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PERSPECTIVES OF USING ANIMAL TISSUES IN THE TREATMENT OF HUMAN DISEASES

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Abstract

The shortage of organs and tissues from deceased donors, which are essential for treating patients with extreme organ failure, is a serious problem in transplantology. The increase in average life expectancy and the expansion of medical indications for the procedure have led to a rise in demand for organs, tissues, and cells for transplantation (e.g., heart, kidneys, Langerhans cells, blood vessels). The gap between the number of available organs and the number of people awaiting transplants is growing every year. Stem cells and tissue engineering are proposed as alternatives to human organs and cells, but they have not yet been implemented in clinical practice. The use of organs, tissues, and cells of animal origin, mainly from transgenic pigs, is being considered more and more often, as organs from genetically modified pigs have already been used for transplants in humans. Some tissues, such as kidneys, show very promising results, while others, such as the heart, liver, or lungs, still require a lot of work. It should be emphasized that Polish scientists are also involved in the preparation of transgenic pigs for xenotransplantation. Of course, different solutions should also be sought in the form of artificial organs and the use of bioartificial organs created using multidimensional bioprinting.

Key words: pigs, transgenesis, gene editing, xenotransplantation, biomedicine, bioprinting

This review provides a narrative overview of the use of animal tissues in the treatment of human diseases, with particular emphasis on the development of xenotransplantation technologies. While selected international achievements are discussed to provide global context, special attention is given to the contributions of Polish research teams, reflecting their role in advancing transgenic animal models and their translational applications. The shortage of organs and tissues necessary for the treatment of organ failure is a significant problem in transplantology. The increasing life expectancy of people has led to an increase in the number of patients suffering from chronic diseases and end-stage organ failure. Additionally, organ failure may also occur in young adults, children, and even in newborns and during infancy. The need for organs, tissues and cells for transplantation (e.g. heart, kidney, Langerhans islets, blood vessels, liver) far exceeds the number of available donors. Although there are currently over one hundred thousand patients (103,223) in the US waiting for a transplant (Health Resources and Services Administration, 2025), the number of organ donors that will become available will be much smaller (around forty thousand), in 2024 the United Network for Organ Sharing (UNOS) reported that 48,149 organ transplants were performed, according to the Organ Procurement and Transplantation Network (OPTN). The gap between the number of organs available and the number waiting for a transplant is growing year by year. Despite the successful introduction of kidney and liver transplantation from related donors, it seems unlikely that the needs of all those awaiting transplant will be met.

The situation is even more difficult in the case of patients waiting for cell transplantation, including pancreatic islets, which mainly affects patients with diabetes. In the United States, many of the nearly 3 million type 1 diabetic patients could benefit from islet transplantation, but the number of human pancreatic islets available will never be sufficient to cure millions of suffering patients.

In Europe, according to Eurotransplant, in 2024 in Austria, Belgium, Croatia, Germany, Hungary, the Netherlands, Slovenia and within Eurotransplant, 514.5 transplants per million population were performed, 28,499 patients remained on the active waiting list at the end of the year (Eurotransplant, 2025). In Poland, according to the Organizing and Coordinating Center for Transplantation “Poltransplant”, 2258 transplants were performed in 2024, and at the end of 2024 there were 1905 patients on the waiting list (Poltransplant, 2025).

What are the alternatives to human organs and cells? Despite recent advances in stem cell biology and tissue engineering, clinical application of techniques in the above fields remains in the distant future. An easily accessible source of human compatible organs, tissues and cells of animal origin (inter-species transplantation, xenotransplantation) would solve the problem. Over the past century, there have been a limited number of clinical trials of the use of organs of animal origin in transplantation, with the majority of the organ sources being primates, excluding humans. Most of the results were unsatisfactory, although there were studies in which the baboon liver functioned in the human body for about 70 days (Starzl et al., 1993), and the kidneys for up to 9 months (Reemtsma et al., 1964; Eisenson et al., 2024). The above trials were promising, the transplant survival time was relatively long, and the reasons the patients did not survive were at least partially unrelated to the problem of transplant rejection. The development of xenotransplantation in the pig-human system may contribute to the solution of the above problem (Kemter et al., 2020; Meier et al. 2021; Goerlich et al., 2023).

Xenotransplantation – generation of transgenic pigs

Xenotransplantation is a procedure for the transplantation, implantation or infusion into the human body of living cells, tissues or organs derived from non-human organisms, as well as body fluids, cells, tissues or organs that have had *ex vivo* contact with cells, tissues and non-human organs. The first animal tissues were transplanted into humans as early as 1682, when a defect in a human skull was replaced with a fragment of a dog's skull. In 1984, interest in xenotransplantation resumed after an attempt to transplant a baboon heart into an infant – the "Baby Fae case" (Bailey et al., 1985). Each of these attempts, like many others, was only partially successful. However, only modern cell engineering methods make it possible to use xenotransplantation as an unlimited source of cells and organs for transplantation (Kemter et al., 2020; Meier et al. 2021; Smorąg et al., 2006, 2013).

Currently, the best research teams in the world are working on xenotransplantation (Kemter et al., 2020; Goerlich et al., 2023; Fatima et al., 2025; Kawamura et al., 2025; Matsumura et al., 2025; Hawthorne et al., 2025; Meier et al., 2025; Tao et al., 2025 a; Beyer, 2025 a, b). Such a team also works in Poland. Since the research results can be used in practice and are associated with obtaining income, the details of research conducted in many centers are not shared. Xenotransplantation is an interdisciplinary undertaking that requires the improvement of many research methods. The research covers a wide range of issues, from molecular biology (obtaining appropriate vectors), through animal reproduction, in particular experimental embryology (introducing gene constructs), pig breeding (keeping animals), immunology (determining the tissue compatibility of the recipient and donor, virus detection) to transplant surgery (Smorąg et al., 2006, 2008, 2013; Hawthorne et al., 2025).

Clinical trials indicate that the domestic pig best meets the criteria for organ suitability for xenotransplantation – the size of the organs, and their physiological capacity is almost identical to the human organs. The following facts also support the choice of a pig as a potential donor of organs for xenotransplantation: the pig is a species of high fertility, cheap and easy to maintain (Goerlich et al., 2023; Juric et al., 2025; Cohen, 2025). Moreover, the pig is a species in which, compared to other large animals, it is relatively easy to make gene modifications (Galli, 2025).

Organ transplantation always carries the risk of organ rejection, which in the case of allografts has been overcome in most cases by the use of immunosuppressive drugs that suppress the activity of the immune system. This is due to the presence of xenoreactive antibodies and differences in the complement system. Acute vascular rejection and delayed rejection are also important. The most serious issue related to transplantation in general, and xenotransplantation in particular, is precisely the problem of the immunological compatibility of the donor organ and the recipient organism.

There is much skepticism regarding xenotransplantation due to the lack of full certainty concerning human safety, but xenotransplantation is in reality a viable and promising solution, despite many aspects that still require improvement (Zhao, 2024). Therefore, we should appreciate not only the teams preparing modified animals, the teams performing the transplants, but above all the patients who, having no other options, undergo xenotransplantation on the basis of admission to the procedure by the appropriate agencies on compassionate grounds (Mohiuddin, 2025; Kögel et al., 2025, 2024). There is also the problem of selecting patients for the first clinical trials in the field of xenotransplantation, in which several criteria should be taken into account: medical necessity, ability to benefit,

patient choice and compliance (used as an exclusion criterion). It seems that clinical trials should rather be based on clearly defined research protocols, especially in cases of compassionate use, which will allow obtaining reliable and valid knowledge about the benefits and risks of xenotransplantation (Kögel et al., 2025, 2024; Ata et al., 2025).

The preparation of pig cells for xenotransplantation is carried out in a multidirectional way, by switching off specific genes (knockout), as well as by inserting additional genes that change the surface antigens of pig cells. Animal transgenesis focuses mainly on the preparation of gene constructs inactivating the gene encoding 1,3-galactosyltransferase (1,3GT) or increasing the expression of the alpha-1,2-fucosyltransferase enzyme competing for the same substrate, human alpha-galactosidase, the major human histocompatibility complex HLA-E and CD59 complement proteins. Several lines of transgenic animals, including double and triple transgenic, fully characterized and available for implementation work, have already been obtained. So far, pigs containing the human 1,2-fucosyltransferase gene, human alpha galactosidase, the main human histocompatibility complex HLA-E, the complement system protein CD59 have been obtained, and the pig genes encoding the glycoprotein binding protein UL-16 (*ULBP1* gene) or alpha-1,3-galactosyltransferase have been disabled (Słomski et al., 2021; Samiec et al., 2022; Wiater et al., 2021 b; Lipiński et al., 2019; Grześkowiak et al., 2016; Zeyland et al., 2014, 2013; Trzcińska et al., 2009).

The most important developments in recent years regarding the use of transgenic pigs for xenotransplantation can be summarized as follows. 1) A factor driving research is the limited availability of organs from the deceased for clinical transplantation. 2) Immediate rejection of a transplant by the human immune system can be improved. 3) The main goals of porcine genetic engineering are to increase the survival of transplanted hearts, kidneys, islets of Langerhans and cornea in primates. 4) Modern pig genetic engineering reduces the risk of transmitting potentially infectious microorganisms and viruses. 5) Approximately 40–60 or more genetic changes have been introduced in pigs, and modified pigs may have up to a dozen changes. At the same time, pigs with fewer modifications (6 to 10 gene edits) are also used for xenotransplantation purposes. 6) Clinical trials related to the transplantation of pig kidneys, heart, blood vessels and Langerhans islets become possible.

An extremely important step in obtaining transgenic pigs is the introduction of gene constructs into animal cells. The most important and oldest method is the micro-injection of the gene construct into the male pronucleus of a fertilized egg. An interesting method accelerating the efficiency of transgenesis is somatic cloning of transgenic animals with confirmed transgene expression. Today, however, the main application is the most modern genome editing approach, which allows animals to be modified in a tightly controlled manner. Before proceeding to further steps, it is necessary to assess cell surface modification, as the main goal is to remove the alpha-1,3Gal epitope from the porcine cell surface, causing immediate rejection of the transplant, and to introduce human proteins regulating the complement cascade (Sikora et al., 2019; Wiater et al., 2021 a). It is also extremely important to determine the transgenesis at the DNA level and to assess its stability. Associated with xenotransplantation is the issue of potential threats related to the risk of infection with viruses in transplant recipients. A transgenic pig can donate different organs, and the transplantation of each of them (heart, liver, kidney, lung, pancreas) is a separate problem in transplant surgery (Meier et al., 2021; Kemter et al., 2022; Goerlich et al., 2023; Sucu et al., 2025). Obtaining trans-

genic pigs for xenotransplantation focuses on three types of modifications. The most important of these, of course, is the exclusion or reduction of glycan antigens on the surface of porcine cells against which natural antibodies are present in humans, thereby reducing the risk of hyperacute and acute transplant rejection. Another type of genome alteration is aimed at regulating processes related to immunity, coagulation and the complement system, through the introduction of selected human genes. The last type of modification is related to the exclusion/deletion of porcine endogenous retroviruses to avoid their transmission and integration into the recipient (Nature Biotechnology, 2024; Anand et al., 2023; Zhou et al., 2024). All groups of modification were undertaken by Polish teams involved in obtaining and characterizing transgenic pigs for xenotransplantation. It should also be noted that the spread of genome editing methods has greatly accelerated the conduct of work in this area.

Polish achievements in the field of pig transgenesis

In Poland, eminent transplant surgeons showed great interest in the advances in research in the field of xenotransplantation. Zbigniew Religa, who performed the first heart transplantation in Poland expressed great interest in the research and supported it. Marian Zembala participated in the project "The use of transgenesis in the genetic modification of pigs for obtaining organs for human transplantation", led by Zdzisław Smorąg from the National Research Institute of Animal Production in Balice (Smorąg et al., 2006, 2008, 2013).

In the last decade, over a dozen Polish research teams have participated in joint research projects in the field of xenotransplantation (Słomski et al., 2021). The last project concerned the development of an innovative technology for the use of transgenic tissues of pigs, which, due to genetic modifications, will be used in xenotransplantation, with particular emphasis on the skin, valves, vessels and, in the future, islets of Langerhans, kidneys and heart. The result of the innovative approach was to obtain pigs whose cells are not recognized by the recipient's immune system and constitute an alternative to stem cells and artificial organs, as well as enable the future use of transgenic tissues in patients waiting for transplants (Smorąg et al., 2006, 2008, 2013). The transgenic pigs obtained in the project have been used in practice, which is a significant achievement not only in national research and development, but also in the field of global research.

The objectives of the research were achieved by the Poznań University of Life Sciences (project leader); National Research Institute of Animal Production; Institute of Human Genetics of the Polish Academy of Sciences; Poznan University of Medical Sciences; Zbigniew Religa Foundation of Cardiac Surgery Development in Zabrze; Stanisław Sakiel Centre for Burn Treatment in Siemianowice Śląskie; and the Laboratory of Molecular Genetics in Poznań.

During the study, concerns were raised about the risk of infection of the recipient by endogenous porcine endogenous retroviruses (PERV), and the project addressed this problem by selecting pigs lacking PERV (Denner, 2024). Virological research was initiated in the team of Tadeusz Wilczok at the Medical University of Silesia in years 1999–2005, the cooperation is continued to this day by his successors. Integrity with the porcine genome makes porcine endogenous retroviruses (PERVs) difficult to remove, posing a very big problem in xenotransplants. A study conducted by a Polish team determined the relationship between the provirus gene sequences and released virions from the porcine PK-15 cell line and the embedded sequence of this retrovirus in infected human HEK-293 and HeLa cells. The sequence of the Pol gene and Pol protein was shown to be less conserved compared to other PERV

genes, and PERVs with some polymorphisms were not released from pig cells and/or did not infect human cells (Gałka et al., 2022).

The considerable phylogenetic distance between pig and human also leads to the immediate rejection of pig organs as a result of the so-called acute immune reaction. It is believed that genetic modification of animals would extend the survival time of zoonotic transplants from several minutes to several years, and this would allow their use in transplantology. A number of problems related to possible transplant rejection have been solved by genetic modification. The conducted breeding procedures allows for obtaining transgenic pigs with a deletion in both alleles of the gene, leading to the exclusion of the Gal antigen.

Completion of the planned stages enables the commercialization of the project. The additional values of the project include showing the possibility of close cooperation between contractors on the same biological material, and also introducing the CRISPR/Cas9 modification technology to research and obtaining the first large animals in the world with switched-off genes conditioning transplant rejection using this method (Hryhorowicz et al., 2019).

The National Research Institute of Animal Production under the supervision of Zdzisław Smorąg developed a system of breeding and obtaining transgenic pig tissues and was involved in reproductive biotechnology (Smorąg et al., 2006, 2008, 2013). The team obtained skin, valves and blood vessels from transgenic pigs for use in biomedicine. Cross-breeding work was carried out to obtain pigs with multi-gene transgenesis necessary for the other tasks of the project. After a few or a dozen days after birth, ear tissue scraps were collected from all piglets and forwarded to the teams from Poznań under supervision of Ryszard Słomski, where transgenic individuals were identified. All transgenic pigs were monitored virologically in the laboratories of the Medical University of Silesia, led by Urszula Mazurek and Ilona Bednarek (Kimsa-Dudek et al., 2015; Mazurek et al., 2013; Matczyńska et al., 2018).

A competent cryobiological team was one of the first in the world to obtain offspring after transplantation of cryopreserved pig embryos. Cryopreserved embryos, like cryopreserved semen from transgenic pigs, constituted a bank of genetic material that, depending on the needs, at any time and place, can be used to recreate a herd of transgenic pigs. The same team increased the potential for obtaining polytransgenic pigs by reproductive biotechnology and for obtaining polytransgenic pigs by somatic cloning. Fibroblastic cell lines were derived from fetal explants derived from potentially transgenic piglets, transgenesis was confirmed by molecular methods. The studies also identified clonal lines of transfected fetal fibroblasts (Samiec and Skrzyszowska, 2014).

The Institute of Human Genetics of the Polish Academy of Sciences in Poznań, under supervision of Ryszard Słomski, was responsible for the development and characterization of new gene structures preventing xenograft rejection. The prepared gene constructs were introduced into pigs at the National Research Institute of Animal Production in Balice and into cell lines *in vitro* at the Poznań University of Life Sciences, and potentially transgenic progeny and cells were analyzed molecularly and cytogenetically. Expression gene constructs were designed and made to introduce human proteins as well as to inactivate gene constructs to switch off the activity of endogenous pig genes. In addition, inactivating-type constructions in the CRISPR/Cas9 technology were prepared. Magnetofection was also adopted in order to obtain transgenic cells by introducing nucleic acids into cells in a magnetic field acting on magnetic nanoparticles that are associated with the nucleic acid (Hryhorowicz et al., 2019; Ryczek et al., 2020).

As part of the multi-parameter characterization of transgenic animals, including genomics, cytogenetics, proteomics and functional tests at the Poznań University of Life Sciences, the integration and expression of transgenes in pig cells and tissues were assessed, the karyotype regularities were determined and the transgene was mapped using the methods of classical and molecular cytogenetics (Słomski et al., 2021).

The Poznan University of Medical Sciences undertook research aimed at using the skin and blood vessels of transgenic pigs (Gabriel et al., 2004). The research led by Grzegorz Oszkinis and Ewa Strauss set out to develop methods of treating human vascular diseases based on the blood vessels of transgenic pigs (Gabriel et al., 2004). *Ex vivo* studies of xenogeneic material obtained from transgenic pigs included comparative morphometric studies of the human and porcine aorta, showing greater flexibility of the vessels of transgenic animals, which was confirmed by preliminary studies, indicating their high clinical usefulness. The transgenic lines have been shown to have half the immunogenicity of hyperacute rejection compared to non-transgenic lines. A preclinical study protocol has been developed to evaluate *in vivo* the properties of full-thickness skin grafts from transgenic pigs as a medicinal substance.

Professor Zbigniew Religa Foundation of Cardiac Surgery Development in Zabrze has developed a technology for the production of innovative heart valve bioprostheses using tissue engineering techniques and molecular biology methods. The team of Piotr Wilczek conducted an *in vitro* evaluation of the biocompatibility of the tested materials, taking into account the processes of induction of an immune reaction, thrombogenicity and susceptibility to calcification. The material for the research were pulmonary valves obtained from transgenic pigs. Tissues from non-transgenic pigs were used as a control group. Both native and decellularized tissues were used for the research (Wilczek et al., 2015). The research was also carried out on cells isolated from the obtained tissues. *In vitro* immunogenicity and thrombogenicity tests were performed on preserved human whole blood obtained from the Regional Blood Center in Katowice. All tests were carried out using bioreactors to ensure close to physiological flow conditions.

At the Dr Stanisław Sakiel Centre for Burn Treatment in Siemianowice Śląskie, Agnieszka Klama-Baryła used in clinical practice skin from animals obtained as part of the xenotransplantation project as a dressing material (Klama-Baryła et al., 2020). As part of earlier work, the patent no. P.404878 was obtained, entitled: “Biotechnological dressing for the treatment of burn wounds, method of making a biotechnological dressing for the treatment of burn wounds and the method of using a biotechnological dressing for the treatment of burn wounds” (Cieślik et al., 2022). The Centre for Burn Treatment in Siemianowice Śląskie has developed two variants of biological dressing made of transgenic pig skin intended for clinical use in patients with burn and chronic wounds, using tissue and cell engineering techniques (Klama-Baryła et al., 2020). In the first stage, procedures for the preparation of a medium-thickness porcine skin dressing, cryopreserved in glycerol, were developed. The skin of transgenic pigs was obtained from animals with a knock-out gene conditioning the formation of the αGal antigen (α-1,3-galactosyltransferase) and with modified cell surface proteins (the human α-1,2-fucosyltransferase gene). Initially, the studies used skin sections collected with a dermatome, which had wound healing properties.

One of the methods of qualitative evaluation of the prepared products was the histopathological analysis of the prepared dressings made of leather preserved in

glycerol. In the next step, methods of removing cells from the extracellular matrix of the dermis of transgenic pigs (ADM) were developed to obtain a matrix for *in vitro* culture of cells. Medical experiments involving patients with donor fields and patients with burn wounds have shown that the use of glycerinated pig skin from transgenic animals reduced the pain experienced by patients, which is important from a clinical point of view. The procedure made it possible to shorten the hospitalization time by an average of 8 days, which significantly reduces the costs of hospitalization. Glycerinated pig skin is comparable to the standard method of treatment in terms of safety of use. In addition, the transplant of the extracellular matrix of the dermis of transgenic pigs with autologous keratinocytes reduces pain experienced by patients in a comparable way to the current treatment method and leads to an average reduction of hospitalization time by 1 day, which is not a statistically significant result, but important from the point of view of reducing hospitalization costs (Kitala et al., 2020). This transplant is as safe as the gold standard, which results from the lack of differences between the parameters tested in the study and control groups.

The Laboratory of Molecular Genetics controlled the quality consistency of the tasks performed and the stability of transgenesis, connecting scientific and business partners. Attention was also paid to the maintenance of appropriate research controls and the smooth transfer of information to the National Research Institute of Animal Production in Balice, which controls the animals and the program of their crossing, as well as the transfer of biological material to all consortium members. The results of transgenesis were also verified with the use of CRISPR/Cas9 technology to obtain new modifications, as well as genetic variability of selected pigs was determined (Ryczek et al., 2020).

Examples of commercialized transgenic animals

In recent years, enormous progress has been made in this field, as several drugs obtained in transgenic animals are commercially available (recombinant human antithrombin III obtained in milk of goats – ATryn®; lysosomal acid lipase obtained in egg white – Kanuma). Interesting is the work carried out by the British company Oxitec, which has developed a genetically modified line of the *Aedes aegypti* (OX513A) mosquito to reduce the population of this mosquito at the site of release. The first transgenic animal approved for consumption was AquAdvantage salmon, now available are other fish and pigs. Nature Biotechnology (2025) has informed about other pigs with gene edition to resist porcine reproductive and respiratory syndrome, which were allowed for consumption in the U.S. Animals were generated by British company Genus, based in Basingstoke.

The research conducted by the Polish teams is compatible with the requirements set by agencies allowing the use of transgenic animals in biomedicine, especially legal regulations related to the use of xenogeneic cells and tissues derived from non-transgenic and transgenic animals based on the recommendations of the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). This includes all works related to the characterization of transgenic animals at the molecular, cytogenetic, cellular and functional levels. These issues range from animals to animal welfare, preparation and characterization of gene constructs, detection of transgenic animals, analysis of the DNA, RNA, protein, cell and animal levels, to the assessment of expression and stability of the transgene, as well as the practical application of skin, vessels and the valves. For now, the risk of infection with PERV viruses may pose a problem, but thanks to genome editing methods, this threat seems to be

limited and in the near future, commercially available pigs for xenotransplantation can be expected, not only in China, which has a huge demand of organs for transplant, but also in the United States and Europe.

The advent of genome editing technology resulted in the acceleration and broad development of research. In December 2020, the U.S. Food and Drug Administration approved the first intended genomic change in a line of domestic pigs: GalSafe® pigs lacking the α1,3Gal epitope on the cell surface. The GalSafe® homozygous pigs are intended for use in both food production and human medicine. Transgenic pigs have been prepared by the company Revivicor, a subsidiary of United Therapeutics. Revivicor inserted 10 genetic modifications in the pigs to ensure that organs do not overgrow, to avoid blood clots, and to limit rejection. Changes in the porcine genome includes turning off genes for improvement of antiimmunogenic properties by knockout of xenogeneic carbohydrates (galactose-α-1,3-galactose GTKO; β1,4-N-acetylgalactosyltransferase B4GalKO, CMP-N-acetylneuraminic acid hydroxylase CMAHKO) and reduction of intrinsic graft growth by knockout of growth hormone receptor. Human transgenes have been added for complement regulation (CD46, decay accelerating factor DAF), with anticoagulation properties (endothelial cell protein C receptor EPCR, thrombomodulin TBM) and with anti-inflammatory function (hemeoxygenase-1 HO-1, CD47) (Griffith et al., 2022).

An interesting analysis of the stability of the genome of pigs with an edited genome was conducted by a team of Chinese scientists for a single line of pigs with the *GGTA1* gene disabled using the CRISPR/Cas9 technology (GTKO), compared to wild-type pigs. The F0 pig generation accumulated approximately 1,205 genetic mutations throughout the genome, and 18 *de novo* mutations were observed in the first generation (F1) offspring compared to wild-type controls and their parents. Most mutations occurred in intergenic regions, did not alter protein function, and were not located in predicted off-target mutation sites. According to transcriptomic and phenotypic data, these mutations did not affect gene expression or cause obvious phenotypic abnormalities. Of course, the data obtained require further study, both in terms of the accuracy of detected changes and the use of other pig breeds, including those with a greater number of modifications. It is also recommended that proteomic studies and functional verification should be introduced (Huo et al., 2025). Additional studies covering usage of immunosuppression approved for human treatment on pig-to-non-human primate (NHP) xenotransplantation models have been performed (Eisenson et al., 2024; Peterson et al., 2024).

Pig to human transplants

The first transplant of a genetically engineered pig kidney obtained from GalSafe pigs into a deceased recipient was performed by Robert Montgomery in 2021 at New York University (NYU) Langone; for 54 hours, doctors tested the kidney's function and watched for signs of rejection (Montgomery et al., 2022; Loupy et al., 2023).

In 2022, scientists at the University of Maryland's Baltimore School of Medicine reported a pig heart transplant to a patient for whom a donor could not be found. It was the first heart transplant between an edited animal and a human (Wang et al., 2022). The recipient was 57-year-old patient David Bennett, and surgery was performed by Bartley P. Griffith. The FDA granted authorization for emergency surgery, which only applies when an experimental medical product, in this case a genetically modified pig heart, became the only treatment option available to the patient. The first patients with modified pig heart lived for two months and died potentially due to complications from a porcine cytomegalovirus; a second transplant recipient – Lawrence Faucette

survived six weeks (Griffith et al., 2025). Pig heart transplants have pointed out several issues that need to be taken into consideration in subsequent transplants, notably attention is paid to the elimination of pig viruses including latent porcine cytomegalovirus (porcine roseolovirus, pCMV/pRV), removal of the administration of potential antibodies to pig antigens as well as the patient own health status – whether they are able to recover fully. There are also thoughts of introducing an appropriate method of immunosuppression, which is being evaluated in systems for transplanting modified pig organs into non-human primates (Cooper and Cozzi, 2024).

Xenotransplantation of modified pig organs is becoming a reality, associated with the reduction of transplant rejection, occurrence of changes in the immune system and matching the size of the organ – mainly the heart to the recipient. Thanks to genome editing methods, this is currently not a difficult task, but it is also important to prevent the transmission of pathogens both from the pig donor and from the human recipient of the transplant. It is also proposed to replace pig heart cells and structures with human equivalents in the process of exogenesis and use pig models to study new cellular and molecular therapies that can be implemented in human treatment (Wolf et al., 2023). Research in the field of xenotransplantation at the University of Maryland was initiated several years earlier by the eminent scholar Muhammad M. Mohiuddin (Goerlich et al., 2023). It should be emphasized that the tissues of transgenic animals – skin, valves, vessels – can be used in the treatment of oncological patients. By participating in the European Union action COST BM1308 “Sharing Advances on Large Animal Models”, we were able to familiarize the international community with the results of work carried out in Poland.

The first transplantation of a genetically modified pig kidney concerning a recently deceased person on life support was performed independently by two teams in 2023. The team of Jayme Locke and her colleagues at the University of Alabama at Birmingham observed normal graft function for seven days after transplantation. In contrast, Robert Montgomery’s team at NYU Langone Health in New York observed the kidney for more than one month with no signs of rejection and no signs of infection from the pig-derived viruses (Judd et al., 2024; Mallapaty and Kozlov, 2024).

The first pig heart transplant to living patient was performed by David Bennett Sr. from the University of Maryland Medical Center (Baltimore, MD, USA) in January 2022, just two months after a pig kidney was transplanted by Robert Montgomery of an academic medical center in New York City. The organ has been supplied by the Revivicor, a subsidiary of United Therapeutics (Loupy et al., 2023; Montgomery et al., 2024; Griffith et al., 2025). In the donor of this heart, a transgenic pig, ten genetic modifications were performed to prevent rejection of the transplant. The danger of swine viruses activation has also been eliminated. The patient died two months after surgery, and the hospital found that the transplanted heart was working well for several weeks with no signs of rejection. It has been suggested that heart transplant rejection may have been related to the level of transgene expression rather than the number of modifications (Ali et al., 2024). The second heart transplant from modified pig into Lawrence Faucette, was performed also at the University of Maryland at Baltimore and enabled surviving of the patient for six weeks. It seems that heart transplantation from modified pigs is an enormous challenge. The most realistic scenario in which such transplants are effective is in little children who do not have a fully developed immune system (Cooper and Cozzi, 2024).

Research on xenotransplantation is developing intensively. Scientists from Ger-

many are also working on breeding pigs with hearts potentially ready for transplantation into humans, as it is associated with high demand and social support (Kemter et al., 2020, 2022). The company XTransplant-LMU aims to develop patent-protected genetically modified donor pigs, as well as to produce donor pigs under conditions declared to be free from pathogens. It is planned to prepare organ distribution channels including the network of XTransplant certified transplant clinics. Technical support during organ transplantation, as well as clinical follow-up of patients with transplant and biobanking are essential. New Zealand Auckland Island pigs were selected for the study due to their small size, which makes their heart more suitable for humans. Eckhard Wolf of the Ludwig Maximilian University of Munich plans to genetically modify donor pigs so that their organs are not rejected after being transplanted into humans. Scientists switch off certain pig genes and add human genes to make transplantation possible. They are focusing on a multimodal phenotyping analysis of transgenic pigs and influence of a protein interaction level on functioning of transplant (Reichart et al., 2024).

Work on transgenesis of pigs for xenotransplantation by other companies is also underway. Biotechnology company eGenesis, based in Cambridge, Massachusetts, in cooperation with PorMedTec of Japan, has obtained genetically modified pigs for use in transplants (Anand et al., 2023). The modification of porcine cells included deletion of three genes involved in the synthesis of glycan antigens associated with hyperacute rejection (8 alleles); insertion of seven human genes involved in the regulation of different pathways that modulate rejection and inactivation of endogenous retroviruses in the porcine genome including 59 copies of PERV. For modifications Genome Engineering and Production (EGEN™) Platform based on multiple parallel gene editing and precise genetic integration has been used. A breed of miniature Yucatan pigs was chosen for the study because the size of their organs is comparable to those of humans, with blood group null (OO) to eliminate ABO blood group incompatibilities. A total of 69 genomic changes were made using genome editing methods, mainly CRISPR/Cas9 technology and recombinase-mediated cassette exchange (Anand et al., 2023). As Nature Biotechnology (2024) informed, the kidney transplant to 62-year-old man Richard (Rick) Slayman with end-stage kidney disease was approved by the U.S. Food and Drug Administration (FDA) under its Expanded Access Program and performed by a team of surgeons at Massachusetts General Hospital in 2024. Japan company PorMedTec has developed a system that uses cloning to reproduce, breed, and conduct pre-transplant virological testing of genetically modified donor pigs developed by the American company eGenesis. Since February 2024, PorMedTec has produced a total of 31 donor pigs for eGenesis and also supplies donor pigs for research related to monkey kidney transplants at Kagoshima University. A Meiji University start-up company gains extensive experience in meeting the demand for kidney transplants, which is greater than in other countries; the average waiting time for a kidney transplant in Japan is fifteen years, compared to four years in the U.S. PorMedTec offers also production and sale of humanized organs (i.a. pancreatic islets) for xenotransplantation using genetically modified pigs, production of genetically modified pigs on demand and technical consulting services in the field of cryopreservation of biomaterials. Despite the enormous progress, the use of long-term mechanical circulatory support devices, with significant clinical benefits, is still associated with serious hemorrhagic complications (i.a. thrombosis, recurrent bleeding and cerebrovascular incidents) and requires further research (Nascimbene et al., 2024).

In April 2024, the first kidney transplant from a pig with a single genome edit and a heart pump was performed at NYU Langone Health in New York City. The left ventricular assist device (LVAD) was implanted by Nader Moazami, and a combination pig thymic and kidney transplant (UThymoKidney, United Therapeutics Corporation, Silver Spring, MD) was performed by Robert Montgomery. However, the heart pump did not supply enough blood to the transplanted pig kidney, and the organ was removed on May 29, ultimately causing the death of the 59-year-old patient on July 7, 2024.

Lisa Pisano received an organ from the pig that had only one genetic edit, while the first patient, Slayman, received an organ from the animal with 69 genetic edits. Scientists must consider how many edits need to be made to enable long-term survival of xenotransplanted organs in humans (Lewis, 2024). It has been suggested that the important factor in porcine organ xenotransplantation is not the number of modifications introduced, but the selection of the set of necessary genetic modifications and their quality with respect to protection against graft rejection and coagulation modifications. Prof. Eckhard Wolf's team also pays attention to the breed and genetic background of donor pigs. He also points out the importance of ancillary procedures related to the preparation of organs and tissues for transplantation for the induction of modifications (preservation, perfusion) (Ali et al., 2024; Hawthorne et al., 2025).

A third kidney xenotransplant was also performed at New York University (NYU) Langone Health on November 25, 2024. The recipient, 53-year-old woman Towana Looney, received a kidney with 10 genetic modifications (UKidney, United Therapeutics), and the immunosuppression regimen was also modified. The UKidney kidney does not contain the immunogenic antigens Gal, Sda and Neu5Gc, the pig growth hormone receptor, in addition, six human genes were included. The treatment also received approval from the U.S. Food and Drug Administration's compassionate use program (Beyer, 2025 b). In March 2025, the U.S. Food and Drug Administration approved United Therapeutics Corporation's Investigational New Drug application (IND) to initiate a clinical study using UKidney™ derived from a pig derived from a 10 gene-edited source pig.

Another company, eGenesis, also received FDA approval for an Investigational New Drug (IND) application (September 2025) to conduct clinical trials using EGEN-2784 in a genetically modified porcine kidney transplant to treat patients with end-stage kidney disease. So far, the first two patients in the study have been living with the genetically modified kidney for several months (Massachusetts General Hospital, January 2025, Tim Andrews, and June 2025, Bill Stewart) (Fieldhouse, 2025 a). The company will focus on analyzing safety, tolerance, and efficacy 24 weeks after transplantation in patients with end-stage renal disease aged 50 or older who are dialysis-dependent and awaiting kidney transplantation. In EGEN-2784 donor pigs, three glycan antigens were deleted to prevent hyperacute immune rejection; seven human transgenes regulating the immune response (reduction of inflammation, coagulation compatibility, and regulation of complement activation) were introduced; and endogenous retroviruses were inactivated.

First documented extracorporeal transplantation of pig liver to brain-dead patient was performed at the University of Pennsylvania in December 2023, pig organ from eGenesis company was functioning for three days (Regalado, 2024).

On March 10, 2024 at the Xijing Hospital of the Air Force Medical University in Xi'an heterotopic auxiliary transplantation of a six-gene-edited pig liver to a brain-dead recipient was performed. The graft function, hemodynamics, and immune and inflammatory responses of the recipient were

monitored over the subsequent 10 days. As a donor Bama miniature pig with six genetic modifications (triple knockout GGTA1-KO, β4GalALNT2-KO and CMAH-KO, expression of human complement regulatory proteins hCD46 and hCD55 and expression of human thrombomodulin hTHBD) provided by Clonorgan Biotechnology in Chengdu, China was used (Mallapaty, 2024; Tao et al., 2025 b; Hara and Wang, 2025; Beyer, 2025 a).

On May 17, 2024, the first pig liver xenotransplantation with 10 modifications was performed for a living 71-year-old man with advanced liver cancer at First Affiliated Hospital of Anhui Medical University in China. According to China Global TV Network (2024), after seven days, the liver was functioning properly, and no symptoms of graft rejection were observed. Genome-edited donor pig (triple knockout GTKO, CMAHKO and β4GalNT2KO, expression of human complement regulatory proteins hCD46, hCD55 and hCD59, expression of coagulation regulatory proteins hTBM, hCD39 and hEPCR, inhibition of macrophage phagocytosis hCD47, tested negative for 47 pathogens) was prepared by the team of Wei Hong-Jiang from Yunnan Agricultural University (Mallapaty, 2024; Xu et al., 2025).

A serious challenge is emerging in the field of lung transplantation. The first studies involved transplanting a pig lung with six modifications into a 39-year-old brain-dead patient on May 15, 2024 at the First Affiliated Hospital of Guangzhou Medical University and the National Clinical Centre for Respiratory Disease (Fieldhouse, 2025 b). Chinese Bama Xiang pig lung was prepared by Clonorgan Biotechnology (GTKO/B4GalNT2KO/CMAHKO/ CD55/ CD46/TBM). The Chinese team monitored lung function for nine days, with the biggest challenge remaining the prevention of transplant rejection and infection. After 24 hours, the researchers observed severe edema resembling primary graft dysfunction, potentially caused by ischemic-reperfusion injury, graft rejection by antibodies on days 3 and 6, with partial recovery on day 9. They also described the immunosuppressive treatment regimen. No cases of hyperacute graft rejection or infection were reported during the study period (He et al., 2025).

Another of the alternatives to save human lives through the use of pig cells and tissues may be the use of transgenic pig cells micro- or macro-encapsulated. Such a strategy would reduce the use of intensive immunosuppression to prevent rejection of the transplant by the immune system and the occurrence of inflammation (Ho et al., 2024). One could also think of mechanisms to inhibit the occurrence of infections with endogenous swine viruses or other zoonosis.

Organ bioprint

Another alternative to transplantation could be 3D bioprinting, which uses biocompatible materials and human cells to create living tissues and organ structures. 3D organs will find applications in regenerative medicine, drug discovery as well as toxicology testing. It is assumed that in the short term it will be possible to use them in organ transplants (Ma et al., 2024). While 3D bioprinting can provide many benefits, it brings a number of challenges and requirements, particularly related to the bioprinting of various tissues, including cells, biotissues and bioprinters, as well as ethical issues, clinical efficacy and cost-effectiveness, making it difficult to integrate 3D bioprinting into routine clinical practice (Veeravalli et al., 2023). One of the novelties is the introduction of 4D bioprinting, which makes it possible to obtain circuits that, by reacting at a certain time, ensure the proper functioning of nerve cells and, in the future, the therapy of neurological disorders and injuries (Bektas et al., 2025). Important is also possibility to guide vascular morphogenesis from individual en-

dothelial cells using time dependent dosing of bioinks (Rana et al., 2025).

Stem cells are an important part of 3D bioprinting, as they determine the ability to prepare functional organs. Stem cells should exhibit the ability to divide, functionality, safety of use, low cost, and the ability to self-organize and recreate normal tissue structures, enabling full functioning of the organ (Ma et al., 2024). *In vitro* studies have yielded three-dimensional structures for liver, kidney, lung, heart, intestine, eyes, skin, nerves and bone, among others (Frankowski et al., 2023). For the purposes of tissue engineering and regenerative medicine, 3D bioprinting is increasingly using decellularized extracellular matrix (dECM), and thought is also being given to preparing bioink based on them (Gadre et al., 2024). Our collaborators have been working on the use of decellularized structures in a xenotransplantation project (Klama-Baryła et al., 2020; Gierek et al., 2023).

The development of cell cultures in three-dimensional systems ensures proper interactions between cells and the extracellular matrix, which makes it possible to reproduce conditions that occur naturally in tissues and organs. Research has largely focused on organoids (Sumbalova Koledova, 2024), derived from stem cells, reproducing the complex structure of organs in *in vitro* systems (Cabral et al., 2024). Three-dimensional printing of organs for transplantation requires overcoming challenges including adequate vascularization of organs, availability of a large number of cells with specific parameters, limitation of the immune response associated with the appearance of animal components, and functionalization of cells forming 3D structures (Ma et al., 2024).

Each new solution has many advantages and disadvantages that may result from the solutions used, available technologies or even ethical approach. In 2022, the BBC reported that a Swedish court had sentenced an Italian surgeon to a suspended sentence for causing injury during an experimental tracheal stem cell transplant (Paterlini and Macchiarini, 2023). Paolo Macchiarini, once seen as a pioneering transplant surgeon, was cleared of two fraud charges. Three patients treated in Sweden died. In October 2023, the Swedish Supreme Court rejected an appeal and upheld the Svea Court of Appeal's sentence of two years and six months for three counts of serious assault in connection with an artificial trachea transplant at Karolinska University Hospital (Karolinska Institutet, 2024). Several articles by Paolo Macchiarini have also been retracted due to misconduct in research. In 2011, Macchiarini enjoyed international recognition for performing the world's first synthetic organ transplant at Sweden's Karolinska University Hospital. His work using an artificial trachea with stem cells opened up prospects for patients who no longer have to wait for donors.

It can be assumed that the first pig organ transplants conducted as the only possible treatment option – compassionate use in both the U.S. and China are due to the huge demand for organs. Starting clinical trials on humans seems a logical step, moreover, researchers will rather focus on indicating the minimal changes to be made to the pig organs as well as ensuring virological safety (Cooper et al., 2024; Ata et al., 2025). Currently obtained data based on non-human primate models do not fully capture the conditions that are associated with the human immune system, with particular attention to the complement system and procedures associated with available immunosuppression protocols (Pullen, 2024). It appears that the diverse activities associated with the modification of animal tissues as well as the use of 3D bioprinting technology may represent a breakthrough in modern approaches to human health.

Summary and future directions

The advances presented in this paper on preparation and characteristics of transgenic pigs and the use of their tissues and organs in preclinical research and clinical applications, as well as alternative approaches based on bioprinting, represent only the first step toward implementation in clinical practice. AJT XenoBulletin team (2025) focused on ethical and regulatory issues, such as questions about the status of animals in light of new genome editing techniques raised in Switzerland (Camenzind, 2024), various regulations that may complicate clinical trials due to the rigorous approach to safety assessment, related to the treatment of xenotransplantation as advanced therapy medicinal products (ATMP) or transplants in the European Union (Andriichuk, 2024). Another problem is the rejection of humans as donors of organs for transplantation (Kaiser et al., 2024). New challenges are posed by the need for the graft to function under physiological conditions in the human body (Zhang et al., 2024). Attention is being paid to the undertaking of basic activities by the transplanted organs and the extension of the period of functioning in the human body. Additional questions arise related to the long-term impact of organs on the human body, the proper regulation of the endocrine system; for example, the kidneys are not only responsible for filtration, but also the production of adrenal hormones, mineral management, etc. In the case of the liver, attention is paid to disorders of the clotting system, thrombocytopenia associated with the possibility of spontaneous hemorrhages. In the case of the pig heart, it is necessary to assess the capacity for the complex activity required of the human heart. Raised is also the question of the complexity of the genome editing performed, protection against zoonotic pathogens (xenosis) as well as the level of immunosuppression. It seems that xenotransplantation is a promising direction that will bring great benefits to humans, but still requires a lot of research. The research conducted by the leaders of Polish teams, co-authors of this article (Ryszard Słomski and Zdzisław Smorąg) fits perfectly into the presented topic and future implementation of xenotransplantation.

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