ENVIGO

Research Models and Services

Inbred Mice

A

Origin

Dr LC Strong, 1921, from a cross between the Cold Spring Harbor and Bagg albino random-bred stocks (and therefore related to BALB/c). In 1928, from Strong to Cloudman, to the Jackson Laboratory, Bar Harbor in 1947. To GD Searle, High Wycombe.

A/JOlaHsd

From GD Searle to OLAC (now Envigo) in 1978.

Research applications

Behavior, lung tumors, carcinogens, teratogenesis, cleft palate, irradiation.

Characteristics

Strain A was the third most widely used strain in cancer and immunology research (Festing, 1969). It is best known for the high incidence of congenital cleft palate in the young (which are usually eaten by the mother), and the high incidence of spontaneous lung tumors. 6-30% incidence of spontaneous lung tumors, which is highly sensitive to the induction of lung adenomas in response to carcinogens (Shimkin and Stoner, 1975).

Animal model

A/J mice are an animal model for human Legionnaire's disease (Brieland *et al*, 1994).

Anatomy

High percent carcass lipid on a high-fat diet (West *et al*, 1992). Small spinal cord, small brain/body weight ratio (Roderick *et al*, 1973). Small relative kidney size (Schlager, 1968). Low total leukocyte count, low erythrocyte count, low hematocrit, low hemoglobin per 100 cm^3 blood (Russell *et al*, 1951). Small thymus/body weight ratio (Belyaev *et al*, 1970). Low proportion acidophilic and high proportion chromophobe cells in adenohypophysis (Keramidas and Symeonidis, 1973). High frequency of mast cells in spleen (Vicklicky, 1967). Low yield of peritoneal exudate cells with low percentage of macrophages and granulocytes but high percentage of lymphocytes (Schwartz *et al*, 1975). Adrenal gland has a high incidence of vacuolisation of the X-zone (Delost and Chirvan-Nia, 1958). Small pituitary (Sinha *et al*, 1975). Number of nipples commonly less than five pairs. Small number of Peyer's patches (Hummel *et al*, 1966). Lower bone mass than C57BL/6 (Kay and Kusy, 1995). Low retinal ganglion cell number (Williams *et al*, 1996). The postnatal cellular proliferation has been described by Crocker *et al* (1970).

Behavior

Low intra-strain aggression (Southwick and Clark, 1966), low food drive and exploratory activity (Thompson, 1953). Low spontaneous bar pressing activity, low open-field activity, low social grooming during aggressive encounters and high tail rattling score during aggressive encounters (Southwick and Clark, 1968).

Low spontaneous locomotor activity (Nikulina *et al*, 1991). High shock avoidance learning (Bovet *et al*, 1966), high avoidance conditioning (Royce *et al*, 1971; Royce, 1972), but poor shock avoidance learning (Wahlsten, 1973), poor T-maze learning (Stasik, 1970). Long latency to attack crickets (Butler, 1973). Long latency to emerge from home cage, low exploration in Y-maze, low rearing, long latency to climb barrier, low hole-in-the-wall entry, low stair climbing (McClearn *et al*, 1970). Poor shock avoidance conditioning and rapid extinction (Schlesinger and Wimer, 1967). Poor performance in a food-seeking task (Henderson, 1970). High social dominance of males in competition for females (De Fries and McClearn, 1970). High open-field defecation in both sexes (Bruell, 1969). Low open-field activity (Bruell, 1964).

Low proportion of paradoxical sleep (Pagel *et al*, 1973), low incidence of tail rattling (St. John, 1973). High shuttle box avoidance (Messeri *et al*, 1972). Low wheel activity (Messeri *et al*, 1972). Low preference for alcohol (Rodgers, 1966).

Drugs

Susceptible to urethane-induced lung tumors (Falconer and Bloom, 1962). Sensitive to induction of pulmonary tumors but resistant to leukemia and liver tumor induction by DMBA given neonatally (Flaks, 1968). Susceptible to the induction of lung tumors by cyclopenta(cd)pyrene (Nesnow *et al*, 1994). Most benzo(a)pyrine-induced lung tumors had K-ras oncogenes inherited from the A/J parent with mRNA transcribed from the allele inherited from strain A/J being 5-20 times more abundant than that from C3H in crosses involving strain C3H (Chen *et al*, 1994) The A/J mouse lung can be used as a model to study the effectiveness of new chemical intervention therapies for controlling malignant tumor growth. (Belinsky *et al*, 1993), and in the study of chemo preventive agents such as dietary and green tea polyphenols (Castonguay and Packer, 1993, Katiyar *et al*, 1993), isothiocyanates (Adam-Rodwell *et al*, 1993, Hecht, 1995), vitamin E (Yano *et al*, 1994b) and other substances (Yun *et al*, 1995). No glycerol-associated effect on active oxygen formation and thiobarbituric acid reactive substances was observed in the lungs of A/J mice treated with 4-nitroquinoline 1-oxide, in contrast with outbred ddY strain mice (Yano *et al*, 1993; Yano *et al*, 1994a). Nicotine decreases shock avoidance learning in J substrain, but increases it in He substrain (Bovet *et al*, 1966). Low ED50 to behavioral effects of nicotine. Resistant to seizures induced by nicotine (Marks *et al*, 1989) Susceptible to skin ulceration by DMBA (Thomas *et al*, 1973). Not sensitive to histamine (Brown, 1965). Susceptible to the teratogenic effect (cleft palate) of cortisone acetate (Dostál and Jelinek, 1973; Kalter, 1965; Kalter 1981). There appears to be a threshold dose of cortisone needed to induce cleft palate (Fawcett *et al*, 1996). Sensitive to teratogenic effect (malformed ribs and vertebre) of hypoxia on ninth day of gestation (Dagg, 1966). Sensitive to X-irradiation (Roderick, 1963; Storer, 1966). Highly susceptible to endotoxin lipopolysaccharide (Heppner and Weiss, 1965). Resistant to hyperbaric oxygen (Hill *et al*, 1968). Susceptible to pulmonary hyaline-membrane formation in 90% oxygen (Lieberman and Kellog, 1967). Low LD50 to X-irradiation (Yuhas and Storer, 1969). Interstitial tumors of testis readily induced with oestrogens (Heston, 1963). Sensitive to chloroform toxicity (Deringer *et al*, 1953). Thalidomide increases congenital malformations such as cleft lip and palate (Szabo and Steelman, 1967). High bronchial reactivity to methacholine and serotonin (Konno *et al*, 1993). Susceptible to daunomycin-induced nephrosis (Kimura *et al*, 1993). Resistant to hepatotoxic effects of cadmium (Shaikh *et al*, 1993). Airways hyperreactive to acetylcholine (Zhang *et al*, 1995). Susceptible to ozone-induced decreases of tracheal potential (Takahashi *et al*, 1995). Clonidene failed to produce an aggressive behavioral response (Nikulina and Klimek, 1993). A diet containing 15% dairy fat, 1% cholesterol and 0.5% cholic acid caused a high incidence of cholesterol gallstones (like SWR, C57L, contrast SM, AKR, DBA/2) (Faulkner *et al*, 1995).

Endocrinology

The adrenal and renal functions have been described by Shire (1968).

Genetics

Coat color genes	- a, b, c : albino
Histocompatibility	- *H-2*^{a}
Biochemical markers	- *Apoa-1*^{b}, *Car-2*^{b}, *Es-1*^{b}, *Es-2*^{b}, *Es-3*^{c}, *Gpd-1*^{b}, *Gpi-1*^{a}, *Hbb*^{d}, *Idh-1*^{a}, *Ldr-1*^{a}, *Mod-1*^{a}, *Pep-3*^{b}, *Pgm-1*^{a}, *Trf*^{b}

This strain carries the *Mus musculus musculus* Y-chromosome, while others have the *M. m. domesticus* type (Nishioka, 1987).

Immunology

Develops autoimmune phenomena, immunological deficits with ageing and autoimmunity following neonatal thymectomy (Yunis *et al*, 1972). Low lymphocyte phytohemagglutinin response (Heiniger *et al*, 1975). Serum antinuclear factor 11% (Barnes and Tuffrey, 1967). 11% incidence of antinuclear antibody by 16 months (Teague *et al*, 1972). Good immune response to small doses of bovine gamma-globulin (Levine and Vaz, 1970). Poor immune response to Cholera A and B antigens (Cerny *et al*, 1971). Good immune response to ovomucoid but poor response to bovine serum albumin (James and Milne, 1972). Good immune response to DNP-keyhole limpet hemocyanin (Borel and Kilham, 1974).

Good immune response to GAT (random terpolymer of Glu^{60}, Ala^{30}, Tyr^{10}) (Dorf *et al*, 1974). Poor primary hemagglutinin immune response to sheep erythrocytes at 3 x 10^{7} and 3 x 10^{8} dose rates, also poor hemolysin response at both doses (Ghaffar and James, 1973). High IgM antibody response to sheep red blood cells compared with C57BL/10ScSn (Vetvicka *et al*, 1993). Non-responder to synthetic polypeptide Glu^{57}, Lys^{38}, m-Ala^{5} (Pinchuck and Maurer, 1965). High antibody affinity to HSA (Petty *et al*, 1972). Erythrocytes have a high agglutinability (Rubinstein *et al*, 1974). Low immune response to ferritin in *A-Thy1.1* (Young *et al*, 1976). Low immune response to dextran (Blomberg *et al*, 1972). Non-discrimination between `H' and `L' sheep erythrocytes (McCarthy and Dutton, 1975). Susceptible to the induction of experimental autoimmune orchitis induced by two or three sc injections with viable syngeneic testicular germ cells without any adjuvants (Tokunaga *et al*, 1993). Resistant to induction of experimental allergic encephalomyelitis (Lindsey, 1996). This strain also suffers from a defect in macrophage function somewhat resembling the mutant *lps* found in C3H/HeJ (Vogel *et al*, 1981). High immune response to ganglio-series gangliosides (Kawashima *et al*, 1992). Interleukin-3 alone does not support hematopoietic colony formation of bone marrow cells from these mice. Interleukin-3R alpha is not detectible on the cell surface by antibody staining, though it is present inside the cells (Ichihara

et al, 1995; Leslie *et al*, 1996). High immunological response to *Salmonella typhi* porins (Gonzales *et al*, 1995). C-5 complement deficient (Ooi and Colten, 1979).

Infection

Resistant to infection by *salmonella typhimurium* strain C5 (Plant and Glynn, 1974; Robson and Vas. 1972). This may be associated with activation of complement (Nakano *et al*, 1995). 100-fold more susceptible to *Listeria monocytogenes monocytogenes* than C57BL/6 when measured by median lethal doses (Sadarangani *et al*, 1980). This seems to be associated with reduced levels of gamma interferon and granulocyte-macrophage colony stimulating factor compared with resistant C57BL/6 mice (Iizawa *et al*, 1993). Susceptible to *Plasmodium berghei* (Most *et al*, 1966). Highly susceptible to mammary tumor virus, which is carried in an acute form in unfostered substrains (Murray and Little, 1967).

High susceptibility to BALB/Tennant leukemia virus (Tennant, 1965). Susceptible to *Herpes simplex* virus (Lopez, 1975). Resistant to oncogenic effects of polyoma virus given at birth (Law, 1966). Susceptible to *Mycobacterium marinum* but poor plateau harvest of M. lepre eight months after infection (Shepard and Habas, 1967). Susceptible to infection by *Mycobacterium marinum* (Yamamoto *et al*, 1991). Resistant to mouse hepatitis virus type 3 infection though Ps substrain susceptible (Le Prevost *et al*, 1975). High mortality in a natural epizootic of ectromelia (Briody, 1966). Resistant to mouse hepatitis virus (Bang and Warwick, 1960). Susceptible to infection with *Ehrlichia risticii* (Williams and Timoney, 1994). Resistant, with low amylase response to the fungus Paracoccidioides brasiliensis (Xidieh *et al*, 1994). Encephalo-myocarditis virus causes diabetes mellitus (Boucher *et al*, 1975). Highly susceptible to infection by measles virus (Rager-Zisman *et al*, 1976).

Legionella pneumophila replicates within and kills thioglycolate-elicited macrophages, in contrast with strain BALB/c. This is associated with differences in availability of intracellular iron (Gebran *et al*, 1994). Develops acute pneumonia that resembles human Legionnaire's disease 24 to 48 hours after intratracheal inoculation of *Legionella pneumophila* (Brieland *et al*, 1994). Susceptibility to most strains of Legionella depends on the *Lgn1* locus (Miyamoto *et al*, 1996). Resistant to the lethal effects of murine hepatitis virus strain 3 (contrast BALB/c), but resistance destroyed by methylprednisolone (Fingerote *et al*, 1995). Highly susceptible to infection with *Candida albicans* (Ashman *et al*, 1996). Mice infected with Sendai virus or MHV had impaired wound healing. However Herpes simplex virus, type 1, did not reduce tensile strength (Kenyon, 1983).

Life-span and spontaneous disease

Primary lung tumors 6% in male, 32% in female and 26% in virgin females in J substrain; 44% in males, 23% in females and 30% in virgin females in He substrains (Hoag, 1963). Zero incidence of lymphatic leukemia in He substrain, 1% in J substrain. Mammary adenocarcinoma zero in males, 1% in virgin females, 28% in breeding females of J substrain and 54% in breeding females of He substrain (Hoag, 1963). Pulmonary tumors 90% in mice at 18 months (Heston, 1963). Leukemia 3% in HeJ substrain (Myers *et al*, 1970). A high proportion of the mammary tumors are of the acinar type (Tengbergen, 1970). Lung adenomas 53-64% in BrA and A substrains, but mammary tumors zero (Muhlbock and Tengbergen, 1971). Lung tumors 4-31% and lymphatic leukemia 10-43% (Festing and Blackmore, 1971). Spontaneous lung tumors occur at rate of 0.21 tumors/mouse at 24 weeks (Poirier *et al*, 1975). Rare spontaneous myoepitheliomas arising from myoepithelial cells of various exocrine glands have been observed in the J and HeJ substrains (Sundberg *et al*, 1991).

Median life-span 16.3 months in A/J males and 19.7 months in A/J females (Storer, 1966). Median life-span 17.1 months in A/Lac males and 18.6 months in A/Lac females (Festing and Blackmore, 1971). Median life-span 22.1 months in A/J males and 22.9 months in A/J females (Goodrick, 1975). Median life-span 15.6 and 17.3 months in A/HeJ males and 19.9 and 20.3 months in A/HeJ females (Les, 1969). Median life-span 18.9 and 21.1 months in A/J males and 18.5 and 25.9 months in A/J females (Les, 1969). Median life-span 21.7 months in A/WySn males and 20.8 months in A/WySn females (Walford, 1976).

Spontaneous congenital cleft palate 4% and high susceptibility to teratogenic effects of cortisone, which may be associated with the H2a allele, (Bonner and Slavkin, 1975). Congenital malformations in new-born mice 10%, including cleft lip and palate and polydactyly (Kalter, 1968). WySn substrain has 20% cranofacial defects due to the action of two genetic loci with unequal duplicate epistasis (Juriloff, 1995). Cleft palate is a function of foetal genotype rather than maternal factors (Yoshida *et al*, 1996). An exclusion map for the major gene causing nonsyndromic cleft lip with or without cleft palate has swept 40% of the mouse genome, with candidate regions on chromosomes 12, 18 and 19 with a few candidate loci (Juriloff, 1993).

Low incidence of virus-like particles in chemically induced sarcomas (Liebelt *et al*, 1970). Can be made obese by a suitable diet (Fenton and Dowling, 1953). Does not develop non-insulin-dependent diabetes mellitus and hypertension when fed a high fat-high simple carbohydrate diet, whereas C57BL/6 mice do (Mills *et al*, 1993). Blood glucose levels and insulin insensitivity in crosses between diet-induced type II diabetes sensitive C57BL/6 and resistant A/J are genetically independent (Surwit *et al*, 1991). High incidence of amyloidosis (Russell and Meier, 1966). No amyloidosis found by Powers *et al* (1976) in He and HeJ substrains, in contrast to previous reports. About 4% incidence of congenital open eyelids (Dagg, 1966). Relatively resistant to secondary amyloidosis which does not appear to be associated with variation in the serum amyloid A gene cluster (Butler and Whitehead, 1994). Incidence of mammary tumors high in breeding females, but very low in virgins (Heston and Vlahakis, 1971). The relationship of genotype, sex, body weight, and growth parameters to lifespan in inbred and hybrid mice have been described by Ingram *et al* (1982). The occurrence of epithelial

and non-epithelial tumors in aging mice have been described by Kawada and Ojima (1977). A review of the life span of aging mice has been described by Myers, (1978).

Miscellaneous

Recommended host for the following transplantable tumors: Anaplastic carcinoma 15091 AK, Hepatoma H6, round cell tumor C 1300 and spindle cell carcinoma Sal. (Kaliss, 1972). Injection of murine C-1300 neuroblastoma cells into the tail vein provides a reproducible model for bone marrow metastasis (Iwakawa *et al*, 1994). A/He mice will be useful for study of teratocarcinogenesis because of the high incidence of experimentally produced teratomas and the extreme low incidence of spontaneous teratomas (Stevens, 1970). Characteristics of the A strain have been described by Festing (1997) and Lyon *et al*, (1996).

Physiology and biochemistry

Low metabolic rate (Storer, 1967). High plasma testosterone level and binding capacity (Hampl *et al*, 1971). Low Na/K ratio in erythrocytes and plasma (Waymouth, 1973). Low serum ceruloplasmin in males but intermediate in females (Meier and MacPike, 1968). Low systolic blood pressure (Schlager and Weibust, 1967). Low peripheral nerve conduction velocity (Hegmann, 1972). High concentration of prostaglandin F in epididymis (Badr, 1975). High glucose-6-phosphate dehydrogenase and nicotinamide-adenine dinucleotide phosphate levels in erythrocytes (Erickson, 1974). High sensitivity to thyrotrophin (Levy *et al*, 1965). Mammary gland insensitive to oestradiol and progesterone (Singh *et al*, 1970). High glucose-6-phosphate dehydrogenase activity (Hutton, 1971). High brain acetylcholinesterase activity (Pryor *et al*, 1966). High rectal but low tail temperature (Shepard and Habas, 1967). Low serum calcium level at four months of age (Barrett *et al*, 1975). Responds by higher growth rate on high fat diets (Fenton and Carr, 1951). Low cell turnover as estimated by slow clearance of DNA-bound radioactivity in J and He substrains, (Heiniger *et al*, 1972). High erythrocyte catalase level (Hoffman and Rechcigl, 1971). Low kidney and liver arylsulphatase activity (Daniel, 1976). High hepatic delta-aminolevulinic acid synthetase activity after DISC treatment (Gross and Hutton, 1971).

High basal serum prolactin level in females of St substrain (Sinha *et al*, 1975). Urine has high osmolality (Silverstein, 1961). Blood catalase has high specific activity (Magdon, 1962). Resistant to the development of atherosclerosis on a semi-synthetic high fat diet. (Nishina *et al*, 1993).

Reproduction

Intermediate breeding performance, litter size 4.9, sterility 11.5% (Nagasawa *et al*, 1973). High ratio of females at birth (Cook and Vleck, 1961).). Low litter size and large proportion of infertile matings (Fernandes *et al*, 1973). Low litter size (Verley *et al*, 1967).

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