Review Article

Bioengineered tissue solutions for repair, correction and reconstruction in cardiovascular surgery

Laura Iop, Tiziana Palmosi, Eleonora Dal Sasso, Gino Gerosa

Cardiovascular Regenerative Medicine, Department of Cardiac, Thoracic and Vascular Surgery, University of Padua and Venetian Institute of Molecular Medicine (VIMM), Padua, Italy

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Correspondence to: Laura Iop. Cardiovascular Regenerative Medicine, Department of Cardiac, Thoracic and Vascular Surgery, University of Padua and Venetian Institute of Molecular Medicine (VIMM), Via G. Orus 2, 35129 Padua, Italy. Email: laura.iop@unipd.it.

Abstract: The treatment of cardiac alterations is still nowadays a dramatic issue in the cardiosurgical practice. Synthetic materials applied in this surgery have failed in their long-term therapeutic efficacy due to low biocompatibility and compliance, especially when used in contractile sites. In order to overcome these treatment pitfalls, novel solutions have been developed based on biological tissues. Patches in pericardium, small intestinal submucosa, as well as engineered tissues of myocardium, heart valves and blood vessels have undergone a large preclinical investigation in regenerative medicine studies. Clinical translation has been started or reached by several of these new bioengineered treatment alternatives. This review will describe the preclinical and clinical experiences realized so far with the application of biological tissues in cardiovascular surgery. It will depict the progressive steps realized in the evolution of this research, as well as it will point out the challenges yet to face in order to generate the ideal biomaterial for cardiovascular repair, corrective and reconstructive surgery.

Keywords: Pericardium; small intestinal submucosa; myocardium; heart valves; blood vessels

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Introduction

Cardiovascular diseases are among the leading mortality cause in the World and the use of cardiac patches remains among the main therapeutic solutions for their surgical treatment.

Currently applied cardiovascular patches can be of synthetic origin or biological derivation. Synthetic materials like Dacron® (Koch Industries, Inc., Wichita, KS, USA) are rigid and not flexible, thus unable to contract simultaneously with the beating heart tissue. Moreover, their biocompatibility is poor. In fact, they are known to induce local inflammatory reactions and endocarditis in the recipient patient (1). As a consequence, thickening, fibrotic processes and calcification may occur, as well as no regeneration of the autologous tissue (2).

A greater clinical interest has been devoted to biologically derived patches and substitutes. A large class of biological devices has been applied or is presently under study for the repair, correction and reconstruction of cardiovascular alterations. Autologous and xenogeneic pericardia, porcine intestinal submucosa extracellular matrix (SIS-ECM), as well as tissue engineered myocardium, blood vessels and heart valves have been proposed as more valid alternatives to synthetic materials for several surgical indications.

This review will offer an overview on the different solutions of regenerative medicine tested at the preclinical level and will discuss the outcomes of their clinical use in the cardiovascular surgical field.

Pericardial patches (PP)

Preclinical experiences

The first application of a chemically stabilized animal pericardium dates back to 1971, when the Ionescu-Shiley bioprosthetic heart valve, manufactured with this tissue, was implanted clinically in aortic position (3). The successful results achieved in the following years encouraged the rapid spread of pericardial xenografts in several other cardiovascular applications (4). The wide use in vascular surgery, correction of congenital and acquired heart diseases, and pericardial closure following heart procedures was sustained by its potentially unlimited availability, low antigenicity thanks to glutaraldehyde (GA) shielding, modest infection incidence, easy handling, and minimal suture line bleeding.

The early literature about the chemical modifications and biological behavior of GA was characterized by the paucity of *in vitro* studies. Initially, cardiac surgeons were more interested about feasibility and functionality of PP implants rather than on their actual biological effects.

Recently, cytotoxicity of commercially available GA-crosslinked bovine pericardial patches (BPPs) was demonstrated by *in vitro* direct contact and extract assays of murine fibroblast culture. Moreover, the activation of human macrophages associated with the release of inflammatory cytokines was observed (5). These results were documented also for commercial GA-treated xenogeneic heart valves by quantifying the ratio among anti-/pro-inflammatory cytokines (6).

Early *in vivo* animal experiments were performed mainly in dogs and revealed the most typical drawbacks related to the use of bioprosthetic GA-treated tissues at the early and mid-term evaluation. GA-treated xenografts were tested to close defects of pericardium (7-9) and atria (9-11), as well as substitutes of mitral chordae (8) and aorta (9). These materials progressively caused fibrotic deposition, patch thickening and shrinkage, chronic inflammation, and several grades of calcification not related to the sutures. Adherences to the epicardium were found in case of pericardial substitutes (7,8) and were particularly severe when cardiopulmonary bypass was performed (12). After one year follow up, they appeared, however, attenuated in respect to those generated with synthetic materials (13).

In general, the comparison of different synthetic polytetrafluoroethylene (PTFE), woven Dacron® and biological materials (canine autologous atrium and pericardium, bovine pericardium) revealed that these severe complications were common and independent from the type of substitute (10,11). Furthermore, the distribution of calcific foci was reported as strongly correlated to implantation site, function, and bloodstream contact with these patches (8,9).

Subcutaneous implants in rats allowed to better investigate the correlation between GA exposure and occurrence of calcification, substantiating the association between treatment duration and rate of BPP mineralization (14,15).

Despite the wide use in the last 50 years, there are still open issues and controversial opinions regarding the effective long-term durability and the biocompatibility of aldehyde-treated PPs. Indeed, GA treatment does not completely prevent host's response and foreign body reactions may occur following implantation (16,17). Nevertheless, the progressive evolution of GA-treated PPs demonstrated their improved performances in terms of hemocompatibility and tissue compliance in respect to the synthetic ones, rendering ordinary their clinical practice.

Clinical applications

Nowadays, the biomedical industry offers a broad range of commercial products based on xenogeneic pericardia, accessible from several species and supplied with different chemical treatments (*Table 1*). Most of these products are GA-treated in order to induce an immunologic barrier, but also to increase their durability and mechanical stability. Moreover, in the last years, the manufacturers began to finally perceive the critical issues related to the indiscriminate use of chemical crosslinking and responded with anti-calcification treatments and procedures directed to stabilize free aldehydes.

Although these biomaterials generally present low thrombogenicity and convenient hemodynamics performances, unfavorable outcomes, such as restenosis, intimal hyperplasia, pseudoaneurysmal deformations, shrinkage, rupture, cartilaginous degeneration, thrombosis, dystrophic calcification, and fibrosis, are not rare reported events.

Pericardial closure

One of the early PP applications was the pericardial closure in case of unfeasible primary suture. Although there is a lack of medical consensus on this procedure, it contributes to prevent cardiac herniation, tamponade, and sternum adherences that might increase post- and re-

Table 1 Overview of the pericardial patches currently available on the market

Product name	Manufacturers	Tissue source	Pre-commercial treatment
CardioCel	Admedus, Malaga, Western Australia	Bovine pericardium	Decellularized, GA-crosslinked and treated with a proprietary anticalcification treatment (ADAPT®) (18)
Edwards Bovine Pericardial Patches	Edwards Lifesciences Irvine, California, USA	Bovine pericardium	GA-crosslinked and treated with a proprietary anticalcification treatment (XenoLogiX) (19)
Matrix Patch™	Auto Tissue Berlin GmbH	Equine pericardium	Decellularized (20)
No-React®	BioIntegral Surgical Mississauga, Ontario, Canada	Porcine pericardium	Proprietary method, heparin based, to prevent the reduction of aldehyde release of GA-crosslinking treatment (21)
Peri-Guard	Baxter International Inc. Deerfield, Illinois, USA	Bovine pericardium	GA-crosslinked (22)
Peripatch-EQ Peripatch-BV	Neovasc Inc. Richmond, British Columbia, Canada	Equine and bovine pericardium	Proprietary method (23)
PhotoFix®	CryoLife Kennesaw, Georgia, USA	Bovine pericardium	Decellularized and photo oxidized (24)
Vascutek Porcine Pericardial Patch	Vascutek LTD Inchinnan, UK	Porcine pericardium	GA-crosslinked (25)
SJM Biocor™ Patch	St. Jude Medical Saint Paul, Minnesota, USA	Bovine pericardium	GA-crosslinked (26)
SJM Pericardial Patch with EnCap™ AC Technology	St. Jude Medical Saint Paul, Minnesota, USA	Bovine pericardium	GA-crosslinked and treated with a proprietary anticalcification treatment (27)
SURGIFOC	FOC Medical Buenos Aires, Argentina	Bovine and porcine pericardium	GA-crosslinked (28)
dCELL® vascular patch	Tissue Regenix Group PLC	Porcine pericardium	Proprietary decellularization process based on SDS and protease inhibitors (29)
Vascu-Guard	Baxter	Bovine pericardium	GA-crosslinked (30)

operative mortality and morbidities, such as hemorrhages and damages to the heart and great vessels (31). In the past, several attempts of pericardial closure were performed with synthetic materials, as Silastic (32), Dacron® (33,34), silicone rubber (35), polyurethane (36), and PTFE (36-38), and with biological tissues, as pleura (39), *dura mater* (34), and *fascia lata* (40-42). Indeed, PPs of bovine, porcine, and equine origin were mostly used with this aim. As an example, the application of GA-treated porcine PPs (PPPs) was clinically successful after 9-month surgery (7) but, in the long term (more than 4 years), it revealed to cause a severe epicardial reaction (43). Results with GA-treated BPPs were controversial. Yakirevich *et al.* disclosed freedom from adhesions and immunoreactions in patients re-operated after 7 years (44), while Skinner and colleagues reported a strong epicardial inflammation (45), which rendered necessary the complete patch removal (46). GA-treated equine pericardial patches (EPPs) demonstrated to be a valid alternative, thanks to the low rate of bioprosthesis-related complications and reduced adhesion in recurrent sternotomy (47).

Congenital and acquired heart defects

GA-treated autologous PPs (APPs) or BPPs were used to correct a wide spectrum of congenital heart defects because of their versatility and easy handling. During the surgery of Tetralogy of Fallot, these patches were applied to reconstruct the right ventricular outflow tract (48) but pulmonary incompetence arose due to the absence of contractility (49). The main side effect observed was the aneurysmal dilatation of the bioprosthetic tissue, which was demonstrated to be size-related to the patch itself (50). For equivalent

considerations, correction of congenital septal defects using autologous and GA-treated heterologous pericardia might undergo the same post-surgery evolution (51-53). Schoof *et al.* reported absent inflammation and tissue thickening of chemically untreated APPs, thanks to the progressive adaptation of the biomaterial (54). After 60 months of follow up, no calcifications were disclosed for BPPs used for the correction of various congenital heart defects (55). Conversely, a case report accounted for the early degeneration of a GA-treated BPP used for mitral valve augmentation. Calcification, fibrosis, pannus formation, thickening, neovascularization, disruption of patch microscopic structure but no immunogenic response were described (56). A comparison between GA-fixed BPPs and cryopreserved homografts used for aortic reconstruction in the correction of the hypoplastic left ventricle (LV) demonstrated that xenografts were less immunogenic, had a similar post-operative recurrent obstruction, besides being cost-effective (57).

Other applications of PPs in congenital heart diseases were represented by the corrections of tricuspid insufficiency in Ebstein's anomaly (58), double outlet of the right ventricle (59,60), complete atrioventricular septum defect (61,62) and reconstruction of the bicuspid aortic valve (63).

PPs were also adopted in valvuloplasty intervention in case of limited amount of autologous tissue. Aortic valvuloplasty with autologous GA-crosslinked APPs generally demonstrated to be effective in the correction of aortic structural defects (fenestration, bicuspid valve) and degenerations (calcification and prolapse) up to 7 years (64). As a result of the GA-treated APP implantation, the timing of re-intervention for pediatric patients was postponed up to 15 years with outcomes superior to the ones obtained in Ross operation and balloon valvuloplasty (65). These biomaterials were also used to enlarge the annulus prior to valve replacement (66).

In the correction of rheumatic disease sequelae, GA-crosslinked APPs served to prevent damages to the conductive system during procedures of tricuspid valve replacement (67), as well as they were adopted to avoid the rupture of the left ventricular myocardium during mitral valve replacement following its calcification (68). Furthermore, in the settings of myocardial infarction, GA-treated APPs (69) or EPPs (70) were applied to elude cardiac rupture.

The dilated wall of ventricular aneurysm might be repaired by isolating the deformation through the endoaneurysmorrhaphy technique. In this case, the application of synthetic substitutes was very often associated with post-operative comorbidities, such as infections and compliance disparity, while the use of crosslinked APPs turned to be more effective, leading to moderate calcifications only (71-73).

As a general consideration, the use of APPs is associated to a lower infection rate, being advantageous also to reconstruct the LV in those patients with severe sepsis (both endocarditis and myocardial abscess) and, hence, considerably reducing the risk of relapses (74). A similar resistance in infected fields was demonstrated for BPPs (75,76). Commonly, the repair of aortic and mitral valves with both bovine and autologous GA-treated PPs increased patient survival over the replacement (77,78).

Vascular surgery

PPs were introduced in vascular surgery in 1991 since their compliance is more similar to native vascular tissues than to artificial grafts. As in other surgical uses, GA treatment helped to stabilize PP tissue and prevent aneurysmal dilatations. In particular, BPPs presented superior hemostatic properties and inferior suture line bleeding in respect to Dacron® (79).

One of the main drawbacks correlated to the use of GA-treated grafts and patches is, however, their challenging endothelialization due to the cytotoxic effects of the gradual and prolonged aldehyde release from the biomaterial surface (80-82). As a consequence, thrombogenicity and graft failure might occur, also as symptomatic of collagen instability with a subsequent predisposition to aneurysmal deformations (83).

In aortic arch and root substitution, GA-treated xenogeneic PPs overcame the limitations of the most common substitute, i.e., Dacron®, such as poor hemostasis and handling. The mid-term follow up evidenced appropriate performances without calcification or tissue deterioration (84). GA-crosslinked PPs were also applied for the reconstruction of valvulated conduits as aortic substitute in combination with porcine stentless aortic cusps, showing no tissue deterioration after more than 5 years from surgery (85).

A preliminary study on the usage of BPPs compared with autologous vein patches for endarterectomy of atherosclerotic carotids revealed that restenosis was uniformly present in both groups but no aneurysms were detected in case of the pericardial substitutes (86). No ruptures, aneurysmal dilatation, occlusions, and infections

were reported by Grimsley *et al.* for implanted GA-treated BPPs at 54 months from carotid endarterectomy (87). In this surgery, BPP-based treatments demonstrated to be durable on both short and long terms (88), with a very low rate of stenosis (89,90). In the early and mid-term comparison, the performance of crosslinked PPs was similar to the one of Dacron®, PTFE, and autologous veins if re-stenosis rate and perioperative bleeding are considered (91,92). Even if generally uncommon, few exceptions of infections and aneurysmal formations have been described (93).

Another successful surgical indication for the use of GA-crosslinked APPs is the reconstruction of the pulmonary artery and superior vena cava (94), as well as angioplasty, as an alternative to bypass grafting (95).

Acellular patches

GA-treated PPs are non-viable tissues, difficultly prone to endothelialization and unlikely disposed to remodeling and regeneration for a full repopulation and integration with the recipient's body.

Besides the countless attempts to reduce calcification potential (96-102) and cytotoxic aldehyde release from crosslinked biomaterials (103,104), new strategies aim at obtaining an improved tissue biocompatibility by means of decellularization. Ideally, decellularization procedures generate scaffolds freed from potentially immunogenic and pro-calcific cell elements, while preserving intact the properties of the ECM through the application of physical, chemical and/or enzymatic treatments (6,105). Several techniques have been proposed for pericardial tissues (6,106-109) and some of the manufactured products have already reached the market as GA-free, decellularized PPs (*Table 1*).

In particular, CardioCel found application for the correction of several congenital heart defects in pediatric patients, showing no evidence of calcification, infections, thickening or hemodynamic alterations on the short and long observations (110,111). Furthermore, explanted patches showed intima formation, neovascularization, and remodeling (112).

SIS-ECM patches

Preclinical experiences

A great attention has been recently addressed to the patches derived from the SIS of porcine origin. This tissue is particularly promising because of several advantages, including superior biocompatibility, manageability, time durability and potential to tissue remodeling and regeneration, with inferior proneness to scarring and calcification. For its peculiarities, SIS has immediately gained wide acceptance within the preclinical and clinical communities.

SIS derives from the jejunal portion of the porcine small intestine, being localized between the mucosal and muscular layers. In order to render it more immunocompatible, several decellularization treatments were developed (113-116). Different preparations are already commercialized as ECM scaffolds of SIS, the so-called SIS-ECMs. They consist of specific matrix proteins, as 90% collagen (predominantly type I with minor amounts of types III, IV, V and VI), fibronectin and laminin, and other non-fibrillar support structures, as glycosaminoglycans (e.g., heparan sulfate and hyaluronic acid, thought to help regulating the matrix density and inhibiting scar formation during the healing process) organized in proteoglycans, as well as growth factors and adhesion molecules able to promote a 'constructive' remodeling (117-122). The collagen fibers of SIS are preferably oriented along the longitudinal axis of the small intestine. This is the result of two types of collagen fibers that are aligned roughly 30° respect to the longitudinal axis of the small intestine (123,124). Probably, this particular spiral arrangement of the collagen fibers facilitates dilatation and retraction, i.e., the typical movements of the small intestine in the transport of the bolus along the digestive lumen. Understanding the alignment of ECM collagen fibers is important for the design of the ideal mechanical behavior of the scaffold and therefore of its strength.

In its acellular version, SIS has an extremely reduced immunogenic behavior (125). In addition, the bioinductive properties of the SIS-ECM confer to this scaffold an important ability of tissue remodeling. In fact, it promotes the viability of the adjacent native tissue. The high regeneration potential inherent to SIS originates from a decellularized tissue very rich in growth factors, such as vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (b-FGF), and transforming growth factor beta (TGF-β), but also owning a high biodegradability. During the scaffold degradation, a release of VEGF, b-FGF and TGF-β occurs, which induces angiogenesis, mitogenesis, and cellular differentiation in a remodeling process stimulating scar development and, thus, encouraging the development of native tissue (119). As previously described (122,124), the dynamics of the

bioinduction process is not yet well deciphered but several hypotheses have been formulated, one not excluding the others. Following the first of these, ECM scaffold degradation occurs through the action of enzymes and monocytes, differentiating in macrophages with M2 phenotype rather than M1. The M2 phenotype stimulates remodeling and integration of the matrix within the tissue through the release of anti-inflammatory cytokines (IL-10 and TGF-β), while the M1 macrophage promotes the release of acidic enzymes that degrade the matrix, as well as the secretion of pro-inflammatory cytokines (126,127). Secondly, the release of growth factors, such as VEGF, TGF-β and other peptides (e.g., endostatin and angiostatin), from the degradable ECM might induce this process (124). As third, the infiltration of the recipient's cells, including bone marrow circulating ones, might support long-term tissue remodeling (127).

CorMatrix® (CorMatrix Cardiovascular, Inc., Roswell, Atlanta, and Alpharetta, GA, USA) is one of the commercial SIS-ECM products to have found large application in cardiovascular surgery. It is marketed as a decellularized porcine SIS material, after treatment of the native tissue with proprietary techniques and following folding in four or six layers, pressed together to form a single membrane of around 100 μm-thickness thanks to the imposition of 1,200 mmHg pressure (121,128). The lyophilized CorMatrix® is available in two sizes and needs to be rehydrated (10 minutes at room temperature in a sterile saline solution) to return flexible and elastic before its application.

Since the beginning, CorMatrix® attracted the interest of scientists and clinicians for its abilities to favor migration, cell growth and differentiation thanks to its three-dimensional structure and to the growth factor content. These features promote, in turn, tissue remodeling, minimizing inflammatory responses by the recipient, as recently reviewed by Mosala Nezhad *et al.* (122). In particular, CorMatrix® is endowed with many characteristics of the ideal scaffold. Its biological and structural properties make it strong and durable over time.

A great number of preclinical studies on different animals evidenced the promising features for the application of SIS scaffolds in the clinical practice. Thanks to a detailed histopathological analysis, it appeared clear that an active remodeling process was undergone on porcine SIS-ECM explants, as proved by surface re-endothelialization, repopulation of the matrix with engrafted cells (fibroblasts and smooth muscle cells) and neoangiogenesis.

The first SIS study in the cardiovascular field was realized in 1989 when Badylak *et al.* tested the use of autologous SIS as a large diameter vascular graft (10 mm) in the canine sub-aorta model. This sensibly improved success rates in this vascular graft surgery with endothelialization of the SIS graft surface and no infection or intimal hyperplasia (125).

A study demonstrating the good perspectives of CorMatrix® cardiovascular use was provided by Mosala Nezhad *et al.* (129): they implanted four different biomaterials, including this commercial SIS-ECM, in the porcine subcutaneous model with a follow up of 12 months after grafting. CorMatrix® underwent a gradual and consistent resorption without leaving residues. In addition, a progressive attenuation of inflammatory and fibrotic responses was documented, facilitating cell migration and subsequent formation of a new viable tissue.

Another successful preclinical experience with this SIS-ECM was described by Padalino *et al.* (121). They evaluated its efficacy as a possible patch in cardiovascular reconstructive surgery, grafting CorMatrix® into the abdominal aorta in a genetically modified rodent model (GFP-transgenic rat). This study stems from the need to find a biological tissue capable of adaptation to the recipient's somatic growth. This ability is often not possessed by other bioprostheses, rendering necessary re-do procedures during the physical development of the pediatric patient. Histopathological analyses of explanted SIS vascular grafts revealed no inflammation or calcifying degeneration, as well as significant neoangiogenetic remodeling and tissue re-endothelialization, originating from the native tissue at the patch graft site.

For the repair of the carotid artery, Fallon *et al.* implanted CorMatrix® (6-ply) as patch in the sheep model. The initial stenosis observed after one month completely disappeared at 90 days from grafting. In addition, a remodeling process interested the graft with SIS-ECM resorption, collagen deposition, endothelialization, neoangiogenesis, and no calcific degenerations (128).

Of all preclinical studies published on SIS-ECM, only one disclosed negative outcomes. In fact, Pavcnik *et al.* demonstrated a high failure rate (70%) at 3–4 months in an ovine carotid graft model due to dilation, stenosis, dissection and aneurysm formation. The authors hypothesized that the possible causes for graft failure could be related to the animal model, the relatively extended length of the graft (10 cm) and the surgical technique, as well as the response to the SIS-ECM material (130).

Clinical applications

Collagen-based connective tissue SIS-ECMs have been applied for over 20 years in the clinics for soft tissue repair and reconstruction in surgery applications in the fields of cardiovascular system (131,132), integument (133,134), body wall (135,136), urinary bladder (137,138), rotator cuff (139,140), intestine (135,141,142), urethra (143), and diaphragm (144). Besides Cormatrix®, already described in the previous section, several commercial products of acellular SIS-ECM are currently available (e.g., Surgisis®, Durasis® and Stratasis®, Cook Biotech, Lafayette, IN, USA; Restore®, DePuy, West Chester, PA, USA). A detailed list of products with information on manufacturers and pre-commercial manipulations can be retrieved in the reviews by Badylak's group (124,126) and Scholl *et al.* (145).

Clinical results with Surgisis® for the treatment of carotid endarterectomy in 76 patients were reported by McCready *et al.*: 7 out of all patients were diagnosed with an asymptomatic pseudoaneurysm, which caused the suspension of the trial. Histopathological analysis revealed a robust presence of myofibroblasts, while biomechanical testing evidenced a strong lot-to-lot variability in the elastic properties of the product (146).

The Food and Drug Administration approved in 2010 the clinical use of Cormatrix® for cardiac and extracardiac indications. Commercialized firstly for the closure of the pericardium, its authorized application was then extended to the repair of intracardiac defect, aortic and great vessels thanks to its high manageability. To date, CorMatrix® has been applied in congenital cardiac and vascular surgery (145,147,148), pericardial reconstruction (149), intraventricular repair (150), arterial and valvular reconstruction in both adults and children, also in the case of endocarditis (151-154), acquired vascular defects at different sites (151) and repair of damaged myocardium after infarction (155). These clinical uses are all facilitated by a large scale manufacturability according to high quality control, thereby ensuring a continuous and standardized supply of material to surgeons.

However, Cormatrix® application in humans did not show the same encouraging outcomes reported in preclinical studies. Several trials have demonstrated that an intense inflammatory response was present after patch implantation. For example, in the study by Rosario-Quinones *et al.*, 25 pediatric patients were treated with CorMatrix® patches (CorMatrix®, Atlanta, GA, USA) for repair of congenital heart malformations. Six of these grafted patients were submitted to re-do intervention and generally, all developed an intense inflammatory infiltration, prevalently of eosinophil type, as well as fibrosis. The severe eosinophilia observed in these explants was correlated to a hypersensitivity reaction to α-gal epitopes (156). These antigens are exposed on the cell surface of porcine tissues, but not on the human counterparts. Thus, this allergic response has to be attributed to the CorMatrix® itself.

In another study, Mosala Nezhad *et al.* used CorMatrix® for the bicuspidation of a severely stenotic unicuspid aortic valve in a 12-year-old boy. In the long-term follow up realized, CorMatrix® remained stable for 2 years. After 4 years from the grafting, the valve underwent complete calcification, fibrotic degeneration, retractions and an intense inflammatory infiltrate (157), rendering necessary a re-intervention.

Deorsola *et al.* applied CorMatrix® to enlarge the isthmic narrowing with the aim of restoring the structure of the original tissue. In 6 months, some stenotic complications appeared at the patch application site, subsequently re-expanded by angioplasty (158). In the case study report by Eckhauser *et al.*, CorMatrix® SIS-ECM (CorMatrix Alpharetta, GA) was for the first time used to reconstruct a traumatic rupture of the aortoinnominate artery (also called brachiocephalic arterial trunk) of a pediatric patient in an emergency intervention. This study highlights the safety, feasibility and usage readiness of CorMatrix® in major arterial reconstruction, also in urgency medicine. However, it is important to note that there are no significant long-term data to support the benefits of this material in artery reconstruction (151).

Quarti *et al.* adopted CorMatrix® ECM in 26 patients for cardiac tissue repair and pericardial closure. No major, post-operative death complications or calcifications were reported but, even in this case, the follow-up length was only 25 months, so too short to evaluate the long-term functionality of this valve repair (147).

All these studies evidenced the main downside in the use of CorMatrix®, i.e., the inflammatory response, often intense and predominantly eosinophil, leading to severe stenosis and complete calcification of the patch (156,157). In addition, no reabsorption of the implanted material, minimal or totally absent tissue remodeling and negligible reconstruction of native tissues were described (158). In all cases, no systematic and long-lasting follow-up demonstrating real and proven clinical efficacy was provided.

Although some reported data are optimistic, the uncertainties on the clinical performance remain, as long

as there are no large scale trials and consequent systematic follow-up. In addition, there is still a lacking consensus on robust protocols aimed at quantifying the pathological and tissue repair process, as well as the host's immune response mechanisms towards SIS-derived patches. Nevertheless, this clinical hesitation is also related to critical ethical doubts about the trial extension to the pediatric population, given that the reoperation rate due to Cormatrix® failure is equal or even higher than 10% for this population.

Bioengineered heart tissues

Preclinical experiences

In the decades around the years 2000, an incredible ferment was generated around the possibility to clinically treat the dramatic consequences of myocardial ischemia with cell cardioplasty. In this therapeutic vision, lost cardiomyocytes could be replaced by the infusion of exogenous cells, as supported by the positive results of preclinical experiments (159-162). In the in-human translation of this concept, skeletal myoblasts, as well as stem cells of hematopoietic, mesenchymal, bone marrow and cardiac origin have been applied in the setting of acute or chronic cardiac ischemia (163-170). Generally, the outcomes of these clinical trials resulted to be not sufficient to restore heart global function, even if a minor to moderate increase of the ejection fraction was documented. The initial hypothesis of transdifferentiation of injected cells into contracting cardiomyocytes was not proved, apart for those cytotypes endowed with an original cardiac commitment. Moreover, the ischemic microenvironment characterized by inflammation, hypoxia and absence of nutrients was not ideal to maintain the viability of infused cells and/or favor their participation to healing. Paracrine effects of cell therapy were therefore the only responsible for the mild amelioration of the ischemic heart function.

The modification of the *milieu* became the essential step towards the target of cardiac myocardium reconstruction. The treatment paradigm shifted from the sole cell therapy to tissue re-establishment by means of cardiac tissue engineering (TE). As firstly described by Langer and Vacanti, the engineering of a tissue can be achieved by opportunely combining and stimulating cells and scaffolds in order to generate a mature and functional bioequivalent (171). First attempts with biomaterial scaffolds were performed with meshes wrapped around the ischemic ventricle to prevent its inexorable dilatation. LV restraints, developed in polypropylene, polyester and recently nitinol, demonstrated to be efficacious in reducing the end-systolic and -diastolic volumes of ischemic ventricles in animal models and clinical trials (172-174), but did not receive further attention for a routine in-human application due to the invasive cardiosurgical intervention.

The classic concept of TE was, instead, widely explored at the preclinical level. Through a multidisciplinary approach, novel solutions were designed and tested in order to offer more biocompatible and viable alternatives to so far used treatments. Scaffolds, cells and stimuli were selected among the several options on the basis of specific criterions, among which their bioactivity and non-immunogenicity. As in the case of cell therapy, cellular elements were chosen on their ability to survive, transdifferentiate into cardiac cytotypes, as well as integrate into the host tissue. Nevertheless, preferred scaffolds had to be biodegradable and easily vascularizable in order to prevent occurrences of core necrosis. First, the ability to be not seen by the recipient's immune system, i.e., biomimesis, was also retained to be an essential property. More recently, the advances on the understanding of the response to implanted biomaterials have evidenced a peculiar role of inflammation and immunoresponse exerted by M2 macrophages in the tolerance/integration process leading to regeneration. Especially in the case of myocardial reconstruction, the *in vitro* integration of cells and scaffolds has to allow the establishment and maintenance of electro-mechanical coupling and pulse propagation. In order to achieve such an objective, the provision of a specific biochemical, biomechanical and electrical conditioning is usually performed with a bioreactor, able to reproduce *in vitro* the physiological environment of the tissue to be reconstructed.

First TE experiences faced the dramatic problem of core necrosis developing soon cell death when the thickness of manufactured tissues exceeded 100 μm. Indeed, the technology proposed by Zimmermann and Eschenhagen in 2000 revolutionized the myocardial TE world. This group advanced a novel concept of myocardial tissue construct, i.e., the engineered heart tissue, a combination of contractile rings realized in Matrigel, i.e., an immature ECM secreted by murine fibroblasts, and neonatal rat cardiac myocytes, able to develop a force superior to 2 mN following mechanical and/or chemical conditioning (175). In a further evolution of this approach, they went closer to the clinical translation by the replacement of the rodent elements with human cardiac myocytes and fibrin (176).

In the TE formulation of a functional tissue, the

provision of adequate stimuli is essential but still a crucial technical issue, especially when driving differentiation of particularly immature cells. Recapitulating in a bioreactor the complex native mechanotransduction is still a difficult task although the increased knowledge in this field. The application of mechanical stimulation is essential in inducing cell alignment and force generation but needs to be precisely tuned to prevent undesired differentiation, fibrotic tissue development and/or apoptosis. A combination of neonatal cardiomyocytes and endothelial cells has demonstrated under cyclic strain to increase the alignment towards the native heart's one, in respect to none or static conditioning (177).

As for LV restraints, not all TE strategies were devised for the *in vitro* reconstruction of the tissue of interest. The development of classical TE equivalents requires a relatively long process, which might be demanding to realize, as well as time-consuming due to extensive culturing in bioreactor. Hence, an associated risk of traditional TE might be the inability to obtain a mature and functional tissue substitute at the end of the conditioning. In addition, developed TE tissues could be available only for elective surgery, thus not representing a therapeutic option for patients to be urgently treated.

In order to skip this limitation, a more straightforward approach was conceived, i.e., *in situ* TE, combining the scaffold and/or the cells directly in the surgical theatre. With such an approach, several biomaterials alone were tested. The formulation of biomaterials available for *in situ* TE was very similar to the one adopted for classical strategies. In particular, hydrogels and patches in natural materials were widely used (178,179). Several types of bioconjugates were generated able to modify their state (liquid to hydrogel) in response to environmental or temperature changes, in addition to gradually release various pro-regeneration proteins. Alginate sulfate was used to create multifunctional scaffolds which, upon progressive degradation, could release drugs and/or growth factors. This was the case of the combined IGF-1/HGF hydrogel: an immediate discharge could be generated for the first growth factor to prevent cell death and increase survival, while a slower release was induced for the second one in order to enhance vascularization and prevent fibrosis (180).

Thermoresponsive polymers were also employed for a different scope, i.e., the creation of sheets of specialized cells. Synthetic materials, as poly(N-isopropylacrylamide) (PIPAAm), were applied by the Japanese group of Okano to create layers of cardiac myocytes. In a traditional culture system, cells need to be detached from their support by the enzymatic effect of trypsin in order to be further used. This treatment induces, however, the rupture of cell-cell and cell-ECM junctions, particularly essential for cardiac syncytium maintenance. Thanks to the PIPAAm technology, a modification in temperature from 37 to 20 ℃ is per se sufficient to cause the detachment of the entire cell layer, by inducing a variation of the polymer hydrophobic properties. As demonstrated in their long experience with PIPAAm, the mono- or multisheets of cardiomyocytes can be submitted to biochemical stimulation with growth factors, vascularized or even fashioned in tube to shape a cardiac pump, similar to a clinically implanted left ventricular assist device (LVAD) (181,182). Cell sheet technology has been realized with several cell types apart from cardiac myocytes, as for example skeletal myoblasts. Some clinical trials evidenced a risk of arrhythmia generated after cell transplantation of these cells. Not only sheets of functional skeletal myoblasts did not induce ventricular tachyarrhythmias when applied as patch, but also their therapeutic effect could be enhanced when mesenchymal stem cells were added, thanks to their pro-survival and anti-apoptotic effects (183,184).

Such an approach was also pursued to overcome the barrier of vascularization. *In vivo* preclinical evaluation evidenced that, in combination with omentopexy, cell sheets promoted arteriogenesis and ameliorated coronary artery perfusion, by mitigating cardiac hypertrophy and scarring (185).

Apart from thermoresponsive materials, great interest was generated by self-assembling peptides, i.e., amphiphilic molecules able to assemble into nanofibers, membranes and hydrogels in a process strictly depending, among the many variables, on the peptide sequence, concentration, pH and presence of salts. After injection, these self-assembling peptides created a suitable intramyocardial environment for the survival of endothelial cells, by downregulating apoptosis and enhancing the angiogenetic program towards a dense tridimensional (3D) net of capillaries (186,187). The possibility to decorate and biofunctionalize these peptide sequences with growth factors further increase the relevance of a potential application in humans (188).

In this panorama of novel technologies, the introduction of 3D bioprinting has allowed to prototype different cardiac tissue constructs by the aid of computational modeling. Differently from other approaches, especially of vascular reconstruction, the use of 3D bioprinters offers the opportunity to generate complex structures, as ramified arterial trees (189-191). The advantage of the easy

switchable combination of cells and scaffold elements might turn to be also a drawback, since as in other TE modalities, the major difficulty is to reproduce the exact spatial distribution and cell maturation of the native tissue in the generated bioequivalent.

Among all preclinical developments in the regenerative medicine of cardiovascular organs and tissues, the adventure of induced pluripotent stem cells (iPS) has definitely signed a step forward, rendering available very plastic stem cells of adult origin able to differentiate into all cardiac lineages, e.g., cardiomyocytes, endothelial and smooth muscle cells, upon appropriate stimulation (192,193). After combination with cell sheet technology, Kawamura *et al.* demonstrated that generated layers of iPS-derived cardiomyocytes could be applied with successful effects in a porcine ischemic cardiomyopathy model upon combination with flap omentum (194). Moreover, Ogasawara *et al.* evidenced that iPS-derived cardiac myocytes co-injected with Matrigel and pro-survival elements could undergo improved engraftment and maturation, in respect with their combination with other biomaterials, as the hyaluronan-based hydrogel HyStem (195). This represents, however, an obstacle in the future clinical application of this therapy intended for the treatment of myocardial infarction: the potential clinical-grade substitute to the xenogeneic Matrigel demonstrated to possess limited ability in sustaining cell viability and differentiation and, hence, a reduced efficacy as therapeutic alternative. As another drawback, this study revealed also the formation of cartilage tissue in the cell/hydrogel injected area. A severe issue in possible iPS application is represented by the ineffective differentiation into the cells of interest, and in particular into cardiomyocytes, which, in turn, might cause lack of integration and genesis of arrhythmic foci. Okano's group demonstrated that it is feasible to remove undifferentiated elements from fabricated cardiac cell sheets in specific culture conditions of methionine deprivation (196). Such a strategy is particularly appealing in the view of implanting beating constructs able to perfectly integrate within recipient's cardiac tissue.

Clinical applications

The large majority of bioengineered myocardial tissues developed so far has not yet reached the clinical arena. The MAGNUM trial was one of the few studies in which the feasibility of implanting a bioartificial myocardium (collagen matrix plus bone marrow cells) was tested in 10 patients by comparison to the sole cell therapy. No mortality cases were disclosed, ascertaining the safety of the procedure (197). Results at 1 year with these implanted constructs revealed a reduction of LV telediastolic volumes and filling deceleration time, as well as an improvement in NYHA classification and ejection fraction (198).

Cell sheet technology found in-human application, too: multilayers of skeletal muscle-derived cell sheets were implanted in patients with dilated cardiomyopathy, treated with LVAD. Upon application onto the LV anterolateral surface, these engineered sheets integrated and induced angiogenesis, systolic wall thickening and regional wall contractility, allowing LVAD removal in 2 out of 4 patients (199). A larger cohort of patients was evaluated in the study of Miyagawa *et al.* In this phase I clinical trial, 15 and 12 patients with respectively ischemic and dilated cardiomyopathy were treated with the ventricular surface application of autologous muscle cell sheets after left thoracotomy. Patients benefited of the treatment, which in general revealed to be safe and feasible. Particularly in the case of patients with ischemic cardiomyopathy, an increase of the ejection fraction and a decrease of LV end-diastolic volume were found to be statistically significant (200). The procedure was reported to be safe also in the case of patients with severe chronic heart failure. This multicenter, phase II clinical trial evaluated the effects of muscle cell sheets in 7 severely affected cardiopatic patients, which at the end of the study revealed ameliorated NYHA class, increased LV ejection fraction and improved physical function (201).

Apart for cell-based strategies, a different therapeutic approach reached the clinical application, i.e. the use of pure biomaterials. Guided tissue regeneration with alginate has been attempted in several clinical trials. Frey *et al.* injected 1% sodium alginate, mixed with 0.3% calcium gluconate, through the coronary artery of 27 infarcted patients with ST-segment elevation (NCT01226563 clinical trial). Not only tissue permeation was demonstrated after 3 minutes from treatment without adverse events for coronary artery perfusion, but also procedure safety was confirmed at 6-month follow-up (202). The trial was extended internationally, enrolling a total of 303 patients, of whom 201 treated with this novel hydrogel scaffold and 102 assigned to the sham (saline injection). Although safety confirmation, no amelioration of the cardiac function could be appreciated in respect to the control group (203). In the international, multicenter, randomized AUGMENT-HF trial, a hydrogel in calcium alginate, i.e., Algisyl®, was injected in 39 patients with advanced heart failure and compared to a similar group of subjects submitted to the

standard medical therapy. At 1-year follow-up, Algisyl®-treated patients presented NYHA increase and ameliorated peak VO_2 (204,205). A second trial, i.e., AUGMENT-HF II (NCT03082508), is now ongoing to demonstrate safety and efficacy in an estimated enrollment of 280 subjects with heart failure.

Up to now, the few therapeutic regenerative medicine approaches reaching the clinical stage to treat heart ischemia and failure have been evaluated in small trials. It is thus imperative to enlarge the studied cohorts in order to fully evaluate the potential effect of these novel therapeutic strategies.

Bioengineered blood vessels

Preclinical experiences

The same TE concept has been applied not only for the myocardium reconstruction but also for the generation of bioengineered vessel replacements. In the last years of the previous century, the group of Mayer has started to develop novel bioequivalent solutions for both heart valves and blood vessels with the aim to overcome the limitations of non 'living' available prosthetic substitutes. By the combination of synthetic polymers, as polyglycolic acid (PGA) and polyhydroxyalkanoate (PHA), and ovine carotid artery cells, vascular constructs were obtained *in vitro* and implanted into the descending aorta of 7 lambs. While acellular polymeric tubes in control animals lost patency progressively, no aneurysmal dilatation was disclosed for TE vascular constructs, which revealed at the microscopic level formation of collagen and elastin, as well as cell population, both accountable for a biomechanical profile similar to the one of a native vessel (206). In the same years, the group also demonstrated the feasibility to generate pulmonary artery autografts starting from identical biomaterials and ovine artery- or vein-derived primary cells. The replacement of the pulmonary artery in the lamb model showed a maintained patency of the novel vessel with its progressive adaptation to the somatic growth of the animal. Although calcium content was particularly high, no gross calcifications were observed and pulmonary artery tissue appeared to be newly created, in terms of endothelialization and ECM synthesis. Also in this study, the polymeric tube used as control underwent thrombosis and loss of patency (207).

By modifying the formulation of the scaffold, Shinoka and Breuer proceeded in the evaluation of TE conduits as inferior vena cava interposition vessels. TE constructs were realized with PGA, coated with a 10% solution of L-lactide and epsilon-caprolactone, and sheep bone marrow mononuclear cells. After 6 months from implantation in 7 juvenile lambs, implanted grafts revealed physiological increase of the diameter and patency, as documented by magnetic resonance angiography. Analyzed tissue composition and ECM distribution were the typical ones characterizing a native vein, also expressing distinctive markers of normal venous formation (208). The extensive studies of the group led to hypothesize in 2010 a mechanism by which vessel tissue repopulation could occur. Following this hypothesis, the bone marrow cells, initially seeded *in vitro*, abandon the scaffold in favor to monocytes soon after implantation, through a program depending on the secretion of chemoattractants by the first cytotype. In turn, this is followed by the infiltration of smooth muscle actin-expressing cells and endothelialization, with monocytes leaving the tissue after scaffold degradation and ECM synthesis (209). It is fascinating that inflammatory response has been so early identified as the main actor in recipient's tolerance and remodeling of TE constructs, even if this formulated theory is not taking into account the real prominence of the scaffold as inductive element of the entire process (210).

Despite the improved formulation, experiences with the sole scaffold revealed to be particularly disastrous in the creation of novel vessels, especially in presence of small diameters (<6 mm). Moreover, the major disadvantage of PGA use was given by the incomplete degradation of the polymeric scaffold able to sensibly modify the proliferation pattern of smooth muscle cells (211). The group of Niklason strongly contributed to the development of more biocompatible blood vessel equivalents. A new scaffold formulation in glycolide and trimethylene carbonate, eventually added with polyethylene succinate, was compared to the classic PGA, showing similar cell bioactivity, but increased induction of collagen production and improved biomechanical properties (212).

In addition, small diameter bioengineered vessels were grown *in vitro* by combining a natural ECM, as fibrin, with bovine smooth muscle cells and human dermal fibroblasts. Pulsatile stretch applied for 30 days on these constructs was able to induce proper synthesis of ECM main proteins, with newly secreted collagen organized in circumferential distribution. Conditioned fibrin-based vessels developed burst pressure and compliance similar to the native counterparts, as well as appropriate suturable

properties (213).

More recently, this group established a novel approach of blood vessel engineering by using decellularized tissues. Acellular umbilical arteries might be used as small diameter vascular grafts thanks to the maintenance of the biomechanical and bioactive properties of their original ECM scaffolding, as demonstrated by Gui *et al.* after treatment with CHAPS and sodium dodecyl sulfate detergents. These human tubular scaffolds were not only prone to endothelialization *in vitro*, but demonstrated also to be patent for 8 weeks *in vivo* in a rat model of abdominal aorta interposition (214).

Clinical applications

Although in a limited number, first in-human applications have been already registered for both synthetic and decellularized arterial vessels. A tubular scaffold in PGA or in poly-L-lactic acid (PLLA) in combination with epsilon-caprolactone has been seeded with bone marrow mononuclear cells and successfully implanted in 25 pediatric patients with no aneurysmal or calcific degeneration up to 15 years, apart for 7 subjects with asymptomatic graft stenosis (215).

In an observational clinical study, Hopkins *et al.* used decellularized allogeneic pulmonary artery patches (MatrACELL; LifeNet Health, Inc., Virginia Beach, VA, USA) for arterioplasty in 106 patients. No degenerative events were reported during follow up, apart from restricted cases of narrowing of the juxtaductal region, without involvement of the implanted graft or stenosis. These results were particularly significant when retrospectively compared with a similar cohort of patients treated with conventional patches in synthetic material, as PTFE, and with cryopreserved pulmonary allografts (14% patch failure) (216). Interestingly, even if not properly a cardiovascular application, human decellularized vessels were effectively applied as dialysis access in 60 patients (217).

Bioengineered heart valves

Preclinical experiences

As previously anticipated, one of the first heart valve TE experiences was realized by the group of Mayer, who attempted the reconstruction of the right posterior cusp of the pulmonary valve with a PGA tissue construct seeded with fibroblasts and lined with endothelial cells. This study evidenced the feasibility of the procedure, particularly with the use of autologous cells, rather than allogeneic ones (218). Trileaflet valves in nonwoven PGA conditioned in a pulse duplicator with ovine myofibroblasts and endothelial cells for 14 days demonstrated to successfully reconstruct the right outflow tract in an autologous lamb model. In addition, the trilayered architecture of the pulmonary cusp was perfectly recreated by deposition of collagen and elastin (219).

PGA was later modified with other more biodegradable polymers, as PLLA and polyhydroxybutyrate (P4HB). Sutherland *et al.* constructed *in vitro* a valve conduit in PGA and PLLA, which was seeded with mesenchymal stem cells in a bioreactor for 1 month, prior to implantation in the juvenile sheep. Even if luminal surface endothelialization was achieved, the ECM distribution after 8 months *in vivo* did not reflect the anisotropic one of a mature native valve (220). With a similar valve composition and testing model, Gottlieb *et al.* demonstrated progressive decrease of the conduit diameter and cusp length after 20 weeks of follow up (221). The group of Hoerstrup introduced a PGA/P4HB copolymeric heart valve scaffold seeded with different cells types and adapted for several implantation modalities, as recently reviewed (222). In particular, they lately moved to the *in situ* heart valve TE concept, which has been adopted by different groups for ease of fabrication, tissue guided regeneration and off-the-shelf availability.

An extensive line of research in heart valve TE has been dedicated to decellularized tissues for the reconstruction of either semilunar or atrioventricular valves. As in the approach with synthetic polymers, the classical concept of TE was initially pursued to generate *in vitro* living heart valve substitutes (223-225), but it later became clear that the decellularized matrix had a well-defined advantage over other scaffolds, i.e. the maintenance of the original 3D architecture and matrikine cues of the native mature ECM, able to home and guide host's cells to its repopulation (226-228). As we previously discussed (105), the choice of the decellularization formula is, hence, pivotal to profit of the benefits of a original ECM scaffold and, at the same time, to get rid of potentially immunogenic cellular components, whether the initial tissue is of allogenic or xenogeneic nature. Human leukocyte antigens (HLA), alpha-gal and/or Neu5GC sialic acids are, in fact, responsible for rejection responses in allo- and/or xenotransplantation (226,229,230). So far, the only decellularization cocktail of detergents proved to remove HLA and alpha-gal is TRICOL, i.e., a

combination of osmotic shock, sodium cholate and Triton X-100 (226,230).

Clinical applications

Although several engineering strategies were applied, the retraction of the valves realized in polymeric materials represents still a sensible issue preventing their clinical application. More recently, an elastomeric valve scaffold in polycarbonate bis-urea has passed brilliantly the preclinical phase research and will be now studied in a multicenter US clinical trial (231).

The promising preclinical experience achieved during the 1990s with xenogeneic models increased the interest for an immediate clinical translation of decellularized porcine heart valves in order to reconstruct the outflow tract of pediatric patients. Clinical outcomes were catastrophic: a hyperacute rejection induced the rapid failure of these decellularized valve grafts (232), analogously to the one observed for similarly treated bovine ureteric conduits used as arterious-venous grafts in adult patients (233).

While the caution decelerated the research with xenogeneic heart valve conduits in the search for more appropriate immunologic models to evaluate tolerance at the preclinical stage, in-human studies with allogeneic valve substitutes demonstrated to be very successful with nowadays long-term observation in pediatric and adult GUCH patients (234). In the wake of these optimal outcomes, two international clinical trials ESPOIR (NCT02035540) and ARISE (NCT02527629) were launched to assess recurrence of adverse events and freedom from dysfunction in a total of 240 patients, treated with decellularized valve conduits either for right or left outflow tract reconstruction.

A multicenter trial has also recently started for the evaluation of TRICOL-decellularized allogeneic valves and preliminary results are indicative of an adequate performance during the initial follow up (unpublished data from our Centre).

Conclusions

Regenerative medicine scientists have designed several strategies in order to overcome the limitations of synthetic materials in the cardiovascular surgery of repair, correction and reconstruction of structural alterations. Shielding approaches, biomaterial fabrication, decellularization, cell reprogramming and differentiation are allowing, among the others, to biologically engineer tissue equivalents in the search for living, biocompatible and long-lasting functional replacements. Preclinical testing experiences, either *in vitro* or *in vivo*, are generally demonstrating effective cardiovascular tissue regeneration. However, the translation in the human routine therapy might find several hurdles, as first the challenging induction of immunotolerance towards the bioengineered graft. Encouraging outcomes on many TE replacements have been achieved in experimental clinical treatments but, so far, their assessment was limited to a reduced number of patients. Enlarged, multicenter clinical trials will therefore shed light on the real efficacy of these more natural surgical solutions.

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Footnote

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