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# THE CASE FOR XENOTRANSPLANTATION

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## Abstract

The availability of organs and cells from deceased humans for transplantation is not meeting the demand. Xenotransplantation, specifically the transplantation of organs and cells from genetically-engineered pigs, could resolve this problem. Diabetic monkeys have remained normoglycemic and insulin-independent after pig islet transplantation for >1 year, and a pig heterotopic (non-life-supporting) heart transplant recently reached the one-year milestone in a baboon. With these encouraging results, why is it that, with some notable exceptions, research into xenotransplantation has received relatively little support by industry, government funding agencies, and medical charitable foundations? Industry appears reluctant to support research that will take more than 2–3 years to come to clinical trial, and the funding agencies appear to have been "distracted" by the current appeal of stem cell technology and regenerative medicine. It has only been the willingness of living donors to provide organs that has significantly increased the number of transplants being performed worldwide. These altruistic donations are not without risk of morbidity and even mortality to the donor. Although with the best of intentions, we are therefore traversing the Hippocratic Oath of doctors to "do no harm". This should be a stimulus to fund exploration of alternative approaches, including xenotransplantation.

### Keywords

Cornea; Islets; pancreatic; Organs; Pig; Xenotransplantation

## Introduction

Organ, tissue, and cell transplantation already plays a major role in medicine in the treatment of end-stage organ failure and cellular deficiencies, such as the lack of insulin in patients with Type I diabetes. However, there is a continuing and critical shortage in the number of organs from deceased donors that become available each year, and this is anticipated to become steadily worse as the global population ages (1). This shortage continues despite the increasing use of organs of marginal quality or from non-heartbeating donors. Particularly with regard to cell transplantation, e.g., transplantation of islets in patients with Type 1 diabetes (or possibly of neuronal cells for Parkinson's disease), the

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deficiency in deceased human donors will become increasingly acute. Furthermore, although in a very few countries there is an adequate number of corneas from deceased donors, worldwide there is a shortage that leaves several hundred thousands, if not millions, of patients blind (2).

Xenotransplantation, i.e., the transplantation of organs, tissues, and cells between different species, e.g., from pig to human, could resolve all of these problems (2–4). If the pig could be utilized for the purposes of clinical transplantation, there would not only be an unlimited supply of organs and cells, but also several other potential advantages (Table 1).

## How far has xenotransplantation research progressed today?

Progress in pig cell xenotransplantation has been rather faster than in organ xenotransplantation. Several different groups worldwide have reported at least six months insulin-independence in diabetic nonhuman primates that received pig islet transplantation, with two groups demonstrating complication-free survival for periods >1 year [(5) and Park C-G, et al, personal communication]. These successes have been related to improvements in the immunosuppressive agents available, e.g., agents that block T cell costimulation, but also to advances in the genetic engineering of the source pigs. There have also been encouraging reports on pig dopamine-producing neuronal cell transplantation in monkeys in which a Parkinson-like state has been induced, with significant functional improvement in several monkeys for periods of months or even a year (6).

Corneal xenotransplantation is also showing encouraging results with decellularized pig corneas remaining transparent in monkeys for >1 year (7). In this regard, corneas from genetically-engineered pigs have not yet been tested, but *in vitro* data strongly suggest they will provide a further improvement in the outcome (8).

Heterotopic (non-life-supporting) heart transplantation between pigs and baboons has recently resulted in >1 year cardiac function (9). In this regard, it is unequivocal that genetic engineering of the pig is playing a major role by (i) knockout of antigens expressed in the pig (but not in the human) to which humans generate antibodies (which initiate early antibody-mediated graft failure) (10), and (ii) the introduction of both human complement- and coagulation-regulatory proteins (11, 12). The orthotopic transplantation of pig hearts into baboons is now being undertaken, though the results do not yet match those of heterotopic transplantation.

Transplantation of other organs has been less successful, although life-supporting pig kidney grafts from genetically-engineered pigs have functioned for up to three months in baboons (13–15), and the period of survival has been extended recently in Pittsburgh to >4 months with an absence of several complications seen previously. Liver and lung xenotransplantation are associated with more complex problems that have limited success to days rather than weeks or months (16, 17), but there is every prospect that these will be overcome through the introduction of pigs with an increasing number of genetic manipulations (18). In this respect, the recent introduction of new techniques of genetic engineering, e.g., zinc finger nucleases (ZFNs), TALENs (transcription activator-like effector nucleases), and the CRISPR (clustered regularly interspaced short palindromic

repeats)/Cas9 system, are increasing the speed with which multiple gene manipulations can be introduced (19). For example, some techniques now allow four transgenes to be inserted simultaneously.

The induction of immunological tolerance is the ultimate goal of transplantation, which would enable the graft to survive without the need for life-long immunosuppressive therapy. In some respects, this may be easier to achieve in xenotransplantation than in allotransplantation, in part because the known availability of the “donor” organ will allow pre-transplant preparation of the potential recipient. If major histocompatibility complex (MHC)-identical pigs might prove advantageous, these could, of course, be immediately obtained by cloning. However, because it would be necessary to have MHC-identical males and females, it would not be possible to follow this by a breeding program, and only previously inbred herds could be used for this purpose.

Of importance, the present evidence is that a patient awaiting an organ transplant who is highly sensitized to human leukocyte antigens (HLA), and who may therefore find it difficult to receive a compatible human organ, will not be at a disadvantage in receiving a pig organ (20, 21). Most studies have indicated that antibodies directed to HLA do not cross-react with those directed against pig antigens. Furthermore, although the data are currently limited, a patient who undergoes a pig organ transplant that fails (and develops sensitization to pig antigens) may not be at a disadvantage when receiving a subsequent allotransplant (22, 23).

Pig heart valves (bioprostheses), specifically the aortic valve, represent a special case as they have been transplanted relatively successfully for many years. Like corneas, the bioprosthetic heart valve is avascular, and therefore to some extent protected from early antibody-mediated rejection. In addition, the valve frequently undergoes a form of processing, e.g., with glutaraldehyde, that may afford some protection of the tissues. Nevertheless, there is increasing evidence that graft failure is related to the presence of pig antigens on the valve against which humans have (or develop) antibodies [reviewed in (24)]. These bioprostheses fail quite rapidly in adolescents and young adults, who have a vigorous immune response, but more slowly in older patients where the response is weaker. There seems little doubt that if the genetically-engineered pigs that are currently available were used as sources of valve bioprostheses, the results would significantly improve, resulting in more prolonged graft survival. This would enable all patients to avoid the potential fatal complications related to the obligatory anticoagulation that is required when a mechanical prosthesis has been implanted.

Why is it, therefore, that, with some notable exceptions, research into xenotransplantation has to date been given so relatively little support globally by industry, government funding agencies, and medical charitable foundations?

## Why has there been a relatively lack of financial support for xenotransplantation research?

### Industry

In the early years of research into xenotransplantation (the 1990s), industry played a leading role, but withdrew when concerns were raised about the potential for the transfer of infectious agents, specifically of porcine endogenous retroviruses (PERV), with the transplanted organ into the recipient, and possibly from the recipient to close contacts in the community (25–27). More recent research by experts in retrovirology and transplant infectious diseases into the potential risk associated with PERV has indicated that it is unlikely to be problematic (28–30). The consensus is that the potential benefits of offering an unlimited supply of organs, tissues, and cells for clinical transplantation far outweigh the potential risks.

Furthermore, any such potential risk associated with xenotransplantation has to be weighed against the real and continuing risk of transfer of an infectious agent with an allograft from a deceased human donor (Table 1). Cytomegalovirus and Epstein-Barr virus are regularly knowingly transferred to the recipients of human organs, and numerous other microorganisms, e.g., rabies, West Nile virus, have been inadvertently transferred with sometimes fatal outcome. Nevertheless, the potential risk of transfer of an infectious microorganism from source pig to human recipient, and possibly then into the community, will require careful monitoring. This field of research would benefit from more input by veterinary and animal disease experts, which has to date been relatively lacking.

Today the pharmaceutical and biotechnology industries appear reluctant to support research in xenotransplantation as they seem focused only on very short-term projects that are likely to come to clinical trial within 2–3 years. Approaches to several companies that have an interest in the treatment of diabetes or in eye diseases, for example, have generally not even received a response, yet alone an expression of genuine interest. This is particularly disappointing as there are millions of patients worldwide awaiting definitive treatment for Type 1 diabetes or corneal blindness whose quality of life would be improved immensely if xenotransplantation could be introduced clinically.

Companies that provide porcine bioprostheses obtain the valves from slaughterhouses for a nominal fee, whereas genetically-engineered pigs specifically bred for these purposes would, at least initially, cost much more. Nevertheless, once one company uses genetically-engineered pigs and can demonstrate prolonged bioprosthetic graft survival, then other companies will have to follow suit. At the present time, if a pig valve fails within a relatively few years, this is not seen as a commercial disadvantage as the company can then provide a second bioprosthesis for re-operation.

### Government, charities, and foundations

The governmental and medical charitable funding agencies appear to have been “distracted” from supporting xenotransplantation by the current appeal of stem cell technology and regenerative medicine. It is perceived that these fields will resolve the shortage of cells and

organs for transplantation. This may eventually be the case, but neither approach can compare with the relative success of xenotransplantation at the present time. To my knowledge, neither approach has yet enabled the successful replacement of viable cells or an organ in a nonhuman primate for any clinically-relevant period of time. It may take years or even decades before a whole organ can be constructed from either stem cells or regenerative techniques that will function long-term in primates. In the meantime, many patients awaiting an organ transplant will die, and the quality of life of many others will deteriorate while they wait for an allograft.

Much research in medicine by the funding agencies is directed to *in vitro* studies or work in mouse models, where sophisticated mechanisms can be investigated. However, some such studies are not closely related to the problems of patients and may never impact clinical medicine. Although it is not always possible to envision the potential clinical significance of a research project, it is surely important for the funding agencies to direct more attention to research that will clearly impact clinical medicine rather than research that is of doubtful clinical relevance.

With a few notable exceptions, the attitude of both funding agencies and industry would appear to be much less positive in Europe and North America than in several Asian countries. For example, the South Korean government has supported xenotransplantation generously for the past decade, and this has resulted in very significant advances by scientists in that country, particularly in the field of islet and corneal xenotransplantation. China is also supporting xenotransplantation significantly, and it is likely that work in both of these countries will advance more rapidly than in the Western world. In Europe, only Germany has played a continuing positive role in financially supporting research in this area, and this support has resulted in considerable progress.

## Comment

Organ allotransplantation remained very limited and relatively unsuccessful until cyclosporine became available in the late 1970s and early 1980s (31). The introduction of this one drug, followed subsequently by even better agents, such as tacrolimus (32), played a major role in establishing organ transplantation as a truly successful mode of therapy. (Indeed, it is still evolving and improving.) As the transplant pioneers realized, there is a limit to the progress that can be made in experimental animals, as in many respects it is easier to manage a patient in the clinic than an animal under laboratory conditions. Xenotransplantation is poised to make a far greater potential impact in clinical medicine than allotransplantation has ever done, and there will soon come a time when progress will be impeded unless clinical trials are initiated.

During the last several decades, significant funding has been allocated towards increasing the number of deceased human donors that become available each year. To a large extent, these efforts have been unsuccessful, and have not convinced families of the deceased to donate more readily. It has only been the willingness of living donors to provide organs that has significantly increased the number of transplants being performed in the U.S. and Europe each year. In many parts of the world, there is a cultural resistance to deceased organ

donation, and transplantation depends almost exclusively on living donors. Living donation, of course, has largely been limited to kidney transplantation, but in some countries the number of partial liver transplants carried out has been greatly impacted, particularly in Japan.

These altruistic donations are not without some risk of morbidity and even mortality to the donor. Although with the best of intentions, we are therefore traversing the Hippocratic Oath of doctors to “do no harm”. Surely this point alone should be a stimulus to make more funding available for exploration of alternative approaches – which would include xenotransplantation.

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## Abbreviations

| | |
|---|---|
| **HLA** | human leukocyte antigens |
| **PERV** | porcine endogenous retrovirus |

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**Table 1**

Potential advantages of xenotransplantation over allotransplantation

| | |
|---|---|
| **1** | There will be an unlimited supply of organs, tissues, and cells suitable for transplantation into the smallest infants or the largest adults. |
| **2** | The organs would be available immediately when required. Patients with end-stage cardiac failure would not need to wait for a suitable organ in an intensive care unit for weeks or months. Patients with renal failure would not require dialysis – and certainly not for years while their general status deteriorates; the length of time a patient is on dialysis negatively impacts the outcome after kidney transplantation (33). Patients with end-stage liver failure, for whom there is currently no mechanical device to sustain them (similar to a left ventricular assist device or renal dialysis), would be able to receive a graft as an emergency. |
| **3** | By definition, all organs obtained from deceased donors have suffered the consequences of the development of brain death, which can be damaging histopathologically as well as metabolically (34). The hormonal changes that take place after brain death impact the immediate function of the organs after transplantation, particularly of the heart, and may impact the development of late graft injury, e.g., graft vasculopathy (35). |
| **4** | Much has been written about the potential risk of transfer of an infectious microorganism with the pig organ to the recipient, and possibly to the community at large (25–27). However, as the pig will be housed under clean conditions and monitored closely, this risk will be significantly less than when organs are transplanted from deceased humans. The decision to transplant the human organ has to be made within hours, resulting in a limited period of time to monitor for infectious microorganisms. The inadvertent transfer of a serious infectious microorganism to the recipients may – and occasionally does – occur, with disastrous outcome (36, 37). Common viruses, e.g., cytomegalovirus and Epstein-Barr virus, which are frequently transplanted with human organs and are detrimental to the outcome of the transplant, may well be able to be eradicated in the pig organ-source herd (38). |
| **5** | Patients who are marginal candidates for organ transplantation, e.g., those who may not be selected by the transplant team as they are unlikely to do well long-term, could be offered a transplant as there would be no shortage of organs. When re- transplantation is indicated, there will be no ethical concerns about providing the patient with a second valuable organ, which might deprive a primary candidate from undergoing a transplant procedure. |
| **6** | In some countries with advanced biotechnology and medical care, most notably Japan, there is a cultural resistance to the use of deceased human organs. In these countries, there is little cultural resistance to xenotransplantation, which will enable organ and cell transplantation to expand dramatically. |
| **7** | Unlike the several ethical concerns currently casting a shadow over allotransplantation in some countries, e.g., paid living organ donation (39, 40), the use of organs from prisoners after execution (39, 41), there should be no ethical concerns with regard to using pigs for this purpose. In the US, approximately 100 million pigs are slaughtered each year for food, and in China it is estimated that approximately 600 million pigs are sources of heparin for the world annually. Pigs have long been used as sources of heart valves and tissues for various orthopedic procedures, and are increasingly used as experimental animals in medical research. If it is acceptable to use pigs for these purposes, surely it will be acceptable to use them as sources of life-saving organs and cells. Indeed, the question should be asked whether it is ethical to allow people to die rather than to use a pig for this purpose. |