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Cardiovascular Research and the Laboratory Mouse

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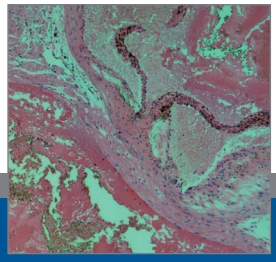
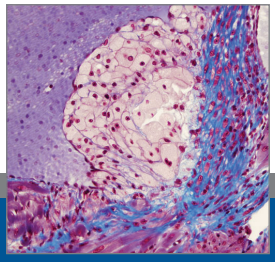
Cardiovascular Research and the Laboratory Mouse

A Jackson Laboratory Resource Manual





This resource manual highlights the importance of cardiovascular research and the extensive resources available for researchers at The Jackson Laboratory.

It briefly describes the following:

- Over 30 JAX® Mice cardiovascular research models
- Summaries of recent mouse-based cardiovascular research
- Comparisons of cardiovascular phenotypes among the Mouse Phenome Project strains
- Resources available through our Center for New Models of Heart, Lung, Blood, and Sleep Disorders
- Courses, online resources and JAX® Services suitable for cardiovascular research

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Cover Photos

Front cover, left: Fatty acid plaque in mouse aortic valve. Courtesy of Karen Svenson.

Front cover, middle: The C57BL/6-Tg(APOA1)1Rub/J (001927) strain has a reduced susceptibility to diet-induced atherosclerosis.

Front cover, right: Fatty acid plaque in mouse aorta. Courtesy of Karen Svenson.

Back cover: B6.129P2-*Apoe*^{tm1Unc}/J (002052) *Apoe*-deficient mice are one of the most relevant models for atherosclerosis research.

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Cardiovascular Research and the Laboratory Mouse

According to the Centers for Disease Control (CDC: www.cdc.gov/heartdisease/facts), heart disease and stroke are the first and third leading causes of death for both men and women in the United States, accounting for nearly 40% of all deaths annually. More than 70 million Americans have some kind of cardiovascular disease. Coronary heart disease is a leading cause of premature, permanent disability in the U.S. workforce. In 2006, the projected cost of heart disease in the U.S. was 256 billion dollars.

Two of the major independent risk factors for cardiovascular diseases are high blood pressure and high blood cholesterol. Other important risk factors include diabetes, tobacco use, physical inactivity, poor nutrition, and obesity. About 30% of U.S. adults have high blood pressure, and 25% have high cholesterol levels. A 12- to 13-point reduction in blood pressure could reduce heart attacks by 21%, strokes by 37%, and all deaths from cardiovascular disease by 25%. A 10% decrease in total blood cholesterol levels could reduce the incidence of coronary heart disease by as much as 30% (CDC: www.cdc.gov/heartdisease/facts).

Although a great deal of cardiovascular research has already been conducted, much more is needed. Our resources, especially our JAX® Mice models and JAX® Services, will undoubtedly play an important role in that research. This Resource Manual briefly describes the role of the laboratory mouse in cardiovascular research, selected JAX® Mice models, JAX® Services, online resources applicable to cardiovascular research, and ongoing cardiovascular research conducted by our scientists.

Atherosclerosis

Atherosclerosis, also called coronary heart disease (CHD), is essentially a chronic inflammatory reaction to modified lipoproteins, primarily oxidized low density lipoprotein (LDL). It is one of the most devastating of human diseases and a leading cause of death in industrialized countries (Kreger et al. 1994; Beckman et al. 2002). Older women and women who begin hormone therapy over 10 years after menopause are at increased risk of developing atherosclerosis (Rossouw et al. 2007). Atherosclerosis is particularly hard to fight because it is influenced by so many genetic and environmental factors, especially diet (Gylling and Miettinen 2001; Cohn 2002).

The laboratory mouse has played a crucial role in atherosclerosis research and will likely continue to do so (Paigen 1995; Rader and Pure 2000; Glass and Witztum 2001; Daugherty 2002; Fazio and Linton 2002; Allayee et al. 2004; Wang et al. 2005a). At least 21 atherosclerosis quantitative trait loci (QTLs) have been identified in the mouse (Wang et al. 2005a): seven in high-fat diet models only, nine in sensitized models (apolipoprotein E- or low density lipoprotein receptor-deficient mice) only, and five in both models.

More than half of the mouse and human atherosclerosis QTLs are likely concordant, having the same underlying genes (Stoll et al. 2000; Sugiyama et al. 2001; Wang et al. 2005a). More mouse QTLs concordant with human QTLs could possibly be found 1) if additional crosses using previously unused parental strains were performed (11 of the 13 crosses performed so far used B6 mice as one of the parents), 2) if, in addition to lesion size, characterization of the atherosclerosis phenotype in the mouse would incorporate plaque stability (as is done in humans), 3) through mutagenesis screens, and 4) by using new genomic and bioinformatics tools (Wang et al. 2005a). Performing additional crosses (with atherosclerosis susceptible strains such as SM/J and SWR/J) would not only reveal new atherosclerosis QTLs but would verify previous QTLs, providing the information necessary to identify QTL genes (Wang and Paigen 2005; Wang et al. 2004).

The genes underlying both human and mouse atherosclerosis QTLs are largely unknown. Of over 80 mouse and at least 17 human genes known to influence atherosclerosis, only about a quarter fall into human atherosclerosis QTLs (Wang et al. 2005a). Only two of the genes underlying the 21 mouse atherosclerosis QTLs have been identified, and half of the human atherosclerosis QTLs have no obvious candidate genes (Wang et al. 2005a). Because of concordance, discovering these genes in the mouse first will be much more cost-effective, less time consuming, and less fraught with ethical issues than would finding them in humans first, especially now that many new genetic, genomic, and bioinformatics tools for the mouse are available.

A map showing the location of mouse atherosclerosis QTLs (and their candidate genes) is available from The Jackson Laboratory's Mouse Heart, Lung, Blood and Sleep Disorders Center (HLBS) website at this URL:

pga.jax.org/qtl/index

The map is linked to resource tables that include chromosome locations, mouse crosses, statistical significances, and references for each QTL.

A map of human atherosclerosis QTLs (at least 27 have been reported) is available from the same website.

Lipid Homeostasis

Given the compelling evidence that HDL protects against atherosclerosis (Brewer 2004; Gotto and Brinton 2004), human atherosclerosis-regulating genes might also be identified by finding the genes underlying mouse HDL QTLs and determining if their orthologs regulate HDL levels and atherosclerosis susceptibility in humans. Many QTLs have been found that regulate plasma levels of HDL cholesterol (37 in mice, 30 in humans), low density lipoprotein (LDL) cholesterol (25 in mice, 20 in humans) and triglycerides (19 in mice, 30 in humans). Ninety-three percent, 100%, and 80% of the human QTLs for HDL cholesterol, LDL cholesterol, and triglycerides respectively have concordant mouse QTLs, suggesting they have the same underlying genes (Wang and Paigen 2005a; Wang and Paigen 2005b). Identifying these genes should be facilitated considerably by analyzing haplotypes (DiPetrillo et al. 2005; Wang et al. 2004), data combined from multiple crosses (Wittenburg et al. 2006; DiPetrillo et al. 2005), and by using the mouse-to-human-to-mouse paradigm (Wang and Paigen 2005b).

Maps of HDL, LDL, and triglyceride QTLs (and candidate genes) found in the mouse can be accessed from the HLBS website: pga.jax.org/qtl/index. Each map is linked to resource tables that include chromosome locations, mouse crosses, statistical significances, and references for each QTL. Maps of human QTLs for the same phenotypes are accessible from the same site.

Blood Pressure

Hypertension

Human hypertension greatly increases the risk of coronary heart disease, congestive heart failure, stroke, and kidney disease. Additionally, it is often associated with and complicated by obesity, dyslipidemia, and non-insulin dependent diabetes mellitus (NIDDM) (Bonora et al. 1998). More than 50 million Americans suffer from hypertension, and 12.7 million of them alleviate its symptoms by taking medicinal drugs (Smith 2000). The alleles associated with essential hypertension in humans have been difficult to find because the genetic backgrounds and environmental influences in human populations are almost impossible to control. These have been much easier to control in inbred rodent populations.

Preeclampsia

Preeclampsia is a disorder that occurs only during pregnancy and the postpartum period and affects both the mother and the unborn baby. Occuring in at least five to eight percent of all pregnancies, preeclampsia is a rapidly progressive condition characterized by high blood pressure and protein in the urine. Although symptoms may include swelling, sudden weight gain, headaches, and changes in vision, some women with rapidly advancing disease report few symptoms.

Typically, preeclampsia occurs after 20 weeks gestation, but it can occur earlier. To diagnose and manage it, proper prenatal care is essential. Preeclampsia and other hypertensive disorders of pregnancy are a leading global cause of maternal and infant illness and death, accounting for at least 76,000 deaths yearly (The Preeclampsia Foundation, www.preeclampsia.org).

The Emergence of the Mouse as a Blood Pressure Model

Until recently, the rodent model most widely used to study hypertension was the laboratory rat. With the advent of genetic engineering and the development of equipment capable of measuring blood pressure in small organisms, the mouse has assumed an increasingly important role as a model in blood pressure studies (Sugiyama et al. 2001a, 2001b, 2002; DiPetrillo et al. 2004; Tsukahara et al. 2004).

Cardiovascular Research at The Jackson Laboratory

Professor Beverly Paigen, Ph.D.

www.jax.org/research/faculty/beverly_paigen

Professor Paigen and her laboratory research the genetic and environmental factors associated with atherosclerosis, hypertension, high density lipoprotein (HDL)-cholesterol levels, and cholesterol gallstone formation. Her staff and colleagues Professor Gary Churchill and Research Associate Renhua Li are pioneers in developing the technology and statistical tools for mapping quantitative trait loci (QTLs) and identifying underlying alleles associated with these diseases. In the past 10 years, they have carried out over 25 QTL mouse crosses and have discovered over 250 disease-associated QTLs. Once they identify the disease-causing alleles in the mouse, they and collaborators seek to identify the orthologous alleles in humans. By using a variety of comparative genetic approaches, they have already identified one allele associated with susceptibility to atherosclerosis and two associated with susceptibility to hypertension in humans.

Professor Paigen and her colleagues have also contributed a considerable amount of cardiovascular related data to the Mouse Phenome Database.

Professor Beverly Paigen (center row, second from right) along with her research staff.

Our Facilities

The Jackson Laboratory comprises two facilities: an East Coast campus in Bar Harbor, Maine and a West Coast campus in Sacramento, California. On both campuses cardiovascular research, services and educational activities take place.

The Jackson Laboratory repository on the Bar Harbor campus is home to more than 4,000 strains of JAX® Mice and growing daily. More than 1,200 of these strains are maintained as live colonies and are available for distribution to biomedical researchers worldwide. All of these strains, including the live colonies, are cryopreserved to ensure they continue to be available to the scientific community for many years to come. This growing resource is the result of the donation of hundreds of unique mouse models every year by researchers around the world in an effort to preserve today what may lead to the prevention and cure many human diseases.

Bar Harbor, ME facility

- Primary production and distribution site for more than 4,000 genetically defined mouse strains
- Research Staff of more than 200 Ph.D.s, M.D.s, and D.V.M.s
- Center for the Mouse Tumor Biology Database (MTB), Mouse Genome Informatics Database, and the Mouse Phenome Database (MPD)
- World-renowned Courses and Conferences, and training programs
- Model preconditioning and surgical services
- Revolutionary cryopreservation and recovery services
- Genetic research services (including gene mapping and speed congenics)
- Microinjection services for new model development
- Comprehensive and integrated mouse breeding and research services designed to provide efficient and cost-effective solutions for mouse-based research

Sacramento, CA facility

- Site of JAX® *In Vivo* Services
- Production and distribution site for our most popular JAX® Mice
- State-of-the-art phenotyping laboratory for characterizing models, validating drug targets, and testing drug efficacy
- Highly trained scientific staff, with experience conducting *in vivo* studies in over 100 mouse models
- Comprehensive and integrated mouse breeding and research services designed to provide efficient and cost-effective solutions for mouse-based research

With nearly 80 years experience breeding and using mouse models of disease, the quality of JAX® Mice & Services offered at our facilities is unmatched. Our commitment drives our mission: We discover the genetic basis for preventing, treating and curing human diseases, and we enable research and education for the global biomedical community.

JAX® Mice Models

Why Choose JAX® Mice

There are many reasons why you should choose JAX® Mice for your cardiovascular research:

- JAX® Mice are the universally recognized *gold standard* for genetically well-defined laboratory mice. Their stable genotypes and phenotypes are the result of our three-component Genetic Quality Control Program. This program includes:
  1) Adherence to best practices in breeding and colony management
  2) The use of molecular test methods to confirm genetic identity and genotypes
  3) Phenotype monitoring
- JAX® Mice colonies are rigorously monitored for both pathogenic and opportunistic agents. Our comprehensive biosecurity program and state-of-the-art facilities ensure the health quality of JAX® Mice.
- JAX® Mice are the most comprehensively characterized laboratory mice as noted below:
  1) The C57BL/6J strain (000664) is the only fully sequenced mouse strain;
  2) The National Institute of Environmental Health Sciences (NIEHS) has resequenced 15 JAX® Mice strains (SNP information available in the Mouse Phenome Database, www.jax.org/phenome);
  3) JAX® Mice were used to construct the most detailed genetic map of any mammal except humans (Shifman et al. 2006);
  4) 40 genetically-diverse and widely-used JAX® Mice strains are being comprehensively characterized by the Mouse Phenome Project (www.jax.org/phenome).
- The JAX® Mice Database (www.jax.org/jaxmice/query) and the Mouse Genome Database (www.informatics.jax.org) are renowned for their wealth of genotypic and phenotypic information.
- JAX® Mice are the most widely published laboratory mice. They have been referenced in more than 20,000 peer-reviewed publications. Over 90% of the published references to B6 substrains cite our C57BL/6J strain.
- Over 4,000 JAX® Mice strains are available, including inbred, hybrid, genetically engineered, recombinant inbred, chromosome substitution, recombinant congenic, and congenic strains.
- JAX® Mice are used for cardiovascular research in medical schools, universities, and research centers all over the world.
- Our Technical Information Support and Customer Service teams leverage the expertise of our research staff and mouse breeding experts to offer comprehensive and integrated support to help you conduct your research with JAX® Mice.
- JAX® Mice users have ready access to JAX® Services, a comprehensive and highly customizable set of mouse breeding and research services designed for the mouse-based biomedical research community (see JAX® Services section in this manual).

Importance of Genetic Background

You may occasionally see the following cautionary note in JAX® Mice strain data sheets:

> *This strain is on a genetic background different from that on which the allele was first characterized. It should be noted that the phenotype could vary from that originally described. We will modify the strain description if necessary as published results become available.*

We include this note because the technology for producing genetically-engineered mice has been substantially refined, resulting in an ever-increasing number, variety, and availability of mutant mouse models. Similarly, the variety of genetic backgrounds and the mutations characterized and published on them are continually increasing. Generally, alleles of interest (such as spontaneous mutations, targeted mutations, transgenes, and congenic regions) are maintained on one to several genetic backgrounds. One background may be more vigorous, better characterized, more amenable to scientific experiments, reproduce better, display a more severe phenotype, or have some other advantages over other backgrounds. However, these alleles are sometimes transferred to backgrounds that are not well characterized. Inattention to a mutant's genetic background can seriously confound research results. Each strain has unique background alleles that may interact with and modify the expression of a mutation, transgene, or other genetic alteration. The likelihood of such modifier genes having a confounding effect is especially high in an uncharacterized background or in a segregating or mixed background of unspecified origin. Even in a well-characterized strain, undiscovered modifier genes may alter results, sometimes making them unexplainable. Thus, before you decide which mouse strain is appropriate for your research, consider its genetic background.

The Mouse-to-Human-to-Mouse Paradigm

Professor Beverly Paigen of The Jackson Laboratory and other investigators have successfully used the mouse-to-human-to-mouse paradigm to identify human disease alleles. The process is as follows:

- Identify disease QTLs and the most promising candidate genes in the mouse.
- Determine if polymorphisms in the human orthologs of these candidate genes are associated with the same disease in humans.
- Return to the mouse to obtain experimental proof that polymorphisms of the gene can cause the disease.

The paradigm has been used successfully to establish the following gene-disease relationships:

- *TNFSF4* (encoding OX40 ligand) is significantly associated with myocardial infarction and coronary artery disease in humans (Wang et al. 2005b);
- *CTLA4* (encoding cytotoxic T-lymphocyte-associated protein 4) is significantly associated with autoimmune disorders, including Graves disease, autoimmune hypothyroidism, and type 1 diabetes (Ueda et al. 2003);
- *POMC* (encoding pro-opiomelanocortin-alpha [MIM 176830]) is significantly associated with obesity (Krude et al. 1998; Hixson et al. 1999);
- *EN2* (encoding engrailed 2 [MIM 131310]) is significantly associated with autism-spectrum disorder (Gharani et al. 2004).

JAX® Mice Models

In the following pages, we describe over 30 of the most commonly used and promising JAX® Mice models suitable for cardiovascular research. The descriptions are abridged from the JAX® Mice Database and scientific journals. For more detailed information and/or comprehensive lists, consult the following:

- **JAX® Mice Database (www.jax.org/jaxmice):** The JAX® Mice Database is the most comprehensive source of JAX® Mice strain information. Many of the strains are described according to mammalian phenotype terms. Strains for cardiovascular research can be searched by research area.
- **The Mouse Phenome Database (MPD, www.jax.org/phenome):** The MPD is the database for the Mouse Phenome Project, a coordinated international effort to establish a collection of baseline phenotypic data for a set of commonly used and genetically diverse inbred mouse strains.
- **The Center for New Mouse Models of Heart, Lung, Blood, and Sleep Disorders (www.nhlbi.nih.gov/resources/pga):** The goal of the JAX® HLBS Center is to provide the biomedical research community with new information, tools, and resources for understanding the genetic bases of atherosclerosis, hypertension, lung function, blood formation, thrombosis, obesity, and sleep function.
- **The Cardiovascular Models Research Page (www.jax.org/jaxmice/research/cardiovascular):** This downloadable pdf lists over 125 JAX® Mice strains suitable for cardiovascular research. Strains are categorized by research area (such as atherosclerosis, hypertension, hypercholesteremia, etc.) and gene symbol.
- **References:** References are provided with each strain description in this manual. Additional ones are available from the strain data sheets in the JAX® Mice Database.

Atherosclerosis

The Mouse Phenome Project Strains

Although many JAX® Mice strains have been used to research atherosclerosis, they have been insufficient for unraveling all the biochemical pathways involved (Wang et al. 2005a). Until recently, choosing other strains was difficult because atherosclerosis susceptibility and its subphenotypes (such as cholesterol and triglyceride levels) in most mouse strains were largely uncharacterized. Professor Paigen of The Jackson Laboratory, her colleagues, and other participants in the Mouse Phenome Project have helped remedy that situation by extensively characterizing these phenotypes for the Mouse Phenome Project strains and submitting their data to the Mouse Phenome Database (www.jax.org/phenome).

Atherosclerosis Susceptibility and Infectious Agents

One of the environmental factors receiving considerable attention as a risk factor for the development of chronic inflammatory diseases, including Crohn's disease, psoriasis, type 2 diabetes, and atherosclerosis, is the aggravating or precipitating influence of infectious agents (Karin et al. 2006 Pellicano et al. 1999). In mice, infections with cytomegalovirus, Chlamydia, or *Porphyromonas gingivalis* have been found to increase the severity of atherosclerosis (Vliegen et al. 2005, 2004, 2002; Chi et al. 2004; Burnett et al. 2001; Hsich et al. 2001). Similarly, in her nearly 20 years of experience researching the genetic determinants of atherosclerosis in mouse models, Dr. Paigen observed that the degree to which mice develop atherosclerosis seemed to depend on the presence of infectious agents in the environment (pers. comm.). To test her hypothesis, she and her colleagues examined the diet-induced susceptibility to atherosclerosis in the Mouse Phenome Project strains in barrier and non-barrier mouse rooms (Table 1) (Paigen et al. 2000a; 2000b). The barrier rooms were regularly monitored for and maintained free of 15 viruses (mouse hepatitis virus, two mouse parvoviruses, reovirus, Theiler's mouse encephalomyelitis virus, ectromelia virus, mouse rotavirus, thymic virus, pneumonia virus of mice, Sendai virus, murine cytomegalovirus, lactic dehydrogenase-elevating virus, K virus, mouse adenovirus, and polyoma virus), 17 bacterial species (including *Helicobacter* spp. and *Pneumocystis pneumotropica*), two *Mycoplasma* species, external and internal parasites, and *Encephalitozoon cuniculi.* Personnel entering these rooms were required to wear caps, facemasks, disposable gowns, shoe covers, and gloves. At the time, the only known infectious agents in the non-barrier facilities were *Helicobacter sp*, *Pneumocystis*, and *Pasturella*.

All mice were fed the same diet: however, whereas mice in the barrier facilities were fed an atherogenic diet for 17 weeks, those in non-barrier facilities were fed the diet for 8 weeks.

Table 1 and the more detailed information in the Mouse Phenome Database should help researchers find more atherosclerosis QTLs, identify the underlying genes, and determine how infectious agents influence susceptibility to atherosclerosis.

A map showing the location of atherosclerosis QTLs identified in the mouse (and their candidate genes) is available at pga.jax.org/qtl/index.

Table 1. Susceptibility to diet-induced atherosclerosis in Mouse Phenome Project strains housed in non-barrier and barrier rooms.

	Resistant mean lesion size: 0 μm²		**Intermediately Susceptible** mean lesion size: 1 to 499 μm²		**Very Susceptible** mean lesion size: > 500 μm²	
	Non-barrier	**Barrier**	**Non-barrier**	**Barrier**	**Non-barrier**	**Barrier**
Females	A/J, BALB/cJ, BPH/2J, BPL/1J, BUB/BnJ, CAST/EiJ, CBA/J, CE/J, CZECHII/EiJ, FVB/NJ, KK/HlJ, MOLF/EiJ, NOD/ShiLtJ, NON/ShiLtJ, NZB/BlNJ, NZW/LacJ, PERA/EiJ, RIIIS/J, SPRET/EiJ, WSB/EiJ	129S1/SvlmJ, A/J, AKR/J, C3H/HeJ, C57BL/10J, C57L/J, CBA/J, CZECHI/EiJ, DBA/2J, FVB/NJ, JF1/Ms, KK/HlJ, MSM/Ms, NZW/LacJ, PERA/EiJ, PL/J, PWK/PhJ, SEA/GnJ, SL/J, SPRET/EiJ,	129S1/SvlmJ, AKR/J, BPN/3J, BTBR *T*⁺ *tf*/J, C3H/HeJ, C57BL/10J, DBA/1J, DBA/2J, I/LnJ, LP/J, P/J, PL/J, RBF/DnJ, RF/J, SJL/J, SWR/J, YBR/EiJ	BALB/cByJ, BUB/BnJ, C57BL/6J, CAST/EiJ, DBA/1J, LP/J, NOD/ShiLtJ, NZB/BINJ, RF/J, RIIIS/J, WSB/EiJ	C57BL/6J, C57BLKS/J, C57BR/cdJ, C57L/J, C58/J, SEA/GnJ, SM/J	BALB/cJ, BTBR *T*⁺ *tf*/J, C57BLKS/J, C57BR/cdJ, C58/J, I/LnJ, MA/MyJ, MOLF/EiJ, NON/ShiLtJ, SEA/GnJ, SM/J, SWR/J
Males	129S1/SvlmJ, A/J, AKR/J, BALB/cJ, BPH/2J, BPL/1J, C57L/J, CAST/EiJ, CBA/J, CE/J, CZECHII/EiJ, DBA/2J, FVB/NJ, KK/HlJ, LP/J, MOLF/EiJ, PERA/EiJ, RF/J, SPRET/EiJ, WSB/EiJ	129S1/SvlmJ, BTBR *T*⁺ *tf*/J, BUB/BnJ, C57BL/10J, C57BR/cdJ, C57L/J, CAST/EiJ, CBA/J, CZECHI/EiJ, DBA/1J, DBA/2J, JF1/Ms, MA/MyJ, MSM/Ms, NOD/ShiLtJ, NZW/LacJ, PERA/EiJ, PL/J, PWK/PhJ, SL/J, WSB/EiJ	BTBR *T*⁺ *tf*/J, C3H/HeJ,C57BL/10J, C57BR/cdJ, DBA/1J, I/LnJ, NOD/ShiLtJ, NON/ShiLtJ, NZB/BlNJ, NZW/LacJ, P/J, RBF/DnJ, RIIIS/J, SEA/GnJ, SWR/J	BALB/cByJ, BALB/cJ, C3H/HeJ, C57BL/6J, FVB/NJ, I/LnJ, LP/J, NZB/BINJ, RIIIS/J, SM/J, SPRET/EiJ, SWR/J	C57BL/6J, C57BLKS/J, C58/J, SJL/J, SM/J	A/J, C57BLKS/J, C58/J, MOLF/EiJ, NON/ShiLtJ

Atherogenic Diet and Cholesterol Homeostasis

Professor Paigen characterized the effects of an atherogenic diet on cholesterol homeostasis in the Mouse Phenome Project strains in the same non-barrier and barrier facilities (Paigen et al. 2000a, 2002). In non-barrier facilities, mice were fed the atherogenic diet for eight weeks; in barrier facilities, they were fed the diet for 17 weeks. All raw data and protocols are published in the Mouse Phenome Database, www.jax.org/phenome.

Cholesterol subphenotypes characterized in non-barrier facilities included total plasma cholesterol, HDL plasma cholesterol, non-HDL plasma cholesterol, % plasma HDL cholesterol, free hepatic cholesterol, esterified hepatic cholesterol, and total hepatic cholesterol.

Cholesterol subphenotypes measured in barrier facilities included HDL cholesterol, non-HDL cholesterol, total cholesterol, fold change in HDL cholesterol, and non-HDL cholesterol.

Atherogenic Diet and Triglyceride Levels

Professor Paigen characterized the triglyceride levels of the Mouse Phenome Project strains maintained in barrier facilities before and after they were fed an atherogenic diet for 17 weeks (Paigen et al. 2002). All raw data and protocols are published in the Mouse Phenome Database, www.jax.org/phenome.

Obesity Mutants

Several obesity mutants may be useful for researching atherosclerosis. Paigen et al. (2000b) determined the diet-induced susceptibility to atherosclerosis of the following four obesity mutants housed in non-barrier rooms:

B6(Cg)-*Tub*^{tub}/J 000562

Homozygotes for the *tubby* spontaneous mutation develop late-onset obesity, recognizable at three to four months in males and at four to six months in females. The increased weight is composed of excess adipose tissue. Blood glucose is normal. Although plasma insulin levels rise before obvious signs of obesity and may be 20 times above normal in six-month olds, tubby mice do not become diabetic (Nishina et al. 1994; Noben-Trauth et al. 1996). When maintained in non-barrier facilities, despite having elevated plasma total cholesterol, triglyceride, and HDL cholesterol levels, B6 mice homozygous for the *Tub*^{tub} mutation are resistant to diet-induced atherosclerosis (Table 2).

BKS.Cg-*m +/+ Lepr*^{db}/J 000642

Homozygotes for the *Lepr*^{db} spontaneous mutation with a BKS background become obese, hyperinsulemic, and hyperglycemic. They are polyphagic, polydipsic, and polyuric. Most die by 10 months of age. They develop peripheral neuropathy and myocardial disease. Wound healing is delayed, and metabolic efficiency is increased. When maintained in non-barrier facilities, this strain is intermediately susceptible to diet-induced atherosclerosis (Table 2).

B6.Cg-A^{y}/J 000021

B6.Cg-A^{y}/J heterozygotes become obese but only mildly diabetic (Reddi and Camerini-Davalos RA 1988; Taylor et al. 1999). When maintained in non-barrier facilities, they are very susceptible to diet-induced atherosclerosis (Table 2).

BKSChpLt.HRS-*Cpe*^{fat}/J 002391

Male BKSChpLt.HRS-*Cpe*^{fat}/J homozygotes become diabetic, grossly obese, and severely hyperglycemic (their glucose levels plateau at about 400-600 mg/dl). Both sexes become obese by six to eight weeks of age and are distinguishable from wild-type littermates by eight to 12 weeks of age. They are severely and permanently hyperinsulinemic by four weeks of age (JAX® Notes 2002; Naggert et al. 1995; Nillni et al. 2002; Weide and Lacy 1991). When maintained in non-barrier facilities, they are very susceptible to diet-induced atherosclerosis (Table 2).

Table 2. Effects of atherogenic diet on susceptibility to atherosclerosis in both sexes of four obesity mutants housed in non-barrier facilities (Paigen et al. 2000b).

Resistant mean lesion size: 0 μm^2	**Intermediately Susceptible** mean lesion size: 1-499 μm^2	**Very Susceptible** mean lesion size > 500 μm^2
B6(Cg)-*Tub*^{tub}/J (000562)	BKS.Cg-*m* +/+ *Lepr*^{db}/J (000642)	B6.Cg-A^{y}/J (000021) BKSChpLt.HRS-*Cpe*^{fat}/J (002391)

The Jackson Laboratory Mouse Heart, Lung, Blood, and Sleep Disorders Center

The Heart, Lung, Blood, and Sleep Disorders Center (HLBS) is producing many chemically-induced mouse models suitable for cardiovascular research. Characterized and proven-heritable mutants are available to academic researchers for the cost of shipping only (for-profit organizations are charged an additional fee). Instructions for ordering are on the Center's website, pga.jax.org.

The Center maintains approximately 200 lines at one of the following three stages of development: not yet proven heritable, heritable and available to ship, and in the process of being mapped. As of May 2008, 37 heritable and ready-to-ship mutants and nine phenotypic deviants have cardiovascular defects: 14 of the heritable mutants and one of the phenotypic deviants have cholesterol disorders (Table 3).

Loci associated with high cholesterol and low HDL have been mapped. For more detailed information about these mapped mutants, consult the Mapped Mutant Matrix at pga.jax.org/resources/mappedmutants.

Register to receive alerts of new JAX® HLBS mutants at pga.jax.org/resources/alert_list.

Table 3. Number of heritable (ready-to-ship) mutants and phenotypic deviants suitable for cardiovascular research identified by the HLBS Center (as of May 2008).

	Cardiovascular Phenotypes	Number of Heritable Mutants	Number of Phenotypic Deviants
Cardiac Dysfunction	Trachycardia	2	2
	Bradycardia (some with prolonged QT* and PR* intervals)	2	1
	Prolonged PR*, QT*, QTC* intervals	2	1
	Dilated cardiomyopathy		1
	High heart rate variability	2	
Cholesterol Disorders	Diet-induced hypercholesterolemia	1	
	Diet-induced hypercholesterolemia and low HDL	1	
	Hypocholesterolemia and low HDL	2	
	High triglyceride levels	2	
	Low HDL		2
	High HDL	6	
	High HDL and triglyceride levels	1	
	Diet-induced high HDL and hypercholesterolemia	1	
Hypertension		15	2

*QT, PR, and QTC refer to heart beat intervals displayed on an electrocardiogram.

Selected JAX® Mice Atherosclerosis Models

B6;129S6-*Abcg5/Abcg8* ^{tm1Hobb}/J 004670

Homozygotes for these targeted mutations of the ATP-binding cassette, sub-family G (WHITE), member 5 (*Abcg5*) and ATP-binding cassette, sub-family G (WHITE), member 8 (*Abcg8*) genes are viable and look and behave normally. Their plasma sitosterol levels are 30 times higher than normal. Their biliary, plasma, and liver cholesterol levels are low. Their plasma and liver cholesterol levels increase rapidly (2.4 and 18 fold, respectively) following cholesterol feeding (Yu et al. 2002).

B6.129P2-*Apoa1*^{tm1Unc}/J 002055

Homozygotes for this apolipoprotein A-I (*Apoa1*) targeted mutation appear to develop normally despite having no APOA1 protein. Additionally, after being fasted overnight, they have severely reduced levels of plasma cholesterol and HDL-cholesterol, and they are deficient in alpha-migrating HDL particles (Williamson et al. 1992). Although *ApoaI* deficiency delays cholesterol absorption, cholesterol is eventually absorbed because of the compensatory *Apob* pathway. Nonetheless, long-term studies involving multiple feedings indicate significant reduction in cholesterol absorption after four days (Iqbal and Hussain 2005).

C57BL/6-Tg(APOA1)1Rub/J 001927

Considerable evidence indicates that a high concentration of APOA1 in the artery wall enhances cellular cholesterol efflux and protects against atherosclerosis. Mice homozygous for the human apolipoprotein A-I (APOA1) transgene (under control of its natural promoter) are viable, fertile, and normal-sized. They have twice as much total plasma cholesterol but over four times less mouse APOAI than normal. They have a reduced susceptibility to diet-induced fatty streak lesions (Rubin et al. 1991).

Major et al. (2001) found that atherosclerotic lesions in mice *Apoe*-deficient and also transgenic for human APOA1 under the control of a macrophage-specific scavenger receptor-A promoter are 96% smaller than those in mice that are only *Apoe*-deficient. Atherosclerosis resistance in these mice has been attributed to the production of human *APOA1* protein and the consequently increased cholesterol efflux by macrophages in the artery wall.

B6.129P2-*Apob* ^{tm1Unc}/J 002053

Mice with this targeted mutation of the apolipoprotein B (*Apob*) gene produce a truncated form of the apolipoprotein B protein (APOB70) and no APOB100, resulting in a condition similar to human familial hypobetalipoproteinemia. These mice express normal amounts of APOB48. Homozygotes have greatly reduced levels of plasma APOB, beta-lipoproteins, total cholesterol, plasma triglycerides, fasting chylomicronemia, and HDL cholesterol. Homozygotes also have a high incidence of exencephaly and hydrocephaly (Homanics et al. 1993).

B6.129P2-*Apoe*^{tm1Unc}/J 002052

Apolipoprotein (apoE) is a glycoprotein synthesized in the liver, brain, and other tissues in both humans and mice. It is a structural component of all lipoprotein particles other than LDL. One of its most important functions is to serve as a high affinity ligand for the apoB and apoE (LDL) receptor and for the chylomicron remnant receptor, thereby allowing the uptake of apoE-containing particles by the liver (Jawien et al. 2004).

Because they are hypercholesterolemic and spontaneously develop arterial lesions, *Apoe*-deficient mice are one of the most relevant models for atherosclerosis research. They develop lesions more quickly if fed a Western diet (containing 21% fat and 0.15% cholesterol), and even more quickly if fed a high-cholesterol diet (containing 15% fat, 1.25% cholesterol, and 0.5% cholic acid) (Jawien et al. 2004).

The progression of atherosclerosis in this model is very similar to that in humans. By three months of age, homozygous mutants develop fatty streaks in the proximal aorta. With age, they develop more lesions with relatively less lipid but more elongated cells, typical of the advanced stage pre-atherosclerotic lesions.

Because atherosclerotic plaques in coronary arteries are particularly critical, future genome scans in mice should perhaps include coronary atherosclerosis as a phenotype (Wang et al. 2005). Advanced atherosclerotic lesions do occur in the coronary arteries of *Apoe*- and/or *Ldlr*-deficient mice and in *Scarb1*-deficient mice fed either chow (Braun et al. 2002) or a high-cholesterol diet (Caligiuri et al. 1999; Calara et al. 2001).

B6.129-*Apoe*^{tm1Unc} *Ldlr*^{tm1Her}/J 002246

Mice homozygous for both *Apoe* and the *Ldlr* targeted, null mutations develop severe hyperlipidemia and atherosclerosis. Even when fed a regular chow diet, they usually develop a more severe atherosclerosis than do *Apoe*-deficient mice. These mice do not have to be fed an atherogenic diet when used to test the anti-atherosclerotic effects of compounds (Jawien et al. 2004).

B6.129S7-*Ldlr*^{tm1Her}/J 002207

These low density lipoprotein receptor-(*Ldlr*-) deficient mice have high serum cholesterol levels (200-400 mg/dl) and very high levels (> 2,000 mg/dl) when fed a high fat diet (levels in normal mice are 80-100 mg/dl). Although they develop atherosclerotic lesions spontaneously when fed a chow diet, the lesions are small and develop slowly. The lesions develop much faster in mice fed either a high cholesterol or a Western diet (Jawien et al. 2004).

B6.129-*Pctp* ^{tm1Bor}/J 006607

Mice homozygous for this targeted mutation of the phosphatidylcholine transfer protein (*Pctp*) gene are viable, fertile, and look and behave normally. *PCTP* is not detected in the liver cytosol of eight day old homozygotes. The lipid content and composition of bile and lung surfactant secretions are normal. Plasma cholesterol and phospholipid levels are not affected in homozygotes fed a normal chow diet, but the accumulation of small alpha-migrating HDL particles increases. When mice are fed a high fat, high cholesterol, cholate-containing lithogenic diet, biliary concentrations of phospholipids, cholesterol, and bile salts decrease, but hepatic accumulations of phospholipids and cholesterol increase. When mice are fed a high fat diet, HDL particles are normal-sized, but plasma cholesterol and phospholipid concentrations are increased.

B6.129P2-*Pltp* ^{tm1Jia}/J 003918

Homozygotes for this targeted mutation of the phospholipid transfer protein (*Pltp*) gene are viable, fertile, and look and behave normally. Their lungs and liver produce no *Pltp* mRNA. No plasma *PLTP* activity is detected. They have marked decreases in plasma HDL phospholipids (66%), cholesteryl esters (69%), free cholesterol (70%), and apoAI. When fed a high fat/high cholesterol diet, similar reductions are observed, as are increases in VLDL and LDL phospholipid, free cholesterol, and cholesteryl ester (Jiang et al. 1999, 2001; Qin et al. 2000).

B6;129S2-*Scarb1*^{tm1Kri}/J 003379

The class B, type I scavenger receptor *Scarb1* is a cell surface HDL receptor that can recognize the apolipoproteins on the surface of the HDL particle. It plays a key role in determining the levels of plasma lipoprotein cholesterol (primarily HDL) and the accumulation of cholesterol stores in the adrenal gland. The plasma cholesterol (primarily HDL) concentrations in *Scarb1*^{tm1Kri} heterozygotes and homozygotes are 31% and 125% higher, respectively, than they are in wild-type controls. Additionally, cholesterol levels in the adrenal tissues of heterozygotes and homozygotes are 42% and 72% lower, respectively, than they are in wild-type controls. The plasma concentrations of APOAI, the major protein in HDL, in these mutants is comparable to that of wild-type controls (Braun et al. 2002).

B6.129P2-*Apob* ^{tm1Unc}/J 002053

Homozygotes for the *Apob*^{tm1Unc} targeted mutation produce a truncated form of the apolipoprotein B protein APOB70 and no APOB100, resulting in a condition similar to human familial hypobetalipoproteinemia. These mice express normal amounts of APOB48. Homozygotes have greatly reduced levels of plasma APOB, beta-lipoproteins, total cholesterol, plasma triglycerides, fasting chylomicronemia, and HDL cholesterol. Homozygotes also have a high incidence of exencephaly and hydrocephaly (Homanics et al. 1993).

DBA/1-*Abca1*^{tm1Jdm}/J 003897

Many homozygotes for this targeted mutation of the ATP-binding cassette, sub-family A (ABC1), member 1(*Abca1*) gene die perinatally. Autopsied pups exhibit perivisceral hemorrhaging. Pups that survive beyond birth have no detectable *Abca1* gene transcript in the liver. Homozygous females have impaired placental development and are unable to produce litters. Plasma lipids and lipoproteins are markedly reduced; plasma cholesterol is decreased by approximately 70%; HDL-C and apoAI are decreased by greater than 99%; and LDL-C and apoB are reduced 70% and 20% respectively. Other characteristics observed are an increase in intestinal absorption of dietary cholesterol, an impaired ability of macrophages to engulf apoptotic cells, and an accumulation of lipid-rich macrophages and type II pneumocytes in the lungs. The pathophysiology of these mice is similar to that associated with Tangier disease (Calpe-Berdiel et al. 2005; Francone et al. 2003; McNeish et al. 2000).

STOCK *Cav1*^{tm1Mls}/J 004585

Homozygotes for this targeted mutation of the caveolin, caveolae protein 1 (*Cav1*) gene are viable, fertile, and look and behave normally. They are intolerant to exercise and slightly hyperphagic. When four to five months old, they are often smaller than their wild-type littermates, and, when a year old, weigh five to seven grams less than those littermates. They are resistant to diet-induced obesity. They produce a reduced amount of white adipose tissue comprised of abnormally small adipocytes, but they have enlarged and hyperplastic brown adipose tissue. Their lipid metabolism and uptake is disrupted, resulting in elevated levels of serum triglycerides and free fatty acids, and reduced levels of leptin. Isolated segments from their aortic tissues have a diminished vasoconstriction response to the alpha-1-adrenergic receptor agonist, phenylephrine, and an enhanced vasorelaxation response to acetylcholine. They have thickened alveolar septa, hypercellularity, reduced alveolar spaces, an increased density of basement membranes and reticulin fibers, and an increased number of endothelial cells. MEF cells derived from these mice are twice as proliferative and denser at confluence than are those of wild-type littermates. Their endothelial cells lack caveolae (plasmalemmal vesicles), and caveolar endocytosis is impaired (Razani et al. 2001).

Blood Pressure

The Mouse Phenome Project Strains

Blood pressure phenotypes of numerous JAX® Mice strains have been characterized and published in the Mouse Phenome Database, www.jax.org/phenome:

- Deschepper and Gallo-Payet (2004) measured the systolic blood pressure and morphologic phenotypes of cardiovascular-related organs in 13 JAX® Mice inbred strains.
- Gavras et al. (2003) measured the effects of diet on blood pressure and heart rate in 11 JAX® Mice inbred strains.
- Svenson and Smith (2005) measured the systolic blood pressure, blood pressure variability across tests, pulse, and pulse variability across tests in 14 JAX® Mice inbred strains.
- Kitten (2003) performed a multi-system analysis of mouse physiology (including various blood pressure and other cardiovascular subphenotypes) in seven JAX® Mice inbred strains.
- Sugiyama and Tsukahara et al. (2007) and Sugiyama et al. (2002) determined the systolic and diastolic blood pressure of 25 inbred mouse strains, most of them JAX® Mice strains (Table 4).

HLBS Mutants

The HLBS Center has produced 15 heritable (ready-to-ship) mutants and two phenotypic deviants suitable for hypertension research (Table 3, page 13).

Strain	Diastolic pressure	Systolic pressure
129T2/SvEmsJ	72.5 ± 6.1	115.7 ± 8.7
A/J	66.8 ± 7.6	106.7 ± 5.6
AKR	79.2 ± 6.4	121.2 ± 2.9
ALS/LtJ	76.1 ± 5.1	120.6 ± 6.6
BALB/cAn	72.3 ± 3.6	107.8 ± 3.6
BTBR	62.2 ± 7.6	101.4 ± 2.7
C3H/HeJ	66.8 ± 3.5	100.5 ± 3.2
C57BL/6J	73.2 ± 2.9	114.6 ± 5.3
C57BLKS/J	71.4 ± 5.0	115.4 ± 3.0
CBA/J	71.1 ± 3.2	106.0 ± 7.0
DBA/1J	69.8 ± 3.4	103.4 ± 2.5
DBA/2J	68.4 ± 5.3	107.8 ± 3.5
FGS/Nga	74.4 ± 1.8	111.8 ± 6.3
FVB/N	70.8 ± 4.5	110.0 ± 4.9
KK/Ta	66.8 ± 1.2	111.8 ± 4.1
LP	62.1 ± 11.1	102.7 ± 7.2
MRL	77.1 ± 10.5	113.5 ± 6.5
NOD	85.2 ± 9.1	127.2 ± 4.4
NON	64.4 ± 6.1	104.8 ± 6.2
NZO/HlLtJ	86.6 ± 6.9	132.4 ± 3.1
NZW	62.5 ± 8.7	106.9 ± 8.2
PL	70.8 ± 70.6	118.9 ± 7.6
RIIIS	70.3 ± 10.9	115.3 ± 6.7
SJL/J	67.7 ± 2.1	100.6 ± 4.4
SWR/J	86.1 ± 4.7	127.1 ± 3.0

Table 4. Mean diastolic and systolic blood pressures (±SD) in 25 inbred mouse strains (Tsukahara et al. 2004; Sugiyama et al. 2002).

Selected JAX® Mice Blood Pressure Models

B6.129P2-*Nos3*^{tm1Unc}/J 002684

Homozygotes for this targeted mutation of the nitric oxide synthase 3, endothelial cell (*Nos3*) gene are viable and fertile. Their blood pressure is about 20 mmHg higher than that of wild-type siblings, and they have a decreased heart rate. Females weigh less than normal wild-type siblings. They are insulin resistant in the liver and peripheral tissues (Shesely et al. 1996).

BPH/2J 003005
BPL/1J 003006
BPN/3J 003004

BPH/2J, BPL/1J, and BPN/3J are descended from an eight-way cross from which hypertensive and hypotensive mouse lines were selected (Schlager and Sides 1997).

BPH/2J mice are hypertensive. By five weeks of age, they have elevated systolic blood pressures; by 150 days of age, their blood pressures are 60mmHg higher than those of BPL/1J mice. They have higher heart rates, larger hearts and kidneys, and higher hematocrit than do BPL/1J mice, and lower renin, aldosterone, and angiotensin I levels than do BPL/1J and BPN/3J mice. BPN/3J mice are normotensive. They were inbred at the same time as and from the same parental strain as BPL/1J and BPN/3J, but in the absence of any selection pressure. They are a normotensive control for hypertensive BPH/2J mice and hypotensive BPL/1J mice.

The original high blood pressure (HBP) and low blood pressure (LBP) selected lines from which the three strains were inbred had several biochemical and physiological differences that have not been re-examined in the inbred strains. These include differences in brain catecholamines, calmodulin concentrations, heat sensitivity, alcohol preference, and longevity. The differences in longevity are striking: the hypotensive selected lines live an average of 200-300 days longer than do the hypertensive selected line. Genetic analysis suggested that three to five genes are responsible for the difference in blood pressures between BPH/2 and BPL/1 mice. A recent genome scan of (BPH/2 x BPL/1)F2 progeny revealed three chromosome locations co-segregating with blood pressure. Two of these sites were verified by candidate gene co-segregation: angiotensinogen on Chr 8 and mouse kallikrein binding protein (*Serpina3c*) on Chr 12 (Schlager and Sides 1997; Uddin and Harris-Nelson 2004).

Observations by some of our scientists (Paigen and Svenson, pers. comm.) suggest that the BPH/2J strain may be a model of preeclampsia. It is a subline originating from an eight-way cross performed by Schlager and Sides (1997) and appears to have some of the same preeclampsia phenotypes (including small litters of one or two pups) as a different subline from the same cross (Dokras et al. 2006; Davisson et al. 2002). We are in the process of characterizing BPH/2J to determine its potential as an preeclampsia model.

B6.129P2-*Agtr1*^{tm1Unc}/J 002682

Homozygotes for this targeted mutation of the angiotensin II receptor, type 1a (*Agtr1*) gene are viable and fertile. Their blood pressures are approximately 24 mmHg lower than those of normal wild-type siblings and do not respond to angiotensin II infusions. Blood pressures of heterozygotes are approximately 12 mmHg lower than those of wild-type siblings and respond qualitatively to angiotensin II infusions (Ito et al. 1995).

Heart Disorders

HLBS Mutants

The HLBS Center has produced 13 mutant models (eight heritable, and ready-to-ship) for researching heart disorders (see Table 3, page 13).

Selected JAX® Mice Models

B6;129S-*Gja1*^{tm1Kdr}/J 002201

Homozygotes for this targeted mutation of the gap junction membrane channel protein alpha 1 (*Gja1*) gene die at birth. The cause of death is a failure in pulmonary gas exchange caused by a swelling and blockage of the right ventricular outflow tract from the heart. The cardiac abnormality involves a delayed looping of the ascending limb of the heart tube, which includes the right ventricle and the outflow tract. This predisposes homozygotes to malformations of the subpulmonary outflow tract and tricuspid valve. The mutation also predisposes homozygotes to lens cataracts and causes a severe reduction of germ cell numbers. Both neonatal and adult heterozygotes have slow ventricular epicardial heartbeats (Reaume et al. 1995).

B6Ei.Cg-*Atp7a*$^{Mo\text{-}blo}$/J 002044

Female heterozygotes for the blotchy allele (*Atp7a*$^{Mo\text{-}blo}$), a targeted mutation of the ATPase, Cu^{++} transporting, alpha polypeptide (*Atp7a*) gene, are viable and fertile. They have irregular patches of light-colored fur. Hemizygous males and homozygous females have reduced viability, and many are infertile. Hemizygotes and homozygotes are light all over with no blotching, are usually small, and occasionally have deformed hind legs. Most hemizygotes and homozygotes have defective aortic elastin and die of an aortic aneurysm. Hemizygous males have enlarged air spaces in their lungs (emphysema), probably because they have defective elastin and collagen (Andrews et al. 1975; Brophy et al. 1988).

B6.129P2-*Nos3*^{tm1Unc}/J 002684

Homozygotes for this targeted mutation of the nitric oxide synthase 3, endothelial cell (*Nos3*) gene are viable and fertile. They have a low heart rate. Females weigh less than normal wild-type siblings (Feng et al. 2002; Li et al. 2004; Ojaimi et al. 2005).

B6.Cg-*Clu*^{tm1Jakh}/J 005642

Homozygotes for this targeted mutation of the clusterin (*Clu*) gene are viable, fertile, and look and behave normally. Clusterin is a widely expressed circulating glycoprotein of unknown function associated with Alzheimer's disease, cerebral palsy, stroke, apoptosis, autoimmune myocarditis and other inflammatory injuries, kidney disease, and skin carcinogenesis (Imhof et al. 2006; McLaughlin et al. 2000). It plays a central role in the remodeling of ischemic damage (Imhof et al. 2006). *Clu*-deficient mice, particularly females, develop more severe myosin-induced myocarditis than do wild-type mice, suggesting that clusterin limits the progression of autoimmune myocarditis and protects the heart from postinflammatory tissue destruction (McLaughlin et al. 2000).

Metabolic Syndrome (Syndrome X)

B6.129S7-*Ldlr*^{tm1Her}/J 002207

Until recently, few animal models were known to display the constellation of obesity, type 2 diabetes, hypertension, atherosclerosis, and other abnormalities collectively called metabolic syndrome or syndrome X. Males of this *Ldlr*-deficient JAX® Mice strain may be such a model. *Ldlr*^{tm1Her} homozygotes have long been used as a model for cardiovascular disease, and recent studies indicate that they may be excellent models of diet-induced metabolic syndrome. Males fed a diabetogenic diet develop hypertriglyceridemia, high serum cholesterol levels, hyperleptinemia, slightly higher insulin and moderately higher plasma glucose levels than do C57BL/6 mice fed a diabetogenic diet, obesity, high vascular calcification, atherosclerotic plaques comparable to those that form in mice of the same strain fed a chow diet, and elevated free fatty acid levels (Merat et al. 1999; Towler et al. 1998, Schreyer et al. 2002).

B6.129-*Pparg*^{tm2Rev}/J 004584

The B6.129-*Pparg*^{tm2Rev}/J strain, developed in the laboratory of Dr. Ronald Evans at The Salk Institute by Dr. Yaacov Barak, currently at The Jackson Laboratory, possesses *loxP* sites flanking exons 1 and 2 of the peroxisome proliferator activated receptor gamma (*Pparg*) gene, which is abundantly expressed in adipocytes. In conjunction with a Cre recombinase-expressing strain, this strain can be used to generate tissue-specific *Pparg* mutants. For example, when this strain is mated to B6.Cg-Tg(Fabp4-cre)1Rev/J (005069), offspring are produced in which *Pparg* is deleted. These offspring develop progressive lipodystrophy and late onset syndrome X-like symptoms, including modestly elevated plasma free fatty acid and triglyceride levels, decreased plasma leptin and ACRP30 levels, increased hepatic glucogenesis, and increased insulin resistance (He et al. 2003; Hevener et al. 2003).

JAX® Services is a comprehensive and integrated set of mouse breeding and research services designed to provide you with efficient and cost-effective solutions to your mouse-based research. The services are based on nearly 80 years of experience in mouse husbandry and genetic research and are conducted in accordance with the highest standards of animal health and genetic quality.

Several services that may be appropriate for cardiovascular research are described below. For more information on these and other services, please contact your Regional Representative (contact information can be found on the following website: www.jax.org/jaxmice/services/manager), visit the JAX® Services website, www.jax.org/jaxmice/services/invivo, or contact JAX® Services at jaxservices@jax.org, 1-800-422-6423, or 1-207-288-5845.

JAX® In Vivo Services

We provide fully customizable target validation and efficacy testing services with access to the world's largest collection of specialized mouse models. Our Study Directors and research scientists bring their expertise and collective knowledge of mouse physiology and genetics research to work for you.

Our state-of-the-art phenotyping laboratory provides a broad array of high-throughput, cost-effective, and non-invasive test platforms for model characterization, evaluation of key physiological parameters, drug target validation, and drug efficacy testing (Table 5). Our in-house services are complemented by a network of providers to offer comprehensive disease endpoint measurements.

We have expertise with a variety of therapeutic areas, including atherosclerosis, osteoporosis, subcutaneous and orthotopic xenograft models of cancer, inflammatory bowel disease, blood disorders, neuromuscular disease, regenerative medicine, autoimmune disorders, pain models, asthma, dermatology, and metabolic disorders, including diabetes and obesity. Our dedicated, experienced staff help select the most clinically relevant model for your protocol. We have performed *in vivo* studies in over 100 mouse models to date.

JAX® *In Vivo* Services are highly customizable. We manage entire projects and work closely with you to ensure that custom protocols are properly executed

Table 5. Summary of JAX® *In Vivo* Services.

Compound Dosing	**Experimental Methods**
IP, IV, SC, PO, ID	Biospecimen collection
High pressure tail vein injections	Digital caliper measurements
Inhalation	*In vitro* cell preparation: cell isolation, culture, characterization
In the food or water	Mouse model induction
Intramuscular, intrarectal	Necropsies, tissue harvests
IV catheters	Surgical techniques
Osmotic minipumps (SC or IP)	SC xenograft and orthotopic transplantation
SC drug pellets	Stem cell engraftment
Physiological and Behavioral Tests*	**Supporting Services**
Activity Monitoring, including locomoter, rearing	Bioanalytical
Body tissue composition by DEXA and MRI	Blood and urine glucose
$C0_2$ production/O_2 uptake, food & water intake	CBC
Glucose tolerance, insulin tolerance, glucose measurement	Clinical chemistry
Heart rate, ECG	Histological services and IHC
Locomotor anxiety test analyzed by SMART software	Immunophenotyping
Morris water maze, Radial arm maze	Lipid distribution
Respiratory function by Whole Body Plethysmograph	Metabolic assays
Rotorod, grip strength, gait analysis	Multiplex analysis of serum hormones and cytokines
Systolic and diastolic blood pressure, pulse	Access to specialized imaging: biophotonic, MRI, micro-CT, PET
Thermal pain reflex	

VCD-induced Menopause

We can produce mouse models that mimic the physiological changes occurring in human perimenopause, enabling researchers to better understand the associations between both menopause and hormone replacement therapy and susceptibility to heart disease.

The only rodent models previously available for modeling menopause were ovariectomized (OVX) rats and mice. However, almost 90% of menopausal women still have their ovaries. Our service uses the industrial chemical 4-vinylcyclohexene diepoxide (VCD) to selectively accelerate the *natural loss* of small primordial and primary follicles without affecting the ovary or other tissues, resulting in an endocrine state that more closely mimics human menopause (Fig. 1) (Mayer et al. 2002).

VCD-induced menopause is a particularly powerful tool because it works with most mouse strains, including models of atherosclerosis. For example, Mayer et al. 2004, 2005) found that when VCD-induced menopausal low-density lipoprotein-(*Ldlr*-) deficient mice (B6.129S7-*Ldlr*^{tm1Her}/J, 002207), which are susceptible to atherosclerosis, receive 17β-estradiol supplements, they develop significantly fewer atherosclerotic plaques than do either non-supplemented controls or non-supplemented OVX mice.

VCD-induced menopause may be particularly appropriate for cardiovascular research when used with the following four JAX® Mice strains: C57BL/6J (000664), an atherosclerosis-susceptible strain; C3H/HeJ (000659), an atherosclerosis-resistant strain; B6.129S7-*Ldlr*^{tm1Her}/J (002207), a strain with normally high serum cholesterol levels and extremely high levels when fed an atherogenic diet; and B6.129P2-*Apoe*^{tm1Unc}/J (002052), another strain with high serum cholesterol levels. A study by our Animal Husbandry and Performance Group demonstrated the efficacy of VCD-induced menopause in these strains. VCD treatments significantly decreased the number of primordial and primary follicles, resulting in a significant increase in FSH levels (JAX® NOTES 2007). For additional cost, this service can be adapted to other strains.

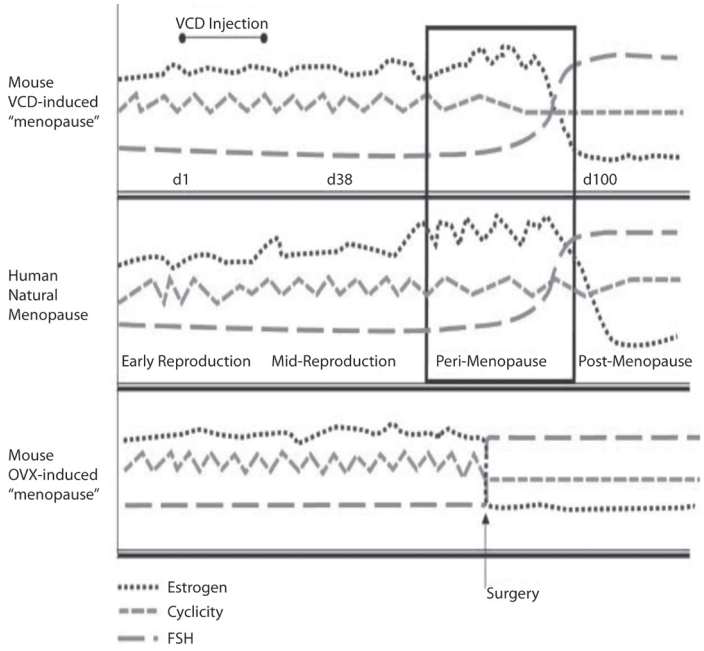
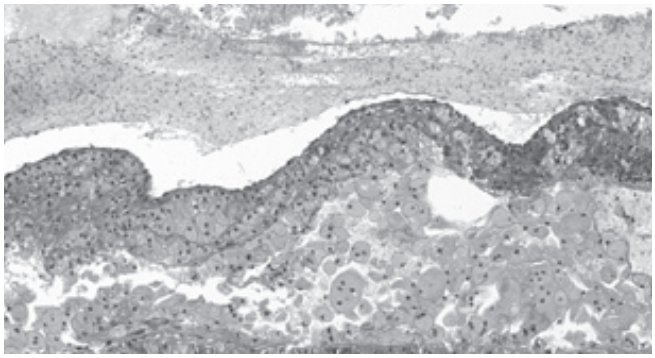


Figure 1. Cyclicity, estrogen levels, and FSH levels are similar in VCD-induced mouse and human menopause. The OVX mouse goes into menopause quickly and skips peri-menopause, (the one to 10 years in humans before menstrual cycles cease). Post-menopause refers to the year after peri-menopause. Values for VCD-induced menopause are relative to the beginning of the 15-day VCD injection protocol.

JAX® Surgical & Tissue Collection Services

Our expert surgeons can perform over 60 types of standard and custom surgical procedures. Conventional techniques can be modified, or new ones can be developed to meet even the most demanding research requirements. All surgeries are performed at an appropriate health status in surgical suites of a barrier facility. We can also collect and provide you with tissues or fluid samples. Table 8 below lists most of our surgical procedures and biospecimens. For a complete list and prices, please visit our website, www.jax.org/jaxmice/services/surgical_pricing.



Foamy macrophages in the subendothelial space of a mouse aorta.

Table 8. Selected surgical procedures and biological samples available from JAX® Services.

Surgical Procedures	Tissue and Fluid Samples
• Adrenalectomy • Adrenal demedullation • Brown adipose fat denervation • Castration - Orchiectomy • Catheter (jugular, femoral, carotid) • Subcutaneous hormone pellet implant • Hysterectomy • Intracerebroventricular cannulation • Intrathymic injections • Kidney capsule implant • Nephrectomy (5/6 and unilateral) • Olfactory bulbectomy • Osmotic pump implants • Ovarian transplant • Ovario-hysterectomy • Ovariectomy • Skin graft (body or tail) • Sialectomy • Splenectomy • Subq implant • Telemetry Implant (PA-C10 BP monitor) • Thymectomy • Thyroid-parathyroidectomy • Vasectomy • Vagotomy	• Bile • Blood, Serum, Plasma (pooled, non-pooled) • Adrenal glands • Aorta • Bone (vertebrae and femur) • Bone marrow • Brain and Spinal cord • Diaphragm • Embryonic tissue • Eyes, Retina • Fat (brown and white depots) • Head • Heart, Liver, Kidneys, Lungs • Leg • Mammary glands • Ovaries, Testicles, Uterus, Prostate • Pineal gland, Pituitary gland • Polyps • Salivary gland - Submandibular • Skeletal muscle • Skin (with or without hair) • Spleen, Thymus • Stomach, Small intestine, Colon, Pancreas

Breeding and Colony Management Services

Offered in Maine, and California, our Breeding and Colony Management Services are designed to save you time, space, money, and to simplify all aspects of managing your mouse colonies.

JAX® Breeding and Colony Management services support your research with the following:

- **Nearly 80 years of experience** in mouse genetics and colony management
- **State-of-the-art technologies** in reproductive science and genetic analysis
- **World-class expertise** with an array of *in vitro* fertilization (IVF) techniques
- **Experience in optimizing animal housing space** to deliver standard and customized breeding projects on schedule, on budget, and according to your specifications
- **Capability to rapidly expand breeding colonies** by drawing from large quantities of breeding stock
- **Breeding strategies customized to your needs**, whether for large or small quantities of mice, from pedigreed stock to preserve genetic integrity

JAX® Breeding Service

This service helps you quickly and efficiently achieve your objectives, whether to relieve capacity constraints at your facility, rederive mice to improve the health of your colonies, or manage complex, multiple-gene crossbreeding projects. Using investigator-supplied or JAX® Mice strains, this service maintains and ships mice to you as needed. Our California facility can also handle projects which require housing mice in flexible film isolators.

JAX® Dedicated Supply Service

Many of our strains are available only from our cryopreserved repository or from small colonies in limited quantities. Our Dedicated Supply Service can custom build a colony of these strains, so you receive the mice you need when you need them. Our Dedicated Supply personnel know all the tricks of the trade for maintaining difficult strains and for expanding colonies of low-demand strains efficiently and cost-effectively.

JAX® Speed Expansion Service

Expanding colonies to meet increased demand or to produce a burst of same-age mice can be expensive and time consuming. Using IVF techniques, we can do this rapidly and cost-effectively. This service is particularly useful for quickly producing large quantities of specific pathogen free (SPF), same-age mice.

Cryopreservation and Recovery Services

JAX® Sperm Cryopreservation & Recovery Service

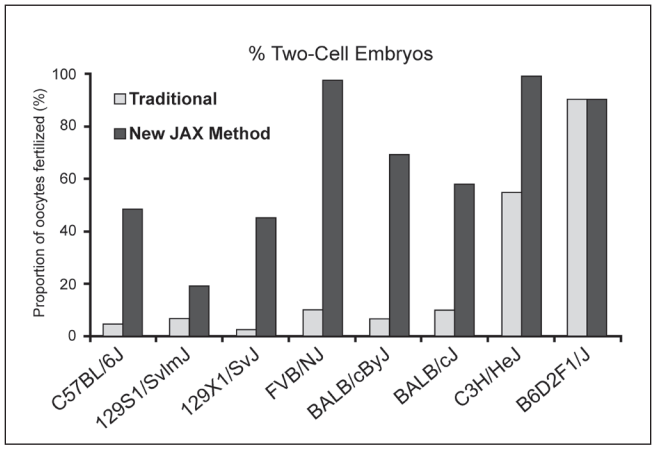
Our scientists have developed the first truly reliable and cost-effective sperm cryopreservation and recovery service for knock-out and transgenic strains with common genetic backgrounds. We recover cryopreserved sperm and use them to quickly produce a large colony of single-age SPF mice. This service includes a quality control check (IVF rate for the frozen sperm) and three years of liquid nitrogen storage (additional years of storage can be purchased).

JAX® Custom (Embryo) Cryopreservation Service

We can cryopreserve embryos of homozygous and hemi/heterozygous inbred, mutant, and genetically modified lines of mice. Cost varies depending on strain background, fertility, and the number of mice provided. This service includes five years of liquid nitrogen storage (additional years of storage can be purchased).

Combined JAX® Speed Rederivation and JAX® Sperm Cryopreservation Service

In this combined service, our JAX® Speed Rederivation Service uses IVF to quickly rederive your mouse strain to SPF status, and, at no extra cost, our JAX® Sperm Cryopreservation & Recovery service cryopreserves sperm from the strain for three years, protecting it from accidental loss or contamination and freeing up valuable mouse room space. This combined service is applicable for strains with transgenes, targeted mutations, or chemically-induced mutations on the most commonly used genetic backgrounds: C57BL/6J, FVB/NJ, NOD/ShiLtJ, BALB/cByJ, BALB/cJ, DBA/1J, DBA/2J, C3H/HeJ, hybrid combinations of these strains, and B6;129 hybrids.



Our new JAX® Sperm Cryopreservation and Recovery Service produces much higher embryo fertilization rates from cryopreserved sperm than traditional methods.

JAX® Genetic Analysis and Research Services

Our scientists have developed a panel of 2,199 informative and easily-assayed single nucleotide polymorphic (SNP) markers. These markers are an average of approximately 1.5 Mb or 0.75cM apart and often represent the informative allele in at least two strains (Petkov et al. 2004a, 2004b). We use this SNP panel for many of our services, including those described below.

Using our SNP panel, we can characterize the genetic make-up of virtually any mouse strain. As examples, we can detect inter-strain genetic contamination, determine the degree of congenicity in congenic strains, and detect cryptic unlinked segments of residual donor DNA in congenic strains.

JAX® Speed Congenic Development Service

This service uses a marker-assisted breeding strategy to produce congenic strains in only 15 to 18 months, reducing the number of mice needed, as well as facility, equipment, and personnel costs.

JAX® Genome Scanning Service

We designed this service for those of you who prefer to construct your own congenic or consomic strains but wish to take advantage of our SNP-marker panel to type and select the offspring for each backcross. The process is easy: simply send us tail samples from backcross offspring (minimum of six to 10 recommended per generation), and we type the tails and tell you which mice to use for the next backcross

JAX® Gene Expression Service

Accelerate your research by using JAX®'s well established Gene Expression Service. The service includes nucleic acid preparation, chip/array hybridization, and detailed statistical analysis, using unique statistical tools developed at The Jackson Laboratory. We have successfully analyzed thousands of mouse tissues for our own scientists, and are now pleased to offer this service to the broader scientific community.

JAX® Gene Mapping Service

Using our SNP-marker panel, we can analyze mouse tissue or processed DNA samples from F2 or N2 progeny and localize a gene of interest. We can also help you select the most appropriate strains to produce the F2 or N2 progeny. You receive results approximately six weeks after we complete the crosses and collect tissue samples. This service is appropriate for mice with single-gene mutations.

JAX® SNP-Assisted QTL Mapping Service

QTL mapping has become a very important tool for finding the alleles that contribute to complex human diseases, such as atherosclerosis and hypertension. These diseases are continuous and modulated by a group of alleles interacting with each other and the environment. Using our SNP marker panel, we can locate and estimate the effect of contributing alleles.

Online Resources for Mouse-based Cardiovascular Research

JAX® Mice Database

You can find more information on over 250 JAX® Mice models suitable for cardiovascular research (including those described herein) in the JAX® Mice Database. Using the Quick Query Form (www.jax.org/jaxmice/query), you may search the database using gene or allele symbols, common names, stock numbers, keywords, phenotype terms from the Mouse Phenotype Ontology vocabulary in the Mouse Genome Database, human disease terms from the Online Mendelian Inheritance in Man (OMIM) vocabulary, or research areas.

Select the strain name to view the Strain Data Sheet. Each Strain Data Sheet includes nomenclature information, genetic and phenotypic characteristics, strain development information, research applications, references, and availability and pricing information.

Mouse Phenome Database

The Mouse Phenome Database (MPD, www.jax.org/phenome) is the database for the Mouse Phenome Project, a coordinated international effort to establish a collection of baseline phenotypic data for a set of commonly used and genetically diverse inbred mouse strains. Housed at The Jackson Laboratory, The MPD includes baseline and diet-induced phenotypic data for many cardiovascular phenotypes, including cholesterol and triglyceride levels, blood pressure, and susceptibility to atherosclerosis.

The database characterizes these and other phenotypes by strain and sex. Investigators may download protocols and raw data, review related data published in the scientific literature, use query tools to analyze data, review current project information, participate in the Mouse Phenome Project, and subscribe to "PHENOME-LIST," a forum for discussing Phenome Project-related items. The Mouse Phenome Database is fully integrated with the Mouse Genome Database (www.informatics.jax.org).

JAX® HLBS Center

The Jackson Laboratory's Center for New Mouse Models of Heart, Lung, Blood, and Sleep Disorders (HLBS) is one of five Programs for Genomic Applications (PGAs) established in September, 2000, by the National Heart, Lung, and Blood Institute to advance functional genomic research related to heart, lung, blood, and sleep (www.nhlbi.nih.gov/resources/pga). The goal of The Jackson Laboratory PGA is to provide the biomedical research community with new information, tools, and resources for understanding the genetic bases of atherosclerosis, hypertension, lung function, blood formation, thrombosis, obesity, and sleep function.

Among the new tools produced by the Center are chemically-induced mutant mice, many of them suitable for cardiovascular research. To produce these mutants, the Center uses N-ethyl-N-nitrosourea (ENU) and B6 mice as the mutagen and strain of choice respectively. Once new mutants are characterized and proven heritable, they are made available to academic researchers for the cost of shipping only (for-profit organizations are charged an additional $250.00 USD). Instructions for ordering are on the Center's website.

To date, the Center has identified over 400 phenotypic deviants, about 100 of which have been proven heritable.

As a participant in the Mouse Phenome Project, the Center is in the process of comprehensively characterizing the heart, lung, blood, and sleep phenotypes of the Mouse Phenome Project strains. This is allowing scientists to choose the strains most appropriate to cross for identifying QTLs associated with cardiovascular, respiratory, and related phenotypes. HLBS and Mouse Phenome Project participants have already characterized coagulation, heart rate, blood pressure, electrocardiogram, plasma lipid, cardiovascular organ weight, atherosclerosis susceptibility (pathogen-accelerated and pathogen-free), lung volume, respiratory rate, airway hyperreactivity, and related phenotypes for some or all Phenome strains. Data are published and publicly accessible in the Mouse Phenome Database. Additionally, the Center has used its strain survey data to carry out QTL crosses for baseline peripheral blood counts, HDL levels, and disordered sleep.

Online Resources

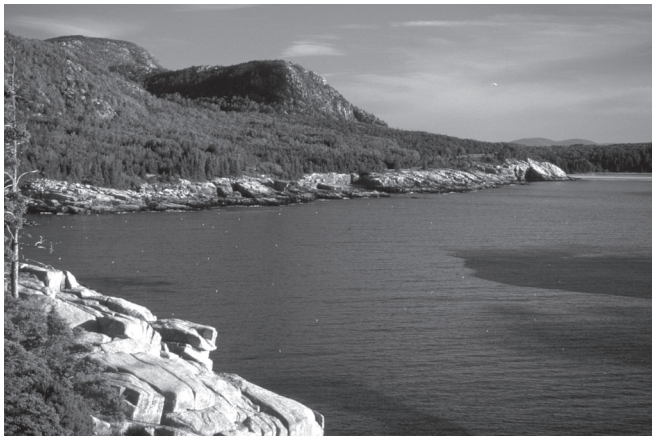
Cardiogenomics PGA and Website

The goal of the Cardiogenomics Program for Genomics Application (PGA) is to characterize the genetic and environmental factors that regulate cardiovascular function and disease. The PGA also provides extensive training in cardiovascular research: ongoing journal clubs and seminars, symposia at major conferences, and workshops relevant to cardiovascular research.

The Cardiogenomics website (cardiogenomics.med.harvard.edu/home) publishes high quality and comprehensive data for the genomics of structural and functional adaptation of the cardiovascular system. It integrates expression data from animal models and human tissue samples, mutation screening of candidate genes in patients, and DNA polymorphisms in awell-characterized general population. This data set will serve as a benchmark for future basic, clinical, and pharmacogenomic studies.

Courses and Conferences

We host several courses that are particularly helpful to cardiovascular researchers. Most of them are offered yearly, are one to two weeks long, and consist of a mixture of lectures, hands-on workshops, discussion groups, and tutorials. Many are held in a retreat-like setting at the High Seas facility overlooking the ocean in Bar Harbor.
To ensure a supportive learning atmosphere with exceptional interaction between students and faculty, the courses are generally limited to 35 participants. We recommend that you register early. For more details on content, registration, enrollment limits, and continuing education credits for Jackson Laboratory courses, see the Courses and Conference website at www.jax.org/courses.



Comprehensive Approaches to the *In Vivo* Assessment of Cardiovascular Function in Mice

This workshop focuses on assessing cardiovascular function in mouse models. Lectures are given by leaders in the field of cardiovascular physiology, pharmacology, and pathology. Participants are taught to use the Visualsonics Vevo 770 system to perform non-invasive high-resolution ultrasound, use telemetry (DataSciences International) and catheter-dependent (ADInstruments) approaches to monitor cardiovascular parameters *in vivo*, analyze data collected during the workshop, perform various surgeries, and administer anesthetics.

Genomic and Proteomic Approaches to Complex Heart, Lung, Blood, and Sleep Disorders

Participants in this highly acclaimed, intensive, nine-day course learn how to use statistics, molecular biology and genetics to analyze complex diseases such as atherosclerosis, hypertension, and asthma in humans and animal models. They learn to detect the genetic basis of disease, perform linkage analysis, conduct genome scans, analyze quantitative trait loci, detect gene interactions, map complex disease genes, clone genes, and characterize gene functions. They are introduced to contemporary approaches of gene discovery, such as mutagenesis and microarray analysis, are introduced to the latest bioinformatics tools (such as OMIM, MGD, Unigene, GeneBank, Blast, Gene-scan, SwissProt, and Entrez), and they engage in in-depth discussions about the social and ethical aspects of generating and using genetic information.

Phenotyping Mouse Models of Human Lung Disease

This five-day workshop provides hands-on training in phenotyping mouse mutants for cardiovascular defects, and heart, lung, blood, and sleep disorders. The course focuses primarily on measuring blood pressure, ultrasound, EKG and coagulation profiles, and the theory and methods used for screening sleep and respiratory mutants.

Annual Short Course on Medical and Experimental Mammalian Genetics

Offered here every summer for nearly 50 years, this two-week course features daily morning and evening lectures and afternoon mini-symposia, workshops, tutorials, and demonstrations. The course implicitly focuses on translational biology and clinical applications of biomedical research. It covers three broad areas:
1) genetics in experimental animals and humans, 2) the relationship of heredity to disease in experimental animals and humans, and 3) the importance of molecular genetics in diagnosing and treating inherited disorders. Many of the lectures, workshops, and symposia are either on or include cardiovascular research.

Annual Workshop on the Pathology of Mouse Models for Human Disease

This week-long workshop provides intensive training sessions in pathology and histopathology and includes didactic sessions on particular diseases and models. Participants interact with prominent mouse pathologists and geneticists from leading research institutions.

Courses and Conferences

Short Course on Systems Genetics

This seven-day course focuses on using the mouse as a paradigm for mathematical approaches to studying complex human diseases. The course objectives are to: 1) help geneticists and statisticians better understand and incorporate each others' skills in analyzing complex phenotypes (most notably, disease); 2) help researchers more critically evaluate the evidence of genetic and biomolecular studies; 3) help investigators use contemporary statistics to design molecular and genetic studies; and 4) develop professional relationships that promote interdisciplinary research.

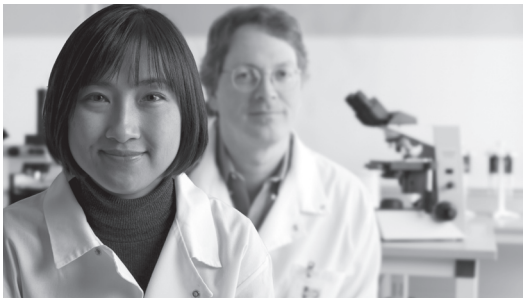
Methods in Human Embryonic Stem Cell Research

This five-day workshop teaches participants state-of-the-art techniques on how to culture, manipulate, and differentiate embryonic stem (ES) cells from humans and other species *in vitro*.

Support Services

Technical Support

Having access to our outstanding staff of research scientists, the members of our highly skilled, informed, and dedicated Technical Information Support team are well equipped to answer your technical questions, help you select mouse models, and give you information to facilitate your research. You can call them at 1-800-422-6423, 1-207-288-5845, send an email to micetech@jax.org, or fill out and send the email contact form at www.jax.org/jaxmice/micetech.



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