

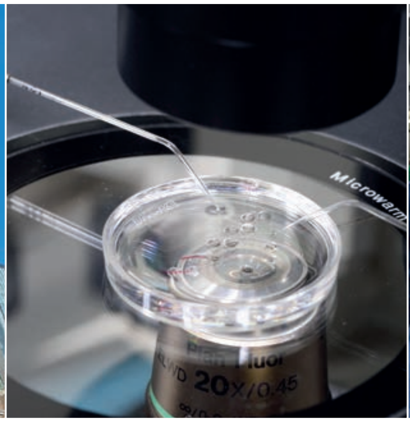


MEIJI UNIVERSITY

NEW MODELS FOR ORGAN PRODUCTION AND TRANSPLANTATION

Meiji University was founded in 1881 during the Meiji era in Japan, when the country was going through major political and economic changes, transforming from a feudal society to a modern industrial state. The university was originally named the Meiji Law School, specializing in the instruction of French law to Japanese students with the idea of building a free society founded on individual rights. In 1903, the school was renamed to its current title to reflect its expansion into other areas of study in the humanities as well as the natural sciences. Today, Meiji University has 10 undergraduate schools, 15 graduate schools and 28 departments that cover a comprehensive range of fields, from political science to agriculture, science and technology.

Meiji University has made great strides in research, thanks to the strategic vision of the Organization for the Strategic Coordination of Research and Intellectual Properties established in 2005 to ensure that the university delivers world-class research. The organization consists of two key branches working in close collaboration — the Research Planning and Promotion Headquarters, responsible for the planning, preparation and implementation of university research policy; and the Research Extension and Intellectual Property Headquarters, tasked with promoting collaborative projects involving industry, academia and the government. Both branches also develop strategies for ensuring a conducive environment for international research at the university.

AGRICULTURE AND MEDICINE

A key institute conducting globally recognized research at Meiji University is the Meiji University International Institute for Bio-Resource Research (MUIIBR). Established in 2011, MUIIBR is comprised of a network of universities, research institutes and companies in Japan and overseas, and has been awarded several research grants from the Japan Science and Technology Agency, including from the Exploratory Research for Advanced Technology (ERATO) and Core Research for Evolutionary Science and Technology (CREST) funding programmes.

> "In agriculture, the concepts of enhancing system efficiency and protecting genetic resources so that they can be passed on to the next generation are very important."

Hiroshi Nagashima is the director of MUIIBR, as well as general manager at the Research Extension and Intellectual Property Headquarters and a professor at Meiji University's School of Agriculture. "In agriculture, the concepts of enhancing system efficiency and protecting genetic resources so that they can be passed on to the next generation are very important," says Nagashima. MUIIBR integrates these agricultural principles and animal

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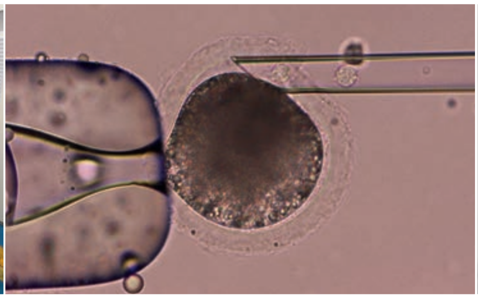

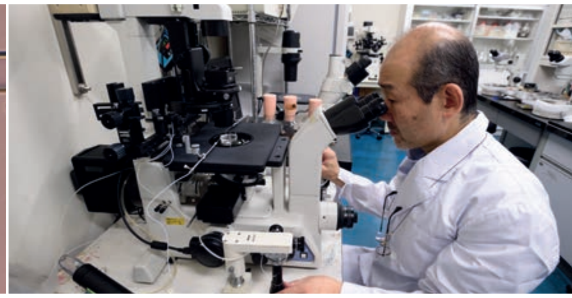

biotechnology methods in the development of new techniques for regenerative medicine and therapies for rare human diseases. To achieve this, MUIIBR relies on the creation, maintenance and utilization of biological resources, with a specific focus on genetically engineered pigs.

TRANSLATIONAL RESEARCH

Translational research creates an important bridge between basic biological and medical investigations using model organisms such as mice and clinical research that can contribute to advances in human well-being. The general consensus within the medical community is that pigs are a useful model in preclinical research because of their physiological and anatomical similarities to humans. MUIIBR therefore focuses on developing pig models for translational research.

In the area of regenerative medicine, MUIIBR uses genetically engineered and cloned pigs to create organs for transplantation. Organ transplantation is the only therapeutic option available for end-stage organ failure, but the procedure is severely limited by shortages in organ availability. The use of induced pluripotent stem (iPS) cells and embryonic stem (ES) cells to generate organs for transplantation offers huge potential for addressing the problem, but difficulties in growing organs derived from iPS and ES cells in cell culture have limited their clinical applicability. Nagashima and his colleagues therefore decided to use pig models to grow organs for transplant surgery.

To fulfil their goal, the researchers first used gene manipulation techniques to create pig models lacking specific organs. They then injected embryonic cells known as blastomeres into the empty space or 'niche' where the original organ would have been to generate an entirely new and viable organ in the vacant niche. In 2010, a team of researchers at the University of Tokyo succeeded in generating a functional pancreas derived entirely from rat iPS cells in a mouse model. Following this, MUIIBR succeeded in taking cells derived from one pig to grow a pancreas in another pig that originally lacked the organ. Researchers at the institute plan to continue these *in vivo* experiments in organ production using different cross-species combinations of model organisms and cells derived from pigs, sheep, cows and even humans.

Hiroshi Nagashima, director of the Meiji University International Institute for Bio-Resource Research, is leading research at the confluence of agriculture and medicine.

In addition to cross-species organ growth, researchers at MUIIBR are also investigating "xenotransplantation", in which pig organs are transplanted to humans. The biggest challenge in applying this method is the potential for the recipient's immune system to reject the foreign organ. One form of rejection known as hyperacute rejection can occur within minutes of transplantation. A key factor in activating hyperacute rejection in pig-to-human transplantation is the presence of natural antibodies in humans against galactose epitopes, which are synthesized on the surfaces of pig cells by the enzyme α1,3-galactosyltransferase. Researchers at MUIIBR therefore developed pig models in which the gene encoding α1,3-galactosyltransferase expression was removed, or knocked out. Only a few researchers in the world have been able to develop α1,3-galactosyltransferase-defficient pig models, and the MUIIBR team was the first to do so in Japan.

NEW MODELS FOR HUMAN DISEASE

Another major project at MUIIBR is the development of pig models for human disease. While many researchers have created mouse models for human disease, the observable characteristics of a mouse model can differ from those phenotypes observed in humans with the same disease. Pigs, on the other hand, are often characterized as having symptoms that more closely resemble those observed in humans. To date, MUIIBR has created pig models for Marfan syndrome, a genetic disorder that affects the connective tissue in the body. The gene expressing for the disorder is dominant, meaning that it is expressed even if only one copy is inherited. Approximately 1 in 5,000–10,000 individuals worldwide have inherited the disease.

Ultimately, the clinical application of MUIIBR's research will depend on the type of organ or disease targeted for research. One prime candidate for clinical application is the transplantation of insulin-producing cells in the pancreas known as the islets of Langerhans. These islet cells deteriorate as soon as the pancreas is damaged. Given the shortage of organ donors, the techniques of growing organs in animal models and transplanting animal organs into patients could offer a temporary solution until clinically applicable methods of pancreas organogenesis from patient-derived iPS cells are developed.

MUIIBR's holistic approach to xenoregeneration-based organ transplantation therapy — from bio-resource development to organ growth and eventual transplantation — has defined its success in the field. Of particular advantage has been the advanced cryopreservation technology established at the institute for safely storing frozen pancreatic islet cells and fertilized eggs. "We are probably the only institute in the world taking such an integrated approach," says Nagashima.