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Animal Models of Disease

Metabolic, Renal and Cardiovascular

GK (Goto-Kakizaki) Rat

Strain Code: 460 Nomenclature: GK/TohiCskCrljCrl Therapeutic Area: Metabolic Control: Crl:WI (Wistar) Origin: The Goto-Kakizaki (GK) rat is a non-obese Wistar substrain that develops adult onset type 2 diabetes early in life. This model was developed in the 1970s by Goto and associates at Tohoku University in Sendai, Japan, by selecting breeder pairs with the highest blood glucose levels (OGTT) from a colony of Wistar rats. Repeated selection of breeders based on OGTT resulted in glucose intolerance after five generations. To Charles River Japan from Chugai Pharmaceutical Co., in 1995. To Charles River North America in 2006. Characteristics: Non-Obese, Type 2 Diabetes, Hyperinsulinemia, Insulin Resistance, Mild Hyperglycemia, Neuropathy, Osteopathy, Retinopathy, Nephropathy. *The GK rat is a non-obese, type 2 diabetes model.*

References: Goto, Y., Kakizaki, M. & Masaki, N. Spontaneous diabetes produced by selective breeding of normal Wistar rats. *Proc. Jpn. Acad.* **51**, 80-5 (1975).

Ostenson, C.G. The Goto-Kakizaki Rat. *Animal Models of Diabetes Frontiers in Research,* 2nd edition. Edited by Eleazar Shafrir. CRC Press, 119-37 (2007).

ZDF (Zucker Diabetic Fatty) Rat

Strain Code: 370 (obese), 380 (lean fa/+), 371 (lean +/?) Nomenclature: ZDF-*Lepr*^{fa}/Crl Therapeutic Area: Metabolic Control: ZDF lean Origin: Originated in a colony of outbred Zucker rats in the laboratory of Dr. Walter Shaw at Eli Lilly Research Laboratories in Indianapolis, Indiana. To Dr. Julia Clark at the Indiana University Medical School (IUMS) in 1977. To Dr. Richard Peterson at IUMS in 1981. To Genetic Models, Inc., in 1991. To Charles River in 2001. Characteristics: Obesity, Insulin Resistance, Hyperinsulinemia, Type 2 Diabetes, Hyperglycemia, Hypertriglyceridemia, Hypercholesterolemia, Nephropathy, Impaired Wound Healing, Mild Hypertension, Neuropathy. *The ZDF rat is a popular obese, type 2 diabetes model.*

References: Belin de Chantemèle, E.J., et al. Type 2 diabetes severely impairs structural and functional adaptation of rat resistance arteries to chronic changes in blood flow. *Cardiovasc. Res.* **81(4)**, 788-96 (2009).

Leonard, B.L., et al. Insulin resistance in the Zucker diabetic fatty rat: a metabolic characterisation of obese and lean phenotypes. *Acta. Diabetol.* **42(4)**, 162-70 (2005).

Schmidt, R.E., Dorsey, D.A., Beaudet, L.N. & Peterson, R.G. Analysis of the Zucker Diabetic Fatty (ZDF) type 2 diabetic rat model suggests a neurotrophic role for insulin/IGF-I in diabetic autonomic neuropathy. *Am. J. Pathol.* **163(1)**, 21-28 (2003).

Overview

Worldwide incidence of cardiovascular, metabolic and renal diseases continues to rise due to growing rates of obesity, type 2 diabetes and hypertension, increasing the priority for developing new methods and technologies to investigate and fight these diseases. Specific animal models for studying these disease conditions can help support research efforts towards finding the necessary cures.

Charles River's Disease Models program supports these efforts by making rodent models available for the study of cardiovascular, metabolic and renal diseases and their related complications. Additionally, through our Discovery and Imaging Services and Preclinical Services groups we have extensive experience using multiple models and species within these therapeutic areas.



Zucker Rat

Strain Code: 185 (obese), 186 (lean +/?) Nomenclature: Crl:ZUC-*Lepr*^{fa} Therapeutic Area: Metabolic Control: Zucker lean Origin: The obese condition appeared spontaneously in the 13M strain when crossed to the Sherman strain. Dr. Theodore and Dr. Lois Zucker maintained the colony at the Laboratory of Comparative Pathology in Stow, MA. Colonies were established at many institutions from this nucleus colony. To Charles River in 1985 from a research colony maintained at a pharmaceutical company. Characteristics: Obesity, Insulin Resistance, Hyperinsulinemia, Hypertriglyceridemia, Hypercholesterolemia, Metabolic Syndrome. *The Zucker rat is commonly used as an obese metabolic syndrome model.*

References: Augstein, P. & Salzsieder, E. Morphology of Pancreatic Islets: A Time Course of Pre-diabetes in Zucker Fatty Rats. *Methods Mol. Biol.* **560**, 159-89 (2009).

Frisbee, J.C. Hypertension-independent microvascular rarefaction in the obese Zucker rat model of the metabolic syndrome. *Microcirculation.* **12(5)**, 383-92 (2005).

Zucker, T.F. & Zucker, L.M. Hereditary obesity in the rat associated with high serum fat and cholesterol. *Proc. Soc. Exp. Biol. Med.* **110**, 165-71 (1962).

Obese Prone (OP-CD) Rat

Strain Code: 463 Nomenclature: Crl:OP(CD) Therapeutic Area: Metabolic, Cardiovascular Control: OR-CD Origin: Developed from a line of Crl:CD(SD) rats by selecting future breeders with accelerated weight gain. Two lines were developed from this outbred colony, the OP-CD (Obese Prone) and OR-CD (Obese Resistant). The OP-CD becomes obese when fed high-fat diets eliminating the subpopulation of non-responders. Polygenic obesity develops despite having a fully functioning leptin receptor. The OR-CD is the control model. Characteristics: Obesity, Metabolic Syndrome, Hypertension, Hypertriglyceridemia, Hyperinsulinemia, Insulin Resistance. *The OP-CD is a polygenic obesity rat model.*

Obese Resistant (OR-CD) Rat

Strain Code: 462 Nomenclature: Crl:OR(CD) Therapeutic Area: Metabolic, Cardiovascular Origin: Developed from a line of Crl:CD(SD) rats by selecting future breeders with accelerated weight gain. Two lines were developed from this outbred colony, the OP-CD (Obese Prone) and OR-CD (Obese Resistant). The OR-CD does not become obese (non-responder) when fed high-fat diets. Characteristics: Obesity Non-Responder, Hyperinsulinemic, Insulin Resistant. *The OR-CD is the control for the OP-CD.*

THE POUND MOUSE™

Strain Code: 457 (obese), 464 (lean +/?) Nomenclature: C57BL/6NCrl-*Lepr*$^{db\text{-}lb}$/Crl Therapeutic Area: Metabolic Control: THE POUND MOUSE™ lean or the standard C57BL/6NCrl Origin: This model was isolated from a C57Bl/6NCrl colony in a Charles River barrier facility in the United States in 2005. The mutation was mapped to a region within less than 2 centimorgan (cM) of the leptin receptor on Chr. 4. Characteristics: Obesity, Hyperinsulinemia, Insulin Resistance, Dyslipidemia, Metabolic Syndrome, Leptin Receptor Deficiency, Fatty Liver Disease. *THE POUND MOUSE™ is a recently established pre-diabetes/metabolic syndrome model.*

ZSF1 Rat

Strain Code: 378 (obese), 379 (lean +/?) Nomenclature: ZSF1-*Lepr*^{fa} *Lepr*^{cp}/Crl Therapeutic Area: Renal, Metabolic, Cardiovascular Control: ZSF1 lean Origin: This hybrid rat is a cross between a ZDF female and an SHHF male rat. It was developed at Genetic Models, Inc. (GMI). Charles River acquired GMI in 2001. Characteristics: Nephropathy, Congestive Heart Failure, Hypertension, Obesity, Type 2 Diabetes, Insulin Resistance, Hyperinsulinemia, Hypertriglyceridemia, Hypercholesterolemia. *The obese ZSF1 is commonly used to study renal failure with additional disease complications.*

References: Dominguez, J.H., et al. Renal injury: Similarities and differences in male and female rats with the metabolic syndrome. *Kidney Int.* **69**, 1969-76 (2006).

Tofovic, S.P., Salah E.M., Jackson, E.K. & Melhem, M. Early renal injury induced by caffeine consumption in obese, diabetic ZDF1 rats. *Renal. Failure* **29**, 891-902 (2007).

Dahl/Salt Sensitive (Dahl/SS) Rat

Strain Code: 320 Nomenclature: SS/JrHsdMcwiCrl Therapeutic Area: Renal, Cardiovascular Control: SS-Chr 13^{BN}/McwiCrl Origin: Inbred from a congenic group of Dahl/SS rats (SS/JrHsd) from Dr. Theodore Kurtz at UCSF. Originally derived from the Harlan SS/Jr colony. To the Medical College of Wisconsin in 1991. To Charles River in 2001. Characteristics: Hypertension, Insulin Resistance, Hyperinsulinemia, Hypertriglyceridemia, Hypercholesterolemia, Nephropathy, Cardiac Hypertrophy, Heart Failure. *The Dahl/Salt Sensitive rat model develops hypertension and renal failure when fed diets with high salt content.*

References: Castrop, H. & Kurtz, A. Differential nNOS gene expression in salt-sensitive and salt-resistant Dahl rats. *J. Hypertens.* **19.7**, 1223-31 (2001).

Chen, P.Y., et al. Hypertensive nephrosclerosis in the Dahl/Rapp rat. Initial sites of injury and effect of dietary L-arginine supplementation. *Lab. Invest.,* **68.2**, 174-84 (1993).

Rapp, J.P. & Dene, H. Development and characteristics of inbred strains of Dahl salt-sensitive and salt-resistant rats. *Hypertension.* **7**, 340-49 (1985).

SS-13^{BN} Rat

Strain Code: 334 Nomenclature: SS-Chr 13^{BN}/McwiCrl Therapeutic Area: Renal, Cardiovascular Origin: A consomic rat model developed at the Medical College of Wisconsin, in which chromosome 13 from the normotensive inbred Brown Norway rat was introgressed into the background of the Dahl/Salt Sensitive rat. Characteristics: Insulin Resistant, Hyperinsulinemia, Hypertriglyceridemia, Normotensive Control. *The normotensive SS-13^{BN} is used as the control for the hypertensive Dahl/Salt Sensitive rat.*

References: Cowley, Jr., A.W., et al. Genetically defined risk of salt sensitivity in an intercross of Brown Norway and Dahl S rats. *Physiol. Genomics.* **2**, 107-15 (2002).

Liang, M., et al. Renal medullary genes in salt-sensitive hypertension: a chromosomal substitution and cDNA microarray study. *Physiol. Genomics*. **28.8**, 139-49 (2002).

SHR (Spontaneously Hypertensive) Rat

Strain Code: 007 Nomenclature: SHR/NCrl Therapeutic Area: Cardiovascular, Metabolic, Renal Control: WKY/NCrl Origin: Okamoto, at the Kyoto School of Medicine in 1963, started with an outbred Wistar Kyoto male with marked elevation of blood pressure and mated him to a female with slightly elevated blood pressure. NIH expanded on the model beginning in 1966. To Charles River in 1973. Characteristics: Hypertension, Insulin Resistance, Hyperinsulinemia, Hypertriglyceridemia, Hypercholesterolemia. *The SHR is the most commonly used genetically hypertensive rat model.*

References: Okamoto, K. Spontaneous hypertension in rats. *Int. Rev. Exp. Pathol.* **7**, 227-70 (1969).

Palmer, B.M., et al. Cardiomyocyte function associated with hyperactivity and/or hypertension in genetic models of LV hypertrophy. *Am. J. Physiol Heart Circ. Physiol*. **290.1**, 463-73 (2006).

Swislocki, A. & Tsuzuki, A. Insulin resistance and hypertension: glucose intolerance, hyperinsulinemia, and elevated free fatty acids in the lean spontaneously hypertensive rat. *Am. J. Med. Sci.,* **306.5**, 282-6 (1993).

SHRSP (Spontaneously Hypertensive Stroke Prone) Rat

Strain Code: 324 Nomenclature: SHRSP/A3NCrl Therapeutic Area: Cardiovascular, Renal Control: WKY/NCrl Origin: Isolated from Wistar-Kyoto rats by Okamoto and Aoki in 1963. A3 subline transferred to NIH in 1975 from Yamori. To Charles River in 2002. Characteristics: Hypertension, Nephropathy, Insulin Resistance, Hyperinsulinemia, Hypertriglyceridemia, Hypercholesterolemia. *When 7-8 week old males are fed Ziegler Brothers Japanese Diet 522880000 along with 1% salt in the water, 80% will develop cerebral hemorrhage at 16-18 weeks of age.*

References: Masineni, S.N., et al. Male gender and not the severity of hypertension is associated with end-organ damage in aged stroke-prone spontaneously hypertensive rats. *Am. J. Hypertens.* **18.6**, 878-84 (2005).

Nagaoka, A., Iatsuka, H., Suzuoki Z. & Okamoto, K. Genetic predisposition to stroke in spontaneously hypertensive rats. *Am. J. Physiol.* **230.5**, 1354-9 (1976).

Sepehrdad, R., Chander, P.N., Singh, G. & Stier, C.T., Jr. Sodium transport antagonism reduces thrombotic microangiopathy in stroke-prone spontaneously hypertensive rats. *Am. J. Physiol. Renal Physiol.* **286.6**, 1185-92 (2004).

SHROB (Spontaneously Hypertensive Obese) Rat

Strain Code: 375 (obese), 376 (lean +/?) Nomenclature: SHROB/KolGmiCrl-*Lepr*^{cp}/Crl Therapeutic Area: Cardiovascular, Metabolic, Renal Control: SHROB lean Origin: Originated in the laboratory of Dr. Simon Koletsky at Case Western Reserve University School of Medicine in 1969. Developed from a cross between an SHR female rat and a normotensive male Sprague Dawley rat. To Genetic Models, Inc., in 2000. To Charles River in 2001. Characteristics: Hypertension, Metabolic Syndrome, Nephropathy, Obesity, Insulin Resistance, Hyperinsulinemia, Hypertriglyceridemia, Hypercholesterolemia. *The lean and obese models exhibit some similar characteristics.*

References: Koletsky, R.J., Velliquette, R.A. & Ernsberger, P. The SHROB (Koletsky) Rat as a Model for Metabolic Syndrome. *Animal Models of Diabetes Frontiers in Research,* Edited by Eleazar Shafrir. CRC Press. 185-207, (2007).

Koletsky, R.J., Velliquette, R. A. & Ernsberger, P. The role of I(1)-imidazoline receptors and alpha(2)-adrenergic receptors in the modulation of glucose and lipid metabolism in the SHROB model of metabolic syndrome X. *Ann. N.Y. Acad. Sci.* **1009**, 251-61 (2003).

SHHF (Spontaneously Hypertensive Heart Failure) Rat

Strain Code: 373 (obese), 374 (lean +/?) Nomenclature: SHHF/MccGmiCrl-*Lepr*^{cp} *Model available in limited supply.* Therapeutic Area: Cardiovascular, Metabolic, Renal Control: SHHF lean Origin: Breed stock for this colony was transferred to Dr. Sylvia McCune at the University of Chicago Medical School in 1983, from the laboratory of Dr. J.E. Miller at G.D. Searle and Company. The animals were developed by backcrossing the SHROB rat to the SHR/N rat. To Genetic Models, Inc., in 1994. To Charles River in 2001. Characteristics: Congestive Heart Failure, Hypertension, Nephropathy, Obesity, Insulin Resistance, Hyperinsulinemia, Type 2 Diabetes, Hypertriglyceridemia, Hypercholesterolemia. *The lean and obese phenotypes exhibit heart failure characteristics, but at different ages.*

References: Emter, C.A., et al. Low-intensity exercise training delays onset of decompensated heart failure in spontaneously hypertensive heart failure rats. *Am. J. Physiol. Heart Circ. Physiol.* **289.5**, 2030-8 (2005).

Heyen, J.R.R., et al. Structural, functional and molecular characterization of the SHHF model of heart failure. *Am. J. Physiol. Heart Circ. Physiol.* **283.5**, 1775-84 (2002).

McCune, S.A., Baker, P. & Stills, H. SHHF/Mcc-cp rat: model of obesity, non-insulin-dependent diabetes, and congestive heart failure. *ILAR News*. **32**, 23-7 (1990).

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