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REVIEW

The future of heart valve replacement: recent developments and translational challenges for heart valve tissue engineering

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Abstract

Heart valve replacement is often the only solution for patients suffering from valvular heart disease. However, currently available valve replacements require either life-long anticoagulation or are associated with valve degeneration and calcification. Moreover, they are suboptimal for young patients, because they do not adapt to the somatic growth. Tissue-engineering has been proposed as a promising approach to fulfil the urgent need for heart valve replacements with regenerative and growth capacity. This review will start with an overview on the currently available valve substitutes and the techniques for heart valve replacement. The main focus will be on the evolution of and different approaches for heart valve tissue engineering, namely the *in vitro*, *in vivo* and *in situ* approaches. More specifically, several heart valve tissue-engineering studies will be discussed with regard to their shortcomings or successes and their possible suitability for novel minimally invasive implantation techniques. As *in situ* heart valve tissue engineering based on cell-free functionalized starter materials is considered to be a promising approach for clinical translation, this review will also analyse the techniques used to tune the inflammatory response and cell recruitment upon implantation in order to stir a favourable outcome: controlling the blood–material interface, regulating the cytokine release, and influencing cell adhesion and differentiation. In the last section, the authors provide their opinion about the future developments and the challenges towards clinical translation and adaptation of heart valve tissue engineering for valve replacement. Copyright © 2016 John Wiley & Sons, Ltd.

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1. Introduction

Valvular heart disease (VHD) is an increasing health problem in both developed and developing countries and is associated with aging of the population and congenital malfunction (Schoen, 2012). Generally, VHDs are characterized by stenosis and/or regurgitation due to an improper opening and closing mechanism caused by the degeneration and/or calcification of the leaflets. Currently, there are no medical treatments for a dysfunctional heart valve and the development of medical therapies is limited by the poor knowledge regarding the pathophysiology and progression of VHD. In case of severe valvular dysfunction, the replacement of the valve is the most effective solution and is currently performed over 300,000 times each year worldwide (Kheradvar *et al.*, 2015). In approximately 55% of the cases a mechanical valve is used, and for the remaining 45% a bioprosthetic valve is chosen. Besides the individual advantages and disadvantages of these valve replacements, which will be described in section 2, their major drawback is the lack of regeneration potential. Therefore, in this review we describe these valves, together with the nondegradable polymeric valves (Figure 1a–c), as nonregenerative replacements, indicating their incapability to adapt to the remodelling potential and the somatic growth of the human body. The implantation technique has an enormous impact on the design of the valve replacements and on the choice of the prostheses for the patient. For these reasons, the differences between the conventional surgical replacement and the rapidly evolving minimally invasive trans-catheter implantation techniques are reviewed in section 3.

The lack of remodelling and growth potential of the clinically available valve replacements has led to the development of innovative valve substitutes with growth capacity, which will be referred to as regenerative valves (Figure 1 d–f) and reviewed in section 4. To manufacture such regenerative valves, different tissue engineering (TE) approaches have been developed to enable lifelong durability by providing physiological-like haemodynamics, haemocompatibility, integration and regeneration in the recipient.

Importantly, the capability to grow and remodel upon implantation is influenced by the immune response to

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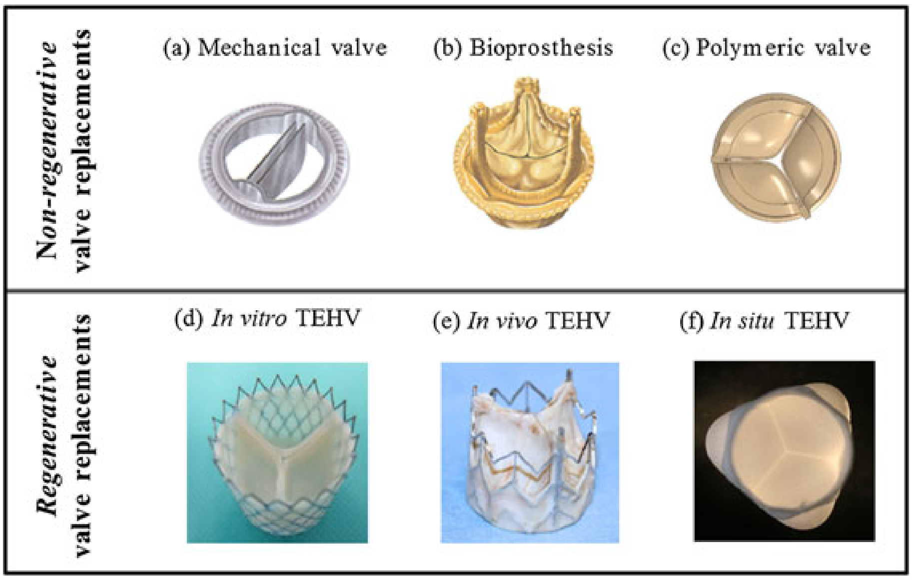

Figure 1. Overview of heart valve replacements: (a–c) standard valves (images adapted from www.pages.drexel.edu) and (d–f) regenerative tissue engineered heart valve replacements (TEHVs). (a) Mechanical valves are durable but they require a life-long anticoagulation treatment. (b) Bioprostheses provide a more physiological haemodynamic profile but they are susceptible to deterioration over time. (c) Polymeric valves, made from nondegradable polymers, are not currently used in clinics due to insufficient mechanical properties. (d) *In vitro* TEHVs are obtained by culturing cells in a scaffold resulting in a living substitute (image courtesy of B. Sanders). (e) *In vivo* TEHVs are created by implanting a mould in the body and taking advantage of the tissue encapsulation of foreign materials (image adapted from (Kishimoto *et al*., 2015) with permission). (f) *In situ* TEHVs, instead, are based on biodegradable porous scaffolds (in figure: an electrospun polymeric valve, image courtesy of M. Simonet, IME Technologies) or decellularized engineered tissues and aim at recruiting cells upon implantation.

the implanted valve. By controlling material properties and/or incorporating bioactive factors into the valve substitute, it will be possible to direct local cellular function, or promote recruitment of specific cell types, as described in section 5. Finally, in the last section, we will discuss the open challenges and the expected future developments towards the successful clinical translation of these innovative and regenerative valve replacements.

2. Nonregenerative valve replacements

The nonregenerative valve replacements (e.g., mechanical, bioprosthetic, and nondegradable polymeric valves) have been developed to ensure long term functionality upon implantation without possibility of integration, remodelling, or growth. Due to this major drawback, in particular young patients have to undergo multiple surgeries and redo interventions to replace the valve substitute over their lifetime, with an increasing risk of morbidity and mortality.

2.1. Mechanical valves

Mechanical valves, currently available in a variety of shapes, sizes and materials, are the gold standard treatment for younger patients (up to 70 years), due to their durability that lead to an average life-span of over 20 years. Since the 1970s, a lot of progress have occurred and mechanical valves developed from the first ball-and-cage valve to the tilting disc design (Zilla *et al.*, 2008). For aortic valves, the most common type is the bi-leaflet valve replacement, which consists of a sewing ring surrounding two semicircular disks generally made by pyrolytic carbon material, resistant to thrombosis (Zilla *et al.*, 2008). However, regardless of the type of mechanical valve implanted, thrombosis is the most significant risk after implantation and the patient must remain on a lifelong anticoagulant treatment. This reduces the patient's ability to participate in activities that can increase the risk of traumatic injuries and, therefore, of major bleeding (Alsoufi, 2014). Moreover, these valves are also contraindicated in young women because the anticoagulation therapy can lead to anomalous fetus development and to increased bleeding risks associated with delivery (Nishimura and Warnes, 2015).

2.2. Bioprosthetic valves

To reduce the thromboembolic complications of the mechanical valves, valve replacements based on xenograft or allograft (homograft) valves have been introduced. Compared to the mechanical prostheses, the geometry and structure of the bioprostheses resemble the native valve. This results in more physiological haemodynamics and reduces platelet adhesion and thrombus formation, mitigating the need for anticoagulants. However, the use of xenogenic or allogenic materials increases the risk for immunogenic reactions and for disease (e.g., the Creutzfeldt–Jakob disease), microorganisms and retroviruses transmission (Neuenschwander and Hoerstrup, 2004). To overcome these limitations, the biological tissue is processed with glutaraldehyde, to obtain a fixed, nonliving and nonresorbable matrix. However, this process causes valve calcification, with altered mechanical properties and compromised functionality that leads to a shorter

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life-span of the valve (Rabkin-Aikawa *et al.*, 2005). For these reasons, their use is particularly limited in paediatric patients who also have a more pronounced immune response that leads to early degenerative failure (Sewell-Loftin *et al.*, 2011).

2.3. Nondegradable polymeric valves

Nondegradable polymeric valves were introduced to combine improved durability with a physiological haemodynamic profile. However, the first polymeric valves with flexible silicon leaflets caused a very high mortality rate due to the valve limited mechanical durability, and thrombogenicity (Roe, 1969). More recently, polytetrafluoroethylene, was used to successfully create leaflets for paediatric pulmonary replacements (Ando and Takahashi, 2009). However, this material was not adopted into clinics, as it previously showed stiffening, calcification (Nistal *et al.*, 1990), thrombosis, and degeneration (Braunwald and Morrow, 1960). Polyurethanes constitute a wide variety of polymers with great biocompatibility, mechanical flexibility, and tunable strength that have been used for the first designs of tri-leaflet valve replacements (Mackay *et al.*, 1996). However, thrombosis and calcification of polyurethanes-based valves became the major causes of failure of these replacements in animal studies (Daebritz *et al.*, 2004, Hilbert *et al.*, 1987, Jansen and Reul, 1992).

Although over the last decade there has been significant progress in the development of durable polymeric valves, their performance did not make them clinically acceptable as valve replacements (Kheradvar *et al.*, 2015). Despite this, they have been recently used for short-term application inside ventricular assist devices to take advantage of their competitive cost and leaflet flexibility (Anderson *et al.*, 2010; Drews *et al.*, 2000; Thuaudet, 2000).

3. Heart valve implantation procedures

The choice of the most suitable valve replacement is individual for each patient and remains particularly critical for young adults and paediatric patients. Based on the patient's age and life style, among others, the surgeon and their team have to choose between the durability of the mechanical valves or the improved haemodynamics related to the bioprostheses. The implantation technique also provides specific demands for the applicability of the valve replacement. While conventional open heart surgery has been the standard of care for many decades, less invasive transcatheter implantation methods have been developed to deliver the valve substitute. Because such innovative transcathether techniques require crimping of the valve replacements, currently, only bioprostheses can be used, as will be further explained in the following sections.

3.1. Surgical heart valve replacement

Conventional surgical heart valve replacement is an invasive procedure requiring temporary cardiac arrest using cardiopulmonary bypass to be successful. This procedure has been performed for decades with good perioperative and long-term results (Brown *et al.*, 2009). Nevertheless, due to an increasing age at surgery, contemporary patients present with more comorbidities (i.e., hypertension, respiratory insufficiency, peripheral arterial stenosis, chronic renal failure) and thus have a greater risk to undergo open heart surgery.

3.2. Transcatheter implantation techniques

Minimally invasive transcatheter implantation procedures are novel techniques acknowledging the increasing preoperative risk profile of our aging patient population suffering from VHD. In 2000, Bonhoeffer *et al*. were the first to apply the catheter-based approach for implanting stented bioprosthetic valves as pulmonary replacements. Two years later, this approach was translated to the aortic position (Cribier *et al.*, 2002) and known as TAVI (transcatheter aortic valve implantation), reaching worldwide clinical acceptance and usage. The main advantage of this method is the reduced invasiveness for the patient, as the need for cardiopulmonary bypass is eliminated and the procedure results in faster recovery (Walther *et al.*, 2007) and better haemodynamic performance than surgically implanted stented valves (Clavel *et al.*, 2009). Taking into consideration the advantages associated with TAVI, this technique is currently offered not only to inoperable or high-risk patients (Sarkar *et al.*, 2013), but also to those with fewer contraindications to surgery (Tamburino *et al.*, 2015), and the results obtained in the intermediate-risk patient cohort are comparable to the surgical replacement (Leon *et al.*, 2016).

However, there is still need to improve implantation techniques and valve designs to reduce the occurrence of paravalvular leakage that affects about 10% of the patients (Rodes-Cabau, 2012) and is known to be associated with an increased mortality (Takagi and Umemoto, 2016). Despite the fact that TAVI is a recent technology, it showed great progression in the past years, with the development of several implantation routes in response to the distinctive clinical needs of the diverse patient population.

3.2.1. Transfemoral approach

The transfemoral approach is the most common route for TAVI, based on a fully percutaneous technique that avoids the need for general anaesthesia. Since this method involves the retrograde insertion of a long catheter through the femoral artery up to the aortic valve, it is still associated (in 5–10% of the implantations) with major vascular complications. To reduce this risk, the approach is currently performed only after an appropriate evaluation of the iliofemoral anatomy of the patient. Since about 30%

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of the patients that principally qualify for TAVI have a poor femoral access, other routes have been introduced, such as the transapical and the transaortic approaches.

3.2.2. Transapical approach

The transapical approach, introduced in 2006 (Ye *et al.*, 2006), accesses the aortic valve antegrade from the left ventricular apex. The main advantage of this technique is the possibility to prevent vascular complications. This makes it a safe and successful approach for patients with advanced atherosclerosis in the ileofemoral system (Walther *et al.*, 2007). However, it is performed by direct puncture of the left ventricle that can lead to bleeding complications and, after the repair, to a reduction of the left ventricular ejection fraction, making the transapical approach not suitable for all the patients.

3.2.3. Transaortic approach

In 2009, surgeons introduced the transaortic approach (Bauernschmitt *et al.*, 2009), where the valve is implanted via an upper mini sternotomy and puncturing of the aortic wall using an introducing sheath system. Due to the access proximity, the positioning of the replacement is simplified and more precise, especially when compared to the transfemoral approach. Moreover, the repair of the aorta is more easily achieved when compared to closure of the ventricle in the transapical approach, suggesting that the transaortic access provides a good alternative solution to transapical access (Dunne *et al.*, 2015). However, patients with severely calcified aortas are contraindicated for this particular type of approach because of the risk of stroke due to embolization of the plaque material during the surgery (Bapat *et al.*, 2012).

3.2.4. Technical requirements for TAVI

The promising minimally invasive valve replacement approach has urged researchers to develop new stents, valves and delivery systems for this application. The delivery system contains the folded stented valve replacement and is connected to a catheter to access the heart where the valve will be deployed. In order to be loaded into such a delivery system, the stented valve should allow for crimping from an average diameter of 23–26 mm down to about 5–10 mm, without any damage. Currently, only bioprostheses mounted on a stent can fulfil this requirement. Over the years, two major stent types, with a broad variety of geometries, have been developed: the self-expanding nitinol stents (e.g., CoreValve, Medtronic), and the stainless steel balloon-expandable stents (e.g., Edwards valves, Edwards Lifescience Corporation). More recently, stent and valve designs for TAVI have been advanced in order to reduce the impact of the crimping on the valve leaflets (Foldavalve, Edwards Lifescience Center for Advanced Cardiovascular Technology), to seal the annulus by capturing the native leaflets (Engager System, Medtronic), to prevent paravalvular leakage with an outer skirt (Acurate TA, Symetis), or to enable the possibility to reposition or retrieve the valve after deployment (JenaValve Technology, JenaValve). Additionally, a great effort is made to guide the surgeon during the implantation and to facilitate the positioning of the valve in the anatomically correct location. As a result of all these improvements, eventually straightforward procedures will be developed that allow for safe and reproducible interventions with an improved success rate and outcome for the patient.

4. Innovative regenerative heart valve replacements

The progression of nonregenerative heart valves has experienced a strong slow down in recent years and the main developments are related to the minimally invasive replacement procedures (Faxon, 2011). However, as currently only bioprostheses are suitable for these techniques, this progress cannot be translated to patients younger than 60 years (Kaneko *et al.*, 2013). In fact, despite several changes implemented to the bioprostheses (i.e., different fixation protocols, anticalcification treatments and stent removal) the improvements obtained in valve durability are not yet sufficient for paediatric usage, because of the enhanced immune response and the lack of growth potential of these prostheses.

Here we suggest that novel crimpable valve prostheses with repair and growth capacity, named as regenerative valves and based on different TE approaches (*in vitro, in vivo* or *in situ,* Figure 1d–f), have the potential to provide a permanent solution for paediatric and young adult patients.

4.1. *In vitro* tissue-engineered heart valves

In 1993, Langer and Vacanti defined the original paradigm to obtain a tissue-engineered heart valve (TEHV), based on a scaffold seeded with autologous cells, *in vitro* tissue formation in a bioreactor, and *in vivo* tissue growth and remodelling upon implantation (Langer and Vacanti, 1993). The key processes of this approach [i.e., cell proliferation and migration, extracellular matrix (ECM) production and organization, and scaffold degradation] require a tight balance to ensure tissue formation and maturation over time. The possibility for the TEHV to repair structural injuries, remodel the ECM and grow is crucial for the long-term success of the living valve replacement (Mendelson and Schoen, 2006). Additionally, the valve requires adequate strength, flexibility and durability to endure the cyclic stresses and strains of the cardiovascular system. Therefore, scaffold design and properties play a crucial role in the success of *in vitro* TEHVs and several types of material have been investigated as potential scaffolds for this application: allogenic and xenogenic heart valves, synthetic biodegradable polymers, and natural polymers.

DOI: 10.1002/term

4.1.1. *Allogenic and xenogenic valves*

Allogenic and xenogenic valves provide the ideal geometry and haemodynamics. However, the seeding of glutaraldehyde-treated porcine- or bovine-derived valves showed very limited cell infiltration and remodelling potential (Tedder *et al.*, 2011). As an alternative to fixation, decellularization of the xenograft valves was introduced to decrease the immunological response (Bloch *et al.*, 2011) and to favour cell infiltration and long-term graft durability (Kasimir *et al.*, 2003). *In vitro* culture of decellularized grafts with endothelial cells was shown to enhance the *in vivo* functionality and endothelialization in a sheep model (Lichtenberg *et al.*, 2006). However, decellularized valves also seeded with myofibroblasts showed thickening of the leaflets, which is hypothesized to indicate excessive matrix formation and cell proliferation that could ultimately lead to improper valve function (Steinhoff *et al.*, 2000). Compared to xenogenic tissues, allogenic valves favour proliferation, differentiation and survival of reseeded cells (Iop *et al.*, 2009). For these reasons, decellularized human pulmonary valves seeded and cultured with autologous endothelial (Dohmen *et al.*, 2011) and endothelial progenitor (Cebotari *et al.*, 2006) cells have been used in clinics and demonstrated excellent haemodynamic performance and good functionality. However, the availability of donor valve allografts is limited. Alternatively, clinical translation of the xenogenic approach has been made by using decellularized porcine pulmonary grafts seeded with autologous endothelial cells (Dohmen *et al.*, 2007). This method proved to be successful and showed good haemodynamic performance but sparse cellular infiltration.

4.1.2. *Biodegradable polymers*

Biodegradable synthetic and natural polymers have been introduced as an alternative to decellularized xenogenic and allogenic matrices. These materials lack the risk of xenogenic diseases and rejection and have the advantage of an unlimited supply. Natural polymers, such as gelatin, collagen and fibrin, are fast-degrading materials produced from biological sources that display no toxic degradation or inflammatory reactions. By contrast, synthetic polymers, such as polyglycolic acid (PGA) and polycaprolactone, can be produced with the desired strength and durability and processed to obtain the required design. However, their degradation products might induce local inflammation. The combination of both natural and synthetic polymers has been also used for TEHV development, to obtain scaffolds with improved mechanical properties and biocompatibility. Seeded with (autologous) cells and subsequently cultured *in vitro*, these material combinations have been shown to be feasible for the development of TEHVs with demonstrated functionality *in vitro* (Del Gaudio *et al.*, 2008; Hoerstrup *et al.*, 2002; Mol *et al.*, 2005; Sodian *et al.*, 2000a, b) and *in vivo* (Flanagan *et al.*, 2009; Gottlieb *et al.*, 2010; Hoerstrup *et al.*, 2000; Robinson *et al.*, 2008; Schmidt *et al.*, 2010; Shinoka *et al.*, 1996; Sodian *et al.*, 2010; Stock *et al.*, 2000; Sutherland *et al.*, 2005; Syedain *et al.*, 2015; Weber *et al.*, 2011) .

In 1995, Shinoka *et al*. replaced a single leaflet of the pulmonary valve of a lamb model with an engineered leaflet based on biodegradable synthetic materials and autologous vascular derived cells. The results showed ECM remodelling, no signs of regurgitation or stenosis, and confirmed that the seeded cells were retained in the scaffold upon implantation (Shinoka *et al.*, 1995, 1996). In a similar approach that allowed for the implantation of a TEHV in pulmonary position of lambs, Hoerstrup *et al*. (2000) showed signs of remodelling and endothelialization of the replacement and physiological-like mechanical behaviour. As previously observed for the xenogenic valves (Steinhoff *et al.*, 2000), the phenomenon of *in vivo* thickening of the leaflets has been also observed for TEHVs based on PGA scaffolds and autologous cells (Gottlieb *et al.*, 2010; Schmidt *et al.*, 2010). This resulted in leaflet retraction and led to valvular insufficiency (Schmidt *et al.*, 2010).

4.1.3. *Self-assembly approach*

Recently, a novel method, based on the self-assembly approach of fibroblast cell-sheet, has shown interesting *in vitro* results. A thick tissue is obtained by stacking together sheets of human fibroblasts that are then used to produce a valve replacements by suturing it on a ring, similarly to what is currently done for the bioprosthesis (Dubé *et al.*, 2014). In another study, the tissue stack was moulded into the complex three-dimensional structure of a valve, leading to an entirely biological valve replacements (Tremblay *et al.*, 2014).

4.2. *In vivo* TEHVs

The *in vivo* TE approach aims at using the human body as a bioreactor to exploit the phenomenon of tissue encapsulation of foreign materials upon subcutaneous implantation of a nondegradable mould (Hayashida *et al.*, 2007). In fact, fibroblasts accumulate around the implanted foreign body and actively produce a collagen-rich matrix forming a fibrotic capsule. Once it is harvested, this membranous tissue with the shape of the mould can be used as an autologous replacement that is nonimmunogenic, nontoxic, and may possess growth and regenerative capacity. In addition, it has been shown that this method can be combined with the minimally invasive transcatheter implantation techniques. In fact, balloon-expandable and self-expandable stented-TEHVs have been obtained by using the *in vivo* TE method and tested *in vivo* as aortic replacements in an acute study in goat (Kishimoto *et al.*, 2015) and *in vitro* under simulated pulmonary conditions (Funayama *et al.*, 2015, Sumikura *et al.*, 2015).

Despite the positive results highlighted here, this methodology has several limitations. Firstly, the collagenous membranous tissue is thrombogenic in nature, and –

DOI: 10.1002/term

similarly to other *in vitro* tissue engineered constructs – lacks other important cardiovascular proteins, such as elastin. Secondly, the regenerative potential of such scar-like tissues in humans is questionable, although proved in rats (Yamanami *et al.*, 2013). In addition, it is not possible to control the thickness of the tissue formed *in vivo* around the mould since it is not related to the time of implantation in humans (Nakayama *et al.*, 2016). Lastly, the *in vivo* tissue formation is an invasive approach that requires a long-term (at least 4 months in humans) (Nakayama *et al.*, 2016) subcutaneous implantation of the mould, excluding its applicability for acute cases.

4.3. *In situ* TEHVs

The third approach of heart valve TE uses the regenerative capacity of the body to remodel and form new tissue upon orthotopic implantation of a cell-free scaffold, by recruiting endogenous (circulating) cells. When compared to the classic TE methods, the *in situ* approach represent a less complex and potentially less costly alternative to produce off-the-shelf available implants that are designed to guide and control cell recruitment and tissue formation while providing initial mechanical functionality (Bouten *et al.*, 2011; van Loon *et al.*, 2013). The material of choice for this approach has a crucial role: the implantation of either natural-derived materials, such as decellularized tissues, or biodegradable polymeric substrates, which will degrade over time while neo-tissue is formed, should generate sufficient mechanical properties at the time of implantation, and a three-dimensional substrate for cell adhesion and growth. By providing instructions to control cell recruitment and differentiation, and to trigger tissue formation, it is intended to obtain a native-like functional living tissue *in situ* (Bouten *et al.*, 2011).

4.3.1. Decellularized native or engineered ECM

Glutaraldehyde-treated porcine valves and bovine pericardium provide limited cell infiltration when used as scaffold material for valve replacements (Tedder *et al.*, 2011). In addition, cell remnants in these tissues have been associated with calcium deposits and immunological response by the host towards the implanted material, as reviewed elsewhere (Schmidt and Baier, 2000). For this reason, researchers developed new options to decrease the immunological response without affecting cellular infiltration or the biomechanical properties of the ECM. By removing the cell component via a process known as decellularization (Kasimir *et al.*, 2003), off-the-shelf available cell-free valve replacements have been developed that worked successfully in sheep (Jordan *et al.*, 2012), pigs (Honge *et al.*, 2011) and dogs (Ota *et al.*, 2007). Several methods to achieve complete decellularization of the tissues have been formulated: hypo- or hypertonic solutions; ionic (e.g., sodium dodecyl sulfate) or nonionic (e.g., Triton X-100) detergents; and enzymes (e.g., trypsin, nucleases), as reviewed by Gilbert *et al*. (2006). A combination of these methods is often more efficient in terms of cell and nucleic acid removal, ensuring preservation of the ECM proteins and elimination of the immunogenic components. As an example, sodium cholate, combined with Triton X-100 and endonucleases (also knowns as TRICOL protocol) proved to be an efficient method to remove not only cell components, but also alpha-Gal (galactose-alpha1–3-galactose) epitopes (i.e., a sugar moiety responsible for the rejection of porcine tissue-based implants) from porcine valves (Naso *et al.*, 2011). This protocol was further validated in a pig model, where the valves showed promising results in terms of cell homing and tissue remodelling during the 15-month follow-up (Iop *et al.*, 2014).

Despite encouraging preclinical results, where physiological growth was shown (Zafar *et al.*, 2015), clinical application of decellularized porcine valves resulted in dramatic results. Even if favourable functionality with freedom from re-operation was reported (Konertz *et al.*, 2011), the residual immunogenicity of the xenogenic decellularized tissues caused severe inflammatory response and valve calcification that led to the death of three paediatric patients (Simon *et al.*, 2003), stenosis and severe thickening (Ruffer *et al.*, 2010; Voges *et al.*, 2013), and degeneration of the material with no signs of integration, remodelling or recellularization (Woo *et al.*, 2016). These results underline the preference of allogenic material for clinical application. Several clinical studies investigated the potential of using decellularized allogenic pulmonary valve during the Ross procedure (Brown *et al.*, 2011; da Costa *et al.*, 2005; Sievers *et al.*, 2003), with promising results in terms of haemodynamics, functionality and reduction of the immunogenic response. Similarly, these valves have been used for pulmonary valve (Cebotari *et al.*, 2011; Sarikouch *et al.*, 2016) and aortic root replacements (da Costa *et al.*, 2010; Zehr *et al.*, 2005), providing good functionality, low immunoreactivity (Hawkins *et al.*, 2003), freedom from reoperation and even signs of adaptive growth in paediatric patients. However, the use of decellularized human valve replacements in clinical studies led to contrary reports about their capacity for endogenous cellular infiltration. Although a single case of complete repopulation of a vessel wall was demonstrated (Konertz *et al.*, 2011), others observed only sparsely cellular infiltration in the wall (Dohmen *et al.*, 2007, Sayk *et al.*, 2005) and leaflets (Miller *et al.*, 2006).

Considering donor shortage and controversial results on cellular infiltration, research has focused on the development of largely available off-the-shelf engineered allogenic replacements. Dijkman *et al*. (2012a) investigated whether the removal of the cellular component of living TEHVs was feasible without affecting the mechanical and biological properties of the replacement. This method proved to be beneficial in overcoming the thickening and retraction of the leaflets upon culture that was previously reported for living TEHVs (Schmidt *et al.*, 2010). The decellularization also provided off-the-shelf availability and a reduced antigenicity of the resulting tissue. In

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addition, the decellularized TEHVs can be produced by using screened and standardize homologous cell sources instead of patient-derived autologous cells, providing consistent results with regards to the *in vitro* tissue formation. Furthermore, these off-the-shelf TEHVs proved to be perfectly suitable for transcatheter implantation, as demonstrated in sheep (Driessen-Mol *et al.*, 2014) and baboons (Weber *et al.*, 2013), showing good early functionality as pulmonary replacement, host cell repopulation, endothelialization and ECM remodelling over time. However, the problem of leaflet shortening upon long-term implantation is not yet solved; computational modelling suggested that this adverse remodelling occurs due to the leaflet compression when the valve is in physiological conditions, and *in vitro* data showed improved valve functionality when a new valve geometry is imposed during culture to counteract for host-cell mediated retraction (Sanders *et al.*, 2015).

4.3.2. Biodegradable polymers

Despite the enhancements in durability and biocompatibility of the standard nonregenerative polymeric valves, these replacements are still not considered as competitive candidates for clinical use. Instead, interest is shifted towards the biodegradable polymeric valves, as they can provide a suitable environment for endogenous cell adhesion upon implantation, potentially leading to ECM formation and remodelling towards a completely autologous tissue replacement.

The use of biodegradable synthetic polymers for valve replacements presents some advantages. Firstly, the mechanical properties can be tuned to obtain strong, but thin and flexible valves that can be safely implanted via catheter techniques without damaging the leaflets. Secondly, degradation of these materials can be designed to provide sufficient mechanical strength at the time of implantation, but also to balance scaffold degradation with endogenous tissue formation over time. Additionally, these materials can be processed to obtain a different level of porosity to control cell infiltration (Balguid *et al.*, 2009) and therewith the immune response upon implantation. Clearly, in order to profit from the full potential of these polymeric materials for valve replacements, multidisciplinary in-depth knowledge is required regarding their material properties, possible methods for scaffold design, and the possible scaffold modifications that can influence the integration and remodelling of the polymeric valves upon implantation. For an overview of the suitable materials and methods of scaffold fabrication for *in situ* cardiovascular tissue engineering we refer the readers to reviews on these particular topics (Bouten *et al.*, 2011; Cheung *et al.*, 2015).

The potential *in vivo* mechanisms that are involved in the integration and remodelling of the implanted valves and the possible polymeric scaffold modifications that can be used to avoid, limit or exploit the natural immune response (Figure 2) will be reviewed in the following section.

5. Valve integration and regeneration upon implantation

The long-term integrity of the native valve is ensured by the endogenous interstitial cells that enable growth and repair of the tissue by synthesizing and remodelling the ECM. This quality is also pursued in an ideal valve replacement to prevent *in vivo* deterioration of the implanted substitute. Thus, for clinical application of the *in situ* TE approach, the scaffold should be able to attract autologous cell adhesion and favour proliferation upon implantation. However, it is still unclear as to what extent endogenous cells will be able to repopulate an implanted scaffold in humans. Since the implantation of any type of biomaterial activates the immune system, the modulation of the natural inflammatory response by tuning material properties is of great interest. Upon implantation, the foreign material will induce a persistent inflammatory response involving granulocytes, macrophages and lymphocytes. The role of these cells is to express inflammatory cytokines and chemokines (e.g., interleukin-8 and monocyte chemotactic protein-1 – MCP-1), which are potent cell attractants and activators. When the inflammatory stimulus is completely eliminated, the inflammatory response will resolve, followed by healing and regeneration. However, a foreign body that is impossible to be eliminated will cause adverse chronic inflammation with the persistent presence of macrophages and giant cells at the site of implantation. This deleterious process can induce some undesired effects (e.g., intimal hyperplasia, fibrosis, calcification) that are almost impossible to treat pharmaceutically (Simionescu *et al.*, 2011). To limit these adverse reactions, research has focused on controlling the blood–material interface and early cell infiltration of the implanted biomaterial. In fact, it is believed that the cells and biomolecules present in the initial phase of the inflammatory response determine the fate of the implanted biomaterial towards either a successful integration or a pathological chronic outcome (van Loon *et al.*, 2013).

5.1. Controlling the blood–material interface

The only fully haemocompatible surface is the endothelial cell lining. Although material developments have reduced haemolytic, toxic and immunological reactions to an extent that these are rarely a matter of concern, thrombotic and thromboembolic complications associated to the implanted biomaterial remain a major concern for cardiovascular devices (Ekdahl *et al.*, 2011).

When the biomaterial is in contact with blood, its surface is immediately covered by a thin monolayer of plasma proteins. The composition and conformation of these proteins is affected by the surface chemistry of the biomaterial (e.g., hydrophilicity/hydrophobicity, charged groups, porosity, roughness) and will determine the adhesion and activation of platelets. To overcome the natural host response to the implant, scaffolds in contact with blood can be coated with unfouling materials (e.g., polyethylene

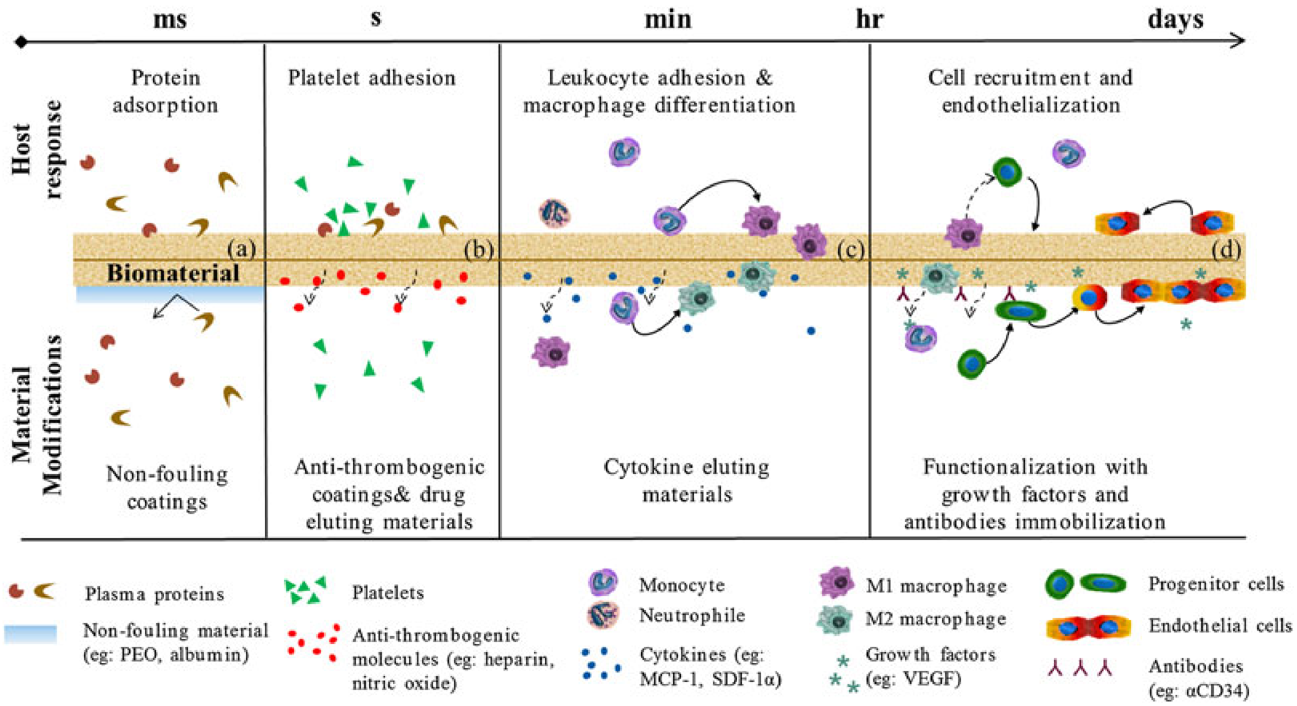

Figure 2. The host response to an implanted biomaterial and the possible interventions to avoid, limit, or exploit the natural immune response: (a) immediately upon implantation, the material is covered in proteins adsorbed from the plasma. This phenomenon can be limited by coating the implant with of nonfouling materials [e.g., polyethylene oxide (PEO), albumin]. (b) Platelet aggregation occurs in the presence of adsorbed and exposed proteins on the material surface. Drug-eluting materials (e.g., heparin, nitric oxide) can inhibit platelet activation. (c) Leucocytes adhere on the biomaterial; among them, monocytes can differentiate towards inflammatory (M1) or regulatory (M2) macrophages. By eluting cytokines (e.g., MCP-1 or SDF1a), it is possible to influence monocyte differentiation towards the favourable M2 type. (d) Cells from the surrounding tissues and the blood will adhere and differentiate towards the main cardiovascular cell components, forming a new endothelial layer. To enhance this process, VEGF or progenitor cell-specific antibodies (e.g., CD34) can be linked to the scaffold.

oxide, albumin) to limit the unspecific protein adsorption (Figure 2a) (Tan and Brash, 2009). Thrombotic complications, instead, can be prevented by inhibiting platelet activation and aggregation by using heparin-coated biomaterials (Liang and Kiick, 2014) or by releasing endogenous anticoagulant molecules, such as nitric oxide (Figure 2b) (Varu *et al.*, 2009). For further information about the role of the complement and coagulation system in the biomaterial-associated thrombosis, the reader is referred to other specific publications (Ekdahl *et al.*, 2011; Gorbet and Sefton, 2004).

5.2. Regulating the cytokine release

Within the first minutes upon contact with blood, a sufficiently porous scaffold is subjected to early infiltration of circulating leucocytes. Among them, neutrophils and monocytes (Figure 2c) adhere on the implant in response to the different types and conformations of the adsorbed proteins (Boehler *et al.*, 2011). These cells are responsible for the early release of cytokines and growth factors, important molecules to control the immune cell infiltration and to modulate the inflammatory response via paracrine and autocrine signalling. A similar role has been identified also for the bone marrow-derived mononuclear cells used to seed the scaffold right before the implantation. These cells release signalling factors that influence positively the tissue development via an inflammation-mediated process, before being rapidly replaced by macrophages (Roh *et al.*, 2010). Macrophages are actively involved in the resolution of the inflammation due to their ability to shift from a proinflammatory state towards a reparative phenotype. Recent studies have demonstrated that biodegradable synthetic grafts implanted in different animal models undergo cell colonization and *in vivo* remodelling over time, becoming functional blood vessels (de Valence *et al.*, 2012; Wu *et al.*, 2012). The inflammatory response involved in the remodelling and regeneration can be influenced by releasing specific cytokines or by functionalizing the material to selectively recruit circulating monocytes into the scaffold. One of the most important cytokines to guide the inflammatory process towards regeneration is MCP-1, a chemokine secreted by macrophages to attract additional inflammatory cells, resulting in a rapid and homogenous infiltration of the starter matrix with blood-derived cells (Talacua *et al.*, 2015). Similarly, stromal cell-derived factor-1α (SDF-1α) is another important cytokine involved in the recruitment of blood-derived tissue-producing progenitor cells and proved to be important to control valve cell phenotype. In addition, it is involved in scaffold remodelling by reducing the inflammatory response (Muylaert *et al.*, 2016; Thevenot *et al.*, 2010) and favouring the endothelialization of valves (De Visscher *et al.*, 2010) and vascular prostheses in a sheep model (De Visscher *et al.*, 2012), stimulating the attraction of stem cells and reducing intimal hyperplasia and thrombosis.

Many other types of cells and biomolecules are involved in the inflammation and remodelling processes, as described elsewhere (Gonzales-Simon and Eniola-Adefeso,

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2012). However, most of the molecular pathways of the remodelling phenomena remain largely unknown and their discovery will be indispensable for the development of new strategies to functionalize biomaterials and modulate the early inflammatory response.

5.3. Influencing cell recruitment, adhesion, and differentiation

When compared to biological materials, polymers are easier to modify in shape, porosity, and mechanical properties and they can be synthetized to obtain *smart* biomaterials capable of inducing specific cell adhesion and/or differentiation by adding different types of bioactive molecules (i.e., material functionalization). In order to mimic native cell–cell and cell–ECM interactions and influence cell adhesion and differentiation, several methods to immobilize specific bioactive components (i.e., antibodies, peptides, growth factors) on biomaterials have been developed. Considering the importance of obtaining an antithrombogenic surface on cardiovascular devices, the focus of this review will be on some of the currently available techniques to enhance endothelialization.

5.3.1. Antibody immobilization

Antibodies are proteins capable of recognizing and binding specific antigens that are present on the cell membrane. One of the most investigated antibodies to enhance endothelialization is against the hematopoietic antigen CD34, a membrane marker of different types of circulating progenitor cells (Avci-Adali *et al.*, 2008). By immobilizing an antibody against CD34 on stents (Lin *et al.*, 2010) or scaffolds (Melchiorri *et al.*, 2015), it was possible to effectively recruit circulating progenitor cells and accelerate the process of endothelium formation. Similarly, antibodies against CD133 have been used to functionalize vascular grafts (Lu *et al.*, 2013) and heart valves (Jordan *et al.*, 2012) favouring endothelialization compared to the uncoated materials. However, both these antibodies are general markers for different subsets of progenitor cells that can lead to undesired effects over time (e.g., intimal hyperplasia in response to an anti-CD34 coating) (Rotmans *et al.*, 2005). Therefore, the potential unspecific differentiation of the recruited cells should be controlled by using antibodies in combination with other biomolecules in order to guide the differentiation towards the desired phenotype.

5.3.2. Peptide immobilization

Peptides are defined as a short sequence of amino acid monomers that resemble an active domain of a specific protein. Different peptides suitable for the functionalization of biomaterials to enhance the *in situ* endothelialization have been identified in the past years. The most common peptide used to enhance cell adhesion onto (cardiovascular) scaffolds is RGD (Arg-Gly-Asp), the general binding site of the protein fibronectin. RGD is involved in the adhesion of circulating and endothelial cells (Ravi *et al.*, 2009), thereby improving the haemocompatibility of the coated implant and enhancing endothelial coverage (Zheng *et al.*, 2012). Fibronectin provides also a more specific binding site for endothelial cells in the domain sequenced as REDV (Arg-Glu-Asp-Val). REDV inhibits platelet adhesion (Rodenberg and Pavalko, 2007) and specifically binds the α5β1-integrin, expressed on the membrane of endothelial (progenitor) cells (Caiado *et al.*, 2011). Similarly, the nonintegrin binding peptide YIGSR (Tyr-Ile-Gly-Ser-Arg) was developed from the protein laminin to promote endothelialization and prevent, at the same time, platelet adhesion (Jun and West, 2005). Thanks to their specificity, peptides are now considered as a good alternative to antibodies in capturing cells from the circulation as they proved to be effective in capturing endothelial cells *in vitro* also under flow conditions (Plouffe *et al.*, 2008). Taken together, these results translated to the use of peptide-functionalized grafts (using, e.g., RGD, REDV or YIGSR) in a rat model. The peptides were retained on the material surface for 10 days in the systemic circulation and, despite the large variability between the groups, endothelialization may be improved by combining different peptides to trigger integrin and nonintegrin binding adhesion sites (Aubin *et al.*, 2016).

5.3.3. Release of growth factors

The incorporation of growth factors into biomaterials is a technique used to efficiently modulate the local cell niche, influencing directly cell functionality. Among several proangiogenic factors, vascular endothelial growth factor (VEGF) plays a major role in the phenomena of vascularization and endothelialization by favoring the recruitment of progenitor cells and enhancing endothelial cell migration and proliferation (Liu *et al.*, 2015). Owning these properties, VEGF has been used to functionalize different types of cardiovascular materials, such as the stent metal alloy nitinol (Liu *et al.*, 2015) and biodegradable polymers based on PGA (Melchiorri *et al.*, 2015). To optimally present the molecule to the cells and protect it from denaturation and degradation, the growth factor can be immobilized to the material via a linker, such as heparin (Smith *et al.*, 2015). This immobilization efficiently enhances cell response and promotes proliferation.

Also, transforming growth factor β1 can be immobilized to a biomaterial to enhance ECM formation and stimulate cell differentiation by emulating the physiological cardiovascular developmental biology (Armstrong and Bischoff, 2004). In this regard, the most studied mechanism is the endothelial to mesenchymal transdifferentiation that occurs when endocardial cells differentiate into mesenchymal cells in the cardiac cushion (Sewell-Loftin *et al.*, 2011). It is hypothesized that the resident endothelial cells that cover the implant can be triggered to undergo transdifferentiation towards a mesenchymal matrix-productive phenotype if correctly stimulated by the bioactive molecules (e.g., transforming growth factor β1 or platelet-derived growth factor) linked to the scaffold

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(Wang *et al.*, 2014). However, this cell differentiation can lead to undesired effects, such as excessive cell proliferation and ECM production that could lead to thickening of the implant.

6. Challenges towards clinical translation of TEHVs

The clinical adaptation and success of the TEHV will depend on their superiority compared to today's bioprostheses. As the life expectancy of humans increases, a greater number of patients would benefit from a valve replacement with life-long durability, such as a TEHV. Nevertheless, due to the improvements in durability and design of glutaraldehyde-fixed bioprosthetic valves and to the use of minimally invasive implantation techniques, the age of patients eligible for a bioprostheses has been lowered by another 10–20 years. For these reasons, the benchmark for clinical application of TEHVs continuously increases.

6.1. Clinical challenges

Today, TEHVs also have to compete with the novel commercially available decellularized homograft (e.g., Espoir PV and Arise AV by Corlife; CryoValve SG and CryoValve Aortic by CryoLife) and xenograft (e.g., Matrix P plus N by Autotissue) valves that are currently in clinical trials. However, the conflicting results obtained from these studies in terms of cellular infiltration (Miller *et al.*, 2006; Sayk *et al.*, 2005) and concerns regarding safety, especially in pediatric patients (Hibino *et al.*, 2015; Simon *et al.*, 2003) favor novel solutions.

The TEHVs will be able to grow and remodel upon implantation, improving dramatically the patient's quality of life, as well as their life expectancy. Moreover, it is hypothesized that cell-free TEHVs based on *in vitro* grown ECM or biodegradable polymers may present better repopulation capacity, thanks to the less mature ECM and the customizable porosity that will favour cell infiltration. However, these hypotheses can only be proven by first clinical studies. For the adaptation of TEHVs in routine clinical practice, the ease of handling of the device, sterility and off-the-shelf availability will be key factors for clinicians to choose the product. Ideally, the advantages of minimally-invasive techniques should be combined with the innovative and promising *in situ* heart valve TE approach. Recent studies investigated the possibility of merging the transcatheter techniques with living and off-the-shelf decellularized TEHVs, showing the feasibility of this approach *in vitro* (Moreira et al., 2015) and *in vivo*, in sheep (Dijkman *et al.*, 2012b; Driessen-Mol *et al.*, 2014) and baboon (Weber *et al.*, 2011, 2015) models. These preliminary results suggest the potential to significantly improve current treatment options for patients suffering from VHD, in particular when the most advanced implantation techniques and devices are used. In this respect, Emmert *et al*. (2014) successfully implanted a TEHV as aortic replacement using a clinically relevant delivery system (JenaValve stent and catheter) in an acute sheep model. Nevertheless, further preclinical investigations have to be performed to support the future clinical studies, where the recipient annulus is usually severely calcified and the consequent valve integration and regeneration may be compromised. The use of diseased animal model to study the regeneration of these valves in clinical-like conditions will also provide important information for the translational approach.

The minimally invasive procedure still remains highly dependent on sophisticated imaging and monitoring instruments and currently available transcatheter prostheses and associated disposables are more expensive than standard prostheses, thus limiting the application in developing countries. In fact, while congenital heart disease is the most common pathology to affect children in Europe and North America (1–2% of newborns), rheumatic fever is the main cause of VHD in young patients in the developing countries (Cheung *et al.*, 2015). The final cost of a TEHV should be, therefore, very competitive to be available for the growing market of China and India, countries with a fast-growing economy that will have substantial demand for affordable treatment options.

Finally, the stent used for minimally invasive heart valve substitution needs to be crimped without inducing damage to the valve. In addition, to accompany the somatic growth of the youngest patients, the stent should either have a continuous, controlled dilatation without inducing regurgitation, or be biodegradable. Promising efforts have been made to prove the feasibility of designing biodegradable self-expandable stents that can be combined with TEHVs (Soares and Moore, 2016). However, the use of biodegradable stents would presume that the implanted prosthesis will be fully integrated at the implantation side, an event that has not yet been demonstrated in humans.

6.2. Technical challenges

Generally, the classic TE approach is limited by the donor-to-donor variability of the isolated cells for cell culture and tissue production. Moreover, the maintenance of the cell line and the optimization of the seeding process are still an issue, especially when considered in large scale production. The *in situ* TE approach may provide an easy solution to these limitations by introducing an off-the-shelf available biodegradable polymeric valve or *in vitro* engineered decellularized valve replacement. However, it seems essential that future scaffolds not only copy native tissues in their composition of structural components, but also duplicate their microstructural organization and mechanical properties. So far, scientists have not been able to create synthetic matrices with the same unique functional characteristics and anisotropic microstructure of the native valve (e.g., flexible and nonresisted motion in systole and durable load bearing behaviour in diastole), obtaining TEHVs inadequate as aortic replacements.

Recently, thanks to the introduction of the tubular leaflet approach, other groups investigated innovative fibrin-based tissues that showed good *in vitro* functionality (Reimer *et al.*, 2015; Weber *et al.*, 2015) and, more recently, sufficient *in vivo* functionality up to 24 weeks in the systemic circulation of sheep with almost complete cell repopulation (Syedain *et al.*, 2015).

Although *in vitro* studies of polymeric valves provide good indications of acute functionality and fatigue resistance of the replacements, they may not be sufficient to ensure the functionality of a biodegradable polymeric valve that will degrade over time. Therefore, collagen production and scaffold degradation should be carefully considered and balanced to always ensure a reliable strong valve replacement at any time. Moreover, cell infiltration should be optimized and the attracted cells should be characterized to understand the tissue remodelling response, as the phenotype of the macrophages in the host response can indicate the direction to either chronic inflammation or remodelling (Brown *et al.*, 2009). By contrast, concerns regarding variability of *in vivo* regeneration among patients are comprehensible, as repopulation and remodelling capacity might be age-dependent and influenced by comorbidities. Such interpatient variability could be further investigated by innovative *in vitro* technologies such as organ-on-a-chip models that are designed to have a predictive capacity for individual blood responses towards implants (Beebe *et al.*, 2013). Moreover, a correct set of markers to monitor the profile of *in vivo* remodelling and healing upon implantation still needs to be assessed. Most importantly, a correlation between animal and human data should be identified, to enable a correct prediction of clinical outcome. For this reason, *in vitro* investigation of correspondences or contradictions between human and animal (cell) responses to the biomaterial can provide important insight in the value of the *in vivo* results obtained in different animal models.

7. Conclusion

Current valve replacements have considerable limitations, but most of all lack regeneration and growth capacity. Therefore, several TE approaches have been developed over recent years with promising *in vitro*, preclinical and even clinical results. Given the widespread scarcity of donor organs and the immunological, infectious, as well as ethical hurdles of cross-species transplants, synthetic or human derived off-the-shelf products hold the potential to offer therapeutic solutions for the increasing numbers of cardiovascular patients worldwide. As long as natural tissues and bioprostheses are superior to synthetic scaffolds in terms of functional behaviour, the clinical translation and implementation of polymer-based TEHVs remains challenging. This implies that scientists have to stay committed to design improved polymeric scaffolds for heart valve replacements. In the coming decades, research will probably focus on intelligent, off-the-shelf available scaffolds that make use of the regenerative capacity of the human body by attracting endogenous cells and stimulating them to produce and remodel living tissue. Moreover, as innovative less-invasive transcatheter implantation techniques rapidly develop, the attractiveness to merge such off-the-shelf engineered heart valves with these new techniques is increasing. Obviously, long-term (preclinical) studies are compulsory to evaluate the remodelling of such optimized biomaterials towards native tissues. Nevertheless, off-the-shelf TEHVs have great potential to eventually replace the use of the current mechanical and bioprosthetic valves. As these valves are designed with regenerative and even growth capacities to function as life-long valve replacements for patients of all ages, they are in future expected to increase life-expectancy and well-being of many patients suffering from VHD worldwide.

Conflict of interest

The authors have declared that there is no conflict of interest.

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Abbreviations

ECM, Extracellular matrix; MCP-1 Monocyte chemoattractant protein-1; SDF-1α, Stromal derived growth factor-1α; TAVI, Transcatheter aortic valve implantation; TE, Tissue engineering; TEHV, Tissue-engineered heart valve; VEGF, Vascular endothelial growth factor; VHD, Valvular heart disease.

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