Have a Heart

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Animals teach us a lot about human health. Researchers study them to make life better for humans and animals alike.

Mizzou's new National Swine Resource and Research Center is a biologically secure fortress. Visitors and researchers have to shower and don sanitized gowns before they're allowed into the building. Packages and lab supplies are decontaminated when they're delivered. Sophisticated air-exchange systems keep out pathogens that could infect the dozens of research pigs housed here.

The center, which opened in the summer of 2006 south of the College of Veterinary Medicine, is the only one like it in the world. Scientists here are developing new strains of genetically modified pigs that medical researchers around the globe will use to search for cures to human diseases.

The swine center was built with a $10 million grant from the National Institutes of Health (NIH). When federal officials announced the grant in 2003, it made a scientific trifecta for MU. A year earlier, the NIH selected Mizzou as the site for its one-of-a-kind national Rat Resource and Research Center. The previous year it picked MU for the Mutant Mouse Regional Resource Center, one of four in the country.

All the centers are responsible for producing new lines of research animals, freezing and storing their cells and reproductive tissues, and making them available to the scientific community. Many of these rats, mice and swine have physical conditions that mimic human diseases, or they've been modified genetically so scientists can use them to trace disease processes.

Cures for all creatures

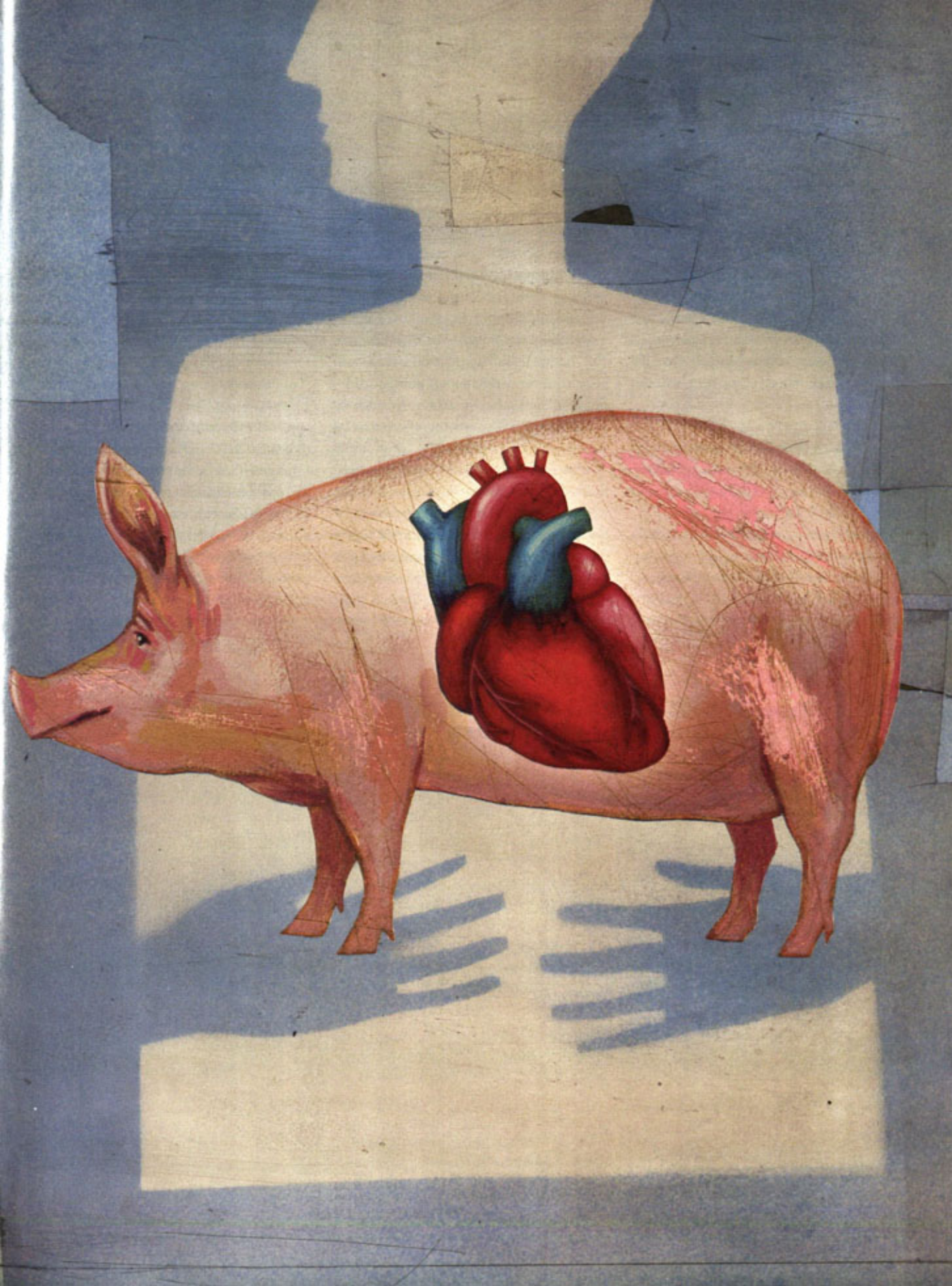
This research approach is called comparative medicine. Simply put, comparative medicine studies diseases in animal models to understand better how the same or similar diseases work in humans. Comparative medicine is offering clues to some of the most puzzling riddles in the health sciences: What is the link between obesity and diabetes? How does a sedentary lifestyle contribute to cardiovascular disease, and why is exercise beneficial? Can gene therapy restore sight to people blinded by retinal disease?

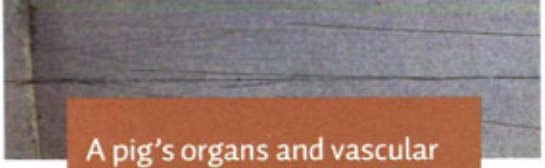
Randy Prather, a Curators Professor of Reproductive Biotechnology, developed many of the swine center's lines of research pigs. These pigs might look like typical barnyard porkers, but they're not. One of his pig lines was genetically engineered to have extremely high levels of heart-healthy omega-3 fatty acids. If pork producers buy into the technology, a BLT sandwich might someday be considered health food.

Every year, thousands of Americans die while they wait for heart, kidney and other organ transplants. Prather is researching how pig organs could be used in human transplants. He has developed another line of swine that lack a sugar compound on the outside of their cells that triggers rejection by human organ recipients. Other experimental pig models are biofactories that can produce human blood products to treat hemophiliacs.

Why use pigs as research animals? "Size counts," Prather says. A pig's organs and vascular system are similar to human organs in size and physiology. Mice and rats are excellent research models for some human diseases, but not all. "Cardiovascular researchers want to measure blood flow," he says. "Well, you can't measure blood flow in a mouse."

Each year, the NIH spends $100 million on research that uses pig models. In comparison,





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the U.S. Department of Agriculture's entire research budget is not quite half that amount. Prather's international reputation for cloning genetically modified pigs is one reason MU was picked for the swine center, but the campus already was a major player in comparative medicine. Mizzou's Research Animal Diagnostic Laboratory (RADIL) is the second largest animal diagnostic lab in the world. Its comparative medicine training program for scientists is one of just a handful around the country.

Strength in diversity

"Another thing that allowed us to be competitive and win those NIH awards was the fact that we put together an interdisciplinary team of individuals who do comparative medicine. There are very few places in the country that have such diversity," says Lela Riley, professor of veterinary pathobiology and RADIL director. "Part of that is the fact that we have a veterinary school, an agriculture school and a medical school. There are just so few universities that have all those pieces in one place."

For example, Riley's research looks at new ways to identify and eliminate pathogens that can infect laboratory animals and invalidate research results. In one project, she's working with biological and computer engineers who are developing miniscule biosensors that use nanotechnology to detect infectious agents.

Finding these bad guys is easy when they make a research animal sick, but sometimes an infected animal can appear perfectly healthy. So Riley and fellow researchers are studying research animals at the molecular level and looking for changes in normal physiology and gene expression triggered by pathogens. She's studying one group of bacteria called Helicobacter, which causes gastric ulcers in humans.

Riley picked those bacteria to study because research animals infected with Helicobacter often don't show any outward signs of illness. It's a different story at the molecular level, though. Riley's research has found subtle genetic changes. "There are 25 genes that no longer behave the way they did before," she says. "We're not exactly sure what happens or how it does that, but we know the animals have altered gene expression, different physiology and immunology than normal ones. It allows us to say, 'That's really something you don't want in your lab animals.' "

The use of animal models in science has evolved tremendously over the last decade, Riley says, as scientists have been able to genetically modify mice and rats and pigs to answer important research questions. In fact, scientists are developing so many lines of genetically altered research animals that it is a challenge to find room to store them all safely and free of pathogens.

Putting the freeze on disease

The need for storage is why John Critser's work is so important. Critser, the Gilbreath McLorn Missouri Professor of Comparative Medicine, directs the Center for Comparative Medicine, a new initiative at Mizzou that is building interdisciplinary teams of researchers. Critser is one of the world's leading experts in a technique called cryopreservation — the science of using super-cold temperatures to preserve animal tissues and reproductive materials under conditions that allow them to be thawed and used later.

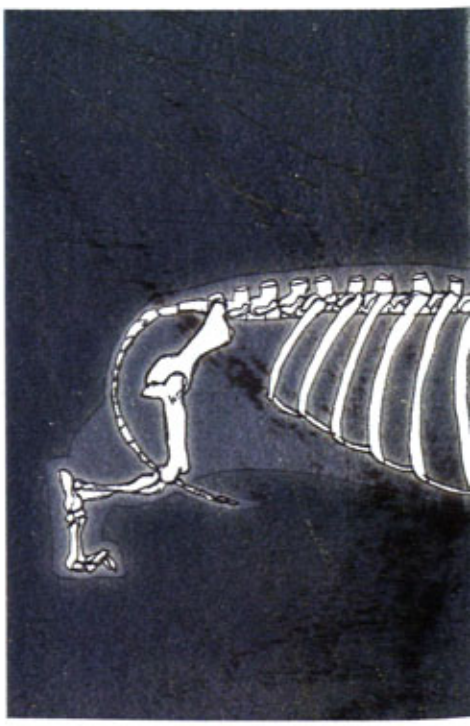
Cryopreservation helps ensure that "you don't lose an animal model because of disease or floods or fires," Critser says. It's also easier and cheaper to ship frozen embryos and tissues than it is a live pig on the hoof. Critser has developed precise techniques to freeze those materials using just the right preservation agent at just the right rate so that ice doesn't form inside the cells and damage them. The rate of cooling and thawing and the type of cryopreservative used is different for different cell types.

His lab routinely freezes tissues and maintains them at minus 196 Celsius, the temperature of liquid nitrogen. "We basically stop all the biochemical processes," Critser says. The preserved material probably will be viable for thousands of years.

A joint solution

Other MU researchers are taking different approaches to comparative medicine. As director of the Comparative Orthopedics Laboratory, veterinary surgeon Jimi Cook and other scientists at the lab are adapting human medical techniques, such as arthroscopic surgery and advanced MRI and X-ray imaging, to treat their four-legged patients. They're also studying animal ailments to learn more about human disease.

The research team focuses on arthritis, which can be as disabling to dogs as it is to millions of humans who develop the



painful joint disorder because of injuries or aging. One common cause of arthritis in the knee is damage to the cartilage — called the meniscus — that cushions the joint. Until now, the only treatment for a torn meniscus was to remove the damaged portion surgically. Without that cushion of cartilage, though, patients usually develop debilitating arthritis down the road.

Cook, the William C. Allen Distinguished Faculty Scholar in Orthopaedics, pioneered a breakthrough several years ago when he implanted bioengineered tissue from pig intestines into dogs' knee joints to regenerate damaged menisci. The results have been amazing in his canine patients, he says, and now the technique is being tested in human clinical trials in Indiana, Tennessee and New Mexico.

"The big thing is that it's been safe and effective," Cook says. "We've seen at minimum a 40 percent regeneration and in some patients up to a 90 percent regeneration of their meniscus. Some patients come pretty close to perfect."

Some day, scientists might even be able to study diseases without using any research subjects. Cook and his team are trying to mimic arthritis by growing cells in specialized test tubes and then treating them with the compounds our bodies produce when we have arthritis.

"When you have arthritis, there are clinical signs and symptoms, and we can take a snapshot of that on many different levels," Cook says. "We can ask, 'What does that look like on an MRI or an X-ray? What's going on in the synovial fluid in your joints? What's happening in your blood and your urine?' Those all may provide signals about what's happening in your knee to cause the arthritis and cause it to progress."

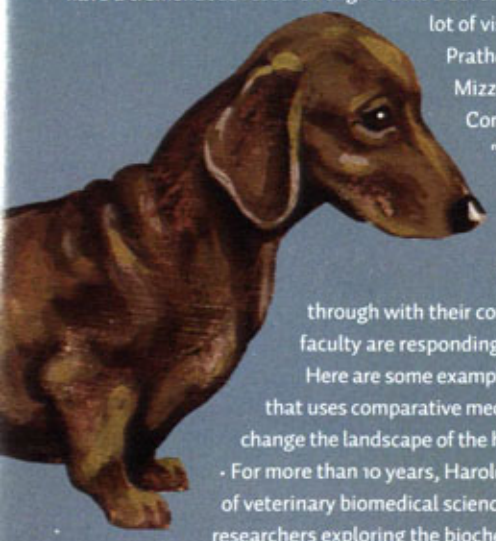
When the human body reacts to arthritis and other diseases, it churns out a stew of protein markers called cytokines. "There are a couple of those proteins that we know are involved in initiating and perpetuating osteoarthritis," Cook says. "So we can take normal cells and tissues and add those guys and turn the cells osteoarthritic. What's neat about that is that I can essentially have 24 little knee joints in a test tube instead of having to have 24 patients. We can make progress in research more quickly and efficiently."

Drug companies already are using Cook's "test tube joints" to screen dozens of different compounds that are possible arthritis treatments. The process also could be used to diagnose arthritis earlier and predict its severity.

"If we could do that, that would really change the world and improve patients' quality of life," Cook says. "That's what our comparative medicine is all about."

Revving the research engine

MU's new focus on comparative medicine is paying off. "We just have a tremendous research engine that's developing; it gives us a lot of visibility," says Randy Prather, co-director of Mizzou's Center for Comparative Medicine. "The administration has made a commitment to life sciences research. They're following through with their commitment, and our faculty are responding."



Here are some examples of faculty research that uses comparative medicine techniques to change the landscape of the health sciences:

- For more than 10 years, Harold Laughlin, professor of veterinary biomedical sciences, has led a team of researchers exploring the biochemical impact that exercise has on cardiovascular disease. To do that, they've been exercising miniature Yucatan pigs on treadmills and then studying the animals' blood chemistry and fatty plaque deposits in their arteries.
- Frank Booth, professor of veterinary biomedical sciences, uses a rat model in his research on the impact a sedentary lifestyle can have on human health. He found that just 48 hours of inactivity can cause a large increase in the amount of fat and size of fat cells in the body and can decrease the body's sensitivity to insulin, which may be a precursor to diabetes and related diseases.
- Kristina Narfstrom, the Ruth M. Kraeuchi Missouri Professor of Veterinary Ophthalmology, is studying how to use gene therapy to correct a defective gene that causes blindness in briard dogs, a large bushy-coated breed that originated around Brie, France. Gene therapy has improved the vision in some of those dogs, and one day it might become a standard treatment for similar human diseases.
- Dongsheng Duan, assistant professor of molecular microbiology and immunology in the School of Medicine, is studying mice that have a genetic defect that mimics Duchenne muscular dystrophy. He's using engineered viruses to deliver a gene therapy that replaces the defective gene with a normal version as a way to fight the deadly disease. The technique could hold promise for treating other human genetic diseases.