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Review

Potential alternative approaches to xenotransplantation

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HIGHLIGHTS

- Several technologies compete with xenotransplantation.
- Mechanical devices are largely limited to cardiac support or replacement.
- Pluripotent stem cells may ultimately cure diabetes.
- Regenerative medicine can replace simple structures, but not yet solid organs.
- Blastocyst complementation is unlikely to replace xenotransplantation.

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ABSTRACT

There is an increasing worldwide shortage of organs and cells for transplantation in patients with end-stage organ failure or cellular dysfunction. This shortage could be resolved by the transplantation of organs or cells from pigs into humans. What competing approaches might provide support for the patient with end-stage organ or cell failure? Four main approaches are receiving increasing attention – (i) implantable mechanical devices, although these are currently limited almost entirely to devices aimed at supporting or replacing the heart, (ii) stem cell technology, at present directed mainly to replace absent or failing cells, but which is also fundamental to progress in (iii) tissue engineering and regenerative medicine, in which the ultimate aim is to replace an entire organ. A final novel potential approach is (iv) blastocyst complementation. These potential alternative approaches are briefly reviewed, and comments added on their current status and whether they are now (or will soon become) realistic alternative therapies to xenotransplantation.

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Abbreviations: ATIIC, alveolar epithelial type II cell; CRISPR/Cas9, clustered regularly interspaced short palindromic repeat-associated system; ECM, extracellular matrix; ESC, embryonic stem cell; iPSC, induced pluripotent stem cell; PSC, pluripotent stem cell; TAH, total artificial heart; VAD, ventricular assist device.

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1. Introduction

Although the science is advancing rapidly, there remain some barriers to successful xenotransplantation (that are reviewed elsewhere in this issue). What alternative approaches are there? In other words, what competing approaches to xenotransplantation might provide support for the patient with end-stage organ or cell failure? Furthermore, how advanced is progress in these fields? Four main approaches are receiving increasing attention – (i) implantable mechanical devices, although these are currently limited almost entirely to devices aimed at supporting or replacing the heart, (ii) stem cell technology, at present directed mainly to replace absent or non-functioning cells, but which is also fundamental to progress in (iii) tissue engineering and regenerative medicine, in which the ultimate aim is to replace an entire organ, and (iv) blastocyst complementation.

2. Implantable mechanical devices

The Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS) now has data on >10,000 patients who have received some form of mechanical circulatory support during the past 8 years [1].

2.1. Ventricular assist devices

Patients in intractable heart failure can now be maintained by a left ventricular (or biventricular) assist device (LVAD, BVAD) in some cases for >2 years [1–3]. Whereas originally they were inserted to support the patient until a heart from a deceased human donor became available (as a 'bridge' to transplant), they are increasingly inserted as 'destination' therapy, implying that no allotransplant will be carried out. In patients with continuous flow pumps, actuarial survival is approximately 80% at 1 year and 70% at 2 years [1–3], compared to survival following heart allotransplantation of approximately 85% and 80%, respectively. Mean hospital stay after implantation of a VAD is only 20 days [4].

Although these results are very encouraging, there are still problems associated with VAD support. The necessity for the patient to wear a portable power source or for the device to be connected to a stationary power source renders the quality of life less than optimal. In addition, in those being bridged to allotransplantation, sensitization to HLA antigens can develop (largely related to the need for blood transfusions), complicating the search for a suitable deceased donor heart [5]. Although data are very limited, this is not thought to be the case if bridging is by a pig xenograft [6].

There are several adverse events associated with long-term VAD support, e.g., thrombosis of the device [7], thromboembolism, and hemorrhage (primarily gastrointestinal) associated with the anticoagulation therapy that is essential [8]. Neurologic events remain significant [9,10]. Infectious complications related to the power lines that traverse the skin, thus providing a route of entry to microorganisms, remain problematic.

2.2. Total artificial hearts

Total replacement of the patient's heart with a mechanical device (total artificial heart, TAH) continues to be an option – or even essential – in specific groups of patients, for example, those with single-ventricle physiology [11], those who are not candidates for isolated left ventricular support by a VAD [12], and those with cardiac allograft failure [13]. Approximately 70% of patients with a TAH are successfully 'bridged' to cardiac allotransplantation, though the mortality on the device is approximately 25% [14]. Systemic infection (incidence of approximately 50%), driveline infection (25%), and thromboembolic/hemorrhagic events (30%) remain major complications.

2.3. Comment

Although in the first few clinical trials of cardiac xenotransplantation it is unrealistic to anticipate that the transplantation of hearts from pigs will be as successful as the current VADs, pig heart transplantation may well offer a viable alternative to a TAH [5]. Experience with VAD implantation extends back 45 years. It is likely that, when comparable experience is gained of cardiac xenotransplantation, the advantages of a natural, fully-implanted pig heart will outweigh those of a VAD.

3. Pluripotent stem cell therapy

Pluripotent stem cells (PSCs) have the capacity for self-renewal and are capable of differentiating into at least one, and sometimes many, specialized cell types. Embryonic stem cells (ESCs) also have this capacity, but concern has been raised about the risk of teratoma