CMAJ Specialty Spotlight
Infectious disease

Xenotransplantation: An animal future?

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Technology: Xenotransplantation
Use: Xenotransplantation uses living nonhuman animal cells, tissues or organs to replace nonfunctioning human tissues or organs.
History: The successes of human–human organ transplantation, coupled with severe limitations in the availability of human organs, have propelled research into the use of nonhuman organs. The earliest in vivo experiments were done in the 1960s (Table). Most attempts at transplanting organs have been desperation measures. Xenotransplantation of tissues and cells is currently being explored.[1] Nonhuman primates were donors in initial studies because of their genetic compatibility. However, they are only 1 or 2 generations removed from the feral state, have a long breeding time and have few offspring. Increased transspecies infection because of genetic compatibility is also of concern. The domesticated pig, now the preferred donor, is a less costly, more available and, possibly, safer source.[1,2]

Xenotransplantation remains experimental, with restrictions in most jurisdictions.[1] Current trials in humans include cells or free-tissue xenografts and extracorporeal therapies with porcine livers or kidneys (Table). The most advanced human clinical trial is a phase I study of intracerebral transplantation of fetal pig neural cells for the treatment of Parkinson's disease.[3] Animal studies of pig–primate organ transplantation are also under way.[2]
Promise: The longer term, utopian view of xenotransplantation is of "spare parts" for the human body to improve survival and quality of life. The shorter term reality is the use of cells or tissues as an adjunct to other therapies to ameliorate chronic diseases characterized by cell death.[3] Also, temporary extracorporeal use of animal organs may provide bridge therapy for severely ill patients awaiting human organs.[1]
Problems: Safety and efficacy have not yet been demonstrated, and information is too preliminary to warrant human trials in most cases. The cultivation and genetic manipulation of animals for human benefit is of ethical concern, as is the issue of obtaining informed consent from patients for clinical trials when the risks are known to be large and no sustained benefits have yet been realized. There are also immunologic barriers, which are greater with pig than with primate donors.[2] Hyperacute rejection occurs within 1–2 hours to an antigen present in all vascularized tissue in pigs, but not present in primates. While transgenic pigs without this antigen have been developed,[2] delayed xenograft rejection occurs and, finally, T-lymphocyte-mediated rejection of the allograft. Another barrier is infection.[4] We are currently coping with 2 remarkable examples of transspecies infection: AIDS and variant Creutzfeld–Jakob disease. The recent Hendra-like virus outbreak in pigs in Malaysia is another cautionary example. Xenotransplantation exposes recipients to endogenous and exogenous infections from the donor animal.[5,6]

Experience with xenotransplantation

Source	Transplant	Comments
Pig	Ex vivo percutaneous liver	Ongoing
Pig	Ex vivo kidney	1990s
Pig	Fetal neural cells injected into brain	Parkinson's studies ongoing Huntington's disease Epilepsy
Pig	Skin grafts	–
Pig	Islet cells	Started 1993
Cow	Adrenal tissue	Relieve pain in terminal cancer
Chimpanzee	Kidney	1964: 6 patients, survival ≤ 9 mo
Baboon	Kidney	1964: 7 patients, survival 4.5–60 d
Rhesus monkey	Kidney	1964: 1 patient, survival 10 d
Baboon	Heart as "bridge"	1984: 1 child, survival 20 d
Baboon	Liver	1992: studies terminated after 2 patients died early
Baboon	Bone marrow	1994: HIV patient; cells did not persist

Porcine retrovirus is of particular concern. If the infectious agent is transmissible to humans beyond the recipient, the spread of these infections in populations is possible.
Prospects: The costs and the unresolved issues surrounding this technology would suggest that further development not be pursued. However, the pressure for organ-replacement options, and industry's interest in cell and tissue transplantation are strong influences. Controlled experiments with tissues in immunologically protected sites such as the brain, or with organs used as bridge therapy, will provide important data to direct further clinical uses. The current development of genetically altered animals will further unravel immunologic mysteries, and animal models of pig–primate transplantation will assist in understanding transspecies biology. Uncontrolled applications in clinically desperate situations should be avoided until further research has provided some hope of feasibility and safety.

Competing interests: None declared.

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