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Functional regeneration at the blood-biomaterial interface

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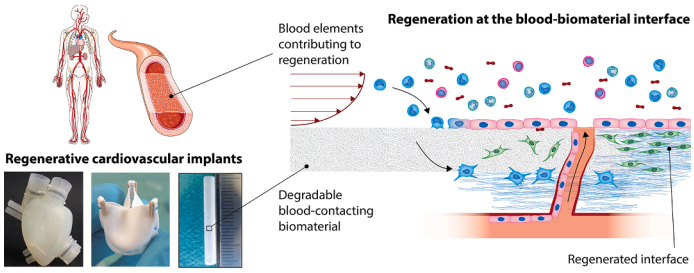
HIGHLIGHTS:

- Contact with the blood poses challenges for implants, but also opportunities.
- Resorbable biomaterials can be used to trigger cardiovascular regeneration *in situ*.
- Circulating immune cells are potent contributors to endothelialization and regeneration.
- Rational engineering offers new opportunities to create hemo-regenerative implants.
- Robust translation requires clinically relevant *in vitro* and *in vivo* testing models.

GRAPHICAL ABSTRACT



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ABSTRACT

The use of cardiovascular implants is commonplace in clinical practice. However, reproducing the key bioactive and adaptive properties of native cardiovascular tissues with an artificial replacement is highly challenging. Exciting new treatment strategies are under development to regenerate (parts of) cardiovascular tissues directly *in situ* using immunomodulatory biomaterials. Direct exposure to the bloodstream and hemodynamic loads is a particular challenge, given the risk of thrombosis and adverse remodeling that it brings. However, the blood is also a source of (immune) cells and proteins that dominantly contribute to functional tissue regeneration. This review explores the potential of the blood as a source for the complete or partial *in situ* regeneration of

Abbreviations: α-SMA, alpha smooth muscle actin; b-FGF, basic fibroblast growth factor; BMMCs, bone marrow mononuclear cells; CNP, C-type natriuretic peptide; DAMPs, damage-associated molecular patterns; EC, endothelial cell; ECM, extracellular matrix; EndMT, endothelial-mesenchymal Transition; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; ePTFE, expanded polytetrafluoroethylene; ET-1, endothelin 1; FBGC, foreign body giant cell; GFP, green fluorescent protein; hBMCs, human bone marrow cells; HBP, heparin-binding peptide; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; iPSC, induced pluripotent stem cell; MCP-1, monocyte chemoattractant protein 1; MHC, myosin heavy chain; MMP-9, matrix metalloproteinase-9; NO, nitric oxide; OCT, optical coherence tomography; PCL, polycaprolactone; PDGF, platelet-derived growth factor; PDMS, polydimethylsiloxane; PEG, polyethylene glycol; PELCL, poly(ethylene glycol)-b-poly(L-lactide-co-ε-caprolactone); PET, polyethylene terephthalate; PGA, polyglycolic acid; PGI2, prostaglandin I2; PLCL, poly(L-lactic-co-ε-caprolactone); PLGA, poly(L-lactide-co-glycolide); PLLA, poly(L-lactic acid); PLVAP, plasmalemma vesicle associated protein; PTGIS, prostaglandin I2 synthase; ROS, reactive oxygen species; SDF-1α, stromal cell-derived factor 1 alpha; SMC, smooth muscle cell; SM-MHC, smooth muscle myosin heavy chain; SMPC, smooth muscle progenitor cell; SIS, small intestinal submucosa; TEHV, tissue-engineered heart valve; TEVG, tissue-engineered vascular graft; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TGF-β, transforming growth factor beta; TM, thrombomodulin; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VIC, valvular interstitial cell; vWF, von Willebrand Factor.

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Vascular graft
Heart valve
Total artificial heart

cardiovascular tissues, with a particular focus on the endothelium, being the natural blood-tissue barrier. We pinpoint the current scientific challenges to enable rational engineering and testing of blood-contacting implants to leverage the regenerative potential of the blood.

1. Introduction

Cardiovascular diseases are major cause for death worldwide [1,2]. Under the wide umbrella of cardiovascular diseases come conditions such as heart failure, valvular diseases, and vascular diseases [1]. The current treatment of choice for these medical conditions, particularly in advanced disease stage, is often dependent on prosthetic devices (e.g., left ventricular assist devices, (endo)vascular grafts/stents, heart valve replacements)[3]. Even though such prosthetic devices are life-saving devices, they all come with critical side-effects, such as the permanent need for anti-coagulation medication, risk for reoperation, device failure, and fibrotic tissue remodeling due to the persistent inflammation in response to the foreign material in the body [4–9]. Consequently, treatment with a cardiovascular prosthesis often leads to a compromised life expectancy and quality of life.

The common denominator among cardiovascular implants is the direct contact of the device with the blood, which is a cause of many complications, such as thrombosis or emboli, as well as inflammation. The risks associated with current cardiovascular devices are for an important part attributable to the fact that such devices cannot mimic the body's natural way of regulating the interactions between the blood and the underlying tissues, such as the endothelium. The endothelium is now acknowledged as a dynamic organ that performs multiple life-determining functions; it contributes to the control of vasomotor tone, proliferation, and survival of underlying tissues. Furthermore, it plays a significant role in maintaining homeostatic processes, including blood vessel permeability, leukocyte trafficking, and hemostasis [10–13]. Endothelial cells (ECs), being structural and functional units of native endothelium, enable all the aforementioned functions. Therefore, novel biomaterial-based implants that can (partly) replicate endothelial functions are being developed to improve hemocompatibility and mitigate risks and complications. Such implants can be generally categorized into three classes: (1) permanent non-degradable implants, (2) resorbable regenerative implants and (3) composite implants that are partly resorbable.

Each of these classes of implants has its own requirements regarding hemocompatibility. Non-degradable implants that are designed to stay permanently in the body (e.g., polyethylene terephthalate (PET, Dacron), expanded polytetrafluoroethylene (ePTFE)) must ensure life-long hemocompatibility [14]. To that end, various material modifications have been developed, such as surface modification with antiplatelet (e.g., nitric oxide [15], Dipyridamol [16]), anticoagulant (e.g., heparin [17], Hirudin [18]), or antifouling molecules (e.g., polyethylene glycol (PEG) [19], zwitterion modification [20]). However, the long-term functionality of some of these modifications remains questionable, as reviewed elsewhere [21].

Alternatively, over the past decades, the concept of *in situ* tissue engineering has been introduced to offer a therapeutic solution for replacement of diseased or damaged cardiovascular tissues [22–24]. This concept relies on implanting a biomaterial that acts as a scaffold that guides neo-tissue regeneration under the influence of the surrounding microenvironment [22,25]. Such an implant can be completely or partly resorbable to allow for the regeneration of autologous cardiovascular tissue or functional parts thereof, such as the endothelium. Examples include regenerative heart valves [26–29], stents [30] and vascular grafts [31–33] based on fully resorbable synthetic materials.

The third type of cardiovascular devices are composite implants, which combine permanent and resorbable, regeneration-inducing materials. The latter type of material is typically represented by a resorbable blood-contacting layer that acts as a scaffold to promote the regeneration of a protective endothelial lining on the blood-material interface. Eventually this scaffold will degrade, leaving behind a functional endothelium adhering to the underlying permeant substrates, thereby preventing thrombus formation and the unwanted inflammatory response that often result in grafts failure [34,35]. One recent example is the Carmat bioprosthetic total artificial heart, in which a xenogeneic pericardial patch was utilized as a regenerative endocardium on the ventricular cavity of the permanent Carmat device [36,37]. *In vitro* [38], *in vivo* [39] and clinical data [40] showed that an endothelial lining regenerates from circulating cells in this manner, eventually creating an endocardium, mimicking the native most inner lining in the human heart [37].

For all these types of cardiovascular implants, the blood undeniably has a dominant impact on short- and long-term functionality. While mainly regarded as a risk for adverse events, such as thrombosis, the recent technological developments in regenerative cardiovascular materials have made clear that the blood also offers a great possibility for regeneration, being a continuous source for proteins and cells. The blood is the first and perhaps the most vital factor contributing to the success of *in situ* regeneration; this ranges from the initial adsorption of the blood proteins that occurs within the first few minutes after implantation to the infiltration of different cellular elements circulating in the blood [41]. The blood is an important and continuous source of immune cells, such as monocytes and monocyte-derived macrophages, which have been shown to play a critical role in *in situ* tissue regeneration [26,42–48]. In addition, several studies have demonstrated the potential of blood-borne cells as a source of functional tissue cells, including ECs and smooth muscle cells (SMCs) [45–47,49–51]. Although the effective contribution of blood-borne cells to reconstitute functional cell populations in relation to other cellularization routes (i.e. transmural and transanastomotic ingrowth) is unclear, as elaborated on later in this review, these studies do show the potential of the blood as a cell source. This is of particular importance given that not all routes of cellularization are accessible for some applications, and are therefore more or even completely dependent on fallout healing from the blood. An example is the application of total artificial hearts, in which transanastomotic and transmural cellularization is restricted due to the design of the implant, leaving the continuous exposure to the blood as the only available cellularization route.

Given that the contribution of the blood to *in situ* regeneration remains a topic of debate, this review explores which roles the blood plays in *in situ* endothelialization and tissue regeneration and elaborates on some of the main current scientific questions:

- What is the contribution of blood-borne cells on *in situ* cardiovascular tissue engineering for various applications?
- To what extent should and can endothelial regeneration be application-specific considering differences in the surrounding tissue and hemodynamic loads?
- How can we engineer blood-contacting implants to leverage the regenerative potential of the blood?
- How can we test such devices in a clinically relevant way, considering strong inter-species differences in regenerative processes, inflammation and endothelialization?

To that end, the heterogeneity in the native endothelium and its relationship with local hemodynamics will be delineated since the native endothelial properties and local hemodynamics are highly dependent on the specific application. Subsequently, we will elaborate

on the process of *in situ* tissue regeneration, focusing on the role of inflammation and the various sources of *in situ* recellularization, especially concerning ECs. State-of-the-art engineering approaches related to scaffold design will be discussed. Finally, the current translational challenges and considerations will be described, with a focus on the recent advances in *in vitro* and *in vivo* testing models and standardizing of appropriate models, analysis methods and reporting thereof.

2. Endothelial heterogeneity in the adult cardiovascular system

Over the past decades, it has become evident that ECs phenotypically differ throughout the cardiovascular system. This biological phenomenon is also known as endothelial heterogeneity, which concerns EC morphology and functionality. EC heterogeneity arises during embryogenesis and is maintained after birth. It is determined by the interplay between site-specific genetic and epigenetic make-up of ECs, as well as by their extracellular milieu, comprising of biochemical and hemodynamic stimuli [52,53]. In general, ECs within the body gain their identity based on their niche (e.g., the organ/anatomical location they are lining). This is dependent on the surrounding microenvironment conditions such as mechanics, signals from parenchymal cells and hormones [54]. Among the hemodynamic stimuli, wall shear stress is considered to be the most potent. Its role has been underscored in endothelial development and the maintenance of EC phenotypes in the adult organism. The dynamic nature of the endothelial heterogeneity is rather complex, but the mechanistic understanding of this phenomenon would ensure that appropriate site-specific EC phenotypes are attained during the *in situ* formation of the endothelium in cardiovascular devices. The EC phenotype is responsible for maintaining the appropriate interactions with the surrounding microenvironment, eventually preserving the native function of tissue-engineered constructs [55]. Thus, when evaluating tissue-engineered structures an in-depth functional and phenotypical evaluation/identification of the present cells should be considered.

Different markers have been used to identify ECs from different origins. The ECs discussed in this review are vascular ECs lining the blood vessels, endocardial ECs lining the inner most layer of the heart (i.e. the endocardium) and valvular ECs lining the blood-contacting surfaces of the heart valves [56–58] (Fig. 1). The expression of such markers varies among ECs from different origins and depends on the local hemodynamic environment they are exposed to (Fig. 1) [59–69].

For instance, KLF2 is a key transcription factor that plays a protective role in adult vasculature and its expression is based on the type of flow (e.g., laminar vs oscillatory) [59,60]. One of its downstream targets is endothelial nitric oxide synthase (eNOS). An observed variation in eNOS distribution is reminiscent of the enzyme's expression patterns in the vasculature and might play a role in the control of cardiac, and arterial tone, as well as contribute to their anti-inflammatory properties [70]. For vascular endothelial cells, increased eNOS expression allows for sufficient production of nitric oxide (NO). In turn, NO inhibits the expression of inflammatory cytokines and cell adhesion molecules on the surface of ECs, thus impeding leukocyte trafficking into the blood vessel wall [71–73]. However, limiting the activity of eNOS is needed, otherwise the generation of reactive oxygen species (ROS) would occur, which may lead to endothelial cytotoxicity [74]. In line with the protective function of NO, it also has a cardioprotective effect by lowering the consumption of O_2 by the myocardium, whether in normal or pathological conditions [75]. In addition to modulating eNOS activity, KLF2 negatively regulates the activity of pro-inflammatory factors, such as NF-κB, leading to reduced endothelial expression of adhesion molecules in vascular ECs [62–66].

Another factor secreted by ECs is Thrombomodulin (TM), an activator of the protein C anticoagulation pathway expressed by vascular ECs. TM is responsible for maintaining the anti-thrombotic behavior of vascular ECs and its expression level is steered via the type of flow to which the cells are exposed [76–78]. Prostaglandin I2 (PGI2), also known as prostacyclin, is an anti-coagulation factor produced by ECs. PGI2 prevents platelet aggregation besides regulating the tone of the overlying cardiac tissue [75,79,80]. PGI2 and NO besides other factors such as endothelin, thromboxane, C-type natriuretic peptide (CNP) and endothelin 1 (ET-1) play a role in controlling vascular tone as well as the progression of intimal hyperplasia [81,82]. Another role of ET-1 secreted by endocardial ECs is to control cardiomyocytes by enhancing the myofilaments' sensitivity to Ca^{2+} [75]. Tissue factor pathway inhibitor (TFPI) and prostacyclin synthase (PTGIS) genes prominently associated with anti-thrombotic protection are also differentially expressed in endocardial ECs at different locations of the ventricular endocardium [56].

Other factors, such as catecholamines and neurohormones, as well as neuregulin secreted by endocardial ECs, are responsible for contractility and ventricular remodeling [75]. Detailed characteristics of different types of ECs are summarized in Table 1.

Overall, *in vitro* and *in vivo* studies of native adult endothelium demonstrate the intrinsic differences that exist among various endothelial sites of the cardiovascular system. In line with this, site-specific types of shear stress are important in the maintenance or alteration of these variations within ECs in different locations [61,68,85,87–94]. Such knowledge should be among the considerations for the

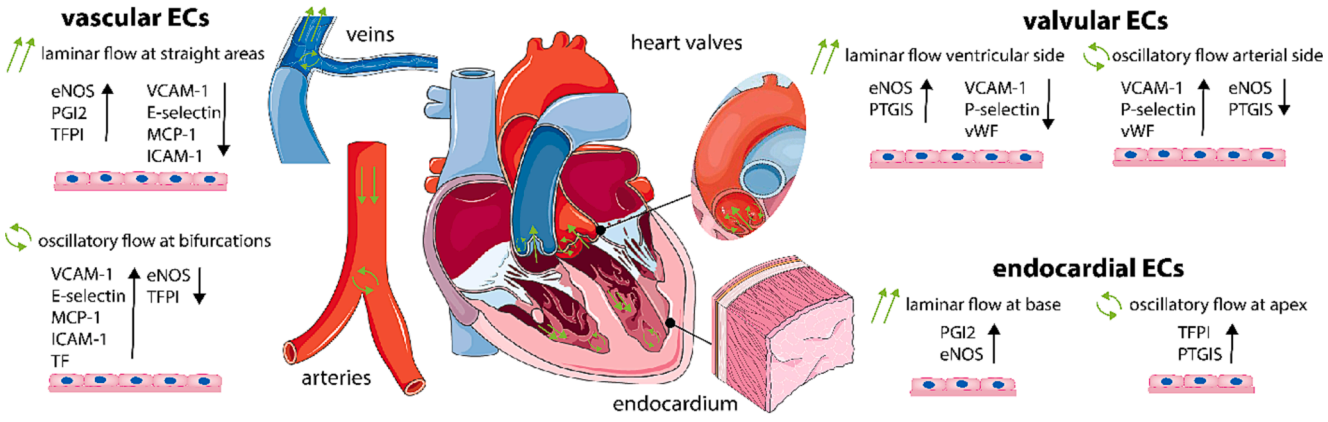

Fig. 1. Endothelial cell (EC) function is dominantly impacted by their functional site and the local hemodynamic environment. Variations in anti-thrombogenic and anti-inflammatory factor secretion have been reported between vascular, valvular and endocardial ECs, under laminar or oscillatory flow conditions. Abbreviations: eNOS, endothelial nitric oxide synthase; PGI2, Prostaglandin I2; TM, Thrombomodulin; TFPI, Tissue factor pathway inhibitor; VCAM-1, vascular cell adhesion molecule 1; MCP-1, monocyte chemoattractant protein 1; ICAM-1, intercellular adhesion molecule 1; TF, Tissue Factor; PTGIS, Prostaglandin I2 Synthase; vWF, von Willebrand Factor.

Table 1
Characteristics of different endothelial cells (ECs).

Vascular endothelial cells	Valvular endothelial cells	Endocardial endothelial cells
Exposed to laminar flow in the straight parts of the vasculature, which becomes oscillatory in bifurcation regions [83]	Exposed to laminar flow on the ventricular side and oscillatory flows on the arterial side [57].	Exposed to laminar flows in the ventricles while the apex and the middle part are exposed to greater oscillatory flows [56].
Align parallel to the flow [84]	Align perpendicular to the flow, which may reflect in the differential expression of thrombogenic factors as compared to other ECs [84]	
Increase expression of pro-inflammatory genes when exposed to steady laminar flow [69]	Decrease expression of pro-inflammatory genes (e.g., IL-1α,IL-8) when exposed to steady laminar flow [69]	Coronary arterial ECs have a higher synthetic capacity and express more eNOS in comparison to coronary venous ECs [85]
	Lower expression of vWF on ventricular side when compared to vascular ECs [61]	Consistent atrial contractions maintain the normal endocardial expression of eNOS
Vascular ECs acquire athero-susceptible phenotype in bifurcations [86]	Possibility of calcification on the arterial side and more protective phenotype on the ventricular side as function of hemodynamics [57]	Endocardial ECs have a protective phenotype in intracardiac regions with disturbed flow [86]. However, laminar flow contributes to the endocardial anti-thrombotic phenotype [67,68]
		Less angiogenic potential when compared to vascular ECs [86]
Control the vascular tone via secretion of vasodilators (e.g., NO, PGI2, endothelial derived hyperpolarizing factor) and vasoconstrictors (e.g., endothelin, thromboxane) that act on the underlying SMCs [81]		Control the underlying myocardium through release of factors such as ET-1, NO, catecholamines and neurohormones, as well as neuregulin [75]
Control the proliferation rate of the underlying SMCs via NO and PGI2, as well as CNP and ET-1 having a pro-proliferative effect [82]		
Upregulate α-SMA expression in the underlying SMCs [55].	Downregulate α-SMA expression in the underlying interstitial cells [55].	
Inhibit matrix deposition by the underlying SMCs when exposed to flow [55].	Increase matrix protein synthesis of the underlying VICs under flow [55].	

development of *in situ* endothelialized tissue-engineered cardiovascular devices. Its appreciation is necessary to ensure that cardiovascular substitutes induce and maintain appropriate EC phenotypes when implanted and exposed to the blood flow. Moreover, for cardiovascular sites with oscillatory blood flow, alternative strategies should be developed for tissue-engineered devices. This particularly concerns arterio-venous grafts, arterial sides of tissue-engineered heart valves (TEHVs), and the blood-contacting surface of cardiac prostheses, such as total artificial hearts.

3. In situ cardiovascular tissue engineering

3.1. Material-driven in situ tissue regeneration

In situ cardiovascular tissue engineering is an approach in which acellular (partly) resorbable implant materials are used to replace and regenerate cardiovascular tissues directly in their functional site, either completely or specific components thereof. This approach relies on the body's immunological response to such a material that is foreign to the body. This immunological response serves as the kick-starter for endogenous tissue regeneration in a phased process that is generally thought to mirror the wound healing cascade, as extensively reviewed previously [22,25] (Fig. 2). In brief, when a synthetic material is implanted in the body and comes in contact with the blood, blood proteins instantaneously adsorb onto the material surface. Consequently, enrichment of the surrounding microenvironment with different factors such as cytokines, growth factors, mitogens and chemoattracts occurs. This is followed by an acute inflammatory phase ruled by the infiltration of immune cells (e.g., neutrophils, monocytes). This eventually leads to a chronic inflammatory phase and potentially a foreign body response, in which other cell types such as fibroblasts and stem cells become involved in a close cross-talk with immune cells coordinating the process (e.g., macrophages, lymphocytes, multinucleated giant cells). Ideally, this cascade leads to the formation of a homeostatic functional tissue and the resolution of inflammation upon degradation of the synthetic implant [22]. In general, immune cells are the main factors contributing to the regeneration process but other cellular elements from the blood such as progenitor cells of various origins (endothelial and smooth muscle progenitor cells), mature ECs and other stem cells also become involved [95–99].

The major translational advantage of this technology is that it is a cost-effective and broadly applicable approach to ensure full or partial regeneration of viable cardiovascular tissues that preserve their ability to adapt and remodel in response to changes in the local environment (e.g., differential hemodynamics), a significant hallmark for the sustained long-term functionality of native cardiovascular tissues [100]. This contrasts with other tissue engineering approaches that use cell preseeding either or not combined with *in vitro* culture before implantation. While proof-of-concept studies have been conducted for various applications, the exact mechanisms of *in situ* tissue regeneration are only beginning to be uncovered [26,101].

3.2. Endogenous cellularization routes for in situ regeneration

Key to the approach of *in situ* tissue engineering is the recruitment of host cells to the acellular implant. Once on site, the host cells will break down the implant material and replace it with functional native-like tissue. For *in situ* tissue engineering of cardiovascular tissues, acellular biomaterials are placed in direct contact with the bloodstream. Therefore, one of the most critical elements in cardiovascular *in situ* regeneration is to regenerate a functional endothelial lining. The exact sources of infiltrating cells in *in situ* engineered tissues remains an active topic of debate. To date, three important cellularization routes have been identified, namely: transanastomotic outgrowth, transmural ingrowth, and fallout healing, as described in more detail in the following sections [102] (Fig. 3A).

While there is *in vivo* evidence for all three cellularization routes from animal experiments, it is important to note that there are strong differences in cellularization routes among species [103]. In this respect, data from animal experiments should be interpreted with species-relevant limitations. Several studies have described ways to mechanistically investigate the cellularization routes in small animal models, for example by isolating specific routes of cell influx by shielding off others [45,104]. However, the applicability of certain cellular influx routes is dependent on the type of application. For example, while transmural ingrowth of cells likely plays a major role in the cellularization of porous

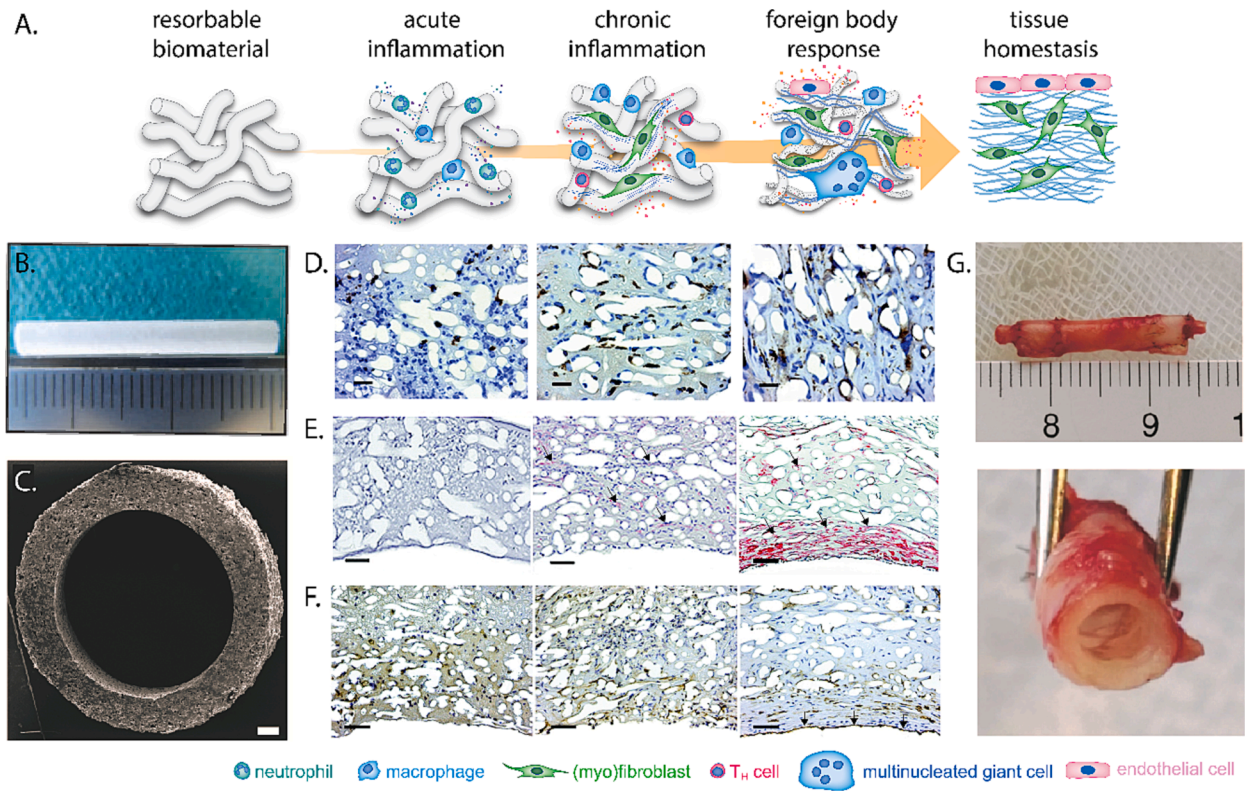

Fig. 2. (A) Schematic representation of the process of *in situ* cardiovascular tissue engineering, mirroring the wound healing cascade and the foreign body response. *In situ* tissue engineering starts from an acellular bioresorbable scaffold (B-C). Upon implantation the scaffold triggers an acute and then chronic inflammatory response, characterized by the influx of neutrophils and macrophages, respectively (D; neutrophils (myeloperoxidase) in blue, macrophages (CD68) in brown). Subsequently, the inflammatory cells attract tissue forming cells, such as smooth muscle cells (E; α-smooth muscle actin in red) and endothelial cells (F; CD34 in brown). These cells produce new tissue while the synthetic scaffold is gradually resorbed, eventually leading to a regenerated tissue (G). Scale bars, 20 μm (D) and 50 μm (E, F). Figure A adapted with permission from De Kort et al. 2021 [25], B, C and F from Bonito et al. 2021 [48], and D-F from Talacua et al. 2015 [45]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

vascular scaffolds, it is not applicable when considering an implant such as a total artificial heart, which consists of an impermeable outer material. Transanastomotic outgrowth is clinically most likely to be a much more relevant cellularization mechanism in heart valve replacements than in small-diameter blood vessels, since valved conduits have a large diameter and a short length (on average 5 cm) which would allow for sufficient endothelialization by mature human ECs [108–110]. Moreover, TEHVs geometrically consist of leaflets with or without a conduit wall, and they are implanted either intraluminally or as interposition grafts in the aorta or the pulmonary artery [27,108–115]. These variations in valve design and implantation procedure are likely to influence the relative contributions of cellularization routes. Preclinical experiments with resorbable synthetic heart valves have shown strong spatiotemporal differences in cellularization routes, for example between the conduit and the valvular leaflets [26]. Moreover, variations have been shown in tissue formation and endothelialization between the ventricular and arterial sides of the leaflets [27]. There is data to suggest that the influx of circulating cells is dependent on the local hemodynamic loads [116,117], as well as the implant site [118]. Hence, it is inherently not possible to pinpoint which cellularization mechanism is the dominant route, without considering the specific application and implant design, as well as the local hemodynamic loads.

3.2.1. *Transanastomotic outgrowth*

Transanastomotic outgrowth is the first identified cellularization mechanism in studies with implanted prosthetic vascular grafts. It relies on a complex signaling network involving ECs, monocytes, platelets, and SMCs. In brief, implantation interferes with normal blood vessel homeostasis and triggers the activation of adjacent native tissue. This promotes an inflammatory response, characterized by the upregulation of leukocyte adhesion molecules, cytokines, and chemokines. In response, recruited monocytes and macrophages initiate a healing process. This combination of factors stimulates the proliferation and migration of native vascular ECs, as well as the migration of SMCs and fibroblasts from the anastomosis sites toward the center of the graft [102]. Hibino *et al.,* showed that infiltrating cells in a porous vascular interposition graft almost exclusively (50%, 72% and 93% increase as the distance to adjacent native vessel increased) originated from transanastomotic outgrowth of the adjacent vessel in mice [106] (Fig. 3Bii).

Indeed, implanted large-caliber and small-caliber tissue-engineered vascular grafts (TEVGs) usually demonstrate complete endothelialization in animal models [119–129]. However, its clinical relevance has been contested, especially in long small-caliber grafts, due to the low proliferative capacity of mature human ECs, which is in contrast to the intrinsically high endothelialization capacity of small animals [103]. As is evident from studies with non-degradable synthetic vascular grafts, transanastomotic endothelialization by mature human ECs does not exceed 1–2 cm from the anastomosis [130]. Moreover, the vast majority of vascular grafts tested in animal models have a length/diameter ratio under 10 cm [131], which may lead to false positives in terms of patency, when compared to clinically used small-diameter grafts [132,133].

3.2.2. *Transmural ingrowth and capillarization*

Transmural ingrowth of cells from the local adventitial tissue into a graft has been pinpointed as a major source of cells in porous cardiovascular implants. Recent studies by Pennel *et al.,* and Liu *et al.,* showed that the surrounding tissue is a major source for smooth muscle-like

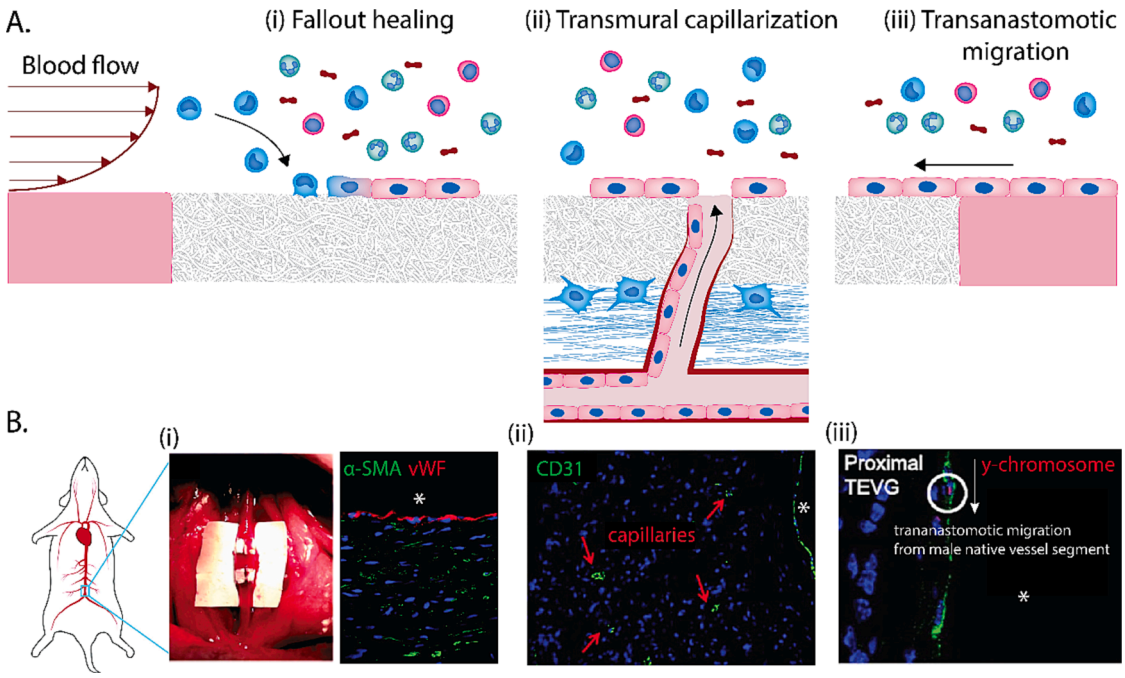

Fig. 3. (A) Schematic representation of the three identified cellularization routes, representing (i) fallout healing by circulating (progenitor) cells, (ii) transmural capillarization and infiltration, and (iii) transanastomotic migration of mature tissue cells. (B) Reported examples for each route, with (i) showing presence of blood-derived α-Smooth Muscle Actin (α-SMA) and von Willebrand Factor (vWF) positive cell populations in GoreTex-shielded vascular grafts in rats. Adapted from Talacua et al. 2015 [45]; (ii) transmural ingrowth of CD31 + capillaries in vascular grafts in rats. Adapted from Liu et al. 2019 [105]; and (iii) transanastomotic migration of mature endothelial cells from a segment of anastomosed native male vessel into a tissue-engineered vascular graft (TEVG) in female mice. Adapted from Hibino et al. 2011 [106]. * Indicates lumen. Subfigure A was inspired by Heath 2017 [107].

cells, immune cells and ECs during *in situ* tissue engineering of blood vessels using resorbable synthetic vascular grafts [105,134] (Fig. 3Biii). Transmural ingrowth and capillarization require the onset and progression of foreign body response and the formation of granulation tissue on the adventitial surface of implanted grafts. Cells confined to the granulation tissue such as fibroblasts and macrophages secrete angiogenic factors that initiate and promote neovascularization and subsequent transmural capillarization towards the luminal surface, however, the reason why the latter process takes place remains unclear [102]. Transmural capillarization might be necessary for a complete TEVGs endothelialization, as seen for ePTFE-based grafts [134]. Bonito and Koch *et al.,* reported on the transmural 'bridging' of neotissue from the adventitia to the lumen in resorbable synthetic vascular interposition grafts in rats [48]. Moreover, Duijvelshoff *et al.,* proposed a dominant role for the surrounding native arterial tissue in the *in situ* regeneration of resorbable nanofibrous endovascular stents [30].

The extent of transmural cellular influx is highly dependent on graft pore size, as previously shown *in vitro* [135,136] and *in vivo* [137,138]. Ideally, graft pore size should be large enough to permit neovascularization and ingrowth of SMCs and fibroblasts [103]. The positive correlation between high scaffold porosity and endothelialization and tissue formation has been demonstrated in synthetic TEVGs [128,139,140]. Furthermore, differences between animal models used for *in vivo* implantation of TEVGs should be acknowledged when assessing the effects of porosity on graft endothelialization [121,122].

3.2.3. Fallout healing

Fallout healing, which is the adhesion and functional differentiation of circulatory cells, is the third discovered mechanism of *in situ* cellularization, and especially endothelialization. It depends on tethering protein adsorption and subsequent adherence, chemotaxis and proliferation of circulating cells [141]. Already in 1998, Kouchi *et al.,* showed that islands of ECs and SMCs were present in impervious Dacron vascular grafts when used as long (64–77 cm) extraanatomical bypasses in dogs, suggesting the recruited cells were of blood-borne origin [99]. More recently, Talacua and Smits *et al.,* showed abundant influx of extracellular matrix (ECM)-producing smooth muscle-like cells and immune cells, as well as extensive endothelialization in arterial interposition grafts in rats in which both transmural and transanastomotic ingrowth were blocked using impermeable ePTFE sheathing [45] (Fig. 3Bi). These findings indicate that circulating cell populations intrinsically have the potential to give rise to various mature vascular cells, although the exact origin of the various cell types was not investigated.

4. In situ regeneration at the blood-biomaterial interface

4.1. Blood proteins

Blood is rich in biological elements that vary from cells, cytokines, and proteins. Such elements play a significant role in controlling the fate of the implanted biomaterial, either for the bad or the good. When a biomaterial is implanted in direct contact with the blood, the material is instantaneously covered by blood proteins that adsorb to the surface of the material. This protein layer consists of blood proteins, including factors from the coagulation and complement (e.g., opsonins) cascades, as well as damage-associated molecular patterns (DAMPs) that may arise from the implantation procedure [142].

Exposure of the blood to a biomaterial leads to the activation of the coagulation cascade, the complement cascade, and leukocytes. This contributes to the inflammation and the adhesion and activation of platelets. Such processes are the main drivers for adverse events, such as thrombus formation and calcifications, which may lead to implant failure [41,143]. These processes are reviewed in detail elsewhere [144,145]. Apart from posing these risk factors, the coverage of material with blood proteins is an important initial step in the regenerative cascade. The protein layer is dynamic in composition (e.g., because of the Vroman effect) and serves as an interface for cells to interact with the

biomaterial [142,146]. Moreover, blood proteins act as a preliminary matrix for cells to modulate inflammation and the subsequent tissue remodeling cascade [147].

Of particular interest in this context is fibrin. Fibrin has been utilized in vascular grafts for its ability to facilitate the invasion/entrapment and arrangement of cells [45,148]. Interestingly, De Kort et al. detected the presence of fibrin in *in situ* TEHVs based on resorbable micro-fibrous synthetic scaffolds even up to 24 months after implantation [26]. Using Raman microspectroscopy, fibrin was found to be surrounding the grafts structure during the full course of the study follow-up time (Fig. 4A). The fibrin was suggested to serve as a provisional matrix as part of the early immune response, facilitating the new tissue formation downstream [26]. The mechanism could be related to the previously reported ability of fibrin to promote the influx of immune cells (e.g., neutrophils and macrophages) and their anti-inflammatory potential [149,150]. In addition, while fibrin itself is the major fibrous component of blood clots, the presence of cross-linked fibrin is in fact associated with anti-thrombotic activity [151]. For instance, the quality of fibrin mesh within the blood clot is based on fiber diameters, packaging, and the size of the pores. If a dense blood clot is formed with thin fibrin fibers, then there is a high chance of increased thrombosis. On the other hand, if a loose blood clot is formed with thick fibrin fibers, then there is a high chance of increased bleeding [152].

Indeed, previous studies have pointed to the beneficial pro-healing effect of the blood clot including fibrin fibers. For example, Burkhardt *et al.,* showed that macrophages entrapped within the blood clot can polarize towards an M2 phenotype, enhancing cell proliferation rate and creating an angiogenic microenvironment (e.g., matrix metalloproteinase-9, MMP-9; vascular endothelial growth factor, VEGF) that can promote the remodeling process [154]. In addition, based on *in vivo* studies using resorbable synthetic vascular and valvular scaffolds in both small and large animals it has been postulated that the deposition of blood proteins may act as a preliminary matrix that acts as an anchoring site for the subsequent development of functional fibrous tissue components, such as collagen and elastin [26,27,30,48]. For example, in resorbable heart valves, there is a consistent development of an appositional collagenous layer on the luminal surfaces of implanted TEHVs [26–28]. Duijvelshoff et al. reported on the subluminal development of mature elastic fibers in resorbable nanofibrous endovascular stents [30] (Fig. 4C). While the exact influence of the blood on these processes is unknown, the consistent finding of a luminal layer in cardiovascular grafts does suggest that blood proteins contribute in some way to the fibrous matrix assembly.

4.2. The blood as a cell source

The blood harbors a continuous source of numerous stem- and progenitor cells, such as endothelial progenitor cells (EPCs), smooth muscle progenitor cells, fibrocytes and immune cells that may play a major role in *in situ* tissue regeneration and endothelialization [95–99]. Table 2 summarizes studies for *in situ* tissue-engineered implants and the role of different cells in the cellularization process.

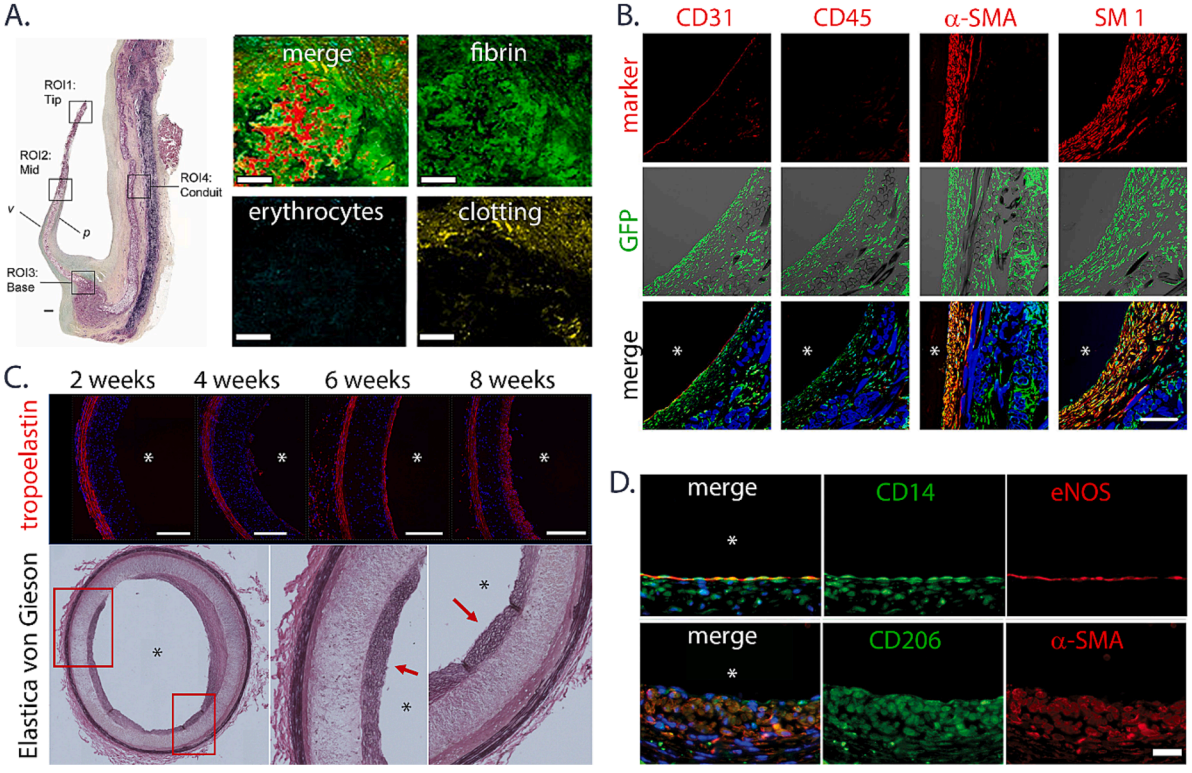

Fig. 4. (A) Detection of fibrin in tissue-engineered heart valves based on micro-fibrous resorbable synthetic scaffolds up to 24-months *in vivo*. Explanted valves were longitudinally sectioned and analyzed with Raman microspectroscopy to determine the tissue composition in localized regions-of-interest (ROIs) as indicated. Displayed are the Raman-derived maps of ROI3 (base of the leaflet) with the synthetic scaffold labeled in red, fibrin in green, erythrocytes in cyan, and clotting proteins in yellow. Scalebars, 100 μm. Adapted from De Kort et al. 2021 [26]. (B) GFP-labelled bone marrow-derived cells were detected to significantly constitute the α-smooth muscle actin (α-SMA) and smooth muscle myosin heavy chain (SM 1) expressing smooth muscle cells and $CD31^{+}$ endothelial cell layers in silk fibroin grafts in rats. Scale bar, 100 μm. Adapted from Enomoto et al. 2010 [153]. (C) Detection of regenerated elastic fibers in nanofibrous resorbable synthetic endovascular stents in rats, with mature elastic fibers organized in the subluminally formed layer. Scale bars, 200 μm. Adapted from Duijvelshoff et al. 2020 [30]. (D) Transdifferentiated $CD14^{+}$ monocytes from the circulation as a cell source contributing to newly formed $eNOS^{+}$ endothelium, as well as α-SMA and CD206 double-positive mural cells on resorbable vascular grafts in mice. Scale bar, 50 μm. Adapted from Nasiri et al. 2022 [46]. * Indicates lumen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Reported roles of various cell types in *in situ* tissue-engineered implants.

Application	Material	Model	Cells involved	Main Findings	Ref
TEVGs	Small intestinal submucosa functionalized with heparin and VEGF	Infrarenal aorta of mouse	Monocytes/ M2 macrophages	Complete endothelialization 1 month post implantation with endothelial cells derived from monocytes.	[51,155]
TEVGs	Electrospun PCL loaded with MCP-1	Rat aorta with anastomotic site and outer surface shielded with Gore-Tex	Monocytes/ M2 macrophages	MCP-1 helped macrophage polarization into M2 that subsequently differentiated into SMCs. Besides the recruitment of angiogenic monocytes as source for endothelial cells.	[45]
TEVGs	Non-woven PGA + poly-L-lactide co– ε -caprolactone sealant	Infrarenal inferior vena cava immunodeficient mouse model.	Monocytes	pre-seeded hBMCs promoted host cellinfiltration in paracrine fashion by secreting MCP-1. Early monocyte infiltration contributed to recruitment of α-SMA^{+} cells and ECs, with consequently vascular remodeling via VEGF secretion in addition to other molecular factors.	[42]
TEVGs	Non-woven PGA + poly-L-lactide co– ε -caprolactone sealant	Infrarenal inferior vena cava immunodeficient mouse model.	Platelets, NK cells, macrophages	Innate immune response is responsible for graft fate.	[156]
TEVGs	Electrospun CE-UPy-PCL-UPy-HBP functionalized with heparin, heparin/IL-4 or bare grafts	Rat aorta with anastomotic sites blocked with Gore-Tex	Macrophages/ M2, α-SMA^{+} and CD31^{+} blood derived cells	Early cellular influx of macrophages in heparin/IL-4 group with polarization of these cells into a pro-healing M2 phenotype which was responsible for downstream healing process.	[48]
TEVGs	PCL scaffolds with different microstructures	Left common carotid artery of rats	Mature SMCs, M2 macrophages, Sca I^{+} stem cells	Microfiber structure promoted high patency, cell infiltration rate and larger lumen. Such structure enhanced SMCs infiltration from surrounding tissue. Sca I^{+} stem cells and M2 macrophages potentially contributed to the regeneration as well.	[105]
TEHVs	Valve leaflets made of ePCL-UPy connected to conduit made of ePC-UPy	Pulmonary valve position in Swifter sheep	Macrophages, progenitor cells, FBGCs, mature α-SMA^{+}, ECs from microvessels withing the leaflets, VICs from EndMT	Presence of FBGCs and macrophages was associated with scaffold resorption. Cell sources could originate from circulating cells, surrounding tissue, transmural ingrowth, and various progenitor cells. The heterogenous hemodynamic environment to which different locations of the valves were exposed perhaps have influenced certain cell populations recruitment.	[26]
TEVGs	Small intestinal submucosa functionalized with heparin and VEGF	Left common carotid artery of a sheep model	Circulating EPCs, possibly ECs from other tissues. M2 macrophages, SMCs	Functional endothelium was present 1 month post implantation. High influx of cells positive for macrophages markers and α-SMA 1 month post implantation that reached similar level as native vessels by 3 months. Absence of fibrillar elastin 3 months post implantation, however the explant still maintained mechanical integrity.	[157]
TEVGs	Electrospun scaffold of PCL and PLLA immobilized with heparin/SDF-1α	left common carotid artery of rats	Circulating EPCs, Mature ECs, smooth muscle progenitor cells	Heparin/SDF-1α grafts were well vascularized with more matrix deposition and intact endothelium at 6 months post implantation. Cells in these grafts were positive for CD34, CXCR7 and CD45. Additionally, smooth muscle progenitors (positive for CXCR4, CXCR7, CD29, CD44) and α-SMA^{+}, CNN1^{+}, MHC^{+} cells were also recruited to the grafts after 1 month.	[158]
TEVGs	High porosity mid graft located within 9 cm looped conduits modified in 4 ways 1) ePTFE wrap, 2) mid graft externally coated with PU, 3) mid graft functionalized either with heparin or 4) with heparin + VEGF + PDGF	Infra-renal aorta-Wistar rats	ECs through transmural route and circulating EPCs	Transmural endothelialization comes first compared to blood-borne. VEGF and PDGF contributed to significantly enhancing endothelialization compared to heparin only functionalized grafts.	[134]
TEVGs	Electrospun PCL modified with RGD	Right carotid artery of rabbits	Mature ECs and SMCs. Possibly EPCs and other stem cells	RGD led to higher cellular influx within the scaffolds. ECs and SMCs migrated through the anastomotic sites to the middle of the grafts aided by RGD.	[159]
TEHVs	Decellularized TEHVs made originally from PGA non-woven meshes	Orthotopic transplantation in pulmonary valve in chacma baboons	α-SMA^{+} from surrounding tissue	α-SMA^{+} cells populated the conduit wall but not the valve leaflets which implied absence of leaflets retraction. Macrophages (MAC-387) influx at 4 and 8 weeks through the leaflets. Less endothelization on the leaflets as compared to the conduit wall.	[114]

(*continued on next page*)

Table 2 (*continued*)

Application	Material	Model	Cells involved	Main Findings	Ref
TEVGs	Multilayered electrospun scaffolds made of PELCL, PLGA, PCL and gelatin functionalized with VEGF and PDGF	Left common carotid artery of rabbits	ECs and SMCs	Controlled release of PDGF compared to VEGF. VEGF promoted complete endothelialization 8 weeks post implantation. PDGF enhanced vascular SCMs excessive proliferation leading to hyperplasia. Vascular SMCs migrated from the outer surface of the grafts to the middle layer.	[160]
TEVGs	Silk Fibroin	Abdominal aorta of rats	SMCs derived from bone marrow. Mature ECs	SMCs were derived from bone marrow and expressing SM1 (differentiated SMC marker), while ECs were derived from surrounding tissues. Macrophages contributed to grafts degradation. Native-like vessel structure was apparent 1 year post implantation.	[153]
TEVGs	Polyester knitted grafts coated with fibronectin and SDF-1α	Sheep carotid artery	$CD34^+$, $CD117^+$ cells and mature ECs	Early high influx of $CD34^+$ and $CD117^+$ cells in coated grafts compared to the noncoated control. Higher endothelium formation rate in coated grafts specifically at the anastomotic sites in line with less neointimal hyperplasia, which reflected on increased flow surface.	[95]
TEHVs	Decellularized native pulmonary valves from human functionalized with CD133 antibody.	*In vitro*	NT2 cells	$CD133^+$ cells (NT2 cells) adhered to the functionalized valves in flow chamber. The adhesion was dependent on the CD133 antibody functionalization concentration.	[161]
TEVGs	Outer scaffold made of elctrospun PLA and inner scaffold made of sponge PLCL	Infrarenal abdominal aortas of mice	c-kit progenitor cells (CD117)	The inhibition of PDGF receptor kinase led to a more quiescent SMCs phenotype, while the inhibition of the c-kit receptor led to less recruitment of c-Kit cells, which are progenitor cells able to give rise of SMCs.	[162]
TEHVs and TEVGs	Photooxidized bovine pericardium bioprosthetic valves/ vascular grafts immobilized with fibronectin and SDF- 1α.	Pulmonary position valve in sheep. Carotid artery in rats	$CD34^+$, $CD117^+$, $CD90^+$	Coating of the grafts steered the phenotype of the adhered cells towards more stem cell phenotypes ($CD34^+$ and $CD177^+$), which differentiate later to mature vascular cells. The dual functionalization prevented leaflets shortening because of the reduction in contractile cells (α-SMA^+).	[96]

4.2.1. Bone marrow mononuclear cells as a source of tissue cell replenishment

Bone marrow-derived mononuclear cells (BMMCs) play various roles in tissue healing and remodeling. Apart from immunological functions, BMMCs have been reported to directly replenish functional cardiovascular cell types, including ECs and SMCs, via recruitment to sites of injury via the blood followed by local differentiation. This can be either through the direct adhesion of circulating cells to the luminal surface of graft, but also via the (transmural) ingrowth of microcapillaries, as also repeatedly reported for regenerative heart valves [26–28].

In mouse models with different induced mechanical vascular injuries, BMMCs were found to be substantially contributing to the cells forming the neointima and medial layers, potentially mediated by secreted chemotactic factors such as VEGF, MCP-1 and SDF-1α [163]. Moreover, studying atherosclerotic plaques from the coronary artery of patient recipients of a bone marrow transplant showed that the fraction of the SMCs in the atherosclerotic arterial wall that came from the donor BMMCs was 100-fold higher than in healthy conditions [164]. Similar findings have been reported in heart valves. Using a mouse model with green fluorescent protein (GFP)-labeled bone marrow cells, Hajdu *et al.,* showed that BMMCs homed to remodeling heart valves where they differentiate into valvular interstitial cells (VICs) and produce collagen as part of normal valve homeostasis [165]. Interestingly, Anstine *et al.,* recently showed that the process of BMMC recruitment to heart valves is dependent on age in mouse models, as evaluated using cell fate tracing of $CD45^+$ cells. In both the aortic and mitral valves, the percentage of $CD45^+$ cells was observed to rise with age [166].

These findings show that BMMCs physiologically contribute to the homeostasis and restoration of native cardiovascular tissues. Similar observations have been made for implanted grafts. GFP-labelled bone marrow was implanted in a recipient rat in which afterward silk fibroin grafts were implanted in the abdominal aorta. The GFP-positive cells were found to significantly constitute the SMC layer (e.g., cells expressing α-SMA and positive for GFP increased up to 50.9% at 3 months) and to a lesser extent the endothelial layer [153] (Fig. 4B).

With respect to prosthetic heart valves, cells positive for vimentin and α-SMA were reported to populate decellularized synthetic scaffolds when implanted as pulmonary valve replacement in sheep, throughout the valvular leaflets, already within 5 h post-implantation, suggesting circulatory cells could be the source [167]. BMMCs have been suggested as a source of VICs in decellularized porcine valves implanted in the pulmonary arterial trunk in dogs. Such immature cells were positive for vimentin, and they were found in scattered lesions underneath the endothelial layer suggesting a blood-borne origin [168]. However, this does not exclude that those vimentin-positive cells could also have originated from mature ECs through Endothelial-Mesenchymal Transition (EndMT) [168]. Similar findings were reported in a study by De Kort *et al.,* in which abundant cells positive for α-SMA and calponin were present directly below the endothelial layer in explanted tissue-engineered pulmonary valves based on resorbable synthetic scaffolds after long-term implantation in sheep [26]. These cells were associated with elevated levels of biglycan and transforming growth factor beta (TGF-β) in addition to enhanced collagen III deposition [26], suggesting that high levels of TGF-β may aid in the differentiation of circulating stem cells into tissue-producing cells [169]. However, it should be noted that cell lineage tracing studies have not been reported for prosthetic heart valves, given that these implants are typically tested in large animal models. Thus, observations regarding cellular origins in such studies remain mostly speculative so far.

Taken together, the aforementioned observations indicate that BMMCs harbor various cellular subpopulations that have the potential to give rise to mature cardiovascular tissue cells, both in native tissues as well as in prosthetic cardiovascular grafts. This is further supported by *in vitro* studies, in which it was shown that BMMCs from peripheral circulation were able to differentiate into SMCs, expressing calponin, Smooth Muscle Myosin Heavy Chain (SM-MHC) and α-SMA [170].

Interestingly, this role of direct differentiation by BMMCs was not observed in studies in which BMMCs were used to pre-seed prosthetic grafts [42,171]. For example, Roh *et al.,* showed that human BMMCs that were pre-operatively seeded into venous grafts implanted in mice did not contribute to the tissue regenerative process in terms of direct cell differentiation [42]. Instead, they explained that the regenerative process is facilitated by paracrine signaling from the BMMCs, rather than direct differentiation, e.g., via abundant monocyte chemoattractant protein-1 (MCP-1) secretion, presumably by the monocytes within the BMMC population [42]. Implanted TEHVs based on resorbable supramolecular elastomers were actually found not to favor the preseeding with BMMCs as it led to calcification and valve regurgitation [171]. This was supported by the upregulation of genes involved in calcification, regurgitation and activated VICs as compared to unseeded valves [171].

4.2.2. Bone marrow-derived stem cells

Many precursor cells are included within the BMMC pool. Therefore, when aiming to actively recruit certain cell fractions from the circulation for *in situ* regeneration, it is important to investigate in further detail the exact cellular origin of tissue-precursor cells within the BMMC population.

BMMCs contain various stem and progenitor populations. Stromal cell-derived factor 1 alpha (SDF-1α) coated vascular grafts revealed a beneficial role for circulating $CD117^+$ (c-Kit) and $CD90^+$ progenitor cells in the functional repopulation and remodeling process of TEVGs [95] and TEHVs [96]. CD90 can be described as a versatile marker that is expressed by various types of cells such as mesenchymal stem cells, NK cells, hematopoietic stem cells, endothelium (mainly in high endothelial venules), myofibroblasts, and a fraction of fibroblasts. Specifically, $CD34^+/CD90^+$ cells showed the ability to differentiate into ECs confirmed by markers such as VEGF, Flk-1, CD31, CD54, and CD44 [172].

CD177 is expressed in certain (circulating) progenitor cells, mesenchymal stem cells, as well as various cells in blood vessels [96,169]. In a mouse model with transplant arteriosclerosis following allograft transplantation, $CD177^+$ $Sca\text{-}1^+$ $CD34^+$ cells were found to contribute to neointima formation [169]. More specifically, $CD177^+$ cells were shown to have a strong influence on the formation of SMCs in the neo-intima [169]. Inhibiting c-Kit function, whether with anti-c-Kit antibody or imatinib, a receptor kinase inhibitor of c-Kit, led to a drop in the neointima formation in both implanted allografts and bioresorbable scaffolds [162,169]. $CD177^+$ cells can originate from the bone marrow as well as other tissues. Although CD177 + cells from bone marrow cannot give rise directly to SMCs, they can promote the formation of the neointima by generating $CD45^+$ leucocytes (e.g., macrophage precursor cells in the adventitia) via an immune reaction [169]. Moreover, cells expressing CD177 were found to contribute to myocardial regeneration following injury [173].

4.2.3. Endothelial progenitor cells

Concerning endothelialization specifically, the most investigated cell source is circulating EPCs [141]. Circulating EPCs are a small population (0.002%) of $CD34^+/VEGFR\text{-}2^+$ peripheral blood mononuclear cells that arise in the bone marrow [174]. These cells have been shown to differentiate to mature ECs *in vitro* and accelerate the repair of vascular endothelium *in vivo* [174,175]. Laminar shear stress induces EPC differentiation into ECs *in vitro* via VEGFR-2 and PI3K/Akt/mTOR signaling pathways [176].

Mobilization of circulating EPCs to the sites of intimal vascular injury is regulated by multiple factors, including SDF-1α, VEGF, and hepatocyte growth factor (HGF) [177–179]. These molecules, together with EPC-associated surface markers, have laid down a pathway for the development of biofunctionalized materials to enhance *in situ* endothelialization [141]. For example, EPCs can be recruited to the surface of an implant decorated with VEGF via binding through VEGFR1 (flt-1) and VEGFR2 (flk-1) [98]. Besides VEGF, SDF-1α is another factor that can be used to induce mobilization of the EPCs in a chemotactic manner from the bone marrow into the peripheral blood. In addition, it can recruit those blood-circulating EPCs to the graft/implant by binding to CXCR4 and CXCR7 receptors on their surface, and promote differentiation into mature ECs [98,158]. A variety of other graft modification strategies have been reported to capture EPCs from the circulation, such as antibodies against CD133, CD34, VEGFR-2, CD31, ECM-peptides, and magnetically coated particles or aptamers [141,161,180–186].

4.2.4. Monocytes as cardiovascular precursor cells

Monocytes make up a large fraction of BMMCs and approximately 10–20% of the circulating mononuclear cell population in humans. In the human peripheral blood, three distinct monocyte subsets have been identified, based on differences in the expression of surface proteins (e.g., CD14/CD16/CCR2/CXCR4), as well as integrins [187,188]. Each monocyte subset has distinct functions. Classical monocytes ($CD14^+/CD16^-/CCR2^+$) are the main monocyte population (e.g., 90% of total monocytes). Such cells are recruited during the early inflammatory phase and contribute towards identifying and removing the foreign body (e.g., through phagocytosis). Intermediate monocytes ($CD14^{++}/CD16^+/CCR5^+$) are the second subset they are recruited during later inflammatory phases. They are antigen-presenting cells, and they can release high levels of chemokines, and pro-inflammatory cytokines. The third population is non-classical monocytes ($CD14^+/CD16^{++}/CX3CR1^+$) and they are continuously patrolling the endothelium in an innate defense mechanism in addition to their association to phagocytosis mediated by Fc-gamma and complement system [189,190]. Interestingly, the ratios of monocyte subsets have been reported to shift after myocardial infarction, suggesting a role in the pathophysiological tissue repair processes after damage [191]. In line with this, the composition of monocyte subsets in the blood has been proposed as a biomarker for certain pathologies [99,190,191].

The importance of monocytes in tissue regeneration is evident in numerous studies. For example, studies by Roh *et al.,* and Talacua and Smits *et al.,* showed that modulating the initial recruitment of monocytes via MCP-1 release, led to various beneficial downstream effects concerning the formation of neotissue in resorbable synthetic vascular grafts [42,45]. Generally, the dominant role of monocytes is attributed to the fact that these cells give rise to macrophages, which are well-established to play key roles in tissue regeneration as well as biomaterial degradation [26,192–198]. Consequently, manipulating macrophage polarization is a widely pursued strategy to modulate tissue regeneration [48].

In addition to their immunological role as mediators of tissue formation and remodeling, monocytes represent a potential source of cardiovascular tissue cells. Particularly, the role of monocytes as potential precursors for ECs has come into the spotlight recently. Monocytes and monocyte-derived macrophages are known to play important paracrine roles in the angiogenesis and vascularization of biomaterials, for instance by secreting large amounts of trophic and angiogenic factors, such as VEGF [199,200]. However, interestingly, VEGF is a chemoattractant for monocytes and macrophages themselves [201], and it has been shown that VEGF can steer the direct trans differentiation of monocyte-derived macrophages into endothelial cells *in vitro* [202–205]. Leveraging this potential, Smith Jr. *et al.,* reported on the use of acellular vascular grafts functionalized with VEGF to stimulate *in situ* endothelialization [47,51,206]. In one of their recent studies, VEGF-functionalized arterial grafts based on small intestinal submucosa (SIS) were found to be populated with cells co-expressing endothelial marker CD144 and M2 marker CD163 after implantation *in vivo* [47]. Additionally, such cells co-expressed the monocyte marker CD14 and the endothelial marker eNOS, suggesting the strong contribution of monocytes to the endothelium formation [47]. Moreover, the majority of cells adhering to the graft lumen were VEGFR1-expressing monocytes, predominantly present within the $CD14^+/CD16^+$ angiogenic monocyte

subset [51,188]. There was no difference between the cell density at mid-graft and the anastomotic sites, therefore it was postulated that the blood was the main source for such cells [47] (Fig. 4D).

In addition to giving rise to ECs, cells of myeloid origin ($CD14^+$, $CD105^+$) within the BMMC population have been indicated as a potential source for vascular SMCs [170]. In line with this, monocytes and macrophages have been shown to transdifferentiate into SMCs and (myo)fibroblast-like cells in various clinical scenarios [207–211]. Interestingly, such cells could be sharing the same precursor with EPCs but the surrounding environment is a deciding factor for the fate of those precursors (e.g., the presence of growth factors, such as basic fibroblast growth factor (b-FGF), platelet-derived growth factor (PDGF)-BB and TGF-β) [212]. However, the role of monocytes and macrophages as precursors for SMCs and VICs in cardiovascular grafts has not been extensively studied so far and remains largely unknown.

4.3. Targeting of circulatory cells for in situ regeneration

Overall, it is clear that the regeneration process is an interplay between multiple cell types in addition to multiple recruitment mechanisms, which include numerous paracrine and cell differentiation processes. Given that progenitor cells, such as EPCs, in the human circulatory system are very low in number and highly variable between individuals, the extent of their contribution to *in situ* regeneration as direct sources of mature tissue cells in humans is to be determined. The pleiotropic influence of the highly abundant circulating immune cells, such as monocytes, in *in situ* tissue engineering, on the other hand, is unmistakably important.

It is apparent that a proper understanding of the regeneration process is still lacking, with multiple studies reporting incomplete results or contradictory outcomes. In addition, it is clear that the markers used for circulating progenitor cells are typically not mutually exclusive and overlap between existing subsets, which makes adequate characterization and comparisons between studies challenging [213,214]. It is however relevant to pinpoint cellular sources since differences in cell origin may affect eventual cell function. For example, SMCs originating from BMMCs were found to display a distinct proteomic profile and produce fewer inflammatory cytokines and proteases when compared to SMCs in the medial layer of arteries [215]. Such phenotypic differences might reflect on their functional profile when recruited to tissue-engineered cardiovascular grafts based on their quiescent versus active profile.

When targeting cell recruitment from the bloodstream using biomaterial modifications, it is important to understand that a specific selection for the cellular elements is needed. For example, utilizing ECM peptides (e.g., RGD, REDV, YIGSR) to enhance cellular infiltration from the blood is a double-edged sword: on the one hand, it can indeed attract cells to populate the implant, but on the other hand, it can also attract undesired elements such as platelets which have a binding domain for fibronectin [141,216]. To mitigate such risks, dual-functionalized materials have been proposed, which combine anti-thrombogenic properties (e.g., via PEG or heparin) with specific cell recruitment- or binding proteins (e.g., VEGF, IL-4) [19,48,217–219].

5. Engineering approaches to promote the success of tissue regeneration

The physical properties of the scaffold can play a major role in determining implant healing based on different aspects. For example, design parameters such as pore size, fiber size and topographies have a strong influence on cellular adhesion, activation, differentiation, and migration on and into implanted scaffolds. As such, the rational engineering of physical implant characteristics represents an important asset to modulate the host response. For instance, scaffold pore size can be tuned to steer cell influx and behavior. Substrate topography is particularly relevant in the context of blood-compatible implants as it is an important determinant for endothelialization. In addition, of particular interest are novel cell-free substrates that are being developed, in which dynamic surface topographies are used as 'self-cleaning' surfaces that are able to avoid thrombus formation and platelet adhesion. The following section deals in more detail with state-of-the-art engineering approaches to create hemocompatible and -regenerative materials.

5.1. Scaffold microstructure

The scaffold microstructure, which is characterized by parameters such as pore size and fiber diameter, affects various aspects of cardiovascular graft performance. Scaffolds with small fiber diameters (fiber ∅ <1 μm) are intuitively thought to be advantageous in tissue engineering as they mimic the native ECM. In line with this, early studies have shown that nanofibrous scaffolds support the growth and maturation of endothelial (progenitor) cells, as opposed to microfibrous scaffolds [220]. Milleret *et al.,* showed that electrospun nanofibrous vascular grafts triggered lower levels of platelet and coagulation activation, as well as thrombin generation when compared to microfibrous grafts (maximum fiber ∅ 5 μm) upon exposure to human blood [221]. When considering endovascular stents, the large strut size, typically in the range of hundreds of micrometers, is known to lead to adverse effects, such as platelet activation and thrombus formation [222]. In contrast, recently developed regenerative stents based on electrospun nanofibers were shown to avoid such problems when implanted in the rat abdominal aorta, and facilitate *in situ* tissue regeneration and endothelialization instead [30].

These findings indeed suggest that a nanofibrous and nanoporous surface may be advantageous for blood-contacting surfaces. However, it is also evident that a nanofibrous structure inhibits cell ingrowth [135,223], and consequently may limit the *in situ* regeneration of new tissue. Similarly, microfibrous scaffolds (fiber ∅ 4.45 μm) with large pores, on the other hand, were found to promote SMCs infiltration on electrospun scaffolds for vascular grafts [105]. Liu *et al.,* recently showed that microfibrous scaffolds (fiber ∅ 6 μm) promoted transmural capillarization, as well as influx and organization of SMCs in bi-layered electrospun vascular grafts when compared to nanofibrous scaffolds (fiber ∅ < 1 μm) when implanted as a vascular interposition graft in the rabbit common carotid artery [105]. Also, blocking vascular graft porosity on its external surface was found to have a negative effect on the cellularity of the graft [134] (Fig. 5A). Interestingly, Fioretta *et al.,* showed that the scaffold microstructure differently affected the ingrowth and alignment of human EPCs when compared to mature human ECs, suggesting that the optimal scaffold microstructure may be cell type-dependent [224].

Interestingly, the scaffold microstructure strongly affects the inflammatory response to scaffolds, in particular macrophage polarization. The observed enhanced influx of SMCs in microfibrous vascular scaffolds as reported by Liu *et al.,* was correlated to the colonization of these scaffolds with anti-inflammatory M2 macrophages [105]. Those cells are thought to secrete growth factors (e.g., PDGF-BB) that trigger the migration and differentiation of cells (e.g., SMCs) responsible for regeneration [105]. Scaffolds with a pore size of 40–60 μm were able to direct macrophage polarization into a pro-healing phenotype M2. Contrarily, increasing the pore size up to 80–100 μm led to a down-regulation of M2 markers, suggesting there is a 'sweet spot' in terms of the ideal pore size to promote favorable macrophage polarization [225]. In addition to pore size, Wissing *et al.,* showed that both the alignment and diameter of electrospun fibers influenced the degradative properties of human macrophages on those scaffolds [196].

Apart from modulating the cellular response, it should be noted that the scaffold microstructure is also a key factor in ensuring the appropriate mechanical properties of an implant. For example, Polycaprolactone (PCL) vascular grafts with pore size of 4 μm exhibited enhanced durability (e.g., resisted wall dilation and expansion) when compared to larger pores of 7, 10 and 15 μm. This was however at the

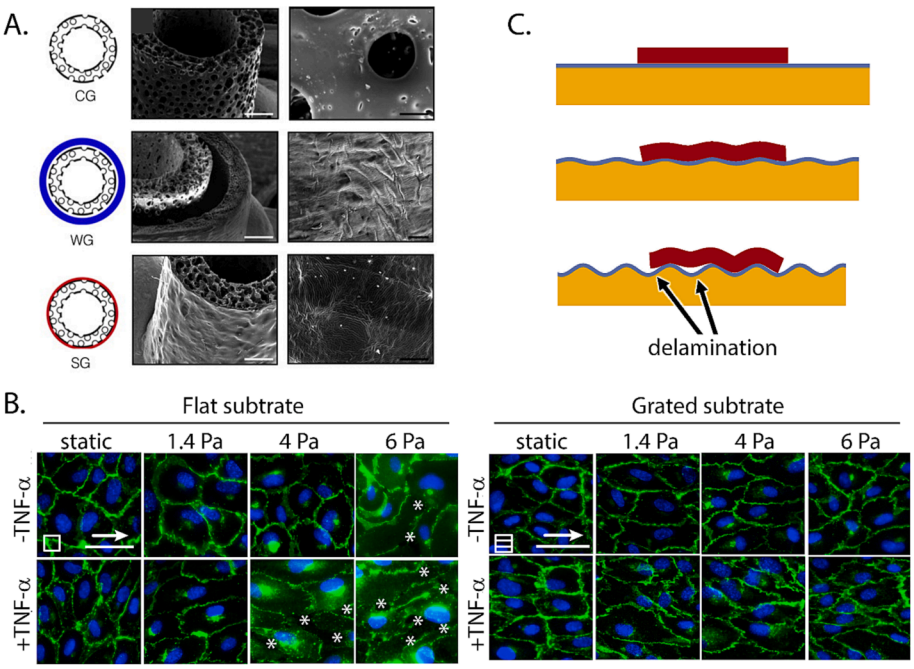

Fig. 5. Engineering approaches to promote cellularization and hemocompatibility. (A) In situ cellularization, and endothelialization in particular, of microporous vascular grafts was compromised by using ePTFE wrapping (WG) or sealant (SG) on the outer wall of the vascular grafts, when compared to porous control grafts (CG) when implanted as infrarenal interposition graft in rats. Scale bars, 500 μm (white) and 50 μm (black). Adapted from Pennel et al. 2018 [134]. (B) Grated surfaces were shown to be protective of endothelial cells when exposed to shear stress and/or tumor necrosis factor-α (TNF-α), when compared to flat surfaces. Arrows indicate direction of flow, * indicate damaged endothelial cells. Scale bars, 50 μm. Adapted from Stefopoulos et al. 2017 [236]. (C) Schematic illustration of thrombus delamination on dynamic wrinkled surfaces. Adapted from Pocivavsek et al. 2019 [237].

expense of cellular infiltration and consequently, the tissue regeneration was delayed at 8 weeks in comparison to grafts with larger pore sizes. Nevertheless, at 1 year follow-up an endothelial lining and smooth muscle layer had formed even with small pores [226]. Multiple studies have reported on the development of multi-layered grafts, including vascular and valvular scaffolds, to mimic both the structure and the mechanical properties of the native tissue counterpart [227–230].

5.2. Topographical substrates

The modification of cardiovascular constructs with defined surface topographies can have a dual influence on hemocompatibility. On the one hand, topographies can be used to enhance cellular alignment, adhesion and migration of ECs, as well as to promote a protective quiescent cellular phenotype [231]. On the other hand, dynamic topographies can be used to create acellular self-cleaning surfaces, which are able to inhibit cellular adhesion, including platelet adhesion, eventually leading to the ultimate goal of developing a hemocompatible construct.

5.2.1. Topography to promote sustained endothelialization

Various studies report on the use of surface topography to favorably steer the interactions between ECs and the underlying substrates, as a potential strategy to be employed in cardiovascular implants and tissue engineering. Franco *et al.*, reported on the use of topographical substrates of grooves and ridges with varied sizes from submicron- to microstructures. Substrates with deep grooves of 1–2 μm were found to favor the rapid spreading of ECs, as well as to induce EC alignment parallel to the grooves [232]. Additionally, focal adhesions were found to be larger and more mature as a function of ridges as compared to flat substrates. Moreover, contact guidance peaked on substrates with a groove depth of 0.6 μm [232]. Similar results on the favorable effect of deep grooves (6–7 μm) on EC retention to the underlying substrates were reported by Pacharra *et al.*, when polyethylene glycol-modified poly-L-lactide substrates were modified with microgrooves [233]. However, undesired effects associated with the microgrooves were shown in terms of elevated platelets adhesion and leucocyte activation. This mandates further consideration for the fabrication and material chemistry which can be the cause for such adverse effects [233].

The ability to create firm and mature adhesion of ECs using surface topography is particularly valuable for cardiovascular replacements that are exposed to stringent hemodynamic conditions. Uttayarat *et al.,* showed that mature ECs were found to sustain their adhesion to the underlying micro-grooved substrate under shear stresses of approximately 6 Pa, a value meeting the highest systolic shear stress within the native abdominal aorta [234]. This was a result of the induction of focal adhesion and actin cytoskeleton organization via the microgrooves, providing strong anchoring sites for the ECs under flow. Additionally, microgrooves were found to guide cellular migration in the direction of the microgrooves when the flow was applied parallel to the patterns [234]. Wu *et al.,* showed that topographies shaped as microwells (e.g., breath-figure honeycomb structures) on biocompatible silicon could aid in forming and maintaining an endothelial lining even under extreme flow conditions and alterations in flow diversions, representative of the flow conditions on the human endocardium [235]. Such topographies were proven effective in diminishing the harmful effects of high flow or directionality changes, in addition to altering the molecular changes within ECs leading to more stable adhesion junctions [235]. Indeed this offers a great advantage as EC organization is controlled by shear stresses [233].

Implementing topographies within implanted cardiovascular tissue-engineered constructs can also hold a protective function for the newly formed endothelial layer upon exposure to an inflammatory environment. Stefopoulos *et al.*, showed that gratings contribute to inhibiting NF-kB nuclear translocation in endothelium growing on gratings as compared to flat substrates [236]. Furthermore, gratings were able to reduce NF-kB nuclear translocation when endothelium was exposed to high shear stresses (4–6 Pa). Besides maintaining endothelial integrity, gratings stabilized the adherence junctions within the endothelial lining and the adherence to the underlying substrates mediated by focal adhesion maturation [236]. Such an approach is particularly beneficial for implementation in cardiovascular devices at risk of exposure to extreme hemodynamic environments that can compromise endothelium integrity (Fig. 5B).

5.2.2. Bio-inspired dynamic topographies as self-cleaning surfaces

Notwithstanding the potential to promote endothelium formation by using topographies, somewhat paradoxically, topographies can also be

used to drive the delamination of cellular adhesion. That approach mainly focuses on self-cleaning and the continuous inhibition of platelet adhesion, eventually creating a cell-free surface that is thrombus resistant. This concept is mainly driven by using the environmental hemodynamic forces to continuously change the surface pattern. In nature, physiological structures such as arteries have topographies in form of wrinkles on their inner lumen, which may act as an endogenous defense mechanism against thrombus formation [238,239]. When pulse pressure is applied, the wrinkled surface stretches into an unwrinkled state, and vice versa, thereby preserving the surface from thrombus formation. Within the body this is driven by the pulsatile blood pressure within the cardiovascular system, dynamically altering the vascular tone from contraction to relaxation [237].

Based on this notion, recent reports investigated implementing such nature-inspired wrinkles on synthetic biomaterials that can be used in vascular tissue engineering [237,238,240]. Pocivavsek *et al.*, investigated such wrinkles by copying them onto polydimethylsiloxane (PDMS) silicone rubber. The developed planar substrates were tested in pneumatic actuation systems where the elastomer is being stretched to transition from a wrinkled to a flat state. Wrinkled surfaces displayed 73% less thrombus formation as compared to flat surfaces under actuation conditions upon contact with blood. When the wrinkled surfaces were shaped into tubes, and different wavelengths were compared under actuation, tubes with a wavelength of 80 μm as compared to 1000 μm showed 80% lower platelet adhesion [237]. The same research group confirmed these results in a later study, manifested by an 86% decrease in platelet adhesion on silicon grafts with dynamic wrinkles in a pulsatile system compared to flat grafts. However, when the wrinkled grafts were tested under non-pulsatile conditions, platelet adhesion was shown to increase significantly, emphasizing the importance of the dynamic topographical changes in the delamination of the platelets. Moreover, the lowest tested wavelengths (e.g., 100 μm) showed the least platelets adhesion [238]. The general theory to explain this delamination is based on the phenomenon that when a solid foulant adheres to a curved surface it will either deform in shape or have reduced contact with that surface. In case it deforms along the surface it will have an elastic energy penalty. However, if it does not deform it will adhere less to the surface. Specifically, when a large thrombus adheres to a curved surface it responds to dynamic changes in the curvature of that surface. As the surface moves into a wrinkled state the thrombus deforms conformally. However, that change in surface curvature enforces the elastic energy penalty. That rise in the elastic energy penalty drives the delamination if the surface curvature exceeds a certain limit [237,240] (Fig. 5C).

6. Translational considerations & recommendations

Despite decades of intensive research into this topic, it is clear that having a sustained hemocompatible blood-contacting surface remains a major challenge in the development of cardiovascular devices. New strategies based on dynamic surface topographies hold great promise for creating acellular devices. In addition, the developments in *in situ* tissue engineering over the past decade have opened up many new avenues for functional regeneration at the blood-biomaterial interface. Nevertheless, it remains highly challenging to replicate or restore nature's intricate ways to actively maintain an anti-thrombogenic and regulating blood-contacting lining on cardiovascular tissues. While the fundamental processes of *in situ* regeneration are slowly being unveiled, a detailed understanding of which processes and aspects at the blood-biomaterial interface are to be harnessed and which can be exploited is still largely missing.

Some aspects have remained particularly underexposed in studies so far, such as the systematic comprehensive characterization of colonizing cardiovascular cells in *in situ* tissue-engineered grafts. Moreover, unraveling the *in vivo* process of *in situ* tissue engineering is challenged by inter-species differences as well as inter-patient differences in regenerative capacity and immunological state. For example, differences in animal models and scaffold design have led to contradicting results [105,134,241]. These aspects, as elaborated on in the following section, are important attention points to move the field forward, the main question being: how can we best test regenerative cardiovascular devices?

6.1. Dynamic (human) in vitro test platforms

In vitro testing of hemocompatibility of medical devices can be done according to standardized protocols (e.g., ISO 10993–4) [242–244]. These tests consist of quantifying thrombogenic potential, as well as coagulation, platelet and complement activation. As such they are exclusively aimed at quantifying the risk of adverse effects evoked by an implanted blood-contacting material, such as thrombus formation. Predicting how well a material will perform in terms of functional regeneration *in vitro* on the other hand, is an unresolved challenge that is actively being pursued by numerous research groups.

Various reductionist *in vitro* culture models based on blood-isolated primary human cells (e.g., neutrophils, mast cells, monocyte-derived macrophages) have been reported to assess the (patient-specific) inflammatory response to a biomaterial [245–253]. These types of static models are highly useful to screen how material choice or material design features affect the initial inflammatory response. Importantly, by using patient-derived cells, such models have the potential to elucidate the *patient-specific* response to an implant. For example, Boersema *et al.,* showed that the response of human macrophages to biomaterials *in vitro* from obese patients was significantly altered compared to those of healthy age-matched donors and that this correlated to differences in circulating monocyte subsets between patients and healthy donors [254].

Although very useful, these models are based on static culture and do not account for the influence of hemodynamic loads on the processes of inflammation and regeneration. Dynamic *in vitro* models, often based on bioreactors, have shown that hemodynamic loads such as cyclic stretch and shear stresses affect inflammation, for example in terms of macrophage polarization [255–262], as well as cell recruitment and adhesion from the bloodstream [117,224,257,263]. For example, Smits *et al.,* developed a custom-developed mesofluidics system to expose 3D scaffolds to circulating peripheral blood mononuclear cells at well-controlled laminar shear stresses [135]. Using that system, Smits and Ballotta *et al.,* showed that the shear stresses heavily impact the recruitment of selective monocyte subsets from the circulation to an electrospun scaffold [116].

Besides the potential of predicting the implant outcome, dynamic bioreactors are eminently suitable to mechanistically unravel specific *in vivo* processes or interactions, which are difficult to systematically study in animal models. For example, it is well-acknowledged that EC physiological function is heavily dependent on flows and shear stresses [189]. Consequently, biomaterial-EC interactions are best studied in conditions of flow, for example using a flow chamber device or more sophisticated bioreactors [264–266]. Moreover, by using smartly designed bioreactors, it is possible to decouple hemodynamic loads, such as shear stress and stretch, in order to study their isolated and combined effects on cell function and cell-material interactions. For example, Sinha *et al.,* described the use of a 2D flex-flow system to systematically study the effect of various combinations of shear stress and anisotropic cyclic stretch on endothelial cells in 2D [267,268]. Van Haaften *et al.*, designed a bioreactor system that allows for the decoupling of shear stress and cyclic stretch on tubular scaffolds, thereby providing a platform that enables a clear distinction of the effects of each hemodynamic load independently in 3D culture conditions [269,270]. Similarly, Bachmann *et al.*, introduced a flow bioreactor that combines wall deformation as well as wall shear stress to mimic the mechanics in heart replacement devices or arterial grafts [271]. An advantage of this system is that wall shear stress can go up to 20 Pa and wall deformation up to 20% in both uniaxial and biaxial directions, with independent control over both

loads. The actuation system in this bioreactor creates compound flow patterns, which in turn yield various conditions for wall shear stresses, as well as multiaxial wall deformation, simulating the hemodynamic environment in larger arteries and heart ventricles [271].

When used as co-culture systems, *in vitro* models are also a valuable tool to probe interactions between cardiovascular cells, which are essential for proper cardiovascular functioning [272,273]. For instance, Helle *et al.,* recently reported on a co-culture system of induced pluripotent stem cell (iPSC)-derived cardiomyocytes and iPSC-derived cardiac ECs [272]. When in co-culture, cardiac ECs were found to upregulate lineage (cardiac) specific genes involved in ECM formation such as ID1 and HAPLN1. Likewise, Plasmalemma vesicle-associated protein (PLVAP), a specific endocardial marker responsible for leukocyte migration, basal permeability and angiogenesis, was found to be upregulated in addition to genes encoding junctional proteins, implying an enhanced function of endothelial junctions and cellular signaling and stability in co-culture [272]. Elucidating such cell–cell interactions is deemed crucial for example in the context of endocardial regeneration, to ensure that the correct cellular interactions are derived from the proper phenotypes [274,275].

All in all, although *in vitro* models are inherently a simplification of the *in vivo* situation, dynamic *in vitro* culture systems have a growing potential as (1) predictive biomaterial screening platforms, and (2) to systematically elucidate cell-biomaterial interactions under hemodynamic conditions. Moreover, by using (primary) human cells, *in vitro* models enable the probing of human-specific cellular mechanisms, avoiding inter-species differences (e.g., in immune cell subsets). As such, *in vitro* models can contribute to the refinement and reduction of animal experiments following the 3R's philosophy, particularly when used *in conjunction with* animal experiments in an iterative fashion; *in vitro* models can be used to systematically investigate observations from *in vivo* experiments, while *in vitro* models can aid in refining the design of animal experiments to test implants in the full complexity of the body.

6.2. Standardizing animal models and reporting

One major challenge for understanding *in situ* tissue engineering is the fact that regenerative processes vary between species. Animal experiments are extremely valuable in testing cardiovascular implants in the full complexity of the body. However, as also described in previous sections, vital differences exist in the key processes underlying *in situ* tissue engineering, including cellularization processes, inflammation, and biomaterial degradation. For example, small animals are considered convenient models in tissue engineering due to relative ease of use, limited costs, and short study durations. Small-diameter vascular grafts implanted in rodents are typically short in length and usually show a high patency rate due to rapid anastomotic endothelialization [131]. Conversely, such small diameter grafts in clinical settings are $>$ 20 cm in length, implying a limited endothelial cell migration through anastomotic sites. Notably, Fukunishi *et al.,* reported that the degradation rates of implanted vascular grafts differed between rats and sheep, with consistently faster resorption in sheep, both in the venous and arterial circulation [276]. Tille *et al.,* compared the host response to PCL-based implants between implant sites in rats (infrarenal abdominal aortic interposition graft versus subcutaneous implantation). They found strong differences in cellularization, inflammation and tissue formation between implant sites, with a significantly enhanced infiltration of macrophages and multinucleated giant cells, as well as enhanced tissue formation and vascularization in arterial grafts when compared to subcutaneous implants [277]. Importantly, various studies have revealed significant and important differences in outcomes (e.g., in terms of intimal hyperplasia, compliance, endothelialization, and calcification risk) even between vascular grafts at different anatomical sites in the same animal [118,278]. Such findings have been reported for both large and small animal models (e.g., dogs and rats).

In addition, the anastomoses construction style plays a significant role in determining the implant remodeling as a result of directly influencing the hemodynamics. For instance, in arterial interposition grafts where end-to-side anastomoses is constructed the full carotid artery is included therefore resulting in high shear flow and stresses due to the arterial blood flow [95]. Indeed, this affects the interpretation of the data from different *in vivo* studies.

These findings all emphasize the importance of the selected *in vivo* model, in terms of species as well as implantation site, the latter underlining the importance of the direct exposure to the bloodstream and the local hemodynamic loads. Although animal studies provide tremendously valuable insights, it should be acknowledged that data of specific readouts (e.g., regarding endothelialization, and patency) is likely not directly translatable to the clinical application. Koch and De Kort *et al.,* recently reported on a systematic review, evidence mapping and *meta*-analysis of all published data from animal experiments to test degradable synthetic vascular grafts. They found that there is tremendous variability in experimental models, methods (e.g., use of anticoagulants), as well as readout methods. Moreover, they identified important lacks in the quality of reporting of animal experiments, which devaluates much of the reported data [131]. Similar results have been reported in a recent systematic review of all preclinical models to test TEHVs [279]. Another consideration is the pathophysiological status of the patient which is also often overlooked and difficult to mimic properly in animals. The vast majority of animal experiments is performed in healthy young animals and patient characteristics such as sex are often not considered part of the experimental design [131]. Such factors may have an impact on outcomes and should be considered for clinical translation, as recently reviewed in detail [25].

Careful evaluation of the used animal models, and reporting thereof (e.g., in accordance with the ARRIVE guidelines) should come as a priority at expense of the feasibility of obtaining fast results to translate the results in light of clinical use. Moreover, standardization of animal models for specific applications would aid in maximizing the knowledge to be gained from animal experiments and accelerating translation.

6.3. Spatial mapping of cellular phenotypes

Another consideration that would greatly improve our understanding of *in situ* regeneration, particularly in the context of animal experiments, is the comprehensive analysis of the cellular infiltrates in explanted samples. As described in the previous sections, cardiovascular tissues consist of similar cells as the building blocks, such as ECs and SMC-like cells, yet they are highly diverse in function across different cardiovascular tissues. For the identification of the cellular phenotype in tissue-engineered constructs, many studies use generic markers as the sole identification of the phenotype, which are not conclusive as standalone markers. In order to evaluate the cellular heterogeneity in *in situ* tissue-engineered implants, it is important to clearly identify the phenotype of recruited cells through (multiplexed) phenotypic markers, as well as cell functionality.

When characterizing endothelial cells, in general, markers such as CD31, Endoglin, PECAM-1, ICAM-1, VEGFR2, or VE-cadherin (CD144) are utilized to identify EC phenotype, disregarding other important aspects such as the response of such cells to mitogens or cytokines or the proper communication with the surrounding microenvironment [280]. In the Carmat total artificial heart, the evaluation of the endothelial lining post-implantation in patients was done based on the absence of von Willebrand syndrome, in addition to scanning electron microscopy visualization of the tight endothelial junctions and staining for endothelial cadherin [281]. vWF staining and low-density lipoprotein were used as the main characterization markers for endothelial cells [54]. The latter one, however, cannot be described as an exclusive endothelial marker as it can be up taken by monocytes/macrophages as well [282].

Clearly, it can be difficult to pick up nuanced differences in cell phenotypes and the question remains to what extent these differences affect cell functionality. Perhaps such differences will have a critical

effect on the functionality indeed. When a tri-leaflet valve construct seeded with vascular cells was implanted in the pulmonary position, cells seemed to have an expression profile similar to the native valves [283]. However, a continuous increase in the leaflet stiffness may refer to the effect of the mismatched phenotype of the implanted cells [55]. Inter-species differences may require the validation of species-specific cell markers to identify specific cellular subsets [284]. De Kort *et al.,* showed that the presence of both VIC-like cells and inflammatory cells in *in situ* TEHVs in sheep was highly heterogeneous in terms of the cellular phenotypes in different regions of the valves and that this correlated to functional outcomes such as tissue formation and scaffold resorption. Here, more sophisticated analysis techniques to spatially map cellular phenotypes, such as multiplexed immunofluorescence [285] and spatial transcriptomics [286,287] could really propel our understanding of the cellular processes and potentially origins in tissue-engineered grafts. Furthermore, the sophisticated use of imaging techniques such as Raman microspectroscopy [26,48,288,289] and Optical Coherence Tomography (OCT) [290] enable the marker-independent monitoring of key functional processes, such as scaffold resorption, endothelialization and neotissue formation and maturation.

7. Conclusion

Being directly at the blood-biomaterial interface, functional regeneration of cardiovascular tissues and the restoration of endothelial functions comes with its challenges and possibilities. The breadth of research on blood-biomaterial interactions over the past four decades and the fact that many aspects remain obscured is manifest in the complexity of the blood-biomaterial interface. The blood-biomaterial interface encompasses multiple dynamic biological processes, such as thrombogenesis, inflammation, endothelialization and cell (trans)differentiation, all of which are dominantly influenced by the continuous and highly heterogeneous hemodynamic loads. Additionally, with our current knowledge, it seems hard to identify the cellular player in the remodeling process at the blood-material interface and to what extent this is application-dependent; this process is rather a collaborative effort by cells from different sources. Our current knowledge of the cellularization routes and origin is biased as a result of the experimental setups that can vary by different grafts design, fabrication techniques, surface functionalization, implantation mode and the animal models in which the constructs are being tested. This is obviously influencing the interpretations of the results from different studies. However, such biased interpretations can still be utilized critically to design the ideal application-specific constructs that can become cellularized and remodeled faster by taking advantage of the continuous contact with blood. Also, the growing recognition of interspecies differences enhanced dynamic human culture models, and more holistic and application-specific methods to map cell phenotypes and functions, represent key focal points to effectively move forward toward application-specific design of hemo-regenerative biomaterials.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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