

ACELLULAR CARDIOVASCULAR TISSUE SCAFFOLDS FROM CONCEPT TO CLINIC

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Introduction

There is a clinical need for regenerative biological grafts for several cardiovascular applications including cardiac valve replacements, replacement of small and large diameter blood vessels and blood vessel repair post endarterectomy. We have developed methods for the decellularisation of human donor and porcine: aortic and pulmonary, valves, blood vessels and pericardium. An overview of the research, development and progress towards clinical translation will be presented.

Methods

Porcine and human donor tissues were decellularised using a process (Booth et al., 2002) based upon sequential treatment with: hypotonic tris buffer (HTB; 10mM Tris pH 8.0, 0.1% (w/v) EDTA, 10KIU aprotinin), 0.1% (w/v) SDS in HTB, nuclease treatment and sterilisation in 0.1% peracetic acid. Analysis methods included histology, immunohistochemistry, extraction and quantification of total DNA from different areas of the tissue, PCR of DNA to detect functional genes, biochemical assays for GAG and collagen content, in vitro contact and extract biocompatibility assays (Wilcox et al., 2005). The acellular porcine tissues were tested for the presence of residual alpha gal epitope by antibody absorption assays. The acellular tissues were subject to biomechanical evaluation including uniaxial tensile testing, pulsatile flow testing (Korossis et al., 2005), burst pressure testing and suture pull-out tests as appropriate. Following development of bioprocesses, the tissues were subject to in vivo biocompatibility tests in rodents (Mirsadraee et al., 2006) and then large animal proof of concept studies.

Results

The decellularisation processes resulted in excellent removal of DNA from the tissues (Wilshaw et al., 2012) as illustrated in Table (1) for human donor cardiac valves. In general decellularisation lead to some loss of GAGs with retention of the biomechanical properties

of the tissues as shown in Figure (1) for porcine pulmonary valves. The tissues were biocompatible in vitro and in vivo. The acellular porcine tissues were devoid of alpha-gal epitope.

Valve	Wall	Junction	Leaflet	Muscle
Aortic	99.2	99.5	97.6	99.1
Pulmonary	99.4	98.1	94.3	99.1

Table (1) Percentage DNA removal from different areas of the human donor cardiac valves

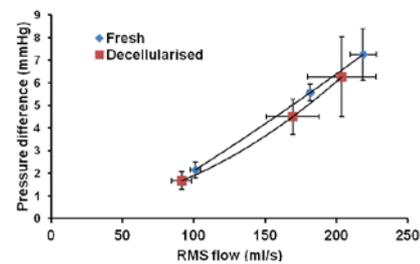


Figure 1: Average pressure difference versus average root mean square (RMS) flow for the fresh (n=6) and decellularised (n=6) porcine pulmonary roots. Mean \pm 95 % C.I.

Discussion

Acellular porcine pericardium has been commercialised marketed in Europe as the dCELL[®] Vascular Patch. Acellular porcine aortic valves have shown regenerative capacity in juvenile sheep and acellular porcine pulmonary valves and blood vessels are currently undergoing long term animal trials. The processes will subsequently be translated to the UK NHS Blood & Transplant (Human tissue) or industry for development of the manufacturing process and clinical studies

References

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