Humanized pigs: How scientists bioengineered swine with human immune systems to accelerate research on viruses, vaccines, cancer and stem cell therapeutics

The U.S. Food and Drug Administration requires all new medicines to be tested in animals before use in people. Pigs make better medical research subjects than mice, because they are closer to humans in size, physiology and genetic makeup.

In recent years, our team at Iowa State University has found a way to make pigs an even closer stand-in for humans. We have successfully transferred components of the human immune system into pigs that lack a functional immune system. This breakthrough has the potential to accelerate medical research in many areas, including virus and vaccine research, as well as cancer and stem cell therapeutics.

Existing biomedical models

Severe Combined Immunodeficiency, or SCID, is a genetic condition that causes impaired development of the immune system. People can develop SCID, as dramatized in the 1976 movie "The Boy in the Plastic Bubble." Other animals can develop SCID, too, including mice.

Researchers in the 1980s recognized that SCID mice could be implanted with human immune cells for further study. Such mice are called "humanized" mice and have been optimized over the past 30 years to study many questions relevant to human health.

Mice are valuable models, but they have limitations. Credit: UnoL/iStock/Getty Images

Mice are the most commonly used animal in biomedical research, but results from mice often do not translate well to human responses, thanks to differences in metabolism, size and divergent cell functions compared with people.

Nonhuman primates are also used for medical research and are certainly closer stand-ins for humans. But using them for this purpose raises numerous ethical considerations. With these concerns in mind, the National Institutes of Health retired most of its chimpanzees from biomedical research in 2013.

Alternative animal models are in demand.

Swine are a viable option for medical research because of their similarities to humans. And with their widespread commercial use, pigs are met with fewer ethical dilemmas than primates. Upwards of 100 million hogs are slaughtered each year for food in the U.S.

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Humanizing pigs

In 2012, groups at Iowa State University and Kansas State University, including Jack Dekkers, an expert in animal breeding and genetics, and Raymond Rowland, a specialist in animal diseases, serendipitously discovered a naturally occurring genetic mutation in pigs that caused SCID. We wondered if we could develop these pigs to create a new biomedical model.

Our group has worked for nearly a decade developing and optimizing SCID pigs for applications in biomedical research. In 2018, we achieved a twofold milestone when working with animal physiologist Jason Ross and his lab. Together we developed a more immunocompromised pig than the original SCID pig – and successfully humanized it, by transferring cultured human immune stem cells into the livers of developing piglets.

During early fetal development, immune cells develop within the liver, providing an opportunity to introduce human cells. We inject human immune stem cells into fetal pig livers using ultrasound imaging as a guide. As the pig fetus develops, the injected human immune stem cells begin to differentiate – or change into other kinds of cells – and spread through the pig's body. Once SCID piglets are born, we can detect human immune cells in their blood, liver, spleen and thymus gland. This humanization is what makes them so valuable for testing new medical treatments.

We have found that human ovarian tumors survive and grow in SCID pigs, giving us an opportunity to study ovarian cancer in a new way. Similarly, because human skin survives on SCID pigs, scientists may be able to develop new treatments for skin burns. Other research possibilities are numerous.

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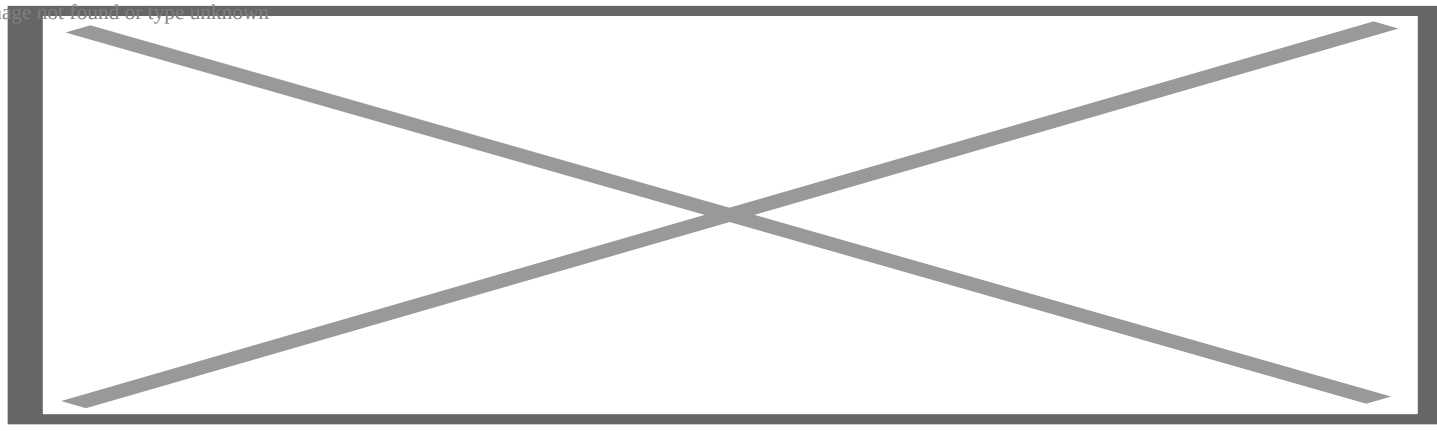

The ultraclean SCID pig biocontainment facility in Ames, Iowa. Credit: Adeline Boettcher

Pigs in a bubble

Since our pigs lack essential components of their immune system, they are extremely susceptible to infection and require special housing to help reduce exposure to pathogens.

SCID pigs are raised in bubble biocontainment facilities. Positive pressure rooms, which maintain a higher air pressure than the surrounding environment to keep pathogens out, are coupled with highly filtered air and water. All personnel are required to wear full personal protective equipment. We typically have anywhere from two to 15 SCID pigs and breeding animals at a given time. (Our breeding animals do not have SCID, but they are genetic carriers of the mutation, so their offspring may have SCID.)

As with any animal research, ethical considerations are always front and center. All our protocols are approved by Iowa State University's Institutional Animal Care and Use Committee and are in accordance with The National Institutes of Health's Guide for the Care and Use of Laboratory Animals.

Every day, twice a day, our pigs are checked by expert caretakers who monitor their health status and provide engagement. We have veterinarians on call. If any pigs fall ill, and drug or antibiotic intervention does not improve their condition, the animals are humanely euthanized.

Our goal is to continue optimizing our humanized SCID pigs so they can be more readily available for stem cell therapy testing, as well as research in other areas, including cancer. We hope the development of the SCID pig model will pave the way for advancements in therapeutic testing, with the long-term goal of improving human patient outcomes.

Adeline Boettcher completed her Ph.D. in Molecular and Cellular Biology at Iowa State University in 2019 where her work focused on the characterization and development of SCID pig biomedical models. Find Adeline on Twitter @adeline_bio

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