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Small intestinal submucosa extracellular matrix (CorMatrix®) in cardiovascular surgery: a systematic review

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Summary

Extracellular matrix (ECM) derived from small intestinal submucosa (SIS) is widely used in clinical applications as a scaffold for tissue repair. Recently, CorMatrix® porcine SIS-ECM (CorMatrix Cardiovascular, Inc., Roswell, GA, USA) has gained popularity for 'next-generation' cardiovascular tissue engineering due to its ease of use, remodelling properties, lack of immunogenicity, absorbability and potential to promote native tissue growth. Here, we provide an overview of the biology of porcine SIS-ECM and systematically review the preclinical and clinical literature on its use in cardiovascular surgery. CorMatrix® has been used in a variety of cardiovascular surgical applications, and since it is the most widely used SIS-ECM, this material is the focus of this review. Since CorMatrix® is a relatively new product for cardiovascular surgery, some clinical and preclinical studies published lack systematic reporting of functional and pathological findings in sufficient numbers of subjects. There are also emerging reports to suggest that, contrary to expectations, an undesirable inflammatory response may occur in CorMatrix® implants in humans and longer-term outcomes at particular sites, such as the heart valves, may be suboptimal. Large-scale clinical studies are needed driven by robust protocols that aim to quantify the pathological process of tissue repair.

Keywords: Cardiovascular surgery • CorMatrix • Small intestinal submucosa • Extracellular matrix • Tissue engineering

INTRODUCTION

Cardiovascular disease (CVD) is a global health challenge and the leading cause of death worldwide [1]. CVD represents a heterogeneous group of diseases; treatment is, therefore, disease- and patient-specific, but surgical options remain at the forefront of the therapeutic armamentarium in both acquired and congenital pathologies. Regardless of aetiology, the surgical treatment of CVD, particularly following the reconstructive approach, frequently requires additional biological or prosthetic tissue to act as an anatomical substitute. Reconstruction with patches, conduits and valves forms the bedrock of congenital cardiac surgery, while synthetic grafts are used to replace damaged, occluded, ruptured, aneurysmal or atherosclerotic vessels. As a result, a wide range of autologous, heterologous and synthetic materials have been developed to meet the needs of different surgical applications, each with their advantages and disadvantages. Traditionally, either autologous or cross-linked xenopericardium has been used for patch repair in cardiac surgery [2], but these are particularly susceptible to fibrosis, thickening, calcification and retraction over time and do not have the capacity to facilitate tissue growth [3]. Homografts of entire valves or a valve leaflet have been used for decades for valve repair, their advantages being favourable haemodynamics, a low incidence of thromboembolic complications, suitability in the presence of infection and no requirement for anticoagulation. However, the long-term outcomes are age-dependent and the homograft supply cannot always meet demand [4]. A synthetic material such as woven nylon (Dacron; Koch Industries, Inc., Wichita, KS, USA) is not intrinsically biocompatible, is fairly rigid and promotes reactive inflammation and endocarditis [5]. In addition, the paediatric population has particular needs since bioprostheses, homografts and xenografts are susceptible to accelerated degeneration in this age group [6]. For all the aforementioned reasons, there is a need for improved materials for use in cardiovascular surgery to overcome these limitations.

One such material that has recently shown promise in experimental and clinical cardiovascular surgery is CorMatrix®, a biological scaffold derived from decellularized porcine small intestinal submucosa (SIS) [7]. CorMatrix® has emerged as the leading commercially available SIS-ECM scaffold for cardiovascular use and is the most widely used SIS-ECM product in cardiovascular surgery; this review, therefore, focuses on CorMatrix® as the exemplar since

it is the material that cardiovascular surgeons are most likely to encounter. In general, SIS-ECM may (i) possess a three-dimensional (3D) architecture to support the ingrowth of host cells (termed 'bioinduction'); (ii) be sufficiently biologically active to initiate and maintain the molecular control of cell proliferation and differentiation (and hence have growth potential); (iii) be absorbable and (iv) lack the immunogenicity to stimulate a host immunological response [8]. These properties would make the material suitable for a wide range of surgical procedures and might ensure longevity of repair of cardiac defects in children. Furthermore, large amounts of the material can be manufactured to quality-assured standards, thereby ensuring a continuous and standardized supply of material to surgeons.

Here, we review the basic biology, preclinical and clinical studies reporting the use of porcine SIS, and particularly CorMatrix®.

SEARCH STRATEGY

We conducted a comprehensive literature search up to October 2015 using the search terms 'CorMatrix' and 'porcine small intestinal submucosa cardiovascular' in the PubMed database; a flowchart of the literature search is shown in Fig. 1. All studies relating to these materials were reviewed. The abstract of the articles was reviewed only if the title of the article and/or keywords were relevant. The full text of all potentially relevant articles was read for inclusion in the study, and the reference lists of included studies were manually searched along with company websites. A total of 47 articles were included and tabulated (Tables 1–5).

WHAT ARE THE IDEAL PROPERTIES OF A CARDIOVASCULAR BIOSCAFFOLD?

The concept of 'inertness'—an absence of antigenicity and toxicity in the grafted material—has traditionally underpinned graft design and development. Indeed, an uncontrolled inflammatory reaction to the implanted graft material might be expected to result in pathological consequences in the form of thrombosis and hyperplasia (in the case of vascular grafts) or calcification, retraction and scarring (in the case of cardiac patches, valves and conduits). However, inertness must be balanced against the need for a scaffold to facilitate controlled (or 'constructive' [55]) remodelling, which is a highly complex and tightly regulated process that produces site-appropriate functional tissue [56]. Furthermore, in the case of congenital heart repairs, an ideal scaffold should promote controlled healing and native tissue formation and have the potential to facilitate native tissue growth over time to avoid or minimize the need for repeat surgery; materials such as Dacron do not change size or shape over time and, therefore, further operations are likely to be needed to accommodate patient growth [36]. Given the complex nature of these endogenous and exogenous interactions (see below), the 'optimal' biological scaffold has yet to be found. An ideal biological scaffold should, therefore, meet a number of important criteria: (i) resist tissue calcification, thickening, retraction or degradation; (ii) be biocompatible and should not promote intense inflammation, fibrosis or be susceptible to infection; (iii) be pliable and easy to handle, while being strong and durable to resist mechanical failure; (iv) have the potential to undergo remodelling and regeneration, ideally with the capacity for adaptive growth and (v) be able to be manufactured in sufficient quantities of standardized quality to meet the demands of a global marketplace. For a comparison of SIS-ECM and other patch materials, we refer the interested reader to the review by Holubec *et al.* [7].

EXTRACELLULAR MATRIX AS A BIOLOGICAL SCAFFOLD

The use of extracellular matrix (ECM) as a biological scaffold for tissue repair and regeneration is not new. SIS was first used in its native form as a large vascular autograft in a dog in 1989 [57], and inverted SIS had been used even earlier in the 1960s in early vascular grafting experiments [58]. ECM has been harvested from a variety of organs and repurposed as a biological scaffold, including

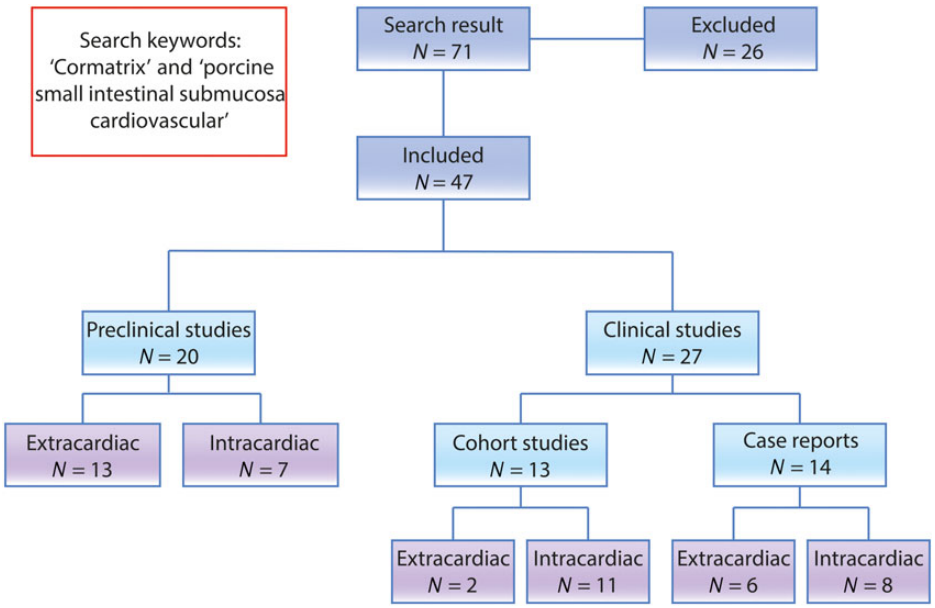

Figure 1: Flow chart demonstrating the study design.

Table 1: Experimental/animal studies of porcine SIS and SIS-ECM used at extracardiac sites or for cardiac regeneration

Study	Year	Indication	Animal model	Number	Follow-up	Outcome measure or method	Result(s)	Reported remodelling process
Sandusky *et al.* [9]	1992	Carotid artery grafting	Dog	$n = 24$	Up to 180 days	Histology, Doppler	SIS thrombosis Day 2, 90 and 180 SIS graft outcome was similar to SVG grafts	Smooth muscle infiltration, neovascularization, endothelialization
Hiles *et al.* [10]	1995	Aortic grafts	Dog	$n = 8$	Up to 60 days	Mechanical testing and histology	Stronger than normal artery, thicker	Remodelling with graft resorption
Robotin-Johnson *et al.* [11]	1998	Superior vena cava graft	Pig	$n = 11$	90 days	Physical properties and histology	No graft material-related deaths. Patent thrombus free grafts. Anastomotic stricture and aneurysm in 2 of 9	Endothelialization, neoangiogenesis
Pavcnik *et al.* [12]	2002	Bicuspid venous valve	Sheep	$n = 12$	Up to 6 months	Venogram, histology	88% good function without leak, one thrombosis. Thickened SIS membrane	Remodeled collagen, fibroblast infiltration with neoangiogenesis
Badylak *et al.* [8]	2003	Myocardial repair	Pigs and dogs	$n = 6$ (pigs) $n = 4$ (dogs)	Up to 24 weeks	Histology, *in vitro* contractility assessment ($n = 2$ dogs)	Scaffold replacement with a mixed cellular infiltrate, including myocytes. 70% contractility of normal	Complete replacement of matrix with connective tissue, cartilage, adipose and myocardium with neoangiogenesis
Yavuz *et al.* [13]	2006	High-pressure implantation in the abdominal aorta	Sheep	$n = 12$ each of SIS, Dacron and ePTFE	Up to 18 weeks	Aortogram, histology	Patent suspended devices without thrombosis or aortic wall contact.	Neointimal formation with endothelialization Dacron > SIS > ePTFE
Pavcnik *et al.* [14]	2009	Carotid artery grafts	Sheep	$n = 13$	Up to 4 months	Doppler, angiography, histology	90% patency at 1 week decreasing to 30% at 3–4 months	Thickened graft wall. Variable endothelialisation: partial in medsection and complete distally
Boni *et al.* [15]	2012	Pulmonary artery reconstruction	Lambs	$n = 6$	Up to 6 months	CT angiography and histology with IHC and electron microscopy	No failures. No stenosis or aneurysm. Endothelialization and smooth muscle infiltration. Patch resorption by 6 months	Neoangiogenesis, c-kit-positive cell infiltration raising the possibility of multipotent cells
Fallon *et al.* [16]	2012	Carotid artery repair	Sheep	$n = 15$	Up to 6 months	Mechanical testing, angiography, histology	Mild stenosis in ECM implant sites at 30 days, resolving by 90 days	Graft resorption, neoangiogenesis, endothelialization
Padalino *et al.* [17]	2012	Vascular patch	Rat	$n = 3$ (sham) $n = 3$ (control) $n = 20$ (treatment)	Up to 6 months	Histology with IHC/IF	Intact aortic wall, no aneurysms. Almost complete remodeled graft by 6 months	Complete graft resorption, neoangiogenesis and endothelialisation, the new intima and media layers found to be of donor origin
Mewhort *et al.* [18]	2014	Ischaemic heart failure	Rat	$n = 13$ (normal) $n = 15$ (sham) $n = 28$ (treatment)	16 weeks	Histology with IHC, echocardiography, invasive hemodynamic assessments	Integration of CorMatrix®, increased FGF expression, enhanced ejection fraction in treatment versus sham ($P < 0.001$)	Patch integration with host myocardium with patch being free from scaring or inflammatory reactivity
Slaughter *et al.* [19]	2014	Ischaemic heart failure	Cow	$n = 11$	N/A	N/A	N/A	Feasibility study of injecting particulate CorMatrix® into ischaemic myocardium
Soucy *et al.* [20]	2014	Ischaemic heart failure	Calves	$n = 12$	60 days ($n = 6$) 90 days ($n = 6$)	Echocardiography, cell proliferation, regional blood flow	P-ECM and HVAD largest functional and biological gains	N/A

SIS: small intestinal submucosa; ECM: extracellular matrix; IHC: immunohistochemistry; SVG: saphenous vein graft; CT: computed tomography; ePTFE: polytetrafluoroethylene, Dacron; IF: immunoflurescence; P-ECM: particulate extracellular matrix; HVAD: HeartWare ventricular assist devices; FGF: fibroblast growth factor.

Table 2: Experimental/animal studies of porcine SIS and SIS-ECM used at intracardiac sites

Study	Year	Indication	Animal model	Number	Follow-up	Outcome measure or method	Result(s)	Reported remodelling process
Matheny *et al.* [21]	2000	Pulmonary valve leaflets	Pig	$n = 4$	Up to 111 days	Echocardiography and histology	Normal valve competence	Replacement with fibrous connective tissue, neoangiogenesis, endothelialization
Rosen *et al.* [22]	2005	Intracardiac patch	Calves	$n = 5$	Up to 6 months	Histology	Macroscopically unremarkable, neointima formation	Thick neointima with collagen and smooth muscle
Ruiz *et al.* [23]	2005	Pulmonary valve replacement	Pig	$n = 12$	Up to 12 months	Echocardiography and histology	No valve misplacements, embolizations or regurgitation	Absent inflammation, fibroblastic infiltration, endothelialization
White *et al.* [24]	2005	Pulmonary valve replacement	Sheep	$n = 4$	Immediate postoperative analysis	Echocardiography and histology	Good function	Red blood cell infiltration
Fallon *et al.* [25]	2014	Prosthetic tricuspid valve	Sheep	$n = 4$	up to 12 months	Echocardiography and histology	Normal gross morphology with coaptation. Structural reorganization, elastin, and GAGs by 5 months	Host cell infiltration with endothelialization
Toeg *et al.* [26]	2014	Aortic valve repair (*ex vivo* porcine aortic roots)	Pig (*ex vivo*)	CorMatrix®, bovine pericardial and Dacron grafts	N/A	Haemodynamic and pressurization studies	Reduced orifice area in CorMatrix® grafts ($P = 0.0001$) and largest quantitative profile difference	N/A
Zafar *et al.* [27]	2015	Tricuspid valve bioprosthesis	Sheep	$n = 8$ ($n = 4$ controls)	Up to 8 months	Echocardiography, ventricular function and histology	One severe regurgitation. Normal ventricular function. Close to normal architecture by 8 months, with separation of collagen, elastin and GAGs layers of the proximal part of the leaflet	Resident mesenchymal cell infiltration and trilaminar ECM organization; no inflammation

SIS: small intestinal submucosa; ECM: extracellular matrix; GAGs: glycosaminoglycans.

Table 3: Clinical studies of porcine SIS-ECM used at extracardiac sites

Study	Indication	Level of evidence	Patients	Follow-up	Outcome measure or method	Result
Boyd *et al.* 2010 [28]	Pericardial reconstruction	III	$n = 111$ (treatment) $n = 111$ (control)	N/A	Postoperative AF	54% reduction in relative risk ($P < 0.001$)
Quarti *et al.* 2011 [29]	Vascular repair at different sites or valve reconstruction	IV	$n = 26$ total	Mean 13.2 months, range (4–25 months)	Echocardiogram	No serious patch-related complications or deaths

SIS: small intestinal submucosa; ECM: extracellular matrix; AF: atrial fibrillation.

from the liver [59], pancreas [60] and urinary bladder [61]. SIS-ECM represents the exemplar ECM for tissue engineering, its biochemical and biomechanical properties have been comprehensively characterized, and SIS-ECM has been used in more than 1 million patients for a variety of reconstructions at multiple sites including the skin [62], rotator cuff [63], urinary tract [64] and intestine [65]. Although clinical results have been variable, ECM materials have gained widespread acceptance within the clinical community. As a result, commercial scaffold materials manufactured from a range of ECM materials from different animals are available, including several porcine SIS products (e.g. Surgisis®, Durasis® and Stratasis®; Cook Biotech, Lafayette, IN, USA; Restore®; DuPuy, West Chester, PA, USA).

However, ECM scaffolds were only recently introduced to cardiovascular surgery in spite of the putative benefits of the material. Of the commercially available SIS-ECM products, CorMatrix® (CorMatrix Cardiovascular, Inc., Roswell, GA, USA) has Food and Drug Administration clearance as a device and a European CE mark for pericardial patch repair and reconstruction, cardiac tissue repair, carotid repair and enveloping implantable electronic devices. It is a decellularized four-ply sheet material made from porcine SIS, which theoretically contains the necessary structural proteins (such as collagens), adhesion molecules and matricellular proteins to promote 'constructive' remodelling. CorMatrix® is also available in 'envelope' form (CorMatrix Cangaroo®) to hold implantable electronic devices *in vivo* to restrict migration, impede infection and improve comfort for the patient. Although other similar commercial ECM products exist for cardiovascular use [such as Autotissue MatrixP®, Germany (decellularized equine pericardial matrix) and CardioCel® (decellularized bovine pericardium; Admedus, Perth, Australia)], these have only recently been introduced to the marketplace and therefore data on their use are very limited.

PHYSICAL AND BIOLOGICAL CHARACTERISTICS OF EXTRACELLULAR MATRIX

ECM represents a complex 3D structural framework that supports cells to provide biological, physical and mechanical properties that dictate cellular and, ultimately, tissue function [66]. Manufacturers of commercial ECM scaffolds therefore aim to remove the cellular components while retaining the intact ECM meshwork and its biomechanical functions to support host cells. Decellularization may involve a combination of physical, ionic, chemical and enzymatic methods tailored to the tissue of interest [67]. It is known that excessive decellularization can impair the release of endogenous growth factors that promote constructive remodelling [67]. Similarly, excessive chemical crosslinking can alter the profile of peptide release during the remodelling process, thereby hampering it [67]. Commercially available ECM products are available in a variety of forms, most frequently multilaminated sheets but also as powders and injectable gels.

ECM can be considered in both mechanical and functional terms. As a mechanical substrate, ECM is a dynamic structure with topologically distinct areas. For instance, the basement membrane is a specialized collagen-rich ECM structure that forms a physical barrier and primarily supports the mucosal epithelium, and the migration of cells through the ECM requires focal remodelling [68]. As a functional substrate, the main ECM components are collagens, glycoproteins, proteoglycans, mucins, elastic fibres and growth factors [69] which, as well as providing the structural support to the tissue, interact with the cell surface via numerous receptors that mediate intracellular signalling pathways that dictate tissue homeostasis and function. The ECM is also tissue-specific, the more obvious examples being the greater quantity of type II collagen and glycosaminoglycans (GAGs) in articular cartilage to confer high resistance to deformation forces [70] or the type I collagen in tendons to resist tensile loading [71].

With these properties in mind, SIS may be considered an ECM well suited to a broad range of applications. Specifically, 90% of the SIS-ECM is collagen (predominantly type I), with minor amounts of type III, IV, V and VI collagens, GAGs, fibronectin and laminin as well as growth factors [72]. Urinary bladder matrix is similar in composition, but with greater amounts of type III collagen and type VII collagen originating from the endothelial basement membrane [72]. In addition to its chemical composition, SIS-ECM has a collagen fibre alignment suited to the mechanical requirements of cardiovascular tissue engineering: there are two distinct populations of collagen fibres orientated ~30° from the longitudinal axis of the small intestine (the 'global preferred fibre alignment') that confer greater strength and stiffness to SIS-ECM than other sources of ECM such as urinary bladder submucosa [55]. This mechanical advantage is further enhanced by lamination.

The mechanisms by which implanted ECM scaffolds undergo remodelling are imperfectly understood, and the mechanical and physical properties of ECM are insufficient to explain all the observed remodelling effects. One useful framework for understanding the remodelling process is the 'bioinduction' model: degradation of the non-native matrix triggers host cell responses that give rise to mature tissue. Bioinduction may occur via several mechanisms: (i) degradation of the ECM scaffold by circulating enzymes and/or early infiltrating cells, particularly M2-type macrophages [73]; (ii) release of growth factors during scaffold

Table 4: Clinical studies of porcine SIS-ECM used at intracardiac sites

Study	Indication	Level of evidence	Patients	Follow-up	Outcome measure or method	Results
Witt *et al.* [30]	*Congenital CV reconstructions*: septal defects (n = 13), vascular augmentation (n = 26), outflow tract augmentation (n = 7), valve reconstruction (n = 3)	IV	n = 37 in 48 locations	411 days *CorMatrix® in situ*: 555 and 23 days, and a biopsy from ASD patch at 336 days	Retrospective review of procedure, implant location, echocardiogram, reintervention and pathology	*Clinical*: 4 deaths not related to the patch. Three reoperations, 2 for patch failure; progressive vascular stenosis (1 RVOT patch and 1 PA patch). *Histological*: thickening and chronic inflammation (eosinophils)
Yanagawa *et al.* [31]	Pericardial patch repair after post-MI complications (n = 7 aneurysm; n = 3 VSD; n = 1 both)	IV	n = 11	Mean 207 days (clinical) Mean 176 days (echocardiography)	Echocardiography	One death and 2 reoperations not related to CorMatrix®. No repair failures
Brinster and Patel [32]	Aortic root enlargement	IV	n = 7	N/A	Postoperative echocardiograms	No reported failures
Gerdisch *et al.* [33]	Tricuspid valve endocarditis repair	IV	n = 18	1–18 months	Echocardiogram	No deaths. *Four reoperations for*: disruption of papillary attachment in n = 3, tricuspid regurgitation [a]n = 1, fungal infection n = 1
Gerdisch *et al.* [34]	Mitral valve repair	IV	n = 19	Mean 10.9 months echocardiography	Echocardiogram	Three deaths, not MV-related. Three MV reoperations, 1 for early tear. Repaired valves showed good function and no evidence of calcification. In 1 patient reported incomplete healing of A2–A3. Histology showed regions of vascularized patch at 18 months
Sundermann *et al.* [35]	Endocarditis (mitral valve)	IV	n = 2	34 days and 3 months	Echocardiography	Successful repair
Zaidi *et al.* [36]	Valve reconstruction in congenital heart disease (17 mitral and 26 aortic)	III	n = 57 patients, n = 9 available for histology	N/A *CorMatrix® in situ*: MV: median 64 days (range 5–261). AV: median 63 days (range 49–198)	Explant histology	*Clinical*: 8 of 17 MV reoperations for valve dysfunction, 6 of 8 patch related. Three of 26 post AV repair, 1 of 3 death, 2 of 3 reoperations for failure *Histological*: 8 of 9 explants; dense chronic inflammatory infiltrates (eosinophils and giant cells). No remodelling or reabsorption of CorMatrix®. In many cases, a thick neointima had formed
Rosario-Quinones *et al.* [37]	Congenital cardiac surgery, various sites	III	n = 25 patients, (n = 6 explants; MV, aortic arch, PV, PA, RVOT and pericardium)	N/A *CorMatrix® in situ*: range: 9 weeks to 13 months	Explant histology	*Clinical*: all patients had significant haemodynamic lesions at the implantation site. Most reoperations related to patch failure. *Histological*: intense inflammation (eosinophils, histiocytes, plasma cells, with granulation tissue and fibrosis). In the patient with reconstructed PV, the scaffold was not grossly identified 13 months after implantation
Luk *et al.* [38]	Endocarditis (1 = MV, 2 = AV and MV)	IV	n = 2 both MV	N/A *CorMatrix® in situ*: 10 and 18 months	Explant histology	*Clinical*: delayed postoperative infection and perforation of MV leaflet *Histological*: intact patches with no resorption of the material. No cellular infiltrates in the tissue. Connective tissue and endothelial cell deposition on the surface. More thickening was observed at 18 months

Woo *et al.* [39]	Paediatric heart reconstructions	III	*n* = 532 patients, *n* = 12 explants from 11 patients (2 mitral, 2 aortic and 8 outflow/septal/conduit patches)	2.5 years *CorMatrix® in situ*: mean 518.6 days (range 77–1294)	Explant histology	*Clinical*: 6 cases had clinical evidence of graft failure before surgery. *Histological*: no evidence of native cells deposition or organized collagenization of CorMatrix. Grade 3 chronic inflammation (giant cells) in 8 of 12 explants and acute inflammation (eosinophil and giant cells) in 3 of 12. Degeneration of material in 9 of 12 but no resorption. Calcification in surrounding tissues in 3 of 12 but not on the CorMatrix®
Padalino *et al.* [40]	Congenital cardiac surgery, various sites	II	*n* = 103 patients, *n* = 132 implants (38 valves; 16 septal reconstructions; 71 arterioplasties; 7 other)	Median 23.3 months (range 0.3–55.23) *CorMatrix® in situ*: median 25.2 months (range: 2.5–34.1)	(i) Reoperation; (ii) interventional procedure and (iii) functional ECM failure. Explant histology also assessed	*Clinical*: short term: no deaths or immediate postoperative complications related to scaffold failure. Mid-term: 6 reoperations and 8 interventional procedures for scaffold failure. *Histological*: intact patch, mild stiffness, mild inflammation (lymphocytes and giant cells) and no calcification was noted in explants

SIS: small intestinal submucosa; ECM: extracellular matrix; CV: cardiovascular; ASD: atrio-septal defect; RVOT: right ventricular outflow tract; PA: pulmonary artery; MI: myocardial infarction; VSD: ventriculo-septal defect; MV: mitral valve; AV: aortic valve; PV: pulmonary valve.
[a]This patient also had disruption of papillary attachment.

degradation; these include vascular endothelial growth factor [74], transforming growth factor beta (TGF-β) [75] and other 'cryptic' peptides (such as endostatin and angiostatin; see ref. [55]); (iii) host cell infiltration, including circulating bone marrow-derived cells that sustain long-term tissue remodelling (notably endothelial and mesenchymal progenitor cells; [73]) and (iv) sustained tissue formation with neoangiogenesis. In this way, ECM degradation may initiate a physiological remodelling process that suppresses an inflammatory response and its resulting fibrous (scar) tissue formation, with rapid replacement of the SIS-ECM (e.g. 60% resorption after 1 month, complete resorption after 3 months in a canine model [76]). Since ECM is thought to provide a stem cell niche (i.e. one suitable for the recruitment and differentiation of stem cells), it also provides the ideal environment to sustain and promote multipotent stem cell development and remodelling of complex tissue structures [66]. ECM scaffolds are not completely immunologically inert and monocytes are recruited to the material as part of the bioinductive process; however, these are thought to differentiate into M2-phenotype macrophages that secrete an anti-inflammatory or 'healing' cytokine profile (IL-10 and TGF-β), rather than M1-phenotype macrophages that promote an inflammatory cascade and scarring [73, 77].

PRECLINICAL STUDIES OF PORCINE SMALL INTESTINAL SUBMUCOSA AND SMALL INTESTINAL SUBMUCOSA-EXTRACELLULAR MATRIX FOR CARDIOVASCULAR USE

As noted above, SIS has been used in experimental models of cardiovascular surgery since the late 1980s, when autologous SIS was used as both small [78] and large [57] diameter vascular grafts in dogs. Follow-on studies in the early 1990s utilized similar models to examine porcine (xenogeneic) SIS [9, 10]. Over the last decade, porcine SIS and the newer SIS-ECM have been used in a variety of cardiovascular applications in a number of different animals, including pigs [8, 11, 21, 23], sheep [12–14, 24] and cows [22], and for a variety of purposes such as arterial or venous grafting [9–11, 14–17], valve replacement [12, 21, 23–26] and myocardial repair or patching [8, 22].

Although the number of animals used in these studies was often small, these were important studies that together laid the ground for the clinical studies using SIS-ECM. The results of these studies are illustrated in Table 1 (extracardiac use) and Table 2 (intracardiac use). In general, results of porcine SIS used under a range of different experimental models, conditions and purposes provided enough evidence to warrant further clinical testing. In contrast to clinical studies of porcine SIS (see below), the material has been tested more frequently in the extracardiac setting although results at all sites appear to be equivalent. In those studies where functional investigations were carried out to assess patency (e.g. by venography or angiography), thrombosis was the main cause of failure (in refs [12] and [9]). Of all the preclinical studies published, only one study by Pavcnik *et al.* [14] reported a high failure rate of 70% at 3–4 months in an ovine model of carotid artery grafting due to dilatation, stenosis, dissections and aneurysm formation. It is uncertain why the failure rate was particularly high in this study: the authors suggested that the animal model used, the graft length (10 cm), the maintenance of anticoagulation or surgical technique could all have accounted for the failures.

Supporting the expectation that porcine SIS-ECM has low immunogenicity, inflammatory reactions were rarely observed at

Table 5: Clinical case reports of porcine SIS-ECM used at intra- and extracardiac sites

Study	Year	Indication	Site	Follow-up	Outcome measure or method	Result
Gilbert *et al.* [41]	2011	Tri-leaflet pulmonary valved conduit	IC	5 months	Echocardiogram	No flow gradient and trivial valvular insufficiency
Eckhauser *et al.* [42]	2013	Repair of innominate artery	EC	8 days	MRI	Repair intact on Day 8
Stelly and Stelly [43]	2013	Pericardial closure	EC	5 years	Redo surgery	Neo-pericardium
Yeen *et al.* [44]	2013	Anomalous pulmonary vein reconstruction	EC	N/A	Postoperative CT	No reported failure
Poulin *et al.* [45]	2013	Atrioventricular continuity reconstruction	IC	N/A	Echocardiogram	Patch dehiscence
Deorsola *et al.* [46]	2014	Aortic coarctation repair	EC	11 months	Serial echocardiograms	Stenosis at 4–5 months
DuBose and Azizzadeh [47]	2014	Repair of arterio-venous fistula aneurysm	EC	4 months	Clinical	Patent AVF
Cua *et al.* [48]	2014	Tricuspid valve replacement	IC	N/A	Postoperative echocardiogram	Moderate regurgitation
Slachman [49]	2014	Aortic root repair	IC	34 months	Autopsy	Death not patch related (myelodysplastic syndrome)
Szczeklik *et al.* [50]	2014	Reconstruction of right atrium and superior vena cava	IC	8 weeks	Echocardiography	Successful repair
Wallen and Rao [51]	2014	Tricuspid valve repair after endocarditis	IC	3 months	Echocardiography and clinical	Mild residual TR
Yanagawa *et al.* [52]	2014	Myocardial regeneration	IC	1 year	Echocardiography	Baseline LVF restored
Holubec *et al.* [53]	2014	Post-MI free wall rupture repair	IC	3 months	Echocardiography	Successful repair
Bibevski and Scholl [54]	2015	Atrioventricular valve	EC	N/A	Echocardiography	Excellent function noted

SIS: small intestinal submucosa; ECM: extracellular matrix; IC: intracardiac; EC: extracardiac; AVF: arterio-venous fistula; TR: tricuspid valve; MI: myocardial infarction; LVF: left ventricular function.

graft sites, even in the xenogeneic setting. Inflammation was observed in the grafts in two studies: a chronic inflammatory infiltrate in bicuspid venous valves [12], and moderate chronic inflammation in carotid artery grafts [16]. The observation of inflammation in sheep and not other animals does not necessarily mean that the ovine model is unsuitable for preclinical testing because (i) inflammation was absent in several other ovine studies and (ii) in general, the physiological arterial pressures reached in sheep closely mimic those found in humans [16]. Thus, sheep can still be considered suitable models for vascular studies. Furthermore, calcification is accelerated in vascular prostheses in sheep [16], and therefore the absence of calcification in any of the ovine SIS-ECM studies positively supports the notion that this material resists calcification during the remodelling process. Indeed, one very recent study in which tricuspid valve bioprostheses were implanted into lambs for 3 or 8 months reported only one failure (regurgitation) in eight experimental grafts [27]. Furthermore, the explanted valves were grossly normal with microscopic features similar to mature native tricuspid valves and evidence of 'growth' of the annular ring, which, as noted above, would be particularly beneficial for the paediatric population.

These animal studies have some limitations including small sample sizes, short follow-up and a lack of standardized functional and histological assessment. However, these preclinical data have the advantage of availability of explant tissue for detailed histopathological analysis, in contrast to most of the reported clinical studies. These results shed light on the remodelling process: the majority of porcine SIS and SIS-ECM explants show at least some degree of matrix repopulation with new cells (fibroblasts and smooth muscle cells), neoangiogenesis and surface endothelialization. At least one study provides direct evidence that infiltrating cells are of host origin using a genetically engineered rat model [17], and there is indirect evidence that the remodelling process may result from repopulation with pluripotent cells: in one study of myocardial repair in pigs and dogs, the infarcted myocardium was replaced with not just myocardium but also adipose tissue and cartilage [8], whereas another study identified a c-kit-positive population of cells within remodelling ECM, raising the possibility that multipotent progenitors participate in the remodelling process [15]. Of note, this principle of native tissue replacement via the inductive properties of CorMatrix® has recently been exploited in a bovine model of cardiac ischaemia, in which particulate (rather than sheet) CorMatrix® was successfully injected into ischaemic myocardium to restore contractility, with the highest levels of cell proliferation and end-organ perfusion in the group receiving particulate ECM ([19, 20] and Table 1).

CLINICAL STUDIES OF CORMATRIX® IN CARDIOVASCULAR SURGERY: EMERGING CONTROVERSIES

CorMatrix® has been used in clinical cardiovascular surgery since 2010. Summaries of clinical studies published to date are presented in Table 3 (extracardiac use) and Table 4 (intracardiac use) [79]. A similar number of case reports describing the use of CorMatrix® are presented in Table 5.

CorMatrix® has been used in congenital cardiac and vascular surgery [29, 30, 36, 41], pericardial reconstruction [28, 31, 43], valve reconstruction in both adults and children [28, 33, 34, 36, 48, 51], endocarditis [33, 35, 51], acquired vascular defects at different sites [42, 47] and to repair damaged myocardium after infarction [52]:

more studies have been conducted in the intracardiac setting (Table 4) than the extracardiac setting (Table 3). The first clinical report of CorMatrix® was as a pericardial substitute [28], which was a retrospective case–control study of 222 patients undergoing pericardial reconstruction after primary isolated coronary artery bypass grafting. The treatment group showed a 54% relative risk reduction of developing postoperative AF although it is uncertain how or why the graft reduced AF and the study was limited by being retrospective, non-randomized and underpowered. Nevertheless, the study provided early evidence that the material might be suitable for cardiac use, prompting greater adoption of the material in a range of cardiovascular applications. As a vascular substitute, one extracardiac study reported a complication of stenosis at the site of coarctation repair treated with a CorMatrix® patch, which was subsequently remedied with balloon angioplasty [46]. However, as noted below, more recent prospective clinical studies have been less than favourable, casting doubt on its use, particularly in the paediatric population.

Extracardiac sites tend to be low mechanical force environments that are likely to facilitate (or at least not hinder) remodelling; results may therefore be expected to be favourable at these sites. However, even at intracardiac sites frequently exposed to high shear forces and mechanical pressures, only minor failures were noted in a limited number of cases in early studies (Table 4). For instance, in a study by Quarti *et al*. [29], 9 patients underwent surgery using CorMatrix® for valve repair (5 aortic, 2 tricuspid, 1 mitral and 1 pulmonary). There were no serious patch-related complications or deaths, and trivial aortic valve regurgitation was only noted in four AV repairs and mild pulmonary valve regurgitation in one PV repair. However, this study was limited by the fact that follow-up was only up to 25 months (mean 13 months), which is far too short to fully assess the functional success of valve repair. Some uncontrolled, and therefore methodologically limited, studies report isolated major complications: patch dehiscence after atrioventricular continuity reconstruction following massive posterior annulus decalcification and mitral valve replacement for mitral stenosis due to dystrophic calcification [45], progressive vascular stenosis in 2 of 37 paediatric patients with CorMatrix® patch repairs for a variety of congenital defects [30] and one fungally infected tricuspid valve 6 months after repair for infective endocarditis (the other three failures in this study being attributed to the surgical technique rather than material failure) [33].

These early results must be considered with caution. To date, there has been only one level II study [40] and only four studies that can reasonably be classified as level III studies [28, 36, 37, 39], the remainder representing level IV studies that are, for the most part, case reports or small case series (Table 5). The majority of published studies only report immediate or very early postoperative findings although a handful of case reports examine outcomes past a year or more.

The most robust study to date is a very recent prospective multicentre (but non-randomized) clinical study of 103 paediatric and adult patients receiving 132 CorMatrix® implants at a variety of sites: 38 valve repairs, 16 septal reconstructions, 71 arterioplasties and 7 at 'other' sites [40]. The surgical experience was regarded as 'positive' by the operating surgeons with good handling characteristics although prolonged washing of the material was sometimes associated with delamination. No immediate postoperative events were attributable to the ECM scaffold, but 6 patients required reoperation due to ECM scaffold failure at a median follow-up of 25.2 months (range 2.5–34.1 months): 5 of 38 were valve replacements for failing aortic valve plasty and 1 for a failed mitral valve plasty. Although no calcifications were seen in the explants, there was a mild chronic inflammatory infiltrate in the explant tissue without signs of regeneration. Eight patients required interventional cardiology procedures at CorMatrix® sites, all of which were on the pulmonary arteries. Surgery on the semilunar valves was a predictor of functional failure in multivariate analysis. These are important data that highlight that there is heterogeneity in clinical responses to SIS-ECM use at different sites, and that further work is required to determine optimal indications for SIS-ECM use.

Recent results have raised some doubt on the *in vivo* biology of CorMatrix® [80]. One level III clinical study on CorMatrix® reports the histological findings from 71 mitral or aortic valvuloplasties using either CorMatrix® or autologous pericardium [36]. Of these, nine CorMatrix® explants subsequently (5–261 days *in situ*) became available at the time of reoperation for valve replacement or valvuloplasty for systematic histopathological analysis although this may have been itself due to a failure of the material in this setting, particularly since the failures were associated with intense chronic inflammation. Contrary to expectations and the manufacturer's claims that the material does not elicit an inflammatory response, 8 of the 9 cases did exhibit an intense chronic inflammatory infiltrate involving the matrix without significant resorption of the implanted material, with little or no remodelling into a structure resembling native valve tissue. Furthermore, these features were apparent as late as 9 months after implantation. These results have prompted recent histopathological studies that have also reported similar findings [37, 80]: in 6 of 25 paediatric patients undergoing reoperation after CorMatrix® implantation, the explanted specimens exhibited dense, mainly eosinophilic inflammatory tissue infiltrates that were frequently accompanied by granulation tissue and fibrosis [37]. In the second study of 532 patients in total (mean follow-up of 2.5 years), 12 CorMatrix® implants were obtained from 11 paediatric patients from a range of sites (4 valves, 2 mitral and 2 aortic; 8 outflow, septal or conduit patches) [39]. Chronic inflammation was observed in adjacent tissue in 11 of 12 explants and, in addition, acute inflammation was seen in 3 cases and tissue necrosis in 5. Notably, these acute inflammation cases were associated with short *in situ* duration (only 103 days on average). Although the CorMatrix® was degraded in 9 of 12 cases, it was not totally resorbed in any case and remodelling was not associated with organized collagen. It is clear that some failures are associated with adverse inflammatory responses although whether these tissue reactions are causative remains to be determined.

One very recent report of the histology of CorMatrix® explants from 2 adult patients describes a multilaminar neo-valvular structure, albeit with one of the layers being composed of non-resorbed biomaterial. However, there was little inflammation except at the anastomosis [38]. Two other case reports describe the histological appearances of a clinical CorMatrix® explants [43, 49]: one mentions the presence of mild chronic inflammation in the explant [49] and both report that calcifications were present within the material examined, a feature reported not to occur with CorMatrix® grafts in contrast to autologous pericardium. Taken together, these studies suggest that CorMatrix® may elicit tissue reactions in human subjects after implantation; Rosario-Quinones *et al*. [37] attributed the intense eosinophilia seen in their explants to a hypersensitivity reaction, perhaps to α-gal epitopes present in the porcine, but not in the human, intestine. As noted in this review, it is also noteworthy that of the

preclinical studies (listed in Tables 1 and 2), only xenogeneic implants elicited measurable inflammatory responses to porcine SIS and SIS-ECM.

In summary, there are few reports of complications when CorMatrix® is used in the low pressure, usually extracardiac environment (i.e. veins), but when used at higher pressure intracardiac sites such as the aortic valve or in semilunar valves, complications are more likely to occur. However, given recent data suggesting that CorMatrix® may elicit significant inflammatory reactions, there is a need to conduct more histopathological evaluations of explant material in order to shed light on this controversy. Further prospective randomized clinical trials to compare patch materials at different sites are needed, and pathological evaluation of explant material in cases of reoperation or failure should be undertaken to better understand how CorMatrix® really behaves in the complex milieu of the human cardiovascular system.

CONCLUSIONS

Porcine SIS-ECM has been used for over 20 years in a range of cardiovascular applications. The preclinical and clinical results support the notion that CorMatrix® may possess many features of an 'ideal' biological scaffold: its intrinsic biological properties render it strong and durable; it has been used in a wide range of clinical applications at different sites and it is easy to manipulate during surgery; the clinical data that are favourable (by no means all) suggest that it does not undergo undue calcification, thickening or retraction; and it has successfully been used in the paediatric population, albeit with the caveat that the explanted tissue did not have a native three-layer structure and inflammation was present.

Although some results have been positive, significant uncertainties still remain—not least from recent prospective data—about whether its clinical performance really meets the expectations set by theory and *in vitro* and *in vivo* preclinical studies. This is mainly due to a lack of large-scale clinical studies, which has been exacerbated by poor systematic reporting of functional and pathological findings in both human and animal studies. Uncertainties also remain about the remodelling process, particularly in the clinical setting and with regard to implant resorption and immunogenicity. This doubt about clinical efficacy raises questions about whether larger clinical studies in the paediatric population are ethically justifiable, given that the reoperation rate for CorMatrix® failure is up to, or even exceeds, 10% in this population in some studies.

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