ORIP

OFFICE OF RESEARCH INFRASTRUCTURE PROGRAMS

SWINE MODELS

Centers and Research 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.

NIH National Institutes of Health
Office of Research Infrastructure Programs

OVERVIEW

The Division of Comparative Medicine within the Office of Research Infrastructure Programs (ORIP) funds a variety of centers and research resources grants that support laboratory animals to study human health and disease. The centers develop, characterize, maintain, cryopreserve, and distribute wild-type strains; mutants; and gene-edited, transgenic, and inbred lines of different species. Large animal models other than nonhuman primates (see ORIP's Nonhuman Primate Resources fact sheet)—such as swine, among others—have similarities to humans in genetics, anatomy, size, metabolism, and physiology and are advantageous for their recapitulation of certain disease phenotypes. They have become valuable models for cardiovascular diseases, diabetes, heart and lung transplantation, and xenotransplantation, and certain large animal models mirror human reproductive physiology, development, and infectious disease behavior. Large animal models also present unique translational opportunities for developing and testing novel devices, diagnostic tools, and therapies that can be used in humans. ORIP is committed to ensuring that scientists have access to these important animal resources.

SWINE RESOURCES

Domestic swine (*Sus scrofa domesticus*) are related closely to humans in terms of anatomy, genetics, and physiology, with their organs sharing common functional features and size. The potential applications of the pig as a model for biomedical studies have been extended by the availability of the pig genome, which NIH supported efforts to sequence, and the identification of many putative disease-causing variants. Swine also have several other advantages, including a favorable reproductive capacity with a short gestation period and large litter sizes. Swine have proven to be useful models for coronary artery disease; diabetes; heart, lung, kidney, and pancreatic islet xenotransplantation; hemophilia; obesity; hypertension; and other cardiovascular diseases and interventions, such as congenital heart disease modeling and pediatrics heart transplantation.

National Swine Resource and Research Center

Established in 2003, the National Swine Resource and Research Center (NSRRC) at the University of Missouri provides invaluable services to the research community by creating, upon request, new genetically engineered swine models. The NSRRC—which is supported by ORIP in partnership with the National Institute of Allergy and Infectious Diseases and the National Heart, Lung, and Blood Institute—is the only national repository that assists swine-based research across multiple disciplines. The Center has facilities with state-of-the-art biosecurity to ensure animals remain specific-pathogen-free for 14 pathogens and laboratories to support its function. In addition, the NSRRC serves as a stock center by importing, preserving, and distributing wild-type and swine model animals, organs, tissues, and cells to investigators throughout the country. The Center also serves as a source of information and training related to the use of these animals in biomedical research as models for human health and disease for the broader research community and performs its own cutting-edge research to advance the technology in this area. Its inventory of live animals represents more than 21 genetic backgrounds. Through their exceptional expertise, NSRRC researchers were the first to (1) add a transgene in pigs through somatic cell nuclear transfer and oocyte transduction, (2) knock out a gene in a pig, and (3) use the CRISPR-Cas9 system to create genetically engineered pigs using embryos. Examples of the models created include the αGal knockout for xenotransplantation; immunocompromised/humanized pigs; models for congenital muscular dystrophy, cystic fibrosis, phenylketonuria, and Fanconi anemia group A; and the oncopig, which has inducible mutations in specific tumor suppressor genes and oncogenes. The Center provides resources and services to the broad research community, in particular to laboratories supported by NIH institutes and centers.

Immunodeficient Pigs for Stem Cell–Based Regenerative Medicine

The team at North Carolina State University (Raleigh, NC) is taking advantage of similarities between humans and pigs to develop a humanized animal model for the testing and expansion of cells that can be transplanted back to human patients, specifically for immunotherapy in cancer and viral diseases and for the expansion of human CD34 cells from cord blood. This application is in addition to the model's potential value in clinical applications where diseased human cells could be expanded in the pig and for the development of treatments that are not possible

with the size and physiological limitations of smaller animal species, such as rodents. The team developed not only an *IL2RG/RAG1* mutant but also a unique cell-tracking line, which is used to understand how engrafted cells behave after allogeneic transplantation. The investigators are improving their model by introducing additional changes in the genome of pigs to enhance their ability to host a human immune system efficiently. They are focusing on reducing phagocytosis of human cells by pig macrophages, enhancing the bone marrow stem cell niche so human cells can engraft at higher efficiencies, and providing a cytokine environment that favors human versus pig cells. Completion of these aims will result in the development of a new large animal model capable of robust and functional engraftment with human hematopoietic stem cells. Generated cell lines, germ cells, and pig founders will be submitted to the NSRRC for distribution to the biomedical community.

Severe Combined Immunodeficient Pigs as a Model for Human Stem Cell Therapy

Immunodeficient animals play an important role in biomedical research by allowing the examination of engrafted human cells under *in vivo* conditions without the risk of rejection. Researchers use these animals to study basic biology, model human diseases, and develop new therapies. Many fields have benefitted from this type of research, including stem cell biology, regenerative medicine, transplantation, infectious diseases, immunology, and cancer. Investigators from Iowa State University (Ames, IA) discovered naturally occurring severe combined immunodeficient (SCID) pigs during a viral challenge study. These investigators currently are characterizing these animals and improving them to create validated SCID models for use in preclinical testing of stem cell–based therapies. To maximize the broad use of these models, the team developed protocols and worked with a vendor to design biocontainment facilities, or "bubbles," to maintain the SCID pigs in a pathogen-free environment. The researchers identified mutations in the *ARTEMIS* gene, which is involved in DNA repair, as the cause of the SCID pig phenotype. The same phenotype exists in humans with *ARTEMIS* mutations. Investigators developed an improved SCID model by introducing mutations into a second gene to further degrade the immune system (*ART-IL2RG* SCID double mutant). The research team is testing the level of humanization, or the development of a human immune system through engraftment of human cells into the pigs' bone marrow, in these double-mutant pigs. Such an advanced model could be used, for example, in vaccine testing and the study of human-specific pathogens. Investigators currently are collaborating on a dozen projects with other universities and biotechnology companies. They will be making the pig models available to other investigators after finishing the characterization and are working to develop procedures and specialized equipment to transport these immunodeficient pigs within a biocontainment space.

Swine Models for the Somatic Cell Genome Editing Initiative

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. Genome-editing technologies present an exciting prospect for treatments—and possibly even cures—for these diseases. The SCGE program is developing quality tools to perform and assess effective and safe genome editing in nonreproductive ("somatic") cells of the body. Animal models provide essential validation of delivery and editing systems within a living organism. Such models also serve as a proving ground for new therapeutics and a detection system for adverse events, including toxicity and immunogenicity. The Swine Somatic Cell Genome Editing Center, which was established at the NSRRC, currently provides pigs, establishes protocols, and evaluates genome-editing tools and delivery systems developed by components of the SCGE consortium.

One goal of the SCGE program is to generate *in vivo* reporter systems that are broadly applicable to many delivery systems and editing technologies, independent of the target cell or tissue type or the specific disease to be corrected. These reporters should have the ability to detect and quantify genome editing in the intended target tissue, as well as editing events resulting from nonspecific delivery to other tissues throughout the body. A team of investigators at

Recombinetics (Eagan, MN) is developing a suite of swine models and vectors capable of reporting gene-editing outcomes with a combination of *in vivo* (whole-animal) and single-cell readouts. The validated reporter constructs now are being integrated into the swine genome at one of three safe-harbor loci prior to animal production by somatic cell nuclear transfer (cloning). Reporter activity in these founder animals and their offspring will be characterized by whole-body imaging and single-cell analysis. The validated reporters, associated data, and animal models then will be provided to the Swine Somatic Cell Genome Editing Center to improve the evaluation of new delivery vehicles and somatic cell genome-editing tools. These novel models will enable new discoveries to characterize therapeutic delivery, DNA repair preferences, and off-target risk for any tissue or cell type in the body.

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