# The Future of Transplant Surgery:
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## Xenotransplantation

Considerable time, money and effort have been invested recently in technology in an attempt try and to restore organ function and/or replace damaged organs. Artificial organs and mechanical devices provide a partial solution in certain types of organ failure (kidney, heart), but they have not yet superseded transplantation as a long-term curative option.
Stem-cell-derived organ and tissue regeneration holds great promise for the future, but advancement in this field towards clinical organ replacement but I believe it will require many years of research.

Therefore, **xenotransplantation** I believe, shows the most promise as a – 'within 5 years' - solution to the scarcity of human organ donors. There has been amazing progress in pig organ transplantation in nonhuman primates. We certainly have a much better understanding of the pathobiology and genetic engineering required and with the improvements in perioperative management, and the development of novel immunosuppressive agents I think it will allow xenotransplantation to become a reality. Already, pig kidney grafts have shown long-term function (10 months), and there is a non–life-supporting heart graft still functioning after more than 2 years.
I think it is reasonable to assume that with better biologics becoming available and further genetic engineering of the pig organs even conventional immunosuppressive therapy will prevent the problem created by the adaptive immune response.

Pancreatic islets xenotransplantation is associated with less immediate transplant-related risk to the recipient. Recent preclinical models provide encouraging results, in which porcine pancreatic islet transplantation led to the reversal of diabetes in non-human primates for more than 6 months. However, the high level of immunosuppression used in these studies would be difficult to justify in diabetic patients, as diabetes is not usually immediately life threatening. An encouraging case report with encapsulated pancreatic islets lead me to think that pancreatic islet xenotransplantation from pigs may prove to be the first area of clinical success with xenotransplantation.
Previous clinical experience with kidney xenotransplantation was limited, but recently, studies using α1,3-galactosyltransferase (α1,3GalT)-deficient pigs indicate that long-term survival and function of porcine kidneys are achievable in non-human primates treated with a T-cell tolerance protocol. Further refinements of the conditioning regimen for tolerance induction may allow for the initiation of kidney xenotransplantation
There is limited and disappointing clinical experience with heart xenotransplantation. Recent studies of α1,3GalT-deficient pig heart transplantation in non-human primates are encouraging, but rejection

uniformly occurred
Progress in liver and lung xenotransplantation has been slow and there has been only one clinical case of pig liver transplantation, but there is now considerable experience with ex vivo pig liver perfusion as a bridge to allo-transplantation. Hyperacute rejection remains a problem, but the use of livers from genetically engineered pigs will improve outcomes. Short-term porcine liver perfusion studies have documented the ability of a pig liver to restore coagulation and clear ammonium from human plasma the question remains as to whether a porcine liver can restore full or nearly full function of a human liver in the long term. Having said that, I believe that porcine liver xenotransplants might most appropriately be evaluated as a bridge to allo-transplantation in patients suffering from acute, fulminant hepatic failure for whom an allogeneic donor is not available and to take it one step further, hepatocyte transplantation obviates the need to remove the native liver, and the latter might offset to a certain degree the incompatibilities in liver-produced proteins between pigs and humans. A recent study showed survival of porcine hepatocytes for about 1–3 months after injection into the spleen of immunosuppressed monkeys130, suggesting that hepatocyte xenotransplantation from pigs could become an option for patients with severe liver failure.
Ultimately, I believe that, with the appropriate genetic modifications, pig organ transplantation will be offered to some patients with terminal organ failure using clinically applicable immunosuppressive therapy. With the current rate of progress in pig-to-nonhuman primate kidney and heart transplantation, I anticipate that clinical trials will begin soon. The issue of obtaining truly informed consent for what is a novel form of therapy of which most patients and their families will have little knowledge is a particular challenge and the ethical dilemma of how a critical or comatose patient would consent for liver xenograft support still has to worked out.


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## Stem Cells and the Liver

Stem cell-based therapy is a promising alternative to LT. Varieties of stem

cells including MSCs, HSCs, EPCs, ESCs and iPSCs have been investigated for their feasibility and/or clinical potential. Among them, MSCs have been most studied and are best understood. There primary mechanism of action has been proposed as paracrine effects rather than trans differentiation. The results from clinical trials seem very promising from the perspectives of functional improvement and clinical parameters. However, long- term efficacy has not yet been proven, and more trials are needed.
Novel technologies such as machine perfusion in liver transplantation may overcome some of the current hurdles related to clinical application of stem cell-based therapy. I think MSCs are an attractive adjunct. Nevertheless, there are still a number of issues to be addressed such as the ideal delivery route of MSCs, which is unstandardized in clinical trials to date. (MSCs differentiate into myofibroblasts instead of hepatocytes depending on the injection route). The optimal dose and number of injections are another practical issue when comparing the results from clinical trials. In addition, methods of tracking engrafted MSCs are still poor. Therefore, it is impossible to predict the fate of transplanted cells, although the survival duration is important for sustained efficacy. Recently, labeling cells with superparamagnetic iron oxide nanoparticles and reporter genes have been suggested with advanced imaging technologies. Finally, the quality of the clinical studies reported to date is far from adequate to reach a definite conclusion. Patient enrollment must differentiate clearly between patients with compensated cirrhosis versus patients with impaired function. Only randomized controlled designs can assess the reliable clinical benefit. Long-term follow-up and histologic evidence should be recommended in cases where they are available


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## Robotic Surgery in Transplantation

Minimally invasive surgical approaches in transplantation are definitely gaining increasing acceptance especially in living donor surgery and many centers are reporting their (mainly laparoscopic) growing experiences. Robotic surgery (RS) within transplantation has been slow to be introduced, largely due to the ‘set-up’ costs and the ‘per-case’ expense. Having said that some enthusiasts expound the potential advantages over traditional laparoscopy. Most of the RS experience has been with living Kidney donor procurement and, to a lesser extent, with RS procedures in the transplant recipient. With the technological advances in the field – mainly by Google and Cambridge Robotics; that may change within the next 5 years.

The available literature suggests that RS appears to be a safe surgical alternative to standard open procedures. RS in living liver donor surgery remains limited, but again enthusiasts report excellent outcomes but more experience is required before commenting on RS-related outcomes. The enhanced precision and ergonomics of the robot may expand its applicability to more widespread use in liver living donation and pancreas transplantation at some point in the next 5 years.
Besides the excessive cost of initial purchase (over a million pounds for a robotic surgical system), depreciation, and maintenance expenses, currently limits its application in the NHS. However, many institutions want to adopt this technology. Recently, in liver surgery, two comparative studies concluded that the perioperative costs were higher for robotic procedures as compared to open but direct costs associated with postoperative care were significantly lower even when compared with the laparoscopic approach.
In general surgery, the total costs of RS were higher when compared to open surgery (P<.001), but not when compared to LS.. While confirming higher direct healthcare costs, the study documented that RS reduced hospital stay and pain, both before and after discharge. Reduced pain associated with essential daily activities during the first week after discharge enhances quality of life. Reduced hospital stays with RS and a trend toward accelerated recovery through less pain and improved quality of life during the first post-discharge week are more cost-efficient and will become more and more important in a 'cash-strapped' NHS.

After reviewing the literature, I believe that RS may be used in living donor surgery to improve postoperative pain and quality of life as an alternative to LS if the robotic approach helps improve the postoperative outcomes. RS for recipients seems to provide advantages for both the surgeon and the patient in obese recipients undergoing KT. RS in pancreas and liver recipient surgery is in its infancy, so more data are needed to draw any meaningful conclusions. RS for organ transplantation should continue to develop as an adjunct tool in minimally invasive surgery. Living donor surgery seems to benefit most from this type of technology. Since 2009, more than 500 RKT procedures have been performed. (70% concentrated in two Indian institutions). Several institutions in Europe have implemented the procedure, mainly using the and a European register (ERUS) has been created that already includes 100 patients who have received a transplant.


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## 3D Bio Printing

Solid organ bioprinting for human transplantation I think is still beyond the bounds of clinical practice, but considerable progress has been made on a basic research level recently. Two strategies have emerged for organ bioprinting: scaffold-free and scaffold-based approaches. Bioprinting holds a significant prospect for incorporation into clinical practice over the next 5 years, through implementation of safe and sterile processes. In situ bioprinting - direct printing of living tissue constructs into the defect site in an operative setting, has tremendous clinical promise to repair body parts directly. The process entails bringing a bioprinter into the desired surgical field in a well-coordinated sterile process.
Its major advantage is that it provides robotic systems that can print different cell types in tandem while positioning them precisely in predefined anatomic locations.
Autologous cells can be obtained intraoperatively and used to prepare a bioink for immediate treatment. The printing system can be integrated with a 3D scanner to scan the defect area, acquire images, and generate a printing plan for robotic movement and deposition.
Successful application of bioprinters into clinical practice will require a product that is simple, easy to use, and seamlessly integrates into the operative process. The process has to be safe, efficient, and capable of adjusting in real time. Several variables need to be accounted for including minor changes in positioning, tight surgical quarters, and the ability to adjust for changes in the printing field, such as clearing fluid accumulation. In situ bioprinting has several advantages. It is an efficient process in that the scanned defect can be repaired rapidly while minimizing surgeon manipulation. Manual interventions, such as implanting prefabricated scaffolds can alter the shape due to swelling, contraction, or deformation. In contrast, in situ bioprinting enables precise positioning of cells, genes, or cytokines. This technique has multiple applications such as craniofacial reconstruction, soft tissue repair, and composite tissue printing and transplantation. I believe this technology although still in its infancy and further research is required has great promise for the future. It can also be used for training and planning of surgery.


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