

Future perspectives

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Contemporary immunosuppressive therapies and modern surgical and perioperative techniques have all contributed to improved outcomes. The principal innovations being investigated for the future are aimed at increasing donor availability and improving the long-term survival. Xenotransplantation has been extensively investigated with the use of transgenic pig hearts. In 1964, Hardy performed a xenotransplant using a chimpanzee heart that beat for 90 minutes before failing, and in 1984 infant Stephanie Fae Beauclair (often referred to as Baby Fae) famously lived for 21 days after receiving a baboon heart. Gene-editing techniques that allow modification of antigen expression are among the biggest technological breakthroughs to support the resurgence of xenotransplantation. Knockout pigs that lack swine leukocyte antigens to reduce organ immunogenicity have led to pig-to-primate allograft survival of up to 945 days. Despite the technical and scientific challenges the first contemporary pig-to-human transplant was undertaken in 2022 at the University of Maryland, USA, with good early clinical xenograft function using a pig heart with 10 genetic modifications, including four knockouts (three responsible for rapid antibody-mediated rejection of pig organ and one to prevent excessive growth) and six human genes added to increase the likelihood of acceptance. Rejection in the medium and long term and the hazard of infection transmission with porcine retroviruses remain of concern. The problems faced by xenotransplantation could be overcome by organ engineering. Decellularised extracellular matrix scaffolds of hearts can be created by removing cellular tissue then repopulating with autologous cardiac cells. Automatic contractility has been demonstrated. In addition to finding new sources of donor organs, improvement of long-term survival remains a priority. New agents to - more favourable side-effect profile remain under investigation. The induction of tolerance of the recipient immune system to donor antigens has promise and T-cell co-stimulation blockade, mixed chimerism (recipient bone marrow engraftment with donor bone marrow cells) and regulatory T-cell infusions are being studied. Personalisation of current immunosuppressants to individual patients may allow for adjustments based on molecular diagnostic techniques to increase efficacy and - reduce side effects. Future perspectives

Bioengineered artificial lung technology using recipient cells grown onto a decellularised lung scaffold is under development and will avoid an immune response; however, it remains a long way from clinical reality. Success would permit lung transplantation without the need for immunosuppression, waiting lists or rejection. Artificial lungs, mimicking the success of VADs in heart transplantation, remain elusive. The physical volume of membrane oxygenators is too great for implantation within the thorax and devices are not durable, lasting weeks rather than months or years. Membranes are thrombogenic and high levels of anticoagulation would be required.

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