

The Ethics of Xenotransplantation

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GLOSSARY

ALLOTRANSPLANTATION is the transplantation of tissue and organs between individuals of the same species.

ANIMAL-TO-ANIMAL studies are preclinical xenotransplantation research studies in which organs, cells or tissues are transferred from one animal species (eg. pig) to another (eg. baboon).

ANTIGENS are substances which are capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibodies or specifically sensitised T-lymphocytes.

FIBROBLASTS are connective tissue cells which differentiate into chondroblasts, collagenoblasts and osteoblasts.

IMMUNOLOGICAL RESPONSE is the mechanism for distinguishing 'self' from 'nonself' and eliminating invading microorganisms or other foreign materials from the body. In xenotransplantation, it can lead to rejection of the transplanted organ, tissue or cells.

IMMUNOSUPPRESSIVE DRUG THERAPY prevents or reduces immune response via the administration of drugs. Immunosuppressive drugs are required after an organ is transplanted from another individual to prevent rejection of the organ.

PANCREATIC ISLET CELLS are cells of the islets of Langerhans in the pancreas that secrete the hormones insulin and glucagon.

RETROVIRUS is a virus whose genetic material is made up of ribonucleic acid (RNA) instead of deoxyribonucleic acid (DNA).

RISK COMMUNICATION is the exchange of unbiased information and opinion among all relevant stakeholders on the risks, benefits, consequences and acceptability of an event.

ZOONOTIC pertains to an animal disease transmissible to humans.

INTRODUCTION

Xenotransplantation is the transplantation of living cells, tissues or organs from one species to another. The term also covers the infusion or transplantation of body fluids, tissues or cells that have had contact with animal tissues or cells outside of the transplant recipient's body (for example, the infusion of blood through an artificial liver containing pig liver cells).

Xenotransplants perform the same functions as the organ, tissue or cells that they replace. The most successful xenotransplants to date have been from pigs to humans but it is conceivable that products from rodents or even fish may be of benefit to humans. The primary reason for conducting research into the benefits of xenotransplantation is an increasing shortage of human tissue and organ donors.

Xenotransplantation from animals to humans is still a largely unproven technique. The research priority at this stage is for further research on ANIMAL-TO-ANIMAL xenotransplantation before animal-to-human trials can begin.

APPLICATIONS

Success in applications of xenotransplantation techniques has showed mixed results. Three such trials are mentioned below.

Pancreatic islet cell xenotransplantation to treat insulin-dependent diabetes has been shown to be relatively successful in Sweden. Post-operative biopsies of patients receiving a simultaneous foetal pig islet and human kidney transplant suggest that pig islet transplants survive immediate cellular destruction with current IMMUNOSUPPRESSIVE DRUG THERAPIES.

There is now experimental evidence to show that the transplantation of **foetal pig neural cells** to treat Parkinson's disease and Huntington's chorea in humans is a potential benefit of xenotransplantation. Preliminary reports of a study conducted in the US suggests that there are relative improvements in the motor capacity of patients suffering from severe parkinsonism.

Further trials are now being conducted in the US and elsewhere. Another xenotransplantation procedure showing some promise is the use of **RETROVIRUS-producing mouse fibroblasts** to treat inoperable brain tumours. Research was first done in 1993 on the transplantation of mouse FIBROBLASTS that release retroviruses containing 'suicide' genes into human malignant brain tissue. Since then, success has been limited. A primary obstacle has been the rapid rejection of the fibroblasts because of the viral ANTIGENS expressed on their surface.

RISKS AND LIMITATIONS

Of concern to the scientific community is that **ZOONOTIC infections** will be transmitted to humans from pigs. These include swine influenza and Japanese encephalitis and the transmission of other, possibly latent or unknown viruses or bacteria.

A primary concern with the **transmission of retroviruses** to humans is the potential risk of infection not only to the transplant recipient, but also their close contacts and the wider community. Strict husbandry management and monitoring strategies may reduce the risk of human infection from source animals.

Porcine endogenous retrovirus or PERV is an animal disease that has raised particular concern with pig xenotransplants. This virus is dormant in pigs but can infect human cells in the laboratory and may infect xenotransplant recipients. For this reason, infectious diseases experts have suggested lifelong monitoring of the recipient and the recipient's close contacts.

Immunological rejection occurs when solid organs are transplanted from one species to another. Further work is needed to overcome this immunological response and to develop procedures that can be shown in animal-to-animal studies to be as successful as ALLOTRANSPLANTATION. The most promising approach at this stage is to genetically modify the source animals so that their organs do not cause immune reaction. Scientists have already produced several genetically modified strains of pigs that show promising results.

Genetic modification of donor animals is the most promising approach to overcoming both the physiological and immunological barriers to xenotransplantation. It is possible to minimize adverse effects resulting from xenotransplantation by inserting key human genes into the donor and treating the recipient with immunosuppressive drug therapy.

ETHICAL AND SOCIAL POLICY ISSUES

The ethical and social policy issues relating to xenotransplantation can be categorized into two sections; (1) issues that relate to research involving human beings and; (2) issues that relate to animal welfare.

Crossing the species barrier is a deep-seated taboo in human culture held by some members of our society. Those who hold this view believe that the integrity of human beings may be compromised if xenotransplants become common practice.

Loss of identity by the human recipient is another concern expressed by opponents of xenotransplantation. The possibility that recipients will experience psychological problems as a result of animal-to-human transplants is another ethical issue that needs further debate.

Some commentators have expressed a concern about an **absence of a relationship between the giver and the receiver** in xenotransplantation. The importance of a giver-receiver relationship has been widely held by professionals working in human organ donation settings. It is yet unknown how the absence of this relationship might affect recipients of xenotransplants.

Lifelong monitoring of xenotransplant recipients and their close contacts is required when participants undergo xenotransplant procedures. This requirement is considered mandatory primarily because of the potential risk of zoonotic infections spreading to the wider community. The preservation of related individuals' privacy and personal autonomy is an issue that has attracted debate in the literature.

Ethical issues with human subject research in xenotransplantation trials include the **voluntary consent** of individuals, respect for the individual's **autonomy**, issues surrounding **risk communication** and issues relating to **equity**. The research conducted must also carry a direct therapeutic benefit to the patient.

Instrumental use of animals has been put forward as a major ethical concern. The current Draft Guidelines require researchers to respect the welfare of source animals and procedures must minimise the impact on animals. The legislation proposed by NHMRC establishes researchers' obligations for keeping animals bred for xenotransplantation research in a natural and comfortable environment.

REGULATION

The NHMRC 2002 Draft Guidelines and Discussion Paper on Xenotransplantation were distributed for public comment in September 2002. Suggested models for future xenotransplantation regulation were put forward

along with a discussion of the scientific and ethical issues involved with xenotransplantation research.

Public response to the document will inform future xenotransplantation research legislation. The document aims to among other things, bring together regulatory controls under one governing body.

Under current Australian legislation, xenotransplantation research is regulated through the NHMRC.

National Statement on Ethical Conduct in Research Involving Humans (1999) covers the human research aspect of xenotransplantation clinical trials. The NHMRC has responsibility for research involving humans through its Australian Health Ethics Committee (AHEC). Its role is to monitor the ethical engagement of participants in research through various institutional human research ethics committee (HRECs).

The Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (1997) (also monitored by the NHMRC) ensures the ethical use of animals in xenotransplantation research.

The Therapeutic Goods Act 1989 (Cth) controls all therapeutic products including medicines and devices for marketing and use. Xenotransplantation products are currently regulated under this Act.

The Gene Technology Act 200 (Cth) provides regulatory guidelines for the genetic modification of source animals.

FURTHER READING

National Health and Medical Research Council (NHMRC) (2002) *Draft Guidelines and Discussion Paper on Xenotransplantation*, Public Consultation Document, Canberra.

Welin, S. (2000) Starting Clinical Trials of Xenotransplantation – Reflections on the Ethics of the Early Phase, *Journal of Medical Ethics*, 26, 231-236.

Organisation for Economic Co-operation and Development (1999) *Xenotransplantation: International Policy Issues*, OECD Proceedings, Paris, France

Fishman, J., Sachs, D. & Shaikh, R. (eds.) (1998) *Xenotransplantation: Scientific Frontiers and Public Policy*, Annals of the New York Academy of Sciences, Vol. 862, New York.

*In the preparation of this factsheet, the author has relied heavily on the NHMRC 2002 Draft Guidelines and Discussion Paper on Xenotransplantation.

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