



NEBRASKA COALITION
FOR ETHICAL RESEARCH

XENOTRANSPLANTATION

Position Paper

POSITION SUMMARY

The Nebraska Coalition for Ethical Research (NCER) supports xenotransplantation (animal-to-human transplantation) research and eventual human clinical trials if the following conditions are met. Researchers must: prevent unnecessary animal suffering; determine that there is a real need for pig xenografts; avoid genetic modifications in the source animals that would alter the biodiversity and balance of the species; verify that the personal identity of the human recipient is not affected; proceed with the greatest caution in human clinical trials because of the presence of health risks to the patients; determine that the prospective human research subjects are not candidates for allotransplantation (human-to-human transplantation); inform the xenograft recipient about his pathology, its prognosis, the nature of the transplantation surgery, the risks of zoonoses, and the need for life-long observation; and be able to demonstrate that the health care costs of xenotransplantation are justified.

EXPLANATION

Science

Xenotransplantation (*xeno* is a Greek suffix meaning foreign) is the transplantation of organs, tissues, or cells from one species into a member of another species. Xenotransplantation in humans (animal-to-human transplants) involves transplanting (foreign) porcine tissues or organs into human recipients. Pigs are the primary source animals for human xenografts because they, first, have a lower risk of transferring disease to humans than have non-human primates such as chimps or baboons and, second, pigs have organs that are comparable in size to those of humans.

Currently, there is an acute allograft (human organ) shortage. More than 75,000 Americans and thousands of Europeans are in need of transplants, and many will die because the supply of human organs, cells, and tissues are severely limited. This shortage of human donor organs for transplant has forced researchers to explore and perfect xenotransplantation. Clinical trials are being conducted on two fronts: (1) experimental trials with pig-to-nonhuman primates (e.g., pig to chimp or baboon) and (2) pig-to-human clinical trials, i.e., transplanting pig cells and tissues into human patients [To date: porcine pancreatic islet cells have been transplanted into a number of patients with diabetes; fetal porcine neural cells have been injected into a number of patients

with Parkinson's, Huntington's disease, and strokes; patients with liver failure have taken part in studies that use pig hepatocytes in artificial livers with promising initial results.]

The research is working to overcome two roadblocks to successful human clinical trials involving transplantation of whole-organ xenografts: (1) infection (or xenozoonoses) and (2) rejection. (1) Scientists have identified over 60 porcine infectious agents that could cause disease in humans and have developed "clean" lines of pigs that are free of these infectious pathogens. The challenge is to eliminate all PERV (porcine endogenous retroviruses) from source pigs. If an unknown pig virus would be transmitted to a human recipient, a benign pig virus could mutate into something lethal for humans. (2) Although there are four kinds of rejection problems connected with xenografts, the solution to two of these is critical before whole organ clinical trials can begin in humans: The first kind is called (A) hyperacute rejection. The human body has natural antibodies that react to animal proteins, for example, a sugar that exists on the surface of pig endothelial cells. Human immune systems recognize this sugar as a foreign antigen and attack the pig cells, leading to hyperacute rejection. The natural antibodies cause blood clotting and the organ is destroyed in approximately one hour. A second kind of obstacle to successful animal transplantation is (B) acute vascular rejection. This process destroys the xenograft five to eight days after transplantation.

To prevent (A) hyperacute rejection, source pigs are genetically altered. The pig sugar-producing gene is 'knocked out' of pig fetal cells and then these engineered fetal somatic cells are fused with enucleated pig egg cells. The resultant "knock out" pig embryos are transferred to a sow who has just come into heat. After successful gestation, multiple cloned piglets are born whose cells, tissues, and organs have a deactivated copy of the sugar-producing gene [galactosyltransferase gene]. When transferred to sheep, the engineered organs of these pigs have survived for months rather than for days. Recently, two biotechnology companies have cloned "knock out" pigs that are considered a major breakthrough in bringing xenotransplantation clinical trials for humans closer to reality.

To prevent (B) acute vascular rejection various solutions are being proposed. Dr. Beshorner (now deceased) and his team at UNMC developed a process that builds up the recipient's immune tolerance without incurring the likelihood of infection through a severe suppression of the patient's immune system. The process is called surrogate tolerogenesis and is done within the pig's body, not that of the human recipient. White cells from the human recipient are injected into fetal pigs. As the pigs develop, the human cells, animal cells, and tissues build immune tolerance over a three to five month period. Dr. Beshorner's team then tested surrogate tolerogenesis using large animal models of sheep. Further development of the process is needed before clinical trials start in humans, but preliminary results in sheep recipients show a prolonged survival for porcine hearts and major blood vessels. In 2008, Beshorner predicted that future refinement of surrogate tolerogenesis would enable his team to conduct pig-to-human transplants in 3-4 years. His work continues today at the research facility (Ximerex) that he founded in Blair, Nebraska. Unfortunately, we have not been able to speak with the researchers at Ximerex to clarify the nature of what they are doing and accomplishing.

Ethical Assessment of Xenotransplantation

Anthropological considerations: Examining the long history of humanity's presence on the earth, we observe that the human being is superior to the rest of creation, including that of animals. The human being has consistently directed human realities by controlling other living and nonliving beings according to determined goals. In a sort of natural cooperation, the human being has made use of animals for his primary needs—food, clothing, work—at the various stages of human progress throughout the ages. Man's superiority over animals is based in human nature, particularly, its rational and spiritual dimensions. Accordingly, the use of animals is moral if it is intelligent stewardship, that is, if it is an intelligent use of the rest of creation. Human stewardship over the created order, including animals, is intelligent when it is both wise and responsible.

Applying these truths about the relationship between humans and animals to xenotransplantation, one concludes that it is moral to use animals for their organs and to transplant them into humans if researchers: (a) prevent unnecessary animal suffering; (b) determine that there is a real need for pig xenografts; (c) avoid genetic modification that could significantly alter the biodiversity and balance of the species; (d) verify that the personal identity of the human recipient is not affected.

To determine whether (d) personal identity is adversely affected, the following must be respected: (i) Because human organs like the brain and the gonads (ovaries and testes) are inextricably linked with the personal identity of the human subject, the transplantation of either animal organ equivalent is morally unacceptable; (ii) Because other human organs such as the heart, kidney, stomach, pancreas, and liver are exclusively functional in nature, there is no ethical objection to replacing these malfunctioning human organs with their porcine equivalents. These kind of xenografts would not alter the human recipient's identity (his or her unrepeatability and essential personal core); (iii) In the case of organs that have somewhat of a personalized significance besides a specific function (e.g., fallopian tubes, cervix, uterus prostate), one has to weigh the moral acceptability of transplanting their porcine equivalent on a case-by-case basis.

Risk: To evaluate the ethics of risk, it must be determined that, first, human patients who request to participate in clinical xenotransplantation trials are (a) not candidates for allotransplants either because of long waiting lists or individual counter-indications; (b) not candidates for alternative treatment or alternative treatments do not exist. Second, it is ethically required that clinical trials involving pig-to-human transplants that present a health risk to the human involved proceed with caution—i.e., in small steps, using the least number of subjects possible, and issuing greater caution according to greater risk-associated damage to human subjects. When the time for human clinical trials arrives, because of the possible occurrence of infections and rejection, volunteer human subjects should agree not to have sex during the trial to avoid both the possibility of genetic recombination that could affect the patient's germ cells and the venereal transmission of possible viruses. Psychological counseling should also be provided in the post-transplant stage in case of any psychological repercussions from the modification of one's bodily schema.

Transgenic animals: Genetically modifying animals for prospective xenotransplantation is morally acceptable when it does not compromise the overall genetic identity of the mutated animal or species and when it brings with it the possibility of significant benefits for human beings without compromising human identity. The question of how many human genes it takes before

the modified pig is no longer a pig, but some kind of pig/human hybrid, is ongoing. The prevailing hypothesis is that one or two human genes characteristic of the genetic engineering necessary for pig-to-human transplants does not cause any kind of essential change in the pig and therefore does not compromise the pig's overall genetic identity.

Informed consent: The xenograft recipient will be able to give his or her free consent only after being thoroughly informed about: his or her pathology and its prognosis; the xenotransplantation surgery and subsequent therapy; the probability of success and the risks of rejection; the real and hypothetical risks of zoonoses; the precaution to be followed in case of zoonoses (including quarantine); the need to remain under medical observation for the rest of his or her life. Relatives of a xenograft recipient should also be informed about what the transplant could entail regarding their contact with the patient and about their possible risk of infection.

Allocation of health care resources: The substantial amount of health care resources used in the case of xenotransplantation is justified by the urgent need to try to save the lives of so many patients who would otherwise have no chance for survival.

Equality of access: Once xenotransplantation becomes approved for general use, persons who are in need of xenografts should not be prevented from accessing this procedure for purely monetary reasons or for reasons connected with race or gender.

Public Policy

We are not aware of any legislation regarding xenotransplantation.