EJT European Journal of Transplantation

2023;1:163-166
DOI: 10.57603/EJT-272

Editorial

THE IMMENSE POTENTIAL OF XENOTRANSPLANTATION

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Summary

Surgeons working in the field of organ transplantation are increasingly directing attention to resolving the shortage of deceased human donor organs by the transplantation of organs from genetically-engineered pigs, a field known as xenotransplantation (cross-species transplantation). If the remaining immunologic hurdles can be overcome, the ready availability of pig organs would enable all suitable patients to receive an organ transplant. Furthermore, the organ graft would be available whenever needed, thus reducing the need for prolonged renal dialysis or other supportive therapies. In addition, with regard to protecting the graft from the human immune response, xenotransplantation provides us the first opportunity of modifying the donor rather than just suppressing the response in the recipient, which may have detrimental effects on the heath of the patient. However, xenotransplantation offers a much greater potential than just organ transplantation. Pig islets could prove to be a cure for diabetes mellitus, corneas for corneal blindness, and pig dopamine-producing cells may reduce the disabilities of Parkinson's disease. Pig red blood cells offer the prospect of a limitless supply for transfusion, and the implantation of gene-edited pig heart valves may increase the viability of these valves far longer than at present. There would be unlimited skin and tissues for the treatment of burns and many other conditions. Importantly, living human donors would no longer be put at risk, and surgeons would no longer have to resort to the transplantation of organs of suboptimal status. Indeed, xenotransplantation could well be the next great medical revolution.

Key words: corneas, organs, pancreatic islets, pig, red blood cells, xenotransplantation

Received: May 16, 2023
Accepted: July 10, 2023

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How to cite this article: Cooper DKC, Cozzi E. The immense potential of xenotransplantation. EJT 2023;1:163-166. https://doi.org/10.57603/EJT-272

INTRODUCTION

The dream of being able to use an animal as a limitless source of organs for transplantation into patients with terminal organ failure has been explored for more than a century, with increasingly sophisticated scientific investigations being carried out during the past 35 years [1,2]. The January 2022 gene-edited pig heart transplant carried out in a patient at the University of Maryland at Baltimore [3-5] generated considerable interest in xenotransplantation (cross-species transplantation) and has stimulated increased activity aimed towards initiating clinical trials of pig heart or kidney transplantation.

An important basic point to note is that, although organ transplantation has been pursued for more than 70 years, xenotransplantation provides us with the first opportunity to modify the donor, rather than just treat the recipient. The more we can do to the donor to make its organs compatible with the recipient, the less treatment (with its detrimental side-effects) we will need to administer to the recipient. This provides immense potential that will change our entire approach to transplantation.

WHY PIGS?

In the early attempts at xenotransplantation, nonhuman primates (NHPs) were the most popular sources of organs [1], but they will not resolve the problem of the shortage of organs for transplantation because i) most NHP species are of inadequate size; ii) their growth is slow (necessitating expensive housing for years before they reach maximum size); iii) they have limited breeding capacity (potentially restricting their availability in large numbers); iv) we are uncertain of the potentially infectious microorganisms they carry, and v) there are ethical concerns about using our 'close relatives' for this purpose.
In the 1980s, pigs were identified as being preferable in all of these respects. However, because of the greater evolutionary divergence of pigs from humans, there is a much more vigorous human immune response against pig organs than against those from NHPs, with rejection often occurring within minutes [6,7].

PREVENTING REJECTION OF PIG ORGANS

The immune barriers have largely been overcome by two approaches – i) the breeding of pigs genetically engineered to protect their organs and cells from the human innate (antibody) immune response, and ii) the administration of novel immunosuppressive agents that suppress the human adaptive (cellular) immune response. The combination of the transplantation of a heart or kidney from a pig with multiple genetic modifications with treatment of the recipient with one of the novel immunosuppressive drugs now available has resulted in pig organs supporting the lives of NHPs for months or even years [8-13]. The transplantation of pig livers and lungs has to date been much less successful, in part because of the more complex nature of the immune response to these organs [14,15].
Although most recent attention has been directed towards the potential impact of pig organ transplantation, xenotransplantation offers potential cures or treatments for several common diseases and conditions.

Diabetes

In patients with diabetes (particularly Type I juvenile diabetes), the transplantation of pig pancreatic islets (that produce insulin) into a diabetic monkey can maintain a state of normoglycemia (normal blood sugar) for more than a year [16-20]. As the patient would be required to take immunosuppressive medication to protect the pig islets from rejection, many diabetologists are reluctant for their patients to exchange one pathological condition (diabetes) for another (the complications of long-term immunosuppressive therapy). With further genetic manipulation of the islet-source pigs, however, the need for immunosuppressive therapy is likely to be reduced. Already it has been demonstrated that pig islets can be engineered to secrete some immunosuppressive agents [21,22], which may eventually allow either no or minimal additional drug therapy to be required.
A diabetic patient may need to receive islets from two or even three human donors if the diabetes is to be fully controlled (in part because some islets are lost during their isolation from the pancreas), but some breeds of pig grow to a much larger size than the largest of humans, and so their pancreases will yield more islets. Furthermore, there are some advantages in the transplantation of islets from newborn (as opposed to adult) donors, but the number of deceased human newborn donors would clearly be very limited, whereas newborn pigs would be readily available.

Corneal blindness

It is estimated that 4 million people in China alone are in need of corneal transplants, and it will be logistically much easier if this need can be fulfilled by pig corneas [23].

Parkinson's disease

Work in Europe demonstrated that the transplantation of pig cells that produce the hormone dopamine into monkeys with a Parkinson-like condition can reverse many of the features of this debilitating disease, e.g., impaired mobility, tremor [24]. With sufficient financial support, these studies might by now have advanced to clinical trials were it not for administrative difficulties that precluded the use of NHPs in research in certain European countries.
Other degenerative neurological conditions, e.g., Huntington's disease, may possibly prove amenable to similar therapy.

Red blood cell transfusion

In many of the world's countries, there are frequent shortages of donated human blood for transfusion. In others, there may be inadequate testing of donated human blood to ensure no potentially infectious microorganisms are transfused with the blood into the patient. Pigs bred and housed under very clean ('designated pathogen-free') conditions will be far less likely to harbor microorganisms than human blood donors and could provide a limitless source of red blood cells for transfusion. This may be particularly valuable in emergencies, e.g., in trauma or war [25,26], and in the treatment of conditions such as sickle cell disease [26].

NEGATING THE NEED FOR LIVING HUMAN ORGAN DONATION

Although the excision of a kidney from a living human donor for transplantation into a patient (usually a relative, spouse, or close friend) is generally a safe procedure, unfortunately it can very occasionally result in the death of the altruistic donor or, more frequently, complications from the operation. The risks to the donor are significantly higher when donating a part of the liver, which is a more complex technical operation. These risks, though rare, would be completely avoided when xenotransplantation becomes routine.

OBVIATING THE NEED TO TRANSPLANT SUBOPTIMAL ORGANS

Because of the continuing shortage of suitable organs for clinical transplantation, surgeons are increasingly accepting organs from deceased human donors that would not have been accepted only a decade ago. Although techniques have been developed that improve the functional quality of these 'suboptimal' organs, this situation is not ideal. From a functional perspective, suboptimal human organs cannot compare with organs from healthy young pigs.

ENSURING EXCELLENT ORGAN FUNCTION

Will a pig organ be able to fulfill all of the functions of a healthy human organ? There is increasing evidence that the pig kidney will provide all of the necessary function of a human kidney [27-29] and, in the absence of rejection, the pig heart appears to support the circulation of primates satisfactorily, although this has not been monitored for more than 9 months [3,10,12,13].

The function of a pig graft is most likely to be questioned in regard to the liver, which produces approximately 2,000 different proteins and other products that are necessary for human life. A pig liver may not produce all of the identical products as a human liver, but gene-editing could correct these discrepancies. For example, if a specific pig protein is found not to be as effective as the comparable human protein, the liver-source pig could be gene-edited to produce the human protein.

There are certain liver diseases, e.g., those where the liver fails to produce one or more essential factors (including 'inborn errors of metabolism' that may prevent the normal development of infants), when the transplantation of isolated liver cells (hepatocytes) alone may be required. Hepatocytes from pigs that have been gene-edited to produce the required product may answer this need.

HEART VALVES FOR VALVE REPLACEMENT IN HUMANS

The implantation of pig heart valves has been routine in cardiac surgery for approximately 50 years, and there is no shortage of valves from domestic (genetically-unmodified) pigs. Because of their simple structure and methods of preservation, they are not at risk for the very rapid rejection seen when a whole heart is transplanted, and so these patients are not administered immunosuppressive drugs. Although successful in older patients, in young patients (in their teens and twenties) the pig valve may deteriorate rapidly and be no longer functional within one or two years [30,31]. This is believed to be related to a number of factors, including a more rigorous immune response and a more active metabolism that may lead to calcification of the valve. Valves from pigs with specific genetic manipulations are likely to function for much longer periods. Indeed, recent studies in Europe have provided clear evidence for this [32].

TISSUE TRANSPLANTATION

Pig tissues, such as ligaments and bone, are increasingly being used to replace or strengthen comparable tissues in human patients. When decellularized, i.e., when the cells within the structures have been eliminated, these tissues generate only a weak immune response from the recipient. When derived from gene-edited pigs, the immune response will be even weaker [33]. Pigs can also provide skin for temporary cover of serious burns [34].

Comment

When our ability to prevent rejection of a pig graft improves to the point that immunosuppressive drug therapy is no longer required, we predict that far more conditions will be rendered treatable by this approach.

"There is nothing more powerful than an idea whose time has come".
Victor Hugo (1802-1885)

Acknowledgements

DKCC acknowledges the grant support he has received from the US NIH NIAID over many years, and the contributions made to some of the studies summarized here by his many former and current collaborators.

Conflict of interest statement

DKCC is a consultant to eGenesis, a biotechnology company in Cambridge, MA, USA, but the opinions expressed in this article are his own and not necessarily those of eGenesis.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

The authors contribuited equally to the work.

Ethical consideration

Not applicable.

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