a; Reith et al. 1990; Tan et al. 1990).

The identification of *c-kit* as the product of the *W* locus strongly suggested that the *Sl* locus may encode a ligand for the *c-kit* receptor (Chabot et al. 1988). Subsequently, a Kit ligand was identified (Flanagan and Leder 1990; Nocka et al. 1990b; Williams et al. 1990; Zsebo et al. 1990a). Cloning of this growth factor and subsequent analyses established that it does indeed map to the *Sl* locus and is rearranged or deleted in independent *Sl* alleles (Anderson et al. 1990; Copeland et al. 1990; Huang et al. 1990; Martin et al. 1990; Zsebo et al. 1990b). Taken together, *W* and *Sl* mutant animals provide elegant genetic evidence for the roles played by Kit-mediated signal transduction pathways in the development of hematopoietic, melanogenic, and germ cell lineages. Questions regarding the function of the Kit signaling pathway remain, particularly in neural tissues where no phenotype is yet apparent in *W* or *Sl* mutants despite expression of both receptor and ligand in these tissues (Matsui et al. 1990; E. Keshet et al., pers. comm.; B. Motro et al., in prep.).

Another example of the roles of growth factor-mediated signaling pathways in development is provided by the *osteopetrotic* (*op*) mutant mouse, in which skeletal defects result from a restricted capacity for bone remodeling due to an osteoclast deficiency (Marks and Lane 1976). A reduction in macrophage numbers has also been noted in this mutant, a consequence of a defective microenvironment rather than an intrinsic stem cell defect (Wiktor-Jedrzejczak et al. 1982; Marks 1984). The mapping of the macrophage growth factor CSF-1 close to *op* on chromosome 3 (Buchberg et al. 1989; Gisselbrecht et al. 1989) provided a suitable candidate gene for this mutant locus. Together with the absence of biologically active CSF-1 in *op/op* cells (Wiktor-Jedrzejczak et al. 1990;

Yoshida et al. 1990) and the identification of a frameshift mutation in the *CSF-1*-coding region in *op* mice (Yoshida et al. 1990), it is likely that the *op* phenotype results from a loss-of-function mutation in the *CSF-1* gene.

Although the phenotype of *op/CSF-1* mutant animals is consistent with the known properties of CSF-1 for in vitro maturation of macrophages and osteoclasts, newborn *op* homozygotes appear normal and no placental defect is apparent despite high levels of *CSF-1* and its receptor *c-fms* during placental development (Bartocci et al. 1986; Pollard et al. 1987; Arcenci et al. 1989; Regenstein and Rossant 1989). A maternal supply of CSF-1, and increased levels of other cytokines in *op/op* cells and tissues (Wiktor-Jedrzejczak et al. 1990), may compensate to some extent for the absence of embryonic CSF-1, thus minimizing the phenotypic consequences of the CSF-1 deficiency in *op/op* mice.

The candidate gene approach has also provided direct genetic evidence for the function of known or putative transcription factors in mammalian development. Mutations at the *undulated* (*un*) locus (chromosome 2) (Wright 1947) confer vertebral abnormalities over the entire length of the vertebral column, a consequence of perturbation in the position of the boundary between anterior and posterior sclerotome halves in the mid-gestation embryo (Gruneberg 1950, 1954). An understanding of the molecular basis of this mutant has been made possible by the mapping of the *Pax-1* gene to the *un* locus (Balling et al. 1988).

Pax-1 was isolated as a potential murine developmental control gene on the basis of its homology to the *Drosophila* paired-box, originally identified in a subset of segmentation genes known to play critical roles during *Drosophila* development (Bopp et al. 1986; Akam et al. 1987). The definition of mutations in *Pax-1* gene structure or expression in three independent *un* alleles (Balling et al. 1988; Kessel and Gruss 1990), and the restriction of *Pax-1* expression to posterior sclerotome halves during normal vertebra development (Deutsch et al. 1988), strongly implicate mutations in *Pax-1* as playing a causal role in the generation of the *un* phenotype. Moreover, the phenotypic consequences of mutation of *Pax-1* suggest that this putative transcription factor may play a directive role in sclerotome determination.

Like coat color or skeletal mutants, genetic dwarfism is one of the more easily assayed mutant phenotypes in mouse breeding stocks and a number of spontaneous dwarf mutant loci have been identified over the years. Two such mutants are *Snell's dwarf* (*dw*) on chromosome 16 (Snell 1929) and *Ame's dwarf* (*df*) on chromosome 11 (Bartke 1964). Mice homozygous for either of these mutations have severely hypoplastic anterior pituitaries and are depleted in somatotroph, lactotroph, and thyrotroph cell types resulting from primary defects intrinsic to the pituitary (Carsner and Rennels 1960). The mapping of the POU domain-containing transcription factor *pit-1* to chromosome 16 (Camper et al. 1990; Li et al. 1990) provided a suitable candidate gene for the *dw* locus.

pit-1 was identified as a transcription factor that can

trans-activate prolactin and growth hormone gene promoters and is restricted to the nuclei of somatotroph, lactotroph, and thyrotroph pituitary cell types (Bodner et al. 1988; Ingraham et al. 1988; Crenshaw et al. 1989; Mangalam et al. 1989; Simmons et al. 1990). The detection of genomic rearrangement of the *pit-1* locus in the *dw^l* allele, and point substitution of a highly conserved tryptophan residue within the POU domain of *pit-1* in the original *dw* allele (Li et al. 1990), provides direct evidence that the *dw* phenotype is a consequence of loss-of-function mutations in the *pit-1* transcription factor. Moreover, this analysis suggests that *pit-1* is essential for the survival and/or proliferation of both lactotroph and somatotroph lineages, in addition to its putative role in mediating hormone expression in these cell types and, furthermore, indicates that *pit-1* may also play a functional role in cells of the thyrotroph lineage.

Physical mapping approaches

An alternative to direct association of a candidate gene with a mutant phenotype is provided by the direct physical mapping and cloning of a mutant locus. The initiation of such an approach requires the availability of cloned markers that map close to the locus of interest. These can be provided in two ways.

Insertional mutagenesis

A number of mouse mutant phenotypes result from disruption of a functional transcription unit by either spontaneous or experimentally induced insertion of DNA elements into a functional locus. It is possible to use the insertional mutagenic element as a "cloning tag" to gain direct access to a mutant locus of interest (Table 2). Tags may take the form of spontaneous insertion of endogenous retroviral elements, as in the case of the *dilute* (*d*) (Jenkins et al. 1981; Copeland et al. 1983; Mercer et al. 1991), *hairless* (Stoye et al. 1988), and *pink-eyed unstable* (Brilliant et al. 1991) loci, or experimental introduction of ecotropic proviruses, as used to generate the *Mov* series of mutant mouse strains (Jaenisch 1976). In addition to these retrovirus insertional events, DNA microinjection into fertilized eggs has provided additional insertional mutagenic events at a frequency estimated to be as high as 5–10% (Jaenisch 1988). Although such tags can greatly facilitate the molecular definition of particular mutant loci, genomic rearrangements at the site of transgene integration (Covarrubias et al. 1986, 1987; Mahon et al. 1988) may complicate molecular analysis. Nevertheless, transgene insertions provide a powerful method of cloning developmentally important loci, as exemplified by the identification of the products of the mouse *limb deformity* (*ld*) locus (Cupp 1960).

ld/ld animals are characterized by fusions and reduction in the distal bones of the limbs that can be traced to a defect in limb bud development (Lyon and Searle 1989; Zeller et al. 1989). The molecular definition of the *ld* locus involved physical mapping and cloning approaches

made possible by the fortuitous generation of novel *ld* alleles by insertional mutagenesis in a transgenic experiment (Woychik et al. 1985). Using the transgene as a "cloning tag," evolutionarily conserved coding sequences of the *ld* locus were cloned and found to encode a variety of novel proline-rich proteins, termed formins, produced from a family of differentially spliced, low-abundance mRNA species expressed in a wide variety of cell types (Zeller et al. 1989; Woychik et al. 1990). In two independent *ld* alleles, a common subset of formin mRNA species are not synthesized (Maas et al. 1990), indicating that functional disruption of the formin locus is causal in the generation of at least some *ld* alleles. The availability of the formin reagents, along with *ld* mutant mice, will make it possible to analyze the functions of this complex family of proteins in limb morphogenesis.

Walking to a mutant locus

In the absence of an insertional cloning tag, the molecular definition of a mutant locus can be achieved only by direct physical mapping, cloning, and chromosome walking procedures. Such analysis is initiated by the use of the cloned markers nearest to the mutant locus; but despite the rapid increase in the number of cloned and mapped probes, markers may be a considerable distance from the locus of interest. A further limitation is imposed by the requirement for a large number of well-defined deletion and/or translocation mutant alleles to facilitate the construction of detailed physical maps of the mutant locus. Nevertheless, this approach has been successful in the identification of certain genes involved in human disease and embryological development (Lee et al. 1987; Riordan et al. 1989; Rommens et al. 1989; Bonetta et al. 1990; Call et al. 1990; Cawthon et al. 1990; Gessler et al. 1990; Sinclair et al. 1990; Viskochil et al. 1990). This strategy is also leading to the molecular cloning of murine developmental loci.

Mutations at the *Brachyury* (*T*) locus (chromosome 17) (Dobrovolskaia-Zavadskaja 1927) induce mild dominant defects in vertebrae development. *T/T* homozygotes die at ~10 days of gestation, a consequence of a primary failure to produce sufficient mesoderm during primitive streak formation at ~7.5–8.5 days of gestation (Chesley 1935; Yanagisawa et al. 1981). A large number of *T* alleles bearing a variety of deletions and chromosomal breakpoints have been isolated in the past 50 years and have provided the basis for physical mapping of the *T* locus to a 75-kb region of DNA (Herrmann et al. 1990). Within this region a single gene was identified, and conserved genomic fragments were used to isolate a cDNA clone of novel nucleotide sequence, *pme75*. Deletion of *pme75*-encoded sequences in many *T* alleles and genomic rearrangement of *pme75* in at least one *T* allele (Herrmann et al. 1990), coupled with the restricted expression of *pme75* in target cell types of *T* mutants (Wilkinson et al. 1990), strongly suggests that this cDNA clone represents a product of the *T* locus and implicates this gene as playing a key role in mesoderm formation. The availability of the *T* protein and *T* mutant mice will fa-

cilitate studies on the interactions between *T* and other proteins involved in mesoderm formation (Rosa 1989; Mitrani et al. 1990; Smith et al. 1990; Thomsen et al. 1990), providing important insights into the molecular mechanisms involved in vertebrate mesoderm formation.

An elegant example of how human and mouse genetic analyses can be used in parallel to identify developmentally important genes is provided by the identification of the mammalian sex-determination gene. In man, analysis of sex-reversed individuals facilitated the construction of detailed genetic and physical maps restricting the testis-determining gene (*TDF* in human; *Tdy* in mouse) to a 60-kb fragment of the Y chromosome. Within this region, a highly conserved Y-specific gene, *SRY*, was identified (Sinclair et al. 1990). Further evidence supporting the notion that *SRY* is the mammalian sex-determining gene has come from the identification of point substitutions in *SRY* in some XY females that lack cytogenetic mutations in Y (Berta et al. 1990; Jager et al. 1990).

In the mouse, a number of mutations have been identified that result in sex-reversed phenotypes. The *Sxr* mutation (Cattanach et al. 1971) results in X/X or X/O individuals developing as males, a consequence of translocation of a small region of the Y chromosome to the distal end of Y that undergoes recombination with X during meiosis. A derivative mutant, *Sxr'* (McClaren et al. 1984), is deleted for some genes translocated in *Sxr* but still gives rise to sex-reversed mice and so represents the smallest region of mouse Y that contains *Tdy*. Another sex-reversed mutant, *Tdy*^{m1} (Lovell-Badge and Robertson 1990), produces XY females and can be complemented by *Sxr'*, suggesting that this represents a loss-of-function mutation in *Tdy*. Consistent with the phenotypes of mouse sex-reversed mutants, the mouse homolog of *SRY* (*Sry*) was found to be present in the translocated region in *Sxr* and *Sxr'* mutants but is deleted in *Tdy*^{m1} mutants (Gubbay et al. 1990). Moreover, *Sry* is a member of a family of at least five closely related mouse genes, all of which contain sequences homologous to DNA-binding domains (Gubbay et al. 1990).

Future prospects

Developmental mutants in the mouse have played a key role in the establishment of mouse genetics and in the elucidation of developmental strategies in mammals. However, only within the last several years has it been possible to address the molecular bases of these mutant phenotypes. This analysis has already brought together proteins with well-defined biochemical properties and mutant strains that have been analyzed by genetic, cellular, and embryological approaches over many years. In addition, this genetic approach has led to the discovery of novel proteins that play key roles in development.

To date, only a very small proportion of the available mouse mutations have been accessed at the molecular level. As exemplified by *W* and *Sl* mutants, identification of the molecular defect in one mutant locus can

facilitate the definition of other loci and also provide a basis for the generation of loss-of-function mutations in related proteins (A.D. Reith et al., in prep.) The continued cloning and mapping of novel genes and anonymous probes will provide ever more detailed genetic and physical maps of both human and mouse genomes. Coupled with the utilization of cloning vectors, such as yeast artificial chromosomes (Schlessinger 1990) and phage P1 vectors (Sternberg et al. 1990), the cloning of candidate genes for a given mutation by walking procedures should become a less formidable task than it is at present. Moreover, the development of techniques to introduce large DNA fragments into the mouse germ line (Richa and Lo 1989; Pavan et al. 1990) promises to provide a basis for genetic complementation assays to functionally define mutant loci, facilitating an entirely new strategy for cloning developmental genes in mammals. Over the next several years, this fusion of complementary genetic, biological, and biochemical approaches will undoubtedly lead to the molecular definition of many pre-existing mouse mutations. These approaches, coupled with gene-targeting strategies to generate novel developmental mutants, will lead to a fuller understanding of the molecular mechanisms that regulate normal mammalian development.

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References

- Adamson, E.D. 1987. Oncogenes in development. *Development* **99**: 449–471.
- Akam, M. 1987. The molecular basis for metameric pattern in the *Drosophila* embryo. *Development* **101**: 1–22.
- Allen, N.D., D.G. Cran, S.C. Barton, S. Hettle, W. Reik, and M.A. Surani. 1988. Transgenes as probes for active chromosomal domains in mouse development. *Nature* **333**: 852–855.
- Anderson, D.M., S.D. Lyman, A. Baird, J.M. Wignall, J. Eisenman, C. Rauch, C.J. March, H.S. Boswell, S.D. Gimpel, D. Cosman, and D.E. Williams. 1990. Molecular cloning of mast cell growth factor, a hematopoietin that is active in both membrane bound and soluble forms. *Cell* **63**: 235–243.
- Arceci, R.J., F. Shanahan, E.R. Stanley, and J.W. Pollard. 1989. Temporal expression and location of colony-stimulating factor 1 (CSF-1) and its receptor in the female reproductive tract are consistent with CSF-1-regulated placental development. *Proc. Natl. Acad. Sci.* **86**: 8818–8822.
- Avner, P., L. Amar, L. Dandolo, and J.L. Guenet. 1988. Genetic analysis of the mouse using interspecific crosses. *Trends Genet.* **4**: 18–23.
- Balling, R., U. Deutsch, and P. Gruss. 1988. *undulated*, a mutation affecting the development of the mouse skeleton, has a point mutation in the paired box of *Pax-1*. *Cell* **55**: 531–535.

- Bartke, A. 1964. Histology of the anterior hypophysis, thyroid and gonads of two types of dwarf mice. *Anat. Rec.* **149**: 225–235.
- Bartocci, A., J.W. Pollard, and E.R. Stanley. 1986. Regulation of colony-stimulating factor 1 during pregnancy. *J. Exp. Med.* **164**: 956–961.
- Berta, P., J.R. Hawkins, A.H. Sinclair, A. Taylor, B.L. Griffiths, P.N. Goodfellow, and M. Fellous. 1990. Genetic evidence equating *Sry* and the testis-determining factor. *Nature* **348**: 448–450.
- Bodner, M., J.-L. Castrillo, L.E. Theill, T. Deerinck, M. Ellisman, and M. Karin. 1988. The pituitary-specific transcription factor GHF-1 is a homeobox-containing protein. *Cell* **55**: 505–518.
- Boettiger, D. 1989. Interaction of oncogenes with differentiation programs. *Curr. Top. Microbiol. Immunol.* **47**: 31–78.
- Bonetta, L., S.E. Kuhn, A. Huang, D.J. Law, L.M. Kallik, M. Koi, A.E. Reeve, B.H. Brownstein, H. Yaeger, B.R.G. Williams, and A.P. Feinberg. 1990. Wilm's tumor locus on 11p13 defined by multiple CpG island-associated transcripts. *Science* **250**: 994–997.
- Bopp, D., M. Burri, S. Baumgartner, G. Frigerio, and M. Noll. 1986. Conservation of a large protein domain in the segmentation gene *paired* and in functionally related genes of *Drosophila*. *Cell* **47**: 1033–1040.
- Bowes, C., T. Li, M. Danciger, L.C. Baxter, M.L. Applebury, and D.B. Farber. 1990. Retinal degeneration in the *rd* mouse is caused by a defect in the β subunit of rod cGMP-phosphodiesterase. *Nature* **347**: 677–680.
- Brilliant, M.H., Y. Gondo, and E.M. Eicher. 1991. Direct molecular identification of the mouse pink-eyed unstable mutation by genome scanning. *Science* **252**: 566–569.
- Buchberg, A.M., N.A. Jenkins, and N.G. Copeland. 1989. Localization of the murine macrophage colony-stimulating factor gene to chromosome 3 using interspecific backcross analysis. *Genomics* **5**: 363–367.
- Call, K.M., T. Glaser, C.Y. Ito, A.J. Buckler, J. Pelletier, D.A. Haber, E.A. Rose, A. Kral, H. Yeger, W.H. Lewis, C. Jones, and D.E. Houseman. 1990. Isolation and characterisation of a zinc finger polypeptide gene at the human chromosome 11 Wilm's tumor locus. *Cell* **60**: 509–520.
- Camper, S.A., T.L. Saunders, R.W. Katz, and R.H. Reeves. 1990. The pit-1 transcription factor gene is a candidate for the murine Snell dwarf mutation. *Genomics* **8**: 586–590.
- Capecchi, M.R. 1989. Altering the genome by homologous recombination. *Science* **244**: 1288–1292.
- Carsner, R.L. and E.G. Rennels. 1960. Primary site of gene action in anterior pituitary dwarf mice. *Science* **131**: 829.
- Cattanach, B.M., C.E. Pollard, and S.G. Hawkes. 1971. Sex reversed mice: XX and XO males. *Cytogenetics* **10**: 318–337.
- Cawthon, R.M., R. Weiss, G. Xu, D. Viskochil, M. Culver, J. Stevens, M. Robertson, D. Dunn, R. Gesteland, P. O'Connell, and R. White. 1990. A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure and point mutations. *Cell* **62**: 193–201.
- Chabot, B., D.A. Stephenson, W.M. Chapman, P. Besmer, and A. Bernstein. 1988. The proto-oncogene *c-kit* encoding a transmembrane tyrosine kinase receptor maps to the mouse *W* locus. *Nature* **335**: 88–89.
- Chesley, P. 1935. Development of the short-tailed mutant in the house mouse. *J. Exp. Zool.* **70**: 429–459.
- Copeland, N.G. and N.A. Jenkins. 1991. Development and application of a molecular genetic linkage map of the mouse genome. *Trends Genet.* **7**: 113–118.
- Copeland, N.G., K.W. Hutchison, and N.A. Jenkins. 1983. Excision of the DBA ecotropic provirus in dilute coat colour revertants of mice occurs by homologous recombination involving the viral LTRs. *Cell* **33**: 379–387.
- Copeland, N.G., D.J. Gilbert, B.C. Cho, P.J. Donovan, N.A. Jenkins, D. Cosman, D. Anderson, S.D. Lyman, and D.E. Williams. 1990. Mast cell growth factor maps near the *Steel* locus on mouse chromosome 10 and is deleted in a number of *Steel* alleles. *Cell* **63**: 175–183.
- Covarrubias, L., Y. Nishida, and B. Mintz. 1986. Early postimplantation embryo lethality due to DNA rearrangements in a transgenic mouse strain. *Proc. Natl. Acad. Sci.* **83**: 6020–6024.
- Covarrubias, L., Y. Nishida, M. Terao, P. D'Eustachio, and B. Mintz. 1987. Cellular DNA rearrangements and early developmental arrest caused by DNA insertion in transgenic mouse embryos. *Mol. Cell. Biol.* **7**: 2243–2247.
- Crenshaw, E.B., K. Kalla, D.M. Simmons, L.W. Swanson, and M.G. Rosenfeld. 1989. Cell-specific expression of the prolactin gene in transgenic mice is controlled by synergistic interactions between promoter and enhancer elements. *Genes & Dev.* **3**: 959–972.
- Cupp, M.B. 1960. *Mouse News Lett.* **22**: 50.
- Dautigny, A., M.G. Mattei, D. Morello, P.M. Alliel, D. Pham-Dinh, L. Amar, D. Arnaud, D. Simon, J.-F. Mattei, J.-L. Guenet, P. Jollès, and P. Avner. 1986. The structural gene coding for myelin-associated proteolipid protein is mutated in *jimpy* mice. *Nature* **321**: 867–869.
- Deutsch, U., G.R. Dressler, and P. Gruss. 1988. *Pax 1*, a member of a paired box homologous murine gene family, is expressed in segmented structures during development. *Cell* **53**: 617–625.
- Dobrovolskaia-Zavadskaja, N. 1927. Sur la mortification spontanée de la queue chez la souris nouveau-née et sur l'existence d'un caractère héréditaire "non-viable." *C.R. Soc. Biol.* **97**: 114–116.
- Dubreuil, P., R. Rottapel, A.D. Reith, L. Forrester, and A. Bernstein. 1990. The mouse *W/c-kit* locus: A mammalian gene that controls the development of three distinct cell lineages. *Ann. N.Y. Acad. Sci.* **599**: 58–65.
- Flanagan, J.G. and P. Leder. 1990. The *kit* ligand: A cell surface molecule altered in *Steel* mutant fibroblasts. *Cell* **63**: 185–194.
- Geissler, E.N., M.A. Ryan, and D.E. Housman. 1988. The dominant-white spotting (*W*) locus of the mouse encodes the *c-kit* proto-oncogene. *Cell* **55**: 185–192.
- Gessler, M., A. Poustka, W. Cavanee, R.L. Neve, S.H. Orkin, and G.A.P. Bruns. 1990. Homozygous deletion in Wilm's tumors of a zinc-finger gene identified by chromosome jumping. *Nature* **343**: 774–778.
- Gisselbrecht, S., B. Sola, S. Fichelson, D. Bordereaux, P. Tambourin, M.-G. Mattei, D. Simon, and J.-L. Guenet. 1989. The murine M-CSF gene is localised on chromosome 3. *Blood* **73**: 1742–1746.
- Gordon, J.W., J. Uehlinger, N. Dayani, B.E. Talansky, M. Gordon, G.S. Rudomen, and P.E. Neumann. 1990. Analysis of the hotfoot (*ho*) locus by creation of an insertional mutation in a transgenic mouse. *Dev. Biol.* **137**: 349–358.
- Gossler, A., A.L. Joyner, J. Rossant, and W.J. Skarnes. 1989. Mouse embryonic stem cells and reporter constructs to detect developmentally regulated genes. *Science* **244**: 463–465.
- Gridley, T., D.A. Gray, T. Orr-Weaver, P. Soriano, D.E. Barton, U. Francke, and R. Jaenisch. 1990. Molecular analysis of the *Mov 34* mutation: Transcript disrupted by proviral integration in mice is conserved in *Drosophila*. *Development* **109**: 235–242.
- Gruneberg, H. 1950. Genetical studies on the skeleton of the mouse. II. Undulated and its "modifiers." *J. Genet.* **50**: 142–173.

- . 1954. Genetical studies on the skeleton of the mouse. XII. The development of undulated. *J. Genet.* **52**: 441–455.
- Gubbay, J., J. Collignon, P. Koopman, B. Capel, A. Economou, A. Munsterberg, N. Vivian, P. Goodfellow, and R. Lovell-Badge. 1990. A gene mapping to the sex-determining region of the mouse Y chromosome is a member of a novel family of embryonically expressed genes. *Nature* **346**: 245–250.
- Herrmann, B.G., S. Labeit, A. Poustka, T.R. King, and H. Lehrach. 1990. Cloning of the *T* gene required in mesoderm formation in the mouse. *Nature* **343**: 617–622.
- Hoffman, E.P., R.H. Brown, and L.M. Kunkel. 1987. Dystrophin: The protein product of the Duchenne muscular dystrophy locus. *Cell* **51**: 919–928.
- Holland, P.W.H. and B.L.M. Hogan. 1988. Expression of homeobox genes during development: A review. *Genes & Dev.* **2**: 773–782.
- Huang, E., K. Nocka, D.R. Beier, T.-Y. Chu, J. Buck, H.-W. Lahm, D. Wellner, P. Leder, and P. Besmer. 1990. The hematopoietic growth factor KL is encoded at the *Steel* locus and is the ligand of the *c-kit* receptor, the gene product of the *W* locus. *Cell* **63**: 225–233.
- Ingraham, H.A., R. Chen, H.J. Mangalam, H.P. Elsholtz, S.E. Flynn, C.R. Lin, D.M. Simmons, L. Swanson, and M.G. Rosenfeld. 1988. A tissue-specific transcription factor containing a homeodomain specifies a pituitary phenotype. *Cell* **55**: 519–529.
- Jackson, I.J., D. Chambers, E.M. Rinchik, and D.C. Bennett. 1990. Characterization of TRP-1 mRNA levels in dominant and recessive mutations at the mouse *brown (b)* locus. *Genetics* **126**: 451–459.
- Jaenisch, R. 1976. Germ line integration and Mendelian transmission of the exogenous Moloney murine leukemia virus. *Proc. Natl. Acad. Sci.* **73**: 1260–1264.
- . 1988. Transgenic animals. *Science* **240**: 1468–1474.
- Jager, R.J., M. Anvret, K. Hall, and G. Scherer. 1990. A human XY female with a frame shift mutation in the candidate testis-determining gene *SRY*. *Nature* **348**: 452–454.
- Jenkins, N.A., N.G. Copeland, B.A. Taylor, and B.K. Lee. 1981. *Dilute (d)* coat colour mutation of DBA/2J mice is associated with the site of integration of an ecotropic MuLV genome. *Nature* **293**: 370–374.
- Keller, S.A., S. Liptay, A. Hajra, and M.H. Meisler. 1990. Transgene-induced mutation of the murine *steel* locus. *Proc. Natl. Acad. Sci.* **87**: 10019–10022.
- Kessel, M. and P. Gruss. 1990. Murine developmental control genes. *Science* **249**: 374–379.
- Kothary, R., S. Clapoff, A. Brown, R. Campbell, A. Peterson, and J. Rossant. 1988. A transgene containing *lacZ* inserted into the *dystonia* locus is expressed in neural tube. *Nature* **335**: 435–437.
- Krulowski, T.F., P.E. Neumann, and J.W. Gordon. 1989. Insertional mutation in a transgenic mouse allelic with Purkinje cell degeneration. *Proc. Natl. Acad. Sci.* **86**: 3709–3712.
- Kwon, B.S., A.K. Haq, S.H. Pomerantz, and R. Halaban. 1987. Isolation and sequence of a cDNA clone for human tyrosinase that maps at the mouse *c-albino* locus. *Proc. Natl. Acad. Sci.* **84**: 7473–7477.
- Lee, W.-H., R. Bookstein, F. Hong, L.-J. Young, J.-Y. Shew, and E.Y.-H.P. Lee. 1987. Human retinoblastoma susceptibility gene: Cloning, identification and sequence. *Science* **235**: 1394–1399.
- Li, S., E.B. Crenshaw, E.J. Rawson, D.M. Simmons, L.W. Swanson, and M.G. Rosenfeld. 1990. Dwarf locus mutants lacking three pituitary cell types result from mutations in the POU-domain gene *pit-1*. *Nature* **347**: 528–533.
- Little, C.C. 1915. The inheritance of black-eyed white spotting in mice. *Am. Nat.* **49**: 727–740.
- Lovell-Badge, R. and E. Robertson. 1990. XY female mice resulting from a heritable mutation in the primary testis-determining gene, *Tdy*. *Development* **109**: 635–646.
- Lyon, M.F. and A.G. Searle. 1989. *Genetic variants and strains of the laboratory mouse*, 2nd ed. Oxford University Press, Oxford.
- Maas, R.L., R. Zeller, R.P. Woychik, T.F. Vogt, and P. Leder. 1990. Disruption of formin-encoding transcripts in two mutant *limb deformity* alleles. *Nature* **346**: 853–855.
- MacGregor, G.R., L.D. Russell, M.E.A.B. Van Beek, G.R. Hanten, M.J. Kovac, C.A. Kozak, M.L. Meistrich, and P.A. Overbeek. 1990. Symplastic spermatids (*sys*): A recessive insertional mutation in mice causing a defect in spermatogenesis. *Proc. Natl. Acad. Sci.* **87**: 5016–5020.
- Mahon, K.A., P.A. Overbeek, and H. Westphal. 1988. Prenatal lethality in a transgenic mouse line is the result of a chromosomal translocation. *Proc. Natl. Acad. Sci.* **85**: 1165–1168.
- Mangalam, H.J., V.R. Albert, H.A. Ingraham, M. Kapiloff, L. Wilson, C. Nelson, H. Elsholtz, and M.G. Rosenfeld. 1989. A pituitary POU domain protein, Pit-1, activates both growth hormone and prolactin promoters transcriptionally. *Genes & Dev.* **3**: 946–958.
- Marks, S.C. 1984. Congenital osteopetrotic mutations as probes of the origin, structure and function of osteoclasts. *Clin. Orthop. Rel. Res.* **189**: 239–263.
- Marks, S.C. and P.W. Lane. 1976. Osteopetrosis, a new recessive lethal skeletal mutation on chromosome 12 of the mouse. *J. Hered.* **67**: 11–18.
- Martin, F.H., S.V. Suggs, K.E. Langley, H.S. Lu, J. Ting, K.H. Okino, C.F. Morris, I.K. McNeice, F.W. Jacobsen, E.A. Mendiaz, N.C. Birkett, K.A. Smith, M.J. Johnson, V.P. Parker, J.C. Flores, A.C. Patel, E.F. Fisher, H.O. Erjavec, C.J. Herrera, J. Wypych, R.K. Sachdev, J.A. Pope, I. Leslie, D. Wen, C.-H. Lin, R.L. Cupples, and K.M. Zsebo. 1990. Primary structure and functional expression of rat and human stem cell factor DNAs. *Cell* **63**: 203–211.
- Matsui, Y., K.M. Zsebo, and B.L.M. Hogan. 1990. Embryonic expression of a hematopoietic growth factor encoded by the *Sl* locus and the ligand for *c-kit*. *Nature* **347**: 667–669.
- McLaren, A., E. Simpson, K. Tomonari, P. Chandler, and H. Hogg. 1984. Male sexual differentiation in mice lacking H-Y antigen. *Nature* **312**: 552–555.
- Mercer, J.A., P.K. Seperack, M.C. Strobel, N.G. Copeland, and N.A. Jenkins. 1991. Novel myosin heavy chain encoded by murine *dilute* coat colour locus. *Nature* **349**: 709–713.
- Mercola, M. and C.D. Stiles. 1988. Growth factor superfamilies and mammalian embryogenesis. *Development* **102**: 451–460.
- Mitrani, E., T. Ziv, G. Thomsen, Y. Shimoni, D.A. Melton, and A. Bril. 1990. Activin can induce the formation of axial structures and is expressed in the hypoblast of the chick. *Cell* **63**: 495–501.
- Nocka, K., J.C. Tan, E. Chiu, T.Y. Chu, P. Ray, P. Traktman, and P. Besmer. 1990a. Molecular bases of dominant negative and loss of function mutations at the murine *c-kit/white* spotting locus: *W³⁷*, *W^v*, *W⁴¹*, and *W*. *EMBO J.* **9**: 1805–1813.
- Nocka, K., J. Buck, E. Levi, and P. Besmer. 1990b. Candidate ligand for the *c-kit* transmembrane kinase receptor: KL, a fibroblast derived growth factor, stimulates mast cells and erythroid progenitors. *EMBO J.* **9**: 3287–3294.
- Pavan, W.J., P. Hieter, and R.H. Reeves. 1990. Modification and transfer into an embryonal carcinoma cell line of a 360-kilobase human-derived yeast artificial chromosome. *Mol. Cell. Biol.* **10**: 4163–4169.

- Pohl, T.M., M.-G. Mattei, and U. Ruther. 1990. Evidence for allelism of the recessive insertional mutation *add* and the dominant mouse mutation *extra-toes* (*Xt*). *Development* **110**: 1153–1157.
- Pollard, J.W., A. Bartocci, R. Arceci, A. Orlofsky, M.B. Ladner, and E.R. Stanley. 1987. Apparent role of the macrophage growth factor, CSF-1, in placental development. *Nature* **330**: 484–486.
- Radice, G., J.J. Lee, and F. Costantini. 1991. H β 58, an insertional mutation affecting early postimplantation development of the mouse embryo. *Development* **111**: 801–811.
- Readhead, C., B. Popko, N. Takahashi, H.D. Shine, R.A. Saavedra, R.L. Sidman, and L. Hood. 1987. Expression of a myelin basic protein in transgenic shiverer mice: Correction of the dysmyelinating phenotype. *Cell* **48**: 703–712.
- Regenstrief, L.J. and J. Rossant. 1989. Expression of the *c-fms* protooncogene and of the cytokine, CSF-1, during mouse embryogenesis. *Dev. Biol.* **133**: 284–294.
- Reith, A.D., R. Rottapel, E. Giddens, C. Brady, L. Forrester, and A. Bernstein. 1990. *W* mutant mice with mild or severe developmental defects contain distinct point mutations in the kinase domain of the *c-kit* transmembrane receptor. *Genes & Dev.* **4**: 390–400.
- Richa, J. and C.W. Lo. 1989. Introduction of human DNA into mouse eggs by injection of dissected chromosome fragments. *Science* **245**: 175–176.
- Rinchik, E.M. 1991. Chemical mutagenesis and fine structure functional analysis of the mouse genome. *Trends Genet.* **7**: 15–21.
- Riordan, J.R., J.M. Rommens, B.-S. Kerem, N. Alon, R. Rozmahel, Z. Grzelczak, J. Zielenski, S. Lok, N. Plavsic, J.-L. Chou, M.L. Drumm, M.C. Iannuzzi, F.S. Collins, and L.-C. Tsui. 1989. Identification of the cystic fibrosis gene: Cloning and characterisation of complementary DNA. *Science* **245**: 1066–1072.
- Rommens, J.M., M.C. Iannuzzi, B.-S. Kerem, M.L. Drumm, G. Melmer, M. Dean, R. Rozmahel, J.L. Cole, D. Kennedy, N. Hidaka, M. Zsiga, M. Buchwald, J.R. Riordan, L.-C. Tsui, and F.S. Collins. 1989. Identification of the cystic fibrosis gene: Chromosome walking and jumping. *Science* **245**: 1059–1065.
- Rosa, F.M. 1989. *Mix.1*, a homeobox mRNA inducible by mesoderm inducers, is expressed mostly in the presumptive endodermal cells of *Xenopus* embryos. *Cell* **57**: 965–974.
- Rossant, J. and A.L. Joyner. 1989. Towards a molecular-genetic analysis of mammalian development. *Trends Genet.* **5**: 116–120.
- Russell, E.S. 1979. Hereditary anemias of the mouse: A review for geneticists. *Adv. Genet.* **20**: 357–444.
- Sarvella, P.A. and L.B. Russell. 1956. *Steel*, a new dominant gene in the house mouse. *J. Hered.* **47**: 123–128.
- Schlessinger, D. 1990. Yeast artificial chromosomes: Tools for mapping and analysis of complex genomes. *Trends Genet.* **6**: 248–258.
- Schnieke, A., K. Harbers, and R. Jaenisch. 1983. Embryonic lethal mutation in mice induced by retrovirus insertion into the $\alpha 1(I)$ collagen gene. *Nature* **304**: 315–320.
- Shawlot, W., M.J. Siciliano, R.L. Stallings, and P.A. Overbeek. 1989. Insertional inactivation of the downless gene in a family of transgenic mice. *Mol. Biol. Med.* **6**: 299–307.
- Sicinski, P., Y. Geng, A.S. Ryder-Cook, E.A. Barnard, M.G. Darlison, and P.J. Barnard. 1987. The molecular basis of muscular dystrophy in the *mdx* mouse: A point mutation. *Science* **244**: 1578–1580.
- Silvers, W.K. 1979. White-spotting, patch and rump-white. In *The coat colors of mice: A model for gene action and interaction* pp. 206–241. Springer-Verlag, New York.
- Simmons, D.M., J.W. Voss, H.A. Ingraham, J.M. Holloway, R.S. Broide, M.G. Rosenfeld, and L.W. Swanson. 1990. Pituitary cell phenotypes involve cell-specific *Pit-1* mRNA translation and synergistic interactions with other classes of transcription factors. *Genes & Dev.* **4**: 695–711.
- Sinclair, A.H., P. Berta, M.S. Palmer, J.R. Hawkins, B.L. Grifiths, M.J. Smith, J.W. Foster, A.-M. Frischauf, R. Lovell-Badge, and P.N. Goodfellow. 1990. A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature* **346**: 240–244.
- Smith, J.C., B.M.J. Price, K. Van Nimmen, and D. Huylebroeck. 1990. Identification of a potent *Xenopus* mesoderm-inducing factor as a homologue of activin A. *Nature* **345**: 729–731.
- Snell, G.D. 1929. "Dwarf," a new Mendelian recessive character in the house mouse. *Proc. Natl. Acad. Sci.* **15**: 733–734.
- Soriano, P., T. Gridley, and R. Jaenisch. 1987. Retroviruses and insertional mutagenesis in mice: Proviral integration at the *Mov-34* locus leads to early embryonic death. *Genes & Dev.* **1**: 366–375.
- Stephenson, D.A., M. Mercola, E. Anderson, C. Wang, C.D. Stiles, D.F. Bowen-Pope, and V.M. Chapman. 1990. Platelet-derived growth factor receptor α subunit gene (*Pdgfra*) is deleted in the mouse *patch* (*Ph*) mutation. *Proc. Natl. Acad. Sci.* **88**: 6–10.
- Sternberg, N., J. Ruether, and K. deRiel. 1990. Generation of a 50,000-member human DNA library with an average DNA insert size of 75–100 kbp in a bacteriophage P1 cloning vector. *New Biol.* **2**: 151–162.
- Stoye, J.P., S. Fenner, G.E. Greenoak, C. Moran, and J.M. Coffin. 1988. Role of endogenous retroviruses as mutagens: The hairless mutation of mice. *Cell* **54**: 383–391.
- Tan, J.C., K. Nocka, P. Ray, P. Traktman, and P. Besmer. 1990. The dominant *W⁴²* spotting phenotype results from a missense mutation in the *c-kit* receptor. *Science* **247**: 209–212.
- Taylor, B.A. 1978. Recombinant inbred strains: Use in gene mapping. In *Origins of inbred mice* (ed. H. Morse), pp. 423–438. Academic Press, New York.
- Thomsen, G., T. Woolf, M. Whitman, S. Sokol, J. Vaughan, W. Vale, and D.A. Melton. 1990. Activins are expressed early in *Xenopus* embryogenesis and can induce axial mesoderm and anterior structures. *Cell* **63**: 485–493.
- Veres, G., R.A. Gibbs, S.E. Scherer, and C.T. Caskey. 1987. The molecular basis of the sparse fur mouse mutation. *Science* **237**: 415–417.
- Viskochil, D., A.M. Buchberg, G. Xu, R.M. Cawthon, J. Stevens, R.K. Wolff, M. Culver, J.C. Carey, N.G. Copeland, N.A. Jenkins, R. White, and P. O'Connell. 1990. Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. *Cell* **62**: 187–192.
- Weiher, H., T. Noda, D.A. Gray, A.H. Sharpe, and R. Jaenisch. 1990. Transgenic mouse model of kidney disease: Insertional inactivation of ubiquitously expressed gene leads to nephrotic syndrome. *Cell* **62**: 425–434.
- Westphal, H. and P. Gruss. 1989. Molecular genetics of development studied in the transgenic mouse. *Annu. Rev. Cell Biol.* **5**: 181–196.
- Wiktor-Jedrzejczak, W., A. Ahmed, C. Szczylik, and R.R. Skelly. 1982. Hematological characterisation of congenital osteopetrosis in *op/op* mice. *J. Exp. Med.* **156**: 1516–1527.
- Wiktor-Jedrzejczak, W., A. Bartocci, A.W. Ferrante, A. Ahmed-Ansari, K.W. Sell, J.W. Pollard, and E.R. Stanley. 1990. Total absence of colony-stimulating factor 1 in the macrophage-deficient osteopetrotic (*op/op*) mouse. *Proc. Natl. Acad. Sci.* **87**: 4828–4832.
- Wilkie, T.M. and R.D. Palmiter. 1987. Analysis of the integrant

- in MyK-103 transgenic mice in which males fail to transmit the integrant. *Mol. Cell. Biol.* **7**: 1646–1655.
- Wilkinson, D.G., S. Bhatt, and B.G. Herrmann. 1990. Expression pattern of the mouse *T* gene and its role in mesoderm formation. *Nature* **343**: 657–659.
- Williams, D.E., J. Eisenman, A. Baird, C. Rauch, V.K. Ness, C.J. March, L.S. Park, U. Martin, D.Y. Mochizuki, H.S. Boswell, G.S. Burgess, D. Cosman, and S.D. Lyman. 1990. Identification of a ligand for the *c-kit* proto-oncogene. *Cell* **63**: 167–174.
- Woychik, R.P., T.A. Stewart, L.G. Lewis, P. D'Eustachio, and P. Leder. 1985. An inherited limb deformity created by insertional mutagenesis in a transgenic mouse. *Nature* **318**: 36–40.
- Woychik, R.P., R.L. Maas, R. Zeller, T.F. Vogt, and P. Leder. 1990. "Formins": Proteins deduced from the alternative transcripts of the *limb deformity* gene. *Nature* **346**: 850–853.
- Wright, M.E. 1947. Undulated: A new genetic factor in *Mus musculus* affecting the spine and tail. *Heredity* **1**: 137–141.
- Xiang, X., K.F. Benson, and K. Chada. 1990. Mini-mouse: Disruption of the pygmy locus in a transgenic insertional mutant. *Science* **247**: 967–969.
- Yanagisawa, K.O., H. Fujimoto, and H. Urushihara. 1981. Effects of the Brachyury (T) mutation on morphogenetic movement in the mouse embryo. *Dev. Biol.* **87**: 242–248.
- Yarden, Y., W.J. Kuang, T. Yang-Feng, L. Coussens, S. Munitz, T.J. Dull, E. Chen, J. Schlessinger, U. Francke, and A. Ullrich. 1987. Human proto-oncogene *c-kit*: A new cell surface receptor tyrosine kinase for an unidentified ligand. *EMBO J.* **6**: 3341–3351.
- Yoshida, H., S.-I. Hayashi, T. Kunisada, M. Ogawa, S. Nishikawa, H. Okamura, T. Sudo, L.D. Shultz, and S.-I. Nishikawa. 1990. The murine mutation osteopetrosis is in the coding region of the macrophage colony stimulating factor gene. *Nature* **345**: 442–443.
- Zdarsky, E., J. Favor, and I.J. Jackson. 1990. The molecular basis of *brown*, an old mouse mutation, and of an induced revertant to wild type. *Genetics* **126**: 443–449.
- Zeller, R., L. Jackson-Grusby, and P. Leder. 1989. The limb deformity gene is required for apical ectodermal ridge differentiation and anteroposterior limb pattern formation. *Genes & Dev.* **3**: 1481–1492.
- Zsebo, K.M., J. Wypych, I.K. McNeice, H.S. Lu, K.A. Smith, S.B. Karkare, R.K. Sachdev, V.N. Yuschenkoff, N.C. Birkett, L.R. Williams, V.N. Satyagel, W. Tung, R.A. Bosselman, E.A. Mendiaz, and K.E. Langley. 1990a. Identification, purification and biological characterisation of hemopoietic stem cell factor from Buffalo rat liver-conditioned medium. *Cell* **63**: 195–201.
- Zsebo, K.M., D.A. Williams, E.N. Geissler, V.C. Broudy, F.H. Martin, H.L. Atkins, R.-Y. Hsu, N.C. Birkett, K.H. Okino, D.C. Murdock, F.W. Jacobsen, K.E. Langley, K.A. Smith, T. Takeishi, B.M. Cattanach, S.J. Galli, and S.V. Suggs. 1990b. Stem cell factor is encoded at the *Sl* locus of the mouse and is the ligand for the *c-kit* tyrosine kinase receptor. *Cell* **63**: 213–224.

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References

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