ENVIGO

Research Models and Services

Inbred Rats

# F344 (Fischer 344)

## Origin

Developed in 1920 by Curtis and Dunning at the Columbia University Institute for Cancer Research, Irvington, NY, USA. The stock was purchased from a commercial breeder called "Fischer". In 1949 to Heston, National Cancer Institute, Bethesda, MD 20205, USA and in 1950 to Hansen, National Institutes of Health, Bethesda, MD 20205, USA. Subsequent sub-lines from either the Dunning or Hansen colonies. From Dr. Carl Hansen, to Laboratory Animals Centre, Carshalton at F43.

### F344/NHsd

In 1977, from Laboratory Animals Centre to OLAC (now Envigo).

## Characteristics

The F344 rat is widely used in gerontology and in carcinogenicity testing programs.

### Animal model

The Fischer rat is useful for the following animal models: phenylketonuria (Anderson, 1982), interstitial cell tumor of the testis, urinary bladder carcinoma, esophageal carcinoma, and Lyme disease (Barthold *et al*, 1988).

### Anatomy

Unlike seven other strains it does not develop brownish skin scales on the dorsum of the body, the perineum and the tail (Tayama and Shisa, 1994). Low relative heart weight in ten weeks old males (Tanase *et al*, 1982).

### Behavior

Low open field defecation in males (Harrington, 1972). Low wheel activity (Harrington, 1971). Moderately easy to handle. Low response to operant morphine-reinforced behavior (Ambrosio *et al*, 1995). Low preference for ethanol and low capability to develop acute tolerance to ethanol hypnosis, like BN/Rij (York and Chan, 1994). Behavioral performance declined more rapidly with aging than in strain BN (Spangler *et al*, 1994). Develops smaller acoustic and tactile startle response than strain LEW, which may be associated with strain differences in hypothalmic-pituitary-adrenal activation (Glowa *et al*, 1992). Unusual in its lack of preference for any concentration of salt. However, there is a dramatic change from aversion to preference following transaction of the chorda tympani nerve, which in other strains causes little change in salt preference (Sollars and Bernstein, 1994). A preference can be induced by depletion of sodium chloride (Breslin *et al*, 1995). F344 rats have been used in anxiety studies (Bert *et al*, 2001).

### Drugs

Neurological toxicity of polybrominated biphynals and acrylamide described by Tilson *et al* (1978) and Tilson and Cabe (1979a,b). Low biliary excretion of copper after intravenous injection of $CuSO_4$ (Nederbragt and Lagerwerf, 1986). Susceptible to the induction of tumors of the tongue by 4-nitroquinoline-1-oxide (Tanaka *et al*, 1993). Susceptible to the development of anaplastic astrocytomas and glioblastomas following treatment with N-methyl-N-nitrosourea in the drinking water (Shibutani *et al*, 1993).

Isolated tracheal rings hyperresponsive to carbachol compared with LEW and F344 (Jia *et al*, 1995). Relatively insensitive to the induction of tumors by N-methyl-N-nitrosourea (MNU) following treatment with cyproterone acetate, which caused a high incidence of tumors in the outbred Cpb:WU strain (Bosland *et al*, 1992a).

However, treatment with cyproproterone acetate for 21 days, testosterone proprionate for three days and a single i.p. injection of MNU results in atypical hyperplasia of the ventral prostate (Bosland *et al*, 1992b). Severity of spontaneous nephropathy in aged rats reduced by treatment with arylsulfonylurea (Milman *et al*, 1979). Exposure of weanling rats to

terephthalic acid or dimethyl terephthalate in the diet induced urolithiasis (Wolkowski *et al*, 1982). Phenylketonurea can be induced by p-Chloro-DL-phenylalanine with L-phenylalanine (Andersen and Guroff 1974; Anderson 1982). Bleomycin induces pulmonary fibrosis, which can be reduced by treatment with indomethacin (Thrall *et al*, 1979). Treatment with 3,2'-dimethyl-4-aminobiphenyl (DMAB) provides the best model for prostatic cancer of five tested (Shirai *et al*, 1990). Slow metabolizer of MPPB (Takahara *et al*, 1993). Morphine does not increase nose-poking behavior, and phenobarbital does not decrease it (Witkin and Goldberg, 1992). Compared with LEW rats, F344 rats show a much lower preference for several classes of drugs of abuse. This may be associated with levels of neurofilament proteins in the ventral segmental area of the brain (Guitart *et al*, 1992). Duration of morphine-induced EEG slow-wave bursts and associated behavioral stupor was less in F344 than in LEW (Mayomichelson and Young, 1993a). F344 rats self-administer less morphine than LEW rats (Gosnell and Krahn, 1993). Duration of EEG slow-wave bursts and behavioral stupor also shorter in F344 than in LEW following administration of ethylketocyclazocine, suggesting differences in opioid-related receptor populations between these strains (Mayomichelson and Young, 1993b). Resistant to the organophosphate diisopropyl fluorophosphate (DFP) in terms of hypothermic response and recovery of day-night difference in core temperature (Gordon and Watkinson, 1995). Resistant (compared with Sprague Dawley rats) to the ventricular hypertrophy and pressure changes induced by monocrotaline. This is associated with pulmonary vascular response rather than hepatic metabolism (Pan *et al*, 1993). Oral administration of hydroquinone for two years resulted in dose-related nephropathy and renal tubule adenomas in males but not females, whereas Sprague Dawley rats were resistant (English *et al*, 1994). Sensitive to the convulsive effects of kainic acid (Golden *et al*, 1995). Relatively resistant to carcinogenic effects of tamoxifen, possibly associated with reduced cell proliferation in the liver (Carthew *et al*, 1995). Intermediate incidence of colorectal cancer after injections of azoxymethane (Kobaek-Larsen *et al*, 2002).

## Genetics

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| Coat color genes | - *a, B, c, h* : albino. |
| Histocompatibility | - *RT1$^{lv1}$, RT2$^{a}$, RT3$^{b}$, RT8$^{b}$*. |
| Immunoglobulins | - Igk-1$^{b}$, Igh-1$^{a}$, Igh-2$^{a}$, Igh-3$^{a}$ (Leslie, 1984). |
| Biochemical markers | - *Acon-1$^{b}$, Acp-2$^{a}$, Ahd-2$^{c}$, Akp-1$^{a}$, Alb$^{a}$, Amyl$^{a}$, Cryg-1$^{b}$, Es-1$^{a}$, Es-2$^{a}$, Es-3$^{a}$, Es-4$^{b}$, Es-6$^{a}$, Es-7$^{b}$, Es-8$^{b}$, Es-9$^{a}$, Es-10$^{a}$, Es-14$^{b}$, Es-15$^{b}$, Es-16$^{b}$, Es-18$^{a}$, Fh$^{b}$, Gc$^{a}$, Glo-1$^{a}$, Gox-1$^{a}$, Hbb$^{a}$, Igk-1$^{b}$, Lap$^{a}$, Mgd-1$^{a}$, Mup-1$^{b}$, Pep-3$^{b}$, Pgd$^{b}$*. (Bender *et al*, 1994). |

## Immunology

Resistant to spontaneous autoimmune thyroiditis (Hajdu and Rona 1969), but susceptible to experimental allergic encephalomyelitis (Gasser *et al*, 1975), experimental allergic neuritis (Levine and Wenk, 1968), and autologous immune complex nephritis (Watson and Dixon, 1966). Relatively insensitive to the induction of experimental autoimmune glomerulonephritis (Sado *et al*, 1986). Susceptible to the development of experimental autoimmune myasthenia gravis (Biesecker and Koffler, 1988). Resistant to the induction of thyroiditis by 3-methylcholanthrene (Glover *et al*, 1969). Resistant to group A *Streptococcus pyogenes* and *Lactobacillus casei*-induced chronic polyarthritis (Lehman *et al*, 1984). Epitope specificities of collagen-induced arthritis studied by Cremer *et al*, (1992). Normally resistant to the development of adjuvant arthritis, but germ-free F344 rats are susceptible, and the use of paraffin oil rather than mineral oil also induces susceptibility (Vandelangerijt *et al*, 1993). Low antibody response to streptococcal group A carbohydrate, not linked to the MHC (Stankus and Leslie, 1976). Neonatal pancreatic islets derived by non-enzymic (in vitro) isolation procedures can be transplanted across MHC barriers without any immune suppression, in contrast with other strains such as ACI (Ketchum *et al*, 1992). Tachykinins cause bronchoconstriction in susceptible F344 mainly by an indirect mechanism that involves stimulation of NK1 receptors and mast cell activation, in contrast with the less sensitive strain BDE where they cause bronchoconstriction by a direct effect on the airway smooth muscle via activation of NK2 receptors (Joos *et al*, 1994). Low primary and secondary response to sheep red blood cells (Tada *et al*, 1974).

Poor producers of reaginic antibody in response to ovalbumin in aluminium hydroxide (Murphy *et al*, 1974). Boulter and Sell (1984) have described the alphafetoprotein and albumin genes and compared these with ACI and BUF.

## Infection

Infection with *Hymenolepis diminuata* cysticercoids results in no worm loss and no mastocytosis in contrast with DA, where there was significant mastocytosis six weeks post infection and low persistence of worms (Ishih, 1992).

## Life-span and spontaneous disease

Life-span and tumor incidence depend both on strain characteristics and the environment. The following has been reported: Median lifespan about 31 months in males and 29 months in females with about 87% survival to 24 months in both sexes. (Sass *et al*, 1975). Cameron *et al*, (1985) found a 75% survival at 26 months of age. Mean lifespan 24 months in both sexes in presence of severe pulmonary infection (Davey and Moloney, 1970). Median lifespan 23-31 months in barrier-reared males and 26-29 months in barrier-reared females (Sass *et al*, 1975, Coleman *et*

*al*, 1977; Jacobs and Huseby, 1967; Hoffman, 1979; Yu *et al*, 1982). Food restriction to 60% of ad-libitum prolongs median lifespan to more than 34 months in males (Yu *et al*, 1982), but food restriction limited to early life and protein restriction caused only a small increase in longevity (Yu *et al*, 1985). Other studies of lifespan and neoplasia include Solleveld *et al* (1984) and Maekawa *et al* (1983). Most animals older than 2 years exhibit small local areas of nephritis; less than 25% show severe nephritis (Snell,1967).

Tumors: Mammary tumors 41% in females and 23% in males, pituitary adenomas 36% in females and 24% in males, testicular interstitial cell tumors 85% in males. Other tumor types less common (Sass *et al*, 1975). Thyroid carcinoma 22% (Lindsey *et al*, 1968). Interstitial cell testicular tumors 65%, mononuclear cell leukemia 24%, subcutaneous fibroadenoma 9% in females. Both sexes have a 5% incidence of nodular hyperplasia of the liver. (Davey and Moloney, 1970). In various studies incidence of leukemia's 23-26% and of testicular interstitial tumors 65-90% (Jacobs and Huseby, 1967; Davey and Moloney, 1970; Moloney *et al*, 1970; Sass *et al*, 1975; Cockrell and Garer, 1976). Uterine polyploid tumors of endometrial origin 21% (Jacobs and Huseby, 1967). In germ-free conditions leukemia 26% in males, 36% in females, mammary tumors 12% in males 20% in females, all other tumors 9% in males, 5% in females (Sacksteder, 1976).

Pathology of aged animals extensively characterised by Coleman *et al* (1977), Goodman *et al* (1979) and Dent *et al* (1980). Aged rats exhibit peripheral retinal degeneration, which is exacerbated by fluorescent light of moderate intensity (32 foot-candles). They also develop cardiomyopathy with myocardial degeneration, fibrosis and chronic interstitial myocarditis (males 33%, females 18%) and nephropathy (67% in males, 39% in females) (Lai *et al*, 1979).

Retinas of both sexes show a steady decline with age in the thickness of the outer nuclear layer and photoreceptor layer, with a drastically accelerated rate of peripheral retinal degeneration seen only in males after 12 months of age (Diloreto *et al*, 1994; Faktorovich *et al*, 1992). Food restriction initiated at six months of age was as effective as food restriction initiated at 6 weeks of age in slowing the progression of chronic nephropathy and cardiomyopathy and in delaying the occurrence of neoplasia (Maeda *et al*, 1985).

Reduction of mineral or protein or fat intake without a reduction of energy had, at most, marginal effects on fatal neoplastic disease (Shimokawa *et al*, 1991).

## Miscellaneous

A detailed account of the pathology of F344 rats is given by Boorman *et al* (1990). Hematological parameters have been described by Lovell *et al* (1981). Effects of restraint, cage transportation, anesthesia and repeated bleeding on plasma glucose levels have been described by Tabata *et al* (1998). Characteristics of the COP strain have been described by Festing (1979) and Greenhouse *et al* (1990).

## Physiology and biochemistry

Growth described by Cameron *et al* (1985). Resistant to the development of salt-induced hypertension (Hall *et al*, 1976). High specific activity but low inducibility of NADP cytochrome C reductase compared with outbred Sprague Dawley rats (Gold and Widnell, 1975). Hepatic microsomal activity before and after induction by phenobarbitone well characterized (Page and Vesell, 1969; Gold and Widnell, 1975; Dent *et al*, 1980). Large pituitaries, susceptible to Cysticercus in infection and rapid absorption of diethylstilboestrol leading to death (Dunning *et al*, 1947). Low LD50 of pentobarbital sodium (70mg/kg) (Shearer *et al*, 1973). Have substantially higher levels of diurnal and stress-related corticosterone levels with higher levels of corticosteroid-binding globulin in plasma, spleen and thymus than LEW or Sprague Dawley rats (Dhabhar *et al*, 1993). Higher concentrations of cortical and hippocampal 5-HT1A receptors compared with LEW rats (Burnet *et al*, 1994). Hippocampal neurones are more vulnerable to ischemic insult than those of other strains (Iwasaki *et al*, 1995).

## Reproduction

Short gestation period: 22.47 ± .36 days (Peters, 1986). Good breeding performance and large litter size. Males reach sexual maturity between 10 and 15 weeks, as determined by sperm production rate and other indicators of testicular and epididymal function (Blazak *et al*, 1985).

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