ORIP

OFFICE OF RESEARCH
INFRASTRUCTURE PROGRAMS

RODENT RESOURCES

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ORIP'S MISSION

ORIP advances the NIH mission by supporting infrastructure for innovation. This support is focused on research resources, including animal models for human diseases, cutting-edge scientific instrumentation, construction and modernization of research facilities, and research training opportunities for veterinary scientists. Through continued engagement with NIH Institutes, Centers, and Offices and the biomedical research community, ORIP empowers and expands existing programs and develops new initiatives to support NIH research at the forefront of scientific progress.

National Institutes of Health
Office of Research Infrastructure Programs

OVERVIEW

Comparative medicine plays an essential role in biomedical discovery by enabling scientists to better understand, diagnose, prevent, and treat human diseases. ORIP's Division of Comparative Medicine (DCM), within the Division of Program Coordination, Planning, and Strategic Initiatives in the Office of the NIH Director, supports an intellectual infrastructure for biomedical research through the creation of models of human disease using animals and cultured cells and management of the infrastructure required to maintain, distribute, and utilize these models.

MODELING HUMAN DISEASES USING RODENT MODELS

Mice and rats are a preferred mammalian disease model because of their high genetic homology with humans, rapid reproduction, efficient and inexpensive housing and husbandry, easily characterized phenotypes, and well-developed resources and tools for genetic manipulation. The use of rodents has enabled the discovery of several noteworthy medical milestones—the discovery of penicillin and the type 2 diabetes drug metformin, as well as the first prophylactic anti-HIV drug, Truvada®, to name a few. Using mice and rats reduces the dependence on higher-order species and allows for easier genetic engineering. The advent of precision (personalized) medicine will benefit greatly from integrative bioinformatics and innovative rodent-based research and validation studies. Over the past several years, there has been a growing awareness of the need for rigorously designed published research studies that are both transparent and reproducible. In response to this need, the NIH launched a formal initiative aimed at improving research reproducibility through an emphasis on scientific rigor and transparency. Eliminating variability in animal research is accomplished by supporting the creation and encouraging the use of animal repositories. NIH-funded rodent repositories ensure the quality and welfare of distributed animals and supply expertise to guide reliable studies.

Through ORIP's DCM grant mechanisms, scientists are equipped with the latest techniques that include CRISPR-Cas9 genomic editing, genotyping, pathogen monitoring, microbiome characterization, and strain tracking. Cryogenic preservation and freeze-dried sperm preservation are ideal methods for biobanking important rodent strains, which limits experimental variability. DCM-funded resources provide high-quality control measures and scientific knowledge to support rigorous, reliable, and reproducible research.

Repositories

DCM has developed strategies to expand access to rodent models through resources. Here are a few examples of the resources that are supported and made available to the biomedical research community.

Mutant Mouse Resource and Research Centers (MMRRC): The MMRRC consortium distributes and cryopreserves scientifically valuable, genetically engineered mouse strains and mouse embryonic stem cell lines. In addition, the MMRRC member facilities develop new technologies to improve the handling of mutant mice, including advances in assisted reproductive techniques, cryobiology, genetic analysis, phenotyping, and infectious disease diagnostics. The MMRRC is comprised of an Informatics, Coordination and Service Center (ICSC, University of California, Davis) and four regional distribution facilities: The Jackson Laboratory; University of California, Davis; University of Missouri; and University of North Carolina, Chapel Hill. mmrrc.org

Rat Resource and Research Center (RRRC): The RRRC at the University of Missouri provides ready access to well-characterized inbred, hybrid, and mutant rat strains; embryonic stem cells; and other related resources. Importantly, this program focuses on cryopreservation of gametes and embryos, *in vitro* fertilization, as well as genotyping and characterizing the gut microbiota. rrrc.us

The Special Mouse Strains Resource (SMSR): The SMSR at The Jackson Laboratory offers special mouse strains and associated tools important for the genetic analysis of complex human diseases. The SMSR imports, cryopreserves, and distributes recombinant inbred and chromosome substitution strains that are necessary for the discovery of quantitative trait loci and genes responsible for complex diseases. jax.org/research-and-faculty/resources/special-mouse-strains-resource

The National Gnotobiotic Rodent Resource Center: This resource at the University of North Carolina allows researchers to evaluate physiologic and pathophysiologic differences between germ-free (sterile), gnotobiotic (i.e., selectively colonized with microbes), and specific-pathogen-free mice. med.unc.edu/ngrrc

Mouse Strains for Testing Regenerative Medicine Therapies: A collaborative project at the University of Massachusetts Medical School and The Jackson Laboratory is improving existing immunodeficient mouse strains to support robust and efficient engraftment of varieties of human tissues. The investigative team is focusing on the early development of a human immune system in mice by expression of human factors required for elaboration of functional lymphoid architecture. Validated humanized mouse models will be an effective platform for evaluating human stem cell–derived cell function *in vivo*.

Cre Driver Strain Resources: The purpose of this resource at The Jackson Laboratory is to create, distribute, and extend characterization of mouse Cre driver lines. The program supports generation and enhancement of Cre driver strain models that include embryonic stem cell resources, congenic Cre driver strains on new genetic backgrounds, and deep functional characterization of these models to enhance their utility. jax.org/research-and-faculty/resources/cre-repository

Hybrid Rat Diversity Panel: This program at the Medical College of Wisconsin offers animal models and baseline molecular and physiological phenotypes under the National Rat Genetics Resource Program. This resource provides phenotypic characterization, genomic sequencing, data analysis, and distribution of hybrid rat models.

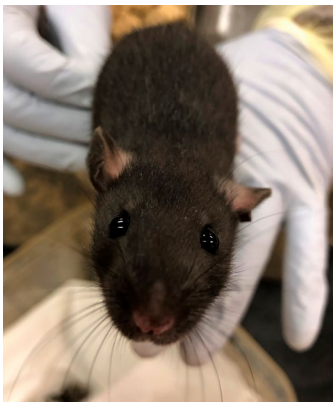
Biorepository of Induced Pluripotent Stem Cell Lines From Diverse Rat Strains: This repository at McLean Hospital in Massachusetts is establishing well-validated and viable rat pluripotent stem cell lines along with their biological and genomic characteristics. The final goal is to use these rat-derived cells to provide insights into the generation of cell replacement therapy for degenerative illnesses.

Mouse Resources for Comparative Mendelian Disease Genomics: The long-term goal of this project from The Jackson Laboratory is to create genomic resources that will facilitate functionalization of naturally occurring variation by employing forward genetic discovery and reverse genetic validation. This resource is focusing specifically on robust discovery and functional validation of variants that cause Mendelian disease phenotypes in mice, with an emphasis on those variants that escape detection by exome sequencing. Investigators are using newly affordable, third-generation, long-read sequencing technologies for the discovery of structural variants and are further developing pipelines integrating these new data types into a data-driven framework for mouse variant interpretation and candidate gene prioritization that is available to the research community. Finally, CRISPR-based engineering and phenotyping is used to prove disease-causation from among a subset of the most relevant candidate genes. jax.org/research-and-faculty/research-labs/the-reinholdt-lab

Precision Rodent Models

DCM supports the Pilot Centers for Precision Disease Modeling. All three Centers develop rodent models that more precisely mirror the genotype and phenotype of human disease processes and promote the creation of new therapeutics.

The program includes three U54 Centers: The University of Alabama's Pilot Center for Precision Animal Modeling, Baylor College of Medicine's Center for Precision Medicine Models, and The Jackson Laboratory's Center for Precision Genetics. The program is focused on creating pipelines for research community–nominated unique human genomic variants linked to diseases for cost-effective, high-throughput testing in a variety of animal model species, including rodents. The diseases modeled include ciliopathy; rasopathy; cohesinopathy; Marfan's syndrome and Ehlers-Danlos syndrome; macular degeneration; and musculoskeletal, cardiovascular, and neurodevelopmental defects. After validation of the expected gene editing, the Centers are establishing assays to conduct comprehensive functional



and phenotypic analysis to evaluate disease-causing variants. The Centers are working to ascertain the relevance of these animal models to the molecular, cellular, pathophysiological, and phenotypic characteristics observed in patients to improve the biological understanding of disease mechanisms, develop diagnostic tools, and test targeted or repurposed therapeutics. The creation and distribution of precision animal model resources and related services are core functions of these Centers. sites.uab.edu/precisionmedicine/center-for-precision-animal-modeling-c-pam; bcm.edu/people-search/jason-heaney-22834; jax.org/research-and-faculty/research-centers/precision-genetics-center

Rodent Testing Centers for Development of Reporter Systems and Evaluation of Somatic Cell Genome-Editing Tools

The NIH Common Fund's Somatic Cell Genome Editing (SCGE) program is working to improve the efficacy and specificity of gene-editing approaches to help reduce the burden of common and rare diseases caused by genetic changes. Central to this effort is a rigorous and innovative approach that requires technology validation via third-party testing in small and large animals. Such models also serve as a proving ground for new therapeutics and a detection system for adverse events, including toxicity and immunogenicity. Target-indication-specific in-animal efficacy and safety studies are currently treated as essential by regulatory authorities for nearly all genome-editing therapeutics being advanced to the clinic. The two Small Animal Testing Centers (SATCs) administered by ORIP—Baylor College of Medicine–Rice University's Resource Center for the Analysis of Somatic Gene Editing in Mice and The Jackson Laboratory's Gene Editing Testing Center—are developing mouse reporter systems because mice are an ideal tool for preliminary testing of new delivery formulations given their small size, low costs, and well-established utility. SATCs centralize animal model expertise to aid investigators in assessing the efficacy, specificity, and safety of novel delivery formulations in both wild-type and reporter mice. The reporter animal models are designed to faithfully activate in all cells and tissues in response to a specific gene-editing event. Fluorescent proteins provide a simple and robust means to detect activity at the single-cell level in situ, allowing for the identification of specific cell types targeted. Importantly, all new reporter animals created in the SCGE program will be available for distribution to the wider biomedical community. commonfund.nih.gov/editing/fundedresearch

Education/Training

Funded by ORIP and the National Institute on Aging, The Jackson Laboratory hosts an annual workshop on mouse model pathology. This workshop offers a week of intensive training in histopathology and pathology, as well as didactic sessions in disease areas and models. jax.org/education-and-learning/course-and-conferences/pathology-of-mouse-models