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Review

Single and multi-functional coating strategies for enhancing the biocompatibility and tissue integration of blood-contacting medical implants

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ABSTRACT

Device-associated clot formation and poor tissue integration are ongoing problems with permanent and temporary implantable medical devices. These complications lead to increased rates of mortality and morbidity and impose a burden on healthcare systems. In this review, we outline the current approaches for developing single and multi-functional surface coating techniques that aim to circumvent the limitations associated with existing blood-contacting medical devices. We focus on surface coatings that possess dual hemocompatibility and biofunctionality features and discuss their advantages and shortcomings to providing a biocompatible and biodynamic interface between the medical implant and blood. Lastly, we outline the newly developed surface modification techniques that use lubricant-infused coatings and discuss their unique potential and limitations in mitigating medical device-associated complications.

1. Introduction

Blood-contacting medical devices such as catheters, vascular grafts and mechanical heart valves are widely used for vascular access and drug delivery, revascularization and repair of defective heart valves. However, all such devices trigger physiological responses that cause complications such as device-associated thrombosis that can lead to device failure [1]. Thrombus formation on medical devices occurs through a series of complex and integrated pathways including protein adsorption, platelet and leukocyte adhesion and activation and thrombin generation. Rapid adsorption of plasma proteins such as fibrinogen is known to be the initiating event (Fig. 1) [2,3].

Since foreign synthetic surfaces are innately thrombogenic, prophylactic treatment with antiplatelet agents such as aspirin or clopidogrel or anticoagulants such as heparin or warfarin is often required to prevent thromboembolic complications [4–6]. However, administration of such agents increases the risk of bleeding, which can be fatal [6–9]. In a comprehensive study conducted on patients who underwent mechanical heart valve replacement between 1988 and 2005, thromboembolism and bleeding were the two leading causes of valve-associated complications [10]. In addition to thrombogenicity, synthetic surfaces suffer from poor biofunctionality and the inability to promote tissue integration. This is problematic for permanent medical implants such as vascular grafts, mechanical heart valves and stents that are commonly used in cardiovascular interventions, because tissue integration and cell infiltration at the site of implantation have been shown to reduce the risk of post-operative device failure and rejection [11].

Cardiovascular disease is the leading cause of mortality and morbidity worldwide, causing about 17 million deaths every year; nearly one third of all deaths. More than 50% of the deaths are caused by ischemic cardiovascular diseases such as ischemic stroke, coronary artery disease or peripheral artery disease [12,13]. These disorders are mainly caused by atherosclerosis, a chronic inflammatory disorder that leads to the thickening of the arterial wall. Atherosclerosis occurs early

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in life and becomes symptomatic when plaques consisting of cholesterol, inflammatory cells, smooth muscle cells, and lipids either enlarge to the point where they obstruct blood flow or are disrupted and trigger the formation of an overlying thrombus that obstructs blood flow [14,15]. In many cases, intervention is needed to open occluded arteries. For example, over 1 million percutaneous coronary interventions and 350, 000 coronary artery bypass procedures are performed each year in the US alone [16]. Consequently, it is predicted that the annual global financial burden of cardiovascular disease will exceed 1 trillion USD by 2030 [17]. The treatment of occluded arteries often requires bypass surgery, where, as the standard of care, autologous vessels such as the saphenous vein or mammary or radial arteries are used [18,19]. However, more than 30% of patients do not have available or appropriate vessels [19,20], because of pre-existing vascular diseases or prior surgery [21–23]. The lack of viable autologous vessels prompted the development and utilization of synthetic graft alternatives.

Synthetic vascular grafts made of stable polymers such as expanded polytetrafluoroethylene (ePTFE, Teflon) or polyethylene terephthalate (PET, Dacron) suffer from low patency rates and are associated with poorer patient outcomes compared with autologous vessels [18,19,22, 24]. This is mainly due to the thrombogenicity of the synthetic graft surfaces, which leads to clot formation and graft occlusion. In addition, thrombus formation on vascular grafts limits coverage of the surface by endothelial cells (ECs) and ultimately thwarts the formation of a healthy endothelium [20]. This is problematic because healthy endothelium has innate anti-thrombotic properties by effectively decreasing platelet and protein adhesion and actively preventing clot formation [25,26]. Moreover, formation of a confluent endothelial layer is critical for integration of permanent prostheses into nearby tissues [18,22] and for prevention of neointimal hyperplasia, which results from proliferation of subendothelial smooth muscle cells [22].

To combat the many issues caused by permanent and non-permanent synthetic blood-contacting interfaces, extensive research has been devoted to developing new surface coatings to enhance hemocompatibility and biofunctionality of permanent implants such as stents and vascular grafts and to eliminate or reduce the need for systemic antithrombotic therapy. This review focuses on single and multifunctional surface modification techniques for blood-contacting medical implants, concentrating on those with dual biofunctionality (promoting endothelial cell adhesion and proliferation) and biocompatibility (preventing non-specific adhesion and clot formation).

2. Surface coating strategies

Surface modification strategies mainly involve coating the surfaces with bioinert polymers [27–30], antithrombotic agents [31–36], or changing the surface charge, wettability, chemical affinity and hydrophilicity using plasma modification techniques [23,37–40]. In addition, EC specific antibodies [41–44] and vascular endothelial growth factors [45,46] have been applied to vascular graft or stent surfaces to enhance their capacity to capture ECs. Coatings used in commercially available vascular grafts or stents have limitations because they mostly focus on a single aspect of hemocompatibility or biofunctionality (*e.g.* promoting endothelialization, Table 1). Although extensive research has been devoted to overcoming these limitations by developing new bi-functional surface coatings, synthesis of stable coatings that integrate biofunctionality and hemocompatibility is challenging (Table 2).

2.1. Bioinert polymeric coatings

2.1.1. Poly (ethylene glycol) (PEG) coatings

PEG (also know as polyethylene oxide (PEO)) is one of the most commonly used synthetic polymers for coating blood-contacting medical interfaces [27,47]. Methods used for PEG surface modification range from physical adsorption [48] to graft polymerization [49] and chemical and covalent coupling [50,51]. Covalent grafting of PEG is the preferred method because this modification procedure creates more stable coatings for long-term applications [52]. The neutrally charged hydrophilic PEG polymer chains have the ability to bind water molecules and form a hydration layer on the surface, which resists nonspecific adhesion of proteins and cells [27,47]. However, studies have shown that the biocompatibility and repellency properties of PEG coated surfaces are highly dependent on the chain length and surface density of the grafted PEG polymer [47,53].

Kim et al. found that increasing the grafting density and chain length of PEO in a polyurethane/polystyrene interpenetrating polymer network created a biocompatible interface that decreased fibrinogen and platelet adhesion *in vitro* [53]. Similar results were found in a study where the adsorption of fibronectin from serum decreased with increasing the PEG chain density up to 0.12 PEG chains/nm^2, and then slightly increased on surfaces with 0.29 PEG chains/nm^2 [47]. PEG coatings have also been applied to ePTFE and PET surfaces to improve their surface biocompatibility and thrombogenicity properties. Like the results obtained from other studies, the PEG surface density and molecular weight affect the hemocompatibility of ePTFE and PET coated surfaces [51,54,55]. ePTFE surfaces modified with 3% weight/volume PEG-600 Da had the best biocompatibility properties compared with 1% and 5% PEG modified surfaces and increasing the PEG surface density to more than 3% reduced biocompatibility [55]. Likewise, PET surfaces coated with PEG-6000 Da were more blood-repellent and exhibited significantly less platelet adhesion than non-treated PET substrates or PET surfaces treated with PEG-200,1000 or 10,000 Da [51]. In a similar study where PEO polymers with different molecular weights (5000, 10,

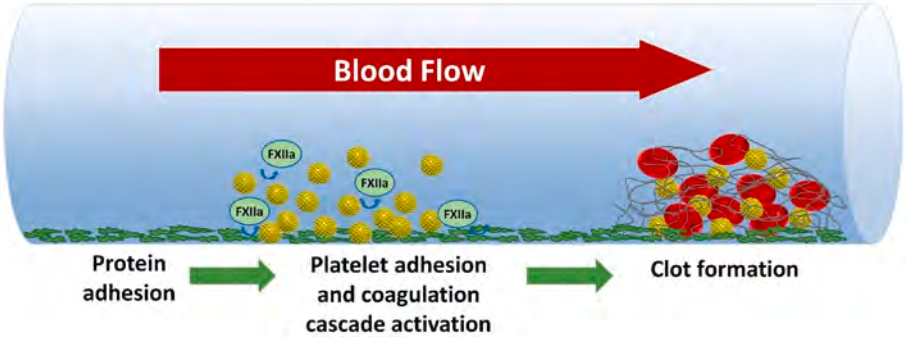

Fig. 1. Schematic representation of the pathways involved in device-associated clot formation. Unlike a healthy endothelium that has innate anti-thrombogenic properties, synthetic surfaces actively induce thrombus formation through a series of complex and integrated pathways. Protein adhesion induces platelet adhesion, activation and aggregation as well as activation of coagulation via the contact pathway. Together, these processes lead to device-associated clot formation.

Table 1
Commercially available vascular grafts and stents modified with different surface coating strategies.

Company	Trade Name	Material	Coating	Pros	Cons	Approval
Vascular Grafts						
W. L. Gore and Associates	GORE® VIABAHN® Endoprosthesis GORE® PROPATEN® Vascular Graft	ePTFE	Heparin Bioactive surface using Carmeda Bioactive Surface (CBAS) Technology [64]	Improved thromboresistance and patency [65]	Not recommended in patients with a history of heparin induced thrombocytopenia (HIT) [66,67]. Toxic chemicals such as polyethyleneimine (a cytotoxic material which has shown to inhibit cell proliferation on biomaterials) has been used in the coating [36]	FDA approved
Maquet Cardiovascular (Gentinge Group)	InterGard Heparin	PET (Dacron)	Heparin-bonded collagen coating	Antithrombotic properties due to the presence of heparin	Not recommended in patients with any history of HIT [68] High thrombogenicity of collagen [36]	FDA approved
	InterGard Silver	Knitted Polyester (Dacron)	Collagen and silver	Prevention of prosthetic infection, early host tissue incorporation of the [69–71]	Potential toxicity caused by silver [72] Failure of silver/collagen-coated prostheses to resist bacterial infection (*Staphylococcus aureus* bacteria) [73–75].	CE marked
	InterGard Synergy	Knitted Polyester (Dacron)	Collagen, silver acetate and triclosan	Faster antimicrobial efficacy [76], Better short term activities in comparison with InterGard silver [77], a more sustainable and efficient 7 days antimicrobial activity than the rifampicin soaked graft [78]	Silver-associated toxicity [72] Triclosan has shown to be an endocrine disrupting chemical and might cause cancer by enhancing hepatocyte proliferation and reactive oxygen species (ROS), and might affect cardiovascular function [79] High thrombogenicity of collagen [36]	CE marked
Vascutek	Gelsoft, Gelseal, Gelweave Vascular Grafts	Knitted Polyester (Dacron)	Gelatin	Decreased early bacterial infection due to decreased porosity using gelatin impregnation [80], prevention of bleedings out of prosthetic wall, no need for pre-clotting [81]	Stimulation of immune response induced by gelatine materials [81], Incidence of Peri-graft Seroma Formation [82] issues related to high thrombogenicity of collagen and gelatin [83]	FDA approved
B. Braun	Uni-Graft® K DV	Knitted Polyester	Absorbable modified gelatine (no glutaraldehyde or formaldehyde used)	No need for pre-clotting (sealed pores using gelatine impregnation), minimized blood loss, athrombogenic, non-cytotoxic, aldehyde free cross-linking, accelerated cellular integration [84].	Stimulation of immune response induced by gelatine materials [81]	FDA approved
Bard Inc.	IMPRA carboflo™ Venaflo Distaflo Dynaflo	ePTFE	Carbon	Reduction in Thrombogenicity (believed to be because of electronegativity and hydrophobicity of carbon [85], Decreased platelet deposition and accumulation on PTFE graft in an animal study model [86]	No significant difference between Carbon PTFE prothesis and standard PTFE prothesis at 36 months (in terms of patency or limb salvage) [87]	FDA approved
Stents						
Biotronik AG	Tenax	316L stainless steel	Amorphous silicon carbide	Hemocompatible and preventing the electron transfer from the fibrinogen molecules to the solid metal stent as a result of having an amorphous silicon carbide coating [88].	Not recommended for patients with a known allergy or hypersensitivity to amorphous silicon carbide [89]. No advantage over the standard steel stent in terms of restenosis rate during the 4.7 ± 1.2-month follow-up period [90]. More premature target lesion revascularization (TLR) rate compared to conventional uncoated stents after 81 ±12 weeks follow-up [90]	FDA approved
Boston Scientific (First Generation Durable Polymer Drug Eluting stent or DP-DES)	TAXUS Express, TAXUS Liberté, TAXUS Element	316L stainless steel or Platinum Chromium Alloy (PtCr)	Poly(styrene-b-isobutylene-b-styrene) (SIBS) polymer with paclitaxel drug	Reduced risk of restenosis and target vessel revascularization (TVR) compared to bare-metal stents (BMS) [91,92]	Lack of bio-compatibility of the polymer, increased risk of very late stent thrombosis (ST) [91,93] of the stent struts [94], considerable long-term death rate and myocardial infarction after 1 year follow-up [95], delayed arterial healing because of persistent fibrin deposition [96]	FDA approved
Abbott (Second Generation DP-DES)	Xience everolimus-eluting stent	cobalt chromium	n-butyl methacrylate (PBMA)– poly (vinylidene fluoride- co-hexafluoropropylene) (PVDF- HFP) with everolimus drug	Reduced thrombus formation as a result of fluoropassivation process, reduced platelet adhesion and activation, faster endothelialization, and healing compared with non-fluoropolymer-coated metallic stents [97], reduced mortality rate and stent thrombosis compared to the first-generation drug-eluting stents [98]	Progressive neointimal growth with similar frequency of neoatherosclerosis in comparison with the first generation DES after 3 years of clinical follow-up [99, 100]	FDA approved

(*continued on next page*)

Table 1 (*continued*)

Company	Trade Name	Material	Coating	Pros	Cons	Approval
Boston Scientific (Second Generation DP- DES)	PROMUS Element EES	Platinum chromium (PtCr)	PVDF-HFP polymer with everolimus drug	Reduced platelet adhesion and activation compared to non-fluoropolymer-coated metallic stents, significantly lower thrombogenicity [97]	Progressive neointimal growth and similar prevalence of neoatherosclerosis compared to first generation DES [101,102]	FDA approved
Medtronic (Second Generation DP- DES)	Endeavor zotarolimus-eluting stent	Cobalt alloy MP35 N	Phosphorylcholine (PC) polymer with zotarolimus drug	Reduced rates of clinical and angiographic restenosis at 9, 12, and 24 months [103]. Similar efficacy compared to first-generation Sirolimus Eluting Stents (SES), but more effective than Paclitaxel Eluting Stents (PES) [104]	Higher rates of TLR and restenosis compared to Resolute zotarolimus-eluting stent (ZES) [105]	FDA approved
Medtronic (Second Generation DP- DES)	Resolute Onyx™ ZES	Cobalt-based alloy shell and a platinum-iridium alloy core	A Parylene C primer coat combined with a coating composed of the zotarolimus and the BioLinx® polymer [106]	Low incidence of cardiac events and stent thrombosis (ST) at 1 year. Low and stable rate between 1 and 5 year [107]. Increased biocompatibility due to hydrophilic polyvinyl pyrrolidinone usage [108,109]	Hypersensitivity reaction report (lymphocytic infiltrate, with eosinophils and giant cells) [106,110]	FDA approved
Cordis Medinol LTD (Second Generation DP- DES)	EluNIR	Cobalt-chromium alloy	Thermoplastic silicone polycarbonate polyurethane and PBMA (PBMA CarboSil 20 55D) with ridaforolimus drug [111]	Better endothelialization, lower inflammation, lower ST and restenosis rates, and uniform drug release because of long term coating integrity and high surface quality. Similar safety and efficacy compared to Resolute™ ZES stents [111,112]	Little information about the vascular response to the polymer (no published preclinical data is available) [99]	FDA approved CE marked
Biotronik (Third Generation Bioabsorbable DES)	Orsiro Sirolimus Eluting Coronary Stent System	Cobalt chromium alloy (L-605)	Active coating: BIOlute bioabsorbable Poly-L-Lactide (PLLA) with a limus drug Passive coating: Amorphous Silicon Carbide	Ion leakage prevention due to a thin passive coating of amorphous silicone carbide (hybrid coating) [113] complete elution of drugs, lower inflammatory response as a result of using a bioabsorbable polymer [114] lower late/very late ST, lower target lesion failure (TLF) and TLR compared to Xience DES after 2 and 5 years follow-up [115,116]	The potential proinflammatory effect elicited by the polymer (like all polymer coated drug eluting stents compared to BMS) [117]	FDA approved
OrbusNeich Medical Technologies (Third Generation Bioabsorbable DES)	Combo Dual Therapy Stent	Stainless Steal 316-L	Biodegradable urethane linked lactide-glycolide multiblock copolymers eluting sirolimus, and a covalently bound anti-CD34 antibody layer	Endothelial coverage acceleration (capturing circulating endothelial progenitor cells by surface immobilized CD34 antibodies), neointimal proliferation control [118,119], low ST, early healing due to the luminal anti-CD34 antibody layer [120], reduced neointimal formation and inflammation [117]	Potential proinflammatory effect elicited by the polymer (like all polymer coated drug eluting stents compared to BMS) [117]	CE marked
Terumo (Third Generation Bioabsorbable DES)	Ultimaster	Cobalt Chromium L605	Bioresorbable Poly (DL-lactide-co-caprolactone) Sirolimus-eluting (Abluminal & gradient coating)	Degradation of the polymer into water and CO_2 (full elimination over 3–4 months) [121]. A low rate of TLF and ST among patients undergoing percutaneous coronary intervention (PCI) in coronary bifurcation; no cases of late or very late ST up to two-year follow-up in a clinical trial [121]; almost complete strut coverage early after implantation [122]	Greater platelet aggregation compared to XIENCE Alpine™ everolimus eluting stents (EES). Thrombus would aggregate on the bare surface of the luminal side [121]	CE marked
B. Braun (Polymer-free DES)	Coroflex® ISAR NEO	Cobalt-chromium alloy L605	Sirolimus as anti-inflammatory and anti-proliferative drug, Probucol as matrix excipient to slow down the release of drug [123]	No more hypersensitivity reactions caused by polymers, delamination or webbing of the polymer coating and problems related to temporary or permanent polymeric residue [124,125]. Low rates of TLR and Major Adverse Cardiac Events (MACE) at 9 months with no ST [123]	Similar clinical and angiographic outcomes to durable polymer zotarolimus-eluting stents [126]	CE marked
Biosensors Interventional Technologies (Polymer-free DES)	BioFreedom Biolimus A9-coated stent	Stainless Steal 316L	Biolimus A9 drug (applied in solvent onto a textured abluminal surface of the stent material)	No hypersensitivity reactions caused by delamination or webbing of the polymer coating and no problems related to temporary or permanent polymeric residue [124,125]. Effective inhibition of neointimal hyperplasia at 12 month follow-up, and similar clinical event rates at 5 years compared with Taxus Liberté paclitaxel-eluting stents [125]. More effective in patients at high risk of bleeding compared to BMS [127]	Higher acute thrombogenicity and platelet adherence compared to the Xience-EES due to selectively textured abluminal surface of the stent. Less anti-inflammatory effect compared to the Xience-EES [97]. An inferior efficacy at inhibiting neointimal hyperplasia in the long course. Higher rate of stent restenosis in comparison with the Xience-EES [128]	CE marked

000, 18,5000, and 100,000 Da) were covalently grafted on PET films, it was concluded that surfaces coated with PEO chains with the molecular weights of 18,500 Da and higher were more biocompatible and they significantly reduced protein adhesion and cellular interaction when compared with samples grafted with lower molecular weight PEO [56]. In contrast, Gombotz et al., reported that only slight decreases in fibrinogen and bovine serum albumin (BSA) adhesion was observed when increasing the molecular weight of the grafted PEO to higher than 3500 Da. The inconsistency in the PEG (PEO) chain length and surface density required for optimal biocompatibility may reflect differences in experimental conditions, grafting methods, incubation times and physical or chemical properties of the underlying coated surfaces. In the case of high-density PEG coated surfaces, some studies have reported that high PEG grafting density could influence and alter the structure of the water molecules that are tightly bound to the PEG chains, resulting in conformational changes and denaturization of the surrounding proteins. This could adversely affect the surface biocompatibility and ultimately increase protein and platelet adhesion on PEG coated surfaces [57,58]. In addition, increasing the surface grafting density could result in obtaining a more porous and rougher surface coating. Surface roughness and surface wettability are important factors that affect protein and cell adhesion on substrates [59].

Although in short-term *in vitro* studies PEG coated surfaces exhibited reduced nonspecific adhesion, the results *in vivo* have not been as promising [54,60]. A major problem with PEG coated surfaces in long-term *in vivo* experiments is the degradation and depletion of PEG chains caused by oxidation. Superoxide anions released by a variety of cells (*e.g.* endothelial progenitor cells, neutrophils and monocytes) during the respiratory burst [61] can attack the ether linkage on the PEG chain and generate a peroxide bond. The peroxide bond can then decompose resulting in a progressive reduction in the chain length and surface density of the PEG layer [62,63]. These findings suggest that PEG coated surfaces are more useful for short-term single-use blood-contacting medical applications [30].

2.1.2. Zwitterionic polymers

As an alternative to PEG coating strategies, other novel bioinert polymers have been developed and investigated for medical applications [129]. Among these, zwitterionic structures, mainly those that contain carboxybetaine [130], phosphorylcholine [30] or sulfobetaine [131], have shown promising results in creating antifouling and hemocompatible surfaces. Zwitterionic polymers are neutrally charged polymers that have equal numbers of anionic and cationic groups on their polymer chains. This unique characteristic renders them highly hydrophilic and resistant to non-specific adhesion [132,133].

The development of zwitterionic materials was inspired by the natural bio-inert properties of the external surface of cell membranes that are rich in phospholipids containing zwitterion head groups [134], which endows them with innate antifouling and antithrombogenic properties (Fig. 2a) [135]. Among the zwitterion structures developed for blood contacting applications, phosphorylcholine (PC)-bearing polymers are the most promising [136]. The low yield and purity of synthetic first generation PC polymers [30] prompted development of a new class of PC polymers called 2-methacryloyloxyethyl phosphorylcholine (MPC) (Fig. 2a). With simplified synthetic processes, large amounts of high purity MPC can be produced [137]. This achievement led to considerable progress in developing various MPC polymers for blood-contacting applications [138–141]. For example, Hong et al., designed a biodegradable and biocompatible fibrous scaffold for vascular tissue development using poly (ester urethane) urea (PEUU) and an MPC-containing polymer poly (2-methacryloyloxyethyl phosphorylcholine-co-methacryloyloxyethyl butylurethane) (PMBU). Both *in vitro* and *in vivo* experiments performed on these surfaces revealed that platelet deposition was dependent on the PMBU content and platelet adhesion was significantly decreased by increasing the PMBU concentration. In addition, a thin layer of endothelial cells and good anastomotic tissue integration were seen on PEUU/PMBU vascular conduits 8 weeks post-implantation, compared with PEUU scaffolds without PMBU. In addition, rat smooth muscle cell (SMC) deposition was inhibited on PEUU/PMBU scaffolds that had higher PMBU content (Fig. 2b) [140].

The amount of protein adhering to blood-contacting devices depends on the free-water fraction of the surface; there is less protein adsorption on surfaces with a higher free-water fraction [142]. MPC polymers have high free-water fraction levels and the PC groups on the polymer chains reduce the protein adsorption force at the interface [136]. Chen et al. observed reduced platelet adhesion and neointimal hyperplasia on ePTFE surfaces coated with MPC through physical absorption compared with uncoated grafts [143]. While these results are promising, shear stress may disrupt the MPC layer because it is not covalently attached. To circumvent this limitation, Chevallier et al. optimized the modification strategy and created a dichloro derivative PC-grafted ePTFE surface by covalently attaching PC polymers to the substrate using radio-frequency glow discharge ammonia plasma treatment [144]. The blood compatibility of the PC-grafted ePTFE surface was investigated by conducting *in vitro* tests such as thromboelastography, and quantification of platelet adhesion and neutrophil adsorption. PC-modified ePTFE grafts exhibited significantly decreased thrombin generation and platelet and neutrophil adhesion compared with control ePTFE grafts [144].

Among the new generation of zwitterionic polymers, poly(sulfobetaine methacrylate) (polySBMA) with a methacrylate main chain has become a popular candidate, mainly because of the low cost, simple synthetic process and its ability to create a strong hydration layer on the coated surface [131,145]. Vascular catheters coated with a non-leaching polySBMA surface using a graft-from redox polymerization process exhibited reduced platelet activation, protein and cells adhesion and prevented clot formation both *in vitro* and *in vivo* (Fig. 2c) [146]. These polymers have also been grafted on hydrogen plasma treated PTFE membranes using atom transfer radical polymerization (ATRP) where the C–F groups on the PTFE surface were used as initiators for the ATRP reaction [147]. Coating the PTFE surface with the polySBMA polymer significantly decreased the hydrophilicity of the PTFE substrate and the coated surfaces were fibrinogen repellent compared with control samples. Film thickness and grafting density affect the blood and plasma protein repellency properties of polySBMA-grafted surfaces [148]; thus, using a controlled polymerization technique such as ATRP for grafting, may be beneficial because it enables control of the molecular weight distribution, molar mass ratios and the architecture of the grafted polymer [149].

2.2. Plasma surface modification techniques

The hydrophobicity of ePTFE and PET vascular grafts limits EC adhesion and growth and promotes platelet activation and clot formation [21]. To render these surfaces more hydrophilic, plasma modification techniques have been used to allow the surfaces to bond with different atmospheric gases, thereby decreasing hydrophobicity [23,37,38]. Plasma treatment also increases the capacity for biomolecule immobilization by creating functional groups such as hydroxyl or carboxyl groups on the surface [162]. Moreover, studies have shown that plasma modification, is an effective way to modify and functionalize biomaterials such as ePTFE to a shallow depth, without altering their surface bulk properties [162]. Results obtained from X-ray photoelectron spectroscopy (XPS) and electron spin resonance (ESR) spectroscopy have revealed that the depth of the plasma radiation can be controlled by the plasma energy and type of plasma gas used. Plasma radiation could be optimized such that it only affects the surface of the substrate to a shallow depth, leaving the bulk properties of the substrate intact [163].

Dekker et al. investigated the effect of nitrogen plasma treatment of ePTFE surfaces on EC spreading and adhesion [37]. Hydrophilicity and

Table 2
Blood contacting biomaterials surface modification techniques for enhancing hemocompatibility and endothelial cell (EC) adhesion.

Surface coating/substrate	Modification technique	Cell marker	Outcomes	Limitations
Heparin/heparin-mimicking multilayers/polyvinylidene difluoride membrane [25]	Layer-by-layer assembly	NA	Reduced platelet adhesion and activation Prolonged clotting times Improved EC adhesion	Non-specific adhesion of heparin [150] Leaching, degradation, depletion and instability of the coating [6,130] Not EC specific
Anti-CD34 antibody immobilization/ePTFE grafts [42]	Covalent attachment through peptide linkages	Anti-CD34 antibody	Rapid endothelialization *in vivo* 95% coverage with ECs after 28 days	Hemocompatibility was not investigated Grafts promoted intimal hyperplasia
Heparin and fibronectin films/titanium surfaces [151]	Electrostatic interaction and co-immobilization technique	NA	Lower hemolysis rate Prolonged blood coagulation time Reduced platelet adhesion and activation More EC adhesion and proliferation	Non-specific adhesion of the coating [150] Leaching, degradation, depletion of the coating [6] Fibronectin is thrombogenic [152] Not EC specific
Poly(1,8-octanediol-co-citrate)-Heparin coating/ePTFE grafts [36]	Chemical immobilization through carboxyl functional groups	NA	Maintained bioactivity *in vitro* Inhibited blood clot formation and platelet adhesion Supported EC adhesion	Non-specific adhesion of heparin [150] Not specific to ECs Non-specific adhesion of SMCs Coating degradation
Heparin/Collagen Multilayer functionalized with anti-CD133 antibody/ePTFE grafts [46]	Layer-by-layer assembly	Anti-CD133 antibody	Prolonged blood coagulation time Reduced platelet adhesion ECs adhered "well" to the ePTFE coated surface *in vitro* Rapid endothelialization *in vivo*	Non-specific adhesion of heparin [150] Thrombogenicity of collagen [83] Instability of the coating [130] Low expression of CD133 on ECs circulating in the blood stream [153]
Anti-CD34 antibody functionalized heparin-collagen multilayer/316L stainless steel stents [154]	Layer-by-layer assembly	Anti-CD34 antibody	Good hemocompatibility Promoted cell attachment and growth Rapid endothelialization *in vivo*	Non-specific adhesion of heparin [150] Thrombogenicity of collagen [83] Instability and degradation of the coating [130]
Co-immobilization of Heparin and Cell-Adhesive Peptides/polyurethane grafts [155]	Chemical immobilization technique	Cell-adhesive peptide	Slightly reduced adhesion of platelets Decreased fibrinogen adsorption Enhanced EC attachment	Non-specific adhesion of fibroblasts, and SMCs to the peptides [155] Non-specific adhesion to heparin [150] Leaching of the heparin coating [6] Not EC specific
Heparin release from PCL/chitosan grafts [156]	Ionic bonding between heparin and chitosan fiber	NA	Reduced platelet adhesion Prolonged coagulation time Promoted EC growth	Non-specific adhesion of heparin [150] Leaching of the heparin coating [6] Not EC specific
Chitosan-Heparin coating/316L stainless steel stents [157]	Layer-by-Layer assembly	NA	Improved hemocompatibility Improved EC adhesion promote re-endothelialization *in vivo*	Non-specific adhesion of heparin [150] Leaching of the heparin coating [6] Instability of the coating [130] Not EC specific
PEG and anti-CD34 antibody immobilization/titanium surfaces [158]	Covalent immobilization	Anti-CD34 antibody	Reduced platelet adhesion Improved EC adhesion	Degradation and depletion of PEG chains caused by oxidation [62] Not suitable for long-term applications [30]
Heparin, fibronectin and VEGF/titanium surfaces [152]	Layer-by-Layer deposition	VEGF	Prolonged clotting time Reduced platelet adhesion and activation Promoted EC adhesion and proliferation	Non-specific adhesion of heparin [150] Thrombogenicity of fibronectin [152] Instability of the coating [130] Risk of tumor development caused by VEGF release [159]
VEGF immobilization/poly(L-lactide-co-ε-caprolactone) elastomer [160]	Multistep chemical immobilization	VEGF	Improved EC adhesion and the formation of an endothelial layer	Hemocompatibility has not been investigated Risk of tumor development caused by VEGF release [159]
Heparin immobilization on plasma treated surface/Polycarbonate-urethane (PCU) grafts [161]	Chemical modification	NA	Antithrombogenic properties Higher patency rates *in vivo* Formation of a more confluent endothelial layer	Non-specific adhesion of heparin [150] Leaching of the heparin coating [6] Not EC specific

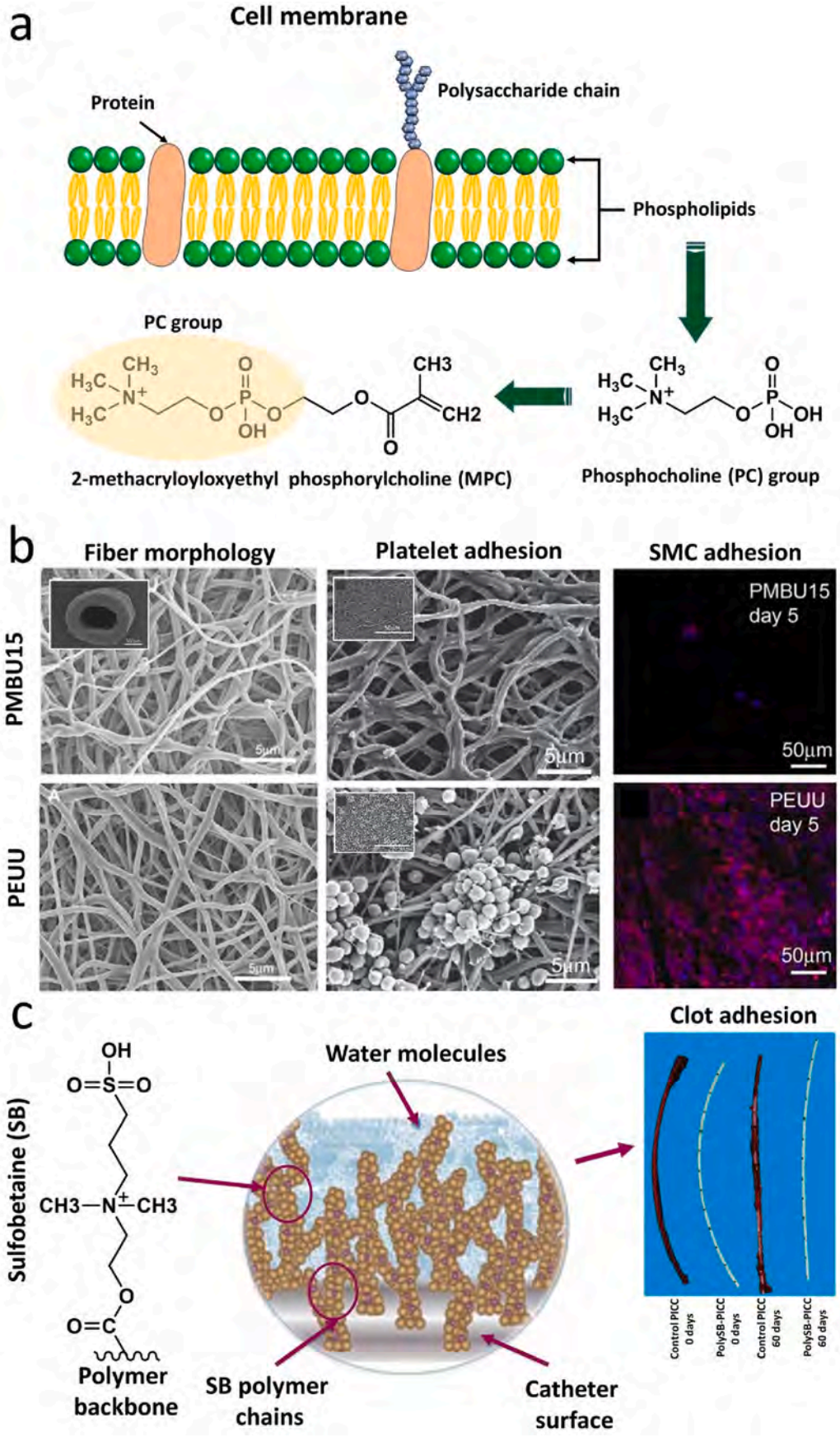

Fig. 2. (a) Schematic illustrations of the synthesis and design of zwitterionic polymers such as MPC which are inspired by the external surface of cell membranes that are rich in phospholipids and contain phosphocholine functional groups. (**b)** Small diameter, fibrous vascular grafts were created with different concentrations of a poly (ester urethane) urea (PEUU) and phospholipid polymer blend (PMBU). No difference was seen in the fibre structure and morphology of the PEUU and PMBU modify grafts. As seen in the SEM images obtained after 4 h of whole blood incubation experiments, surfaces that had the highest amount of PMBU (PMBU15) significantly decreased platelet adhesion compared with PEUU grafts. In addition, PMBU15 grafts significantly inhibited SMC adhesion. Adapted with permission from Ref. [140]. Copyright 2009 Elsevier. **(c)** Peripherally inserted central catheters were modified with polymeric sulfobetaine (SB) chains and their thrombogenicity was investigated. PolySB coated catheters significantly reduced human cell adhesion and activation (e.g. platelet, lymphocytes and PMNs) and thrombus accumulation after 60 days of incubation in serum. Adapted from with permission from Ref. [146]. Copyright 2012, American Association for the Advancement of Science.

wettability of the treated surfaces changed with the plasma treatment time, with longer plasma treatment times resulting in greater hydrophilicity and lower water contact angles. In addition, there was more EC cell spreading and adhesion after 6 h of incubation on plasma treating ePTFE surfaces than on unmodified ePTFE substrates [37]. Ammonia plasma treatment of PET and PTFE significantly increased cell adhesion by 1.3-fold and 5.5-fold respectively compared with their unmodified counterparts and the number of adherent cells continued to increase over a 7-day time period [164]. Despite the enhanced EC adhesion on these surfaces, their hemocompatibility and their ability to prevent blood protein and platelet adhesion still needs to be investigated.

A number of studies from Laroche's laboratory have focused on ammonia plasma treatment as an initial step in multistep functionalization procedures for PTFE surfaces [39,144,165]. Ammonia plasma treatment was used to generate amino functional groups on the PTFE surface, which were then utilized to covalently attach biomolecules such as fibronectin [39], vascular endothelial growth factor (VEGF) [165] or zwitterionic phosphorylcholine polymer [144]. The main purpose of these studies was to assess the blood compatibility [144], biological activity [39], and endothelialization [165] of the modified PTFE surfaces compared with unmodified substrates. In addition to ammonia, argon plasma treatment has also been used to covalently attach specific bioactive molecules, such as collagen IV or prostaglandin E1 on ePTFE and PET surfaces in order to enhance their hemocompatibility, without significantly altering graft structure [166]. These coatings reduced fibrinogen adsorption, platelet and bioactive molecule adhesion and significantly improved the biocompatibility of the vascular grafts.

2.3. Antithrombotic agents and biologically active coatings

2.3.1. Heparin

Attachment of anticoagulant and biologically active agents alone or in combination with other bioactive and bioinert molecules has been extensively investigated as a method for synthesizing antithrombotic blood-contacting surfaces [130]. Of the anticoagulants, heparin has been studied the most (Table 2) [23,167]. Heparin is an anionic polysaccharide with a linear structure, containing carboxylic, sulfonic, and sulfanilamide functional groups [130]. Heparin acts as an anticoagulant by binding to antithrombin and enhancing its capacity to inhibit clotting proteases such as thrombin and factor Xa [168]. Several techniques have been used to immobilize heparin on the surfaces including covalent attachment **(**Fig. 3a, b and c) [31,36,155,169], physical adsorption [170,171], electrostatic attachment via the negatively charged sulfate groups of heparin [172] and layer-by-layer deposition (Fig. 3d and **e)** [25,157]. The efficiency of the heparin coated layer in preventing non-specific adhesion and preventing thrombin generation depends on several factors such as the stability of the heparin coating and whether the heparin molecule remains biologically active after the modification process [162]. Physical adsorption of heparin results in creating unstable heparin coatings that deplete overtime [173]. For example, ePTFE grafts coated with silyl-heparin though physical adsorption lose 98% of the heparin activity after 7 days of implantation and because of poor heparin retention, the patency rates of heparin coated ePTFE surfaces were similar to those of uncoated ePTFE surfaces [173].

In order to circumvent this limitation, covalent immobilization of heparin is the preferred method for creating heparin-coated surfaces. The covalent immobilization strategy used to attach the heparin molecule on the surface plays an important role in the biological activity of the immobilized heparin molecule. Each heparin molecule has several free carboxyl groups that can create multiple covalent linkages with other functional amino or hydroxyl groups on the biomaterial, thereby yielding robust covalent immobilization of heparin. Although multiple covalent linkages could better stabilize heparin on the surface, nonspecific immobilization impairs the free movement of heparin molecules, which can limit the bioactivity of the heparin layer [130]**.**

To better understand this problem, Gore et al., investigated the impact of the heparin immobilization technique on the hemocompatibility and protein resistant properties of coated surface in human whole blood [168]. End-point attachment of heparin using Carmeda® BioActive Surface technology (CBAS-ePTFE) was compared with multivalent attachment techniques, such as heparin immobilization using carbodiimide crosslinking chemistry which results in nonspecific linkage of the heparin molecule. In contrast to multivalent carbodiimide crosslinking, end-point immobilization of heparin results in attachment via a single covalent bond at the end of the heparin chain. Heparin bound at its end retains its natural configuration and biological activity. Consequently, surfaces with end-point attached heparin exhibited less platelet adhesion, activation and clot formation than surfaces that had heparin attached using multivalent techniques [168]. Several studies have reported the effectiveness of end-point immobilization for synthesizing blood-compatible heparin-coated surfaces [65,161,174,175]. For example, Begovac et al. demonstrated higher patency rates and less thrombus deposition with end-point immobilized heparin coated Gore-Tex® ePTFE vascular grafts than with unmodified grafts 1 and 12 weeks after implantation [65]. Therefore, end-point immobilization is considered the optimal method for heparin immobilization.

Introducing a hydrophilic spacer between the heparin molecule and the biomaterial surface is an effective method for creating biofunctional, bioactive and hemocompatible heparin coatings and to protect the heparin molecule from denaturation [176]. PEG is one of the most common hydrophilic spacers used for heparin immobilization [155,177,178]. Pan et al. investigated the blood compatibility and EC adhesion of titanium surfaces modified with heparin-PEG (Fig. 3f and g) [178]. When titanium surfaces were oxygen plasma treated and modified with heparin-PEG using the carbodiimide coupling chemistry, they exhibited less plasma fibrinogen and platelet adhesion than control surfaces and there was prolongation of the activated partial thromboplastin time. In a similar study, the negatively charged heparin-PEG coated surfaces were cell compatible and showed better EC adhesion and spreading compared with unmodified surfaces [178]. The chain length of the PEG spacer affects the bioactivity and antithrombotic properties of heparin [179,180]. By increasing the PEG chain density, the bioactivity of heparin increases and 1000 Da PEG appears to provide the optimum heparin dynamic motion required to prevent platelet adhesion and clot formations [155].

In recent studies, heparin has been co-immobilized with other biomolecules (Table 2), [151,152,156,181,182]. For example, aminosilanized titanium surfaces were biofunctionalized with heparin and fibronectin (Hep/Fn), an extracellular matrix (ECM) protein [151]. Blood experiments showed that co-immobilization of Hep/Fn prolonged the blood clotting time, decreased fibrinogen adhesion and platelet activation and aggregation compared with unmodified titanium substrates. In addition, there was more EC attachment and proliferation on biofunctionalized surfaces than on uncoated, NaOH-activated and silanized titanium surfaces [151]. Neointimal hyperplasia caused by smooth muscle cell migration and proliferation is a major cause of restenosis after cardiovascular intervention [22]. Cai et al. demonstrated that, compared with control surfaces, titanium surfaces coated with Hep/Fn resisted smooth muscle cell proliferation for up to 5 days [183].

Collagen is another ECM protein that has been co-immobilized with heparin [181,184]. In one study, ePTFE films biofunctionalized with a Hep/collagen complex that included an EC adhesive peptide exhibited less platelet adhesion and aggregation and a longer blood clotting time than unmodified surfaces [181]. In addition, the EC adhesive peptide enhanced EC adhesion and proliferation compared with control ePTFE films.

Although collagen and fibronectin are used to promote cell adhesion and improve cell compatibility on biomaterials [36,152,185], they are highly thrombogenic and could promote platelet adhesion and activation [83,186]. Therefore, the use of these highly thrombogenic materials on blood-contacting implants that have not yet been completely covered

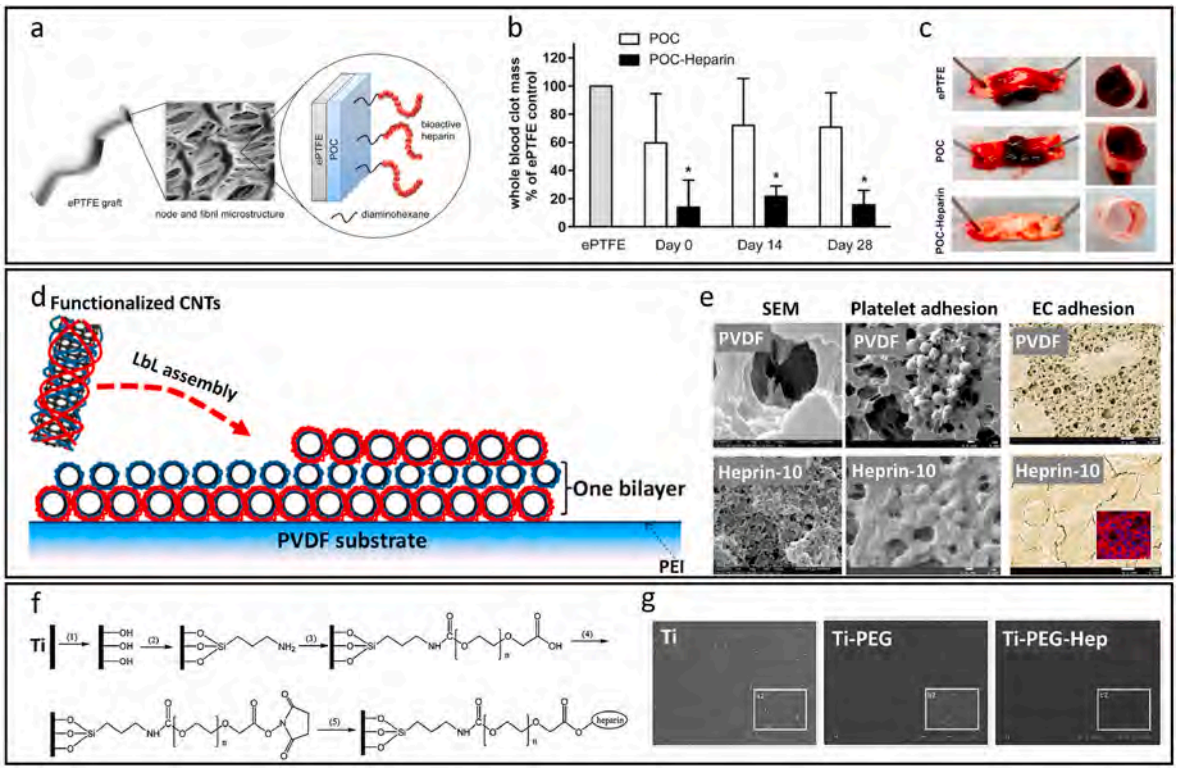

Fig. 3. **(a)** The inner lumen of ePTFE grafts were functionalized with a poly(1,8-octanediol-co-citrate) (POC)-Heparin layer. Heparin was covalently attached to POC through its carboxyl functional groups. **(b–c)** Whole blood and vascular cell compatibility of the surfaces was investigated *in vitro*. POC-Heparin ePTFE vascular grafts remained functional after 28 days of incubation in PBS and they significantly attenuated blood clot adhesion when compared with control ePTFE and POC modified vascular grafts. Panels a–c reproduced with permission from Ref. [36]. Copyright 2013 Elsevier. **(d)** Schematic representation of nanofibrous multilayers prepared by layer-by-layer (LbL) assembly of heparin or oxidized carbon nanotubes functionalized with heparin-mimicking polymer (oCNT/CS/Hep) immobilized on commercially available polyvinylidene fluoride (PVDF) membrane substrates. **(e)** Surfaces coated with 10 bilayers of oCNT/CS/Hep (Hep-10) exhibited the best blood compatibility with nearly no platelet adhesion. In addition, as observed in the EC SEM images, only a few ECs were spread on the PVDF membrane and cells tended to spread and fully cover the Hep-10 functionalized surfaces. With the increase in the layer numbers, the endothelial cell layer became much thicker. Panels d and e adapted with permission from Ref. [25]. Copyright 2015 American Chemical Society. **(f)** PEG is used as a spacer in order to covalently attach heparin on titanium (Ti) substrates. **(g)** Ti surfaces functionalized with Ti-PEG-Hep coating significantly decreased platelet adhesion compared with untreated Ti and Ti-PEG treated surfaces. Panels f and g adapted from Ref. [178] with permission from The Royal Society of Chemistry.

with an endothelial layer could be problematic [83,152]. Hence, these ECM proteins have to be co-immobilized with other antithrombotic agents (*e.g.* heparin) and their surface density of must be optimized so that they promote endothelialization without compromising the antithrombotic properties of the coating.

Surface modification of biomaterials with heparin coatings is an established method for creating hemocompatible substrates. However, challenges remain. The anticoagulant activity of heparin relies on its capacity to bind circulating antithrombin [168]. This could be problematic in occluded vessels with higher blood velocity [187]. Furthermore, heparin binds plasma proteins other than antithrombin. These proteins include fibronectin, vitronectin and growth factors [150]. This nonspecific interaction could decrease the anticoagulant activity and efficiency of the coating. Lastly, the heparin present on coated surfaces are prone to depletion and leaching off of the surface over time, which could result in the gradual loss of their anticoagulant properties [6,7].

2.3.2. *Other agents*

In addition to heparin, other agents with different mechanisms of action have been coated on blood-contacting devices to enhance thromboresistance. These include corn-trypsin inhibitor (CTI) [188,189], thrombomodulin (TM) [190], direct thrombin inhibitors such as hirudin, bivalirudin, or argatroban [191–193], and nitric oxide (NO) releasing coatings [169,194]. CTI is a protein derived from corn kernels that inhibits FXIIa [1]. In order to inhibit both FXIIa and FXII autoactivation and decrease plasma protein deposition, CTI has been co-immobilized with PEG (PEG-CTI). Surfaces coated with PEG-CTI conjugates inhibit FXII autoactivation, reduce fibrinogen adhesion and thrombin generation and prolong plasma clotting times compared with non-coated surfaces or surfaces coated with PEG alone or with a PEG-albumin conjugate [189,195,196]. When PEG-CTI modified catheters were implanted in the jugular veins of rabbits, the time to occlusion was 2.5-fold longer than that of unmodified catheters or catheters modified with PEG alone [188].

TM is another anticoagulant agent used for coating blood-contacting medical devices. TM, which is expressed on the surface of ECs, is a receptor for thrombin. The thrombin-thrombomodulin complex supresses coagulation by binding thrombin and neutralizing its procoagulant properties and by promoting protein C activation which ultimately results in inhibition of thrombin generation by inactivation of FVa and FVIIIa. Several groups have immobilized TM alone [197–200] or in combination with other anticoagulants such as heparin [201] to create biocompatible surfaces that locally prevent coagulation and thrombin generation. These surfaces have shown promising short-term results in reducing clot formation, thrombin generation, platelet adhesion and activation [197,199–201] and inhibiting neointimal hyperplasia [198]. One of the main disadvantages of the modification techniques used in these studies is the random orientation and inherent reduction in the bioactivity of TM after immobilization. This is mainly due to the non-targeted conjugation and immobilization of the protein on the substrate in a manner that limits the capacity of TM to bind thrombin [202]. In order to retain TM activity, several site-specific, targeted

binding strategies have been developed [203–205]. For example, Qu et al., reported a novel technique to site-specifically immobilize TM on ePTFE surfaces by using a molecular engineering and bioorthogonal chemistry approach [204]. In this technique, human TM fragments expressing a signal C-terminal azide moiety were synthetized and immobilized onto the luminal surface of polyurethane coated ePTFE vascular grafts using the Staudinger ligation reaction chemistry. The TM coated surfaces were stable *in vitro* and significantly reduced platelet adhesion and activation and clot formation *in vivo* over a 60-min perfusion period. Despite these promising results, the complex synthetic procedure, low yield and scalability of the reaction limits the implementation of this modification technique for clinical applications.

Nitric oxide (NO) generating and releasing substrates are another class of surface coating that has been explored. NO is a signalling molecule synthesized and released by ECs, which regulates several biochemical processes in the vascular system [206]. Most importantly, the protective role of the endothelium has mainly been attributed to the presence of NO which causes vasodilation and has shown to prevent platelet adhesion and activation, clot formation and SMC proliferation [207]. Smith et al., were the first to apply a NO-releasing polyethylenimine coating on PTFE surfaces by incorporating diazeniumdiolate groups ($[N(O)NO]^-$) in polymeric matrices [208,209]. NO-releasing polyethylenimine coated PTFE vascular grafts exhibited potent antiplatelet activity and were significantly less thrombogenic than untreated PTFE surfaces *in vivo* [208]. Several other modification approaches have been developed for obtaining diazeniumdiolate NO-releasing functional surfaces. A major disadvantage of diazeniumdiolates as a NO donor is that the amount of NO released from these surfaces is limited and decreases over time. Consequently, coated substrates lose their anticoagulant properties with long-term applications [210]. Because of these limitations, other surface coating techniques have been explored. These incorporate catalytic agents to convert endogenous NO donors such as S-nitrosoglutathione, S-nitrosocysteine and S-nitrosoalbumin to NO and thereby generate a sustained source of NO [211–214]. These surface coatings have shown to reduce restenosis, collagen-induced platelet activation and enhance human umbilical vein EC (HUVEC) adhesion.

2.4. Surface coating with EC specific growth factors and antibodies

The endothelium consists of a monolayer of ECs that line the lumen of vessels and is in direct contact with blood. The endothelial layer plays a crucial role in regulating inflammation and clot formation [159]; therefore, the establishment of a healthy and confluent endothelial layer on newly implanted vascular grafts, stents and heart valves is essential to prevent occlusion [23,159]. To address this requirement, several research groups have investigated *in vitro* EC seeding onto synthetic vascular grafts (Fig. 4), [215,216]. Although this technique improves the patency and performance of the grafts, it remains impractical because it requires harvesting and culturing autologous ECs and seeding them onto the luminal surface of the grafts prior to implantation (Fig. 4) [14,217]. This process is costly and time consuming because it can take up to 8 weeks to generate a sufficient number of cells in culture during which time there is a risk of contamination and infection [14,154,159]. In addition, the stability of the pre-seeded endothelial monolayer during and after implantation is unconcern. These drawbacks have prompted alternate technologies, particularly *in situ* endothelialization techniques using EC specific ligands and cell adhesive molecules [159].

2.4.1. Vascular endothelial growth factor (VEGF) coated surfaces

VEGF promotes angiogenesis and stimulates the proliferation, differentiation and migration of ECs [218,219]. Surface immobilization of VEGF alone or in combination with other biomolecules promotes EC adhesion, proliferation, migration and growth *in vitro* (Table 2), [45,160,220]. In a recent study, Randall J. et al. used a microfluidic device to investigate the ability of VEGF/heparin coated surfaces to capture ECs under various flow conditions [45]. VEGF remained biologically active after immobilization and selectively captured ECs and not other cell types such as human dermal or mouse fibroblast. In addition, these surfaces were able to capture ECs from whole blood under high shear conditions. As an alternative approach, Xu et al. incorporated VEGF-loaded polylactic-co-glycolic acid microparticles onto surfaces coated with an anti-CD34 antibody and investigated the effect of VEGF release on endothelialization and hemocompatibility [221]. Although sustained release of VEGF decreased platelet activation and significantly improved endothelial cell adhesion and proliferation, high levels of VEGF may lead to neovascularization and tumor formation [222]; therefore, its safe usage for promoting *in vivo* endothelialization of biomaterials should be closely investigated.

Despite the promising results obtained from *in vitro* experiments using VEGF immobilization, *in vivo* experiments suggest that VEGF coated surfaces not only capture ECs, but also promote the non-specific adhesion of other cell types. *In vivo* studies with ePTFE vascular grafts coated with a VEGF/ECM [223] or fibrin/VEGF [224] complex have shown that, in addition to increasing EC capture, these surface coatings also promote SMC adhesion and growth, thereby promoting neointimal hyperplasia and reducing long-term patency rates [223,224].

2.4.2. Promoting endothelialization by immobilizing endothelial cell targeting antibodies

Endothelial Progenitor Cells (EPCs) are mononuclear cells that are mainly accumulated in the bone marrow and can be found in low concentrations in the peripheral blood stream. After entering the blood stream, EPCs differentiate into mature ECs and attain EC specific markers and antigens [153,159]. Peripheral blood contains at least two types of “early” and “late” EPC populations, which are fundamentally different. Early EPCs, which are also called colony forming unit-endothelial cells (CFU-ECs), have low proliferative capacity and express hematopoietic and monocytic features in addition to endothelial cell characteristics. In contrast, late EPCs or endothelial colony forming cells (ECFCs) have high proliferative capacity, express EC specific markers and phenotype but have no hematopoietic or monocytic characteristics [14,159]. In general, EPCs in the bone marrow express CD34, VEGFR-2 and CD133 surface markers. However, EPCs in the blood stream lose CD133 expression and express EC specific markers such as VE-cadherin (CD144) and von Willebrand factor (vWF) in addition to CD34 and VEGFR-2 (Fig. 5) [153,225].

Circulating ECs can be captured by immobilizing monoclonal antibodies against these endothelial specific surface markers on the surface of vascular implants. Anti-CD34 antibody is one of the most frequently used EC capturing antibodies [154,158,226–231]. Genous™ stents, designed by OrbusNeich Medical Technologies (Hong Kong), where the surface of the 316L stainless steel stents are covalently modified with a polysaccharide layer and functionalized with monoclonal anti-human CD34 antibodies [159] are the first commercially available EPC capturing stents [14]. In the first clinical study these stents appeared safe, and promoted rapid endothelialization with no stent thrombosis observed at 30 days or 6 months post implantation [232]. EPC capturing stents have also been evaluated in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. Rates of major adverse cardiac events 30 days and 6 months after implantation were 4.2% and 5.8%, respectively [233] and remained low at 12-months [234]. Additional studies are needed to evaluate the utility of these bioengineered stents compared with conventional third generation stents.

Lin et al. integrated an anti-CD34 antibody with heparin-collagen in a functionalized multilayer to investigate *in situ* endothelialization and hemocompatibility of intravascular stents [154]. In addition to good hemocompatibility, *in vitro* studies suggested that the anti-CD34 antibody attracted ECs and not SMCs, something that was not observed with surfaces functionalized with heparin/collagen alone. In addition, ECs adhering to anti-CD34 antibody functionalized surfaces exhibited

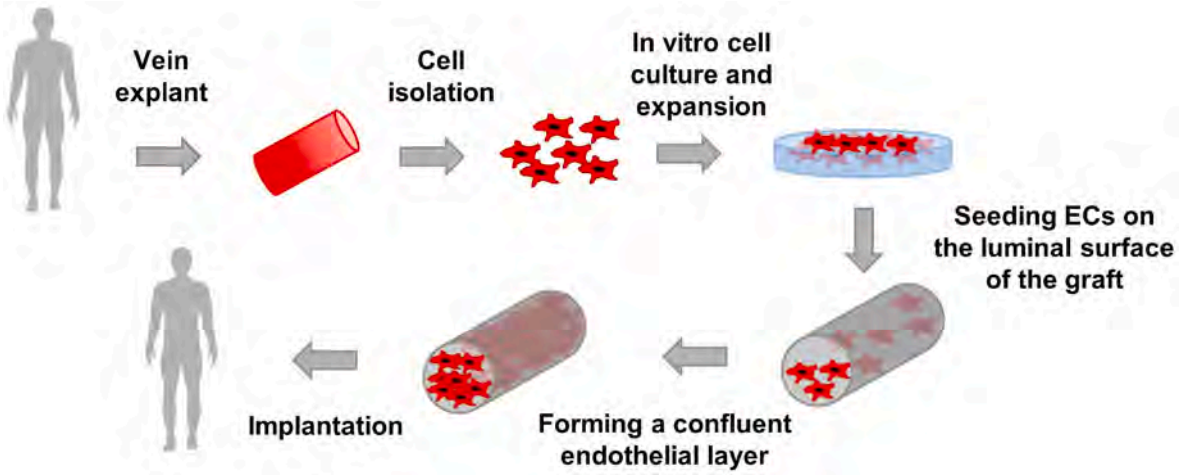

Fig. 4. Schematic representation of in vitro EC seeding on synthetic vascular grafts. ECs are extracted from the patient's vein and further cultured *in vitro*. Once the cells are ready and the desired cell population is achieved, they are seeded on the luminal surface of the synthetic vascular graft and cultured until a confluent and functional endothelial layer is created. The EC seeded vascular graft is then implanted in the patient's body.

enhanced viability and metabolic activity compared with ECs adherent to non-antibody functionalized surfaces. Lastly, results obtained from *in vivo* experiments revealed that surfaces functionalized with heparin-collagen/antiCD34 antibody significantly inhibited neointimal hyperplasia compared with nonfunctionalized surfaces or surfaces coated with heparin/collagen alone [154]. In a similar approach, Chen et al. incorporated PEG into the coating and studied the biocompatibility and endothelialization of PEG/anti-CD34 antibody functionalized titanium surfaces (Fig. 6*a*) [158]. In this technique, 3-(2-amino-ethylamino) propyltrimethoxysilane was used as the base coupling agent for grafting PEG polymer chains and further, anti-CD34 antibodies were immobilized on the PEG functionalized surfaces using carbodiimide crosslinker chemistry. The results obtained from *in vitro* experiments confirmed the superior performance of PEG/anti-CD34 antibody functionalized surfaces compared to control samples. These surfaces significantly decreased platelet adhesion, promoted targeted ECs adhesion and inhibited SMC adhesion [158].

In contrast to vascular stents, anti-CD34 antibody immobilization on synthetic vascular grafts has not been fully investigated. In the limited studies performed on ePTFE substrates, anti-CD34 antibody immobilization has been shown to inhibit platelet adhesion [44] and stimulate endothelialization [42,44] in short-term applications; however, the long-term efficacy of these grafts and their capability to promote *in vivo* endothelialization is unknown (Fig. 6*b*).

Although CD133 expression is lost when EPCs enter the peripheral blood stream and differentiate (Fig. 5) [14], a few studies have investigated anti-CD133 antibody immobilization for capturing ECs as well [46,235–237]. Stents coated with anti-CD133 antibody have exhibited improved endothelialization *in vitro* [235,236]*;* however, long-term *in vivo* experiments showed an increase in non-specific adhesion of other cell types and no difference in endothelial recovery [235,236] or neointima formation [236] compared with uncoated surfaces. Lu et al. coated ePTFE synthetic grafts with a heparin/collagen multilayer functionalized with anti-CD133 antibody (HEP/COL-CD133 antibody) using a layer-by-layer technique (Fig. 6c). In a pig common carotid artery transplantation model [46], explanted HEP/COL-CD133

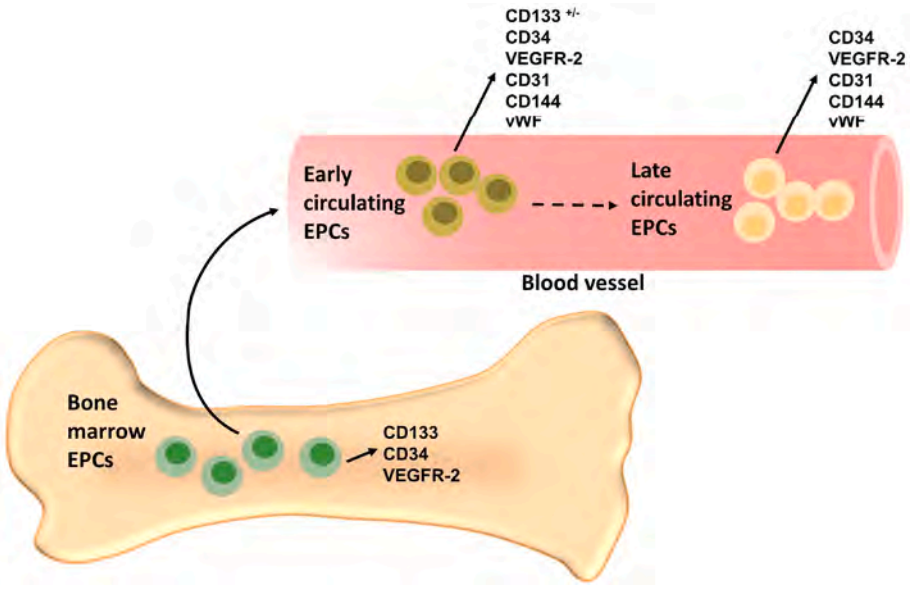

Fig. 5. Schematic representation of the expression of different markers during the differentiation and migration of EPCs from the bone marrow into the blood stream. Bone marrow EPCs express CD133, CD34 and VEGFR-2 markers. EPCs in the blood stream loose gradually loose CD133 expression and express EC specific markers such as CD144 and von vWF in addition to CD34 and VEGFR-2.

antibody-modified ePTFE grafts exhibited a luminal surface free of any identifiable clot formation. In contrast, the bare ePTFE grafts and HEP/COL modified grafts without anti-CD133 antibody, exhibited some areas of red thrombus on the luminal surface and no evidence of luminal cellularization was seen on these surfaces. In addition, the SEM imaging and histopathological analysis of explanted grafts suggested that the HEP/COL-CD133 antibody-modified ePTFE grafts promoted EC adhesion compared with surfaces modified with HEP/COL alone and bare ePTFE grafts (Fig. 6d) [46].

Mature and circulating ECs highly express VEGFR-2, also known as kinase insert domain receptor (KDR) [153]; hence, immobilizing antibodies against this receptor on the surface of biomaterials is another technique that promoted EC adhesion and growth [238–240]. However, surfaces coated in this manner appear less effective at promoting EC spreading, adhesion and differentiation compared with VEGF coated substrates [241,242]. To study this phenomenon, Matsuda et al. investigated the capture of EPCs on surfaces coated with either VEGF or anti-VEGF receptors [241]. These biomarkers were covalently attached to hydroxyl terminated poly (ethylene-co-vinyl alcohol) surfaces and EC adhesion and differentiation was studied. VEGF coated surfaces significantly increased cell differentiation after 2 weeks and the number of cells expressing VEGF receptors were significantly higher on these surfaces compared with anti-VEGFR coated surfaces, making them a better candidate for EC capture.

2.5. Lubricant-infused surfaces

2.5.1. Design principals

Recently, lubricant-infused surfaces (LIS) have gained attention as a promising approach for solving the ongoing problem of non-specific adhesion in medical and non-medical applications (Fig. 7a) [243]. Inspired by the repellent and non-sticky liquid-infused surfaces widely present in nature [244–247], scientists have integrated liquids into their surface engineering designs and investigated the repellency properties of these substrates [248–253]. The thin, lubricant layer, integrated within the solid substrate creates a mobile liquid interface with new surface properties that repel organic, aqueous and complex biological liquids [248,252,254–257] and prevent cell adhesion and biofilm formation [248,258–260].

The solid underlying substrate and the immobilized liquid layer are

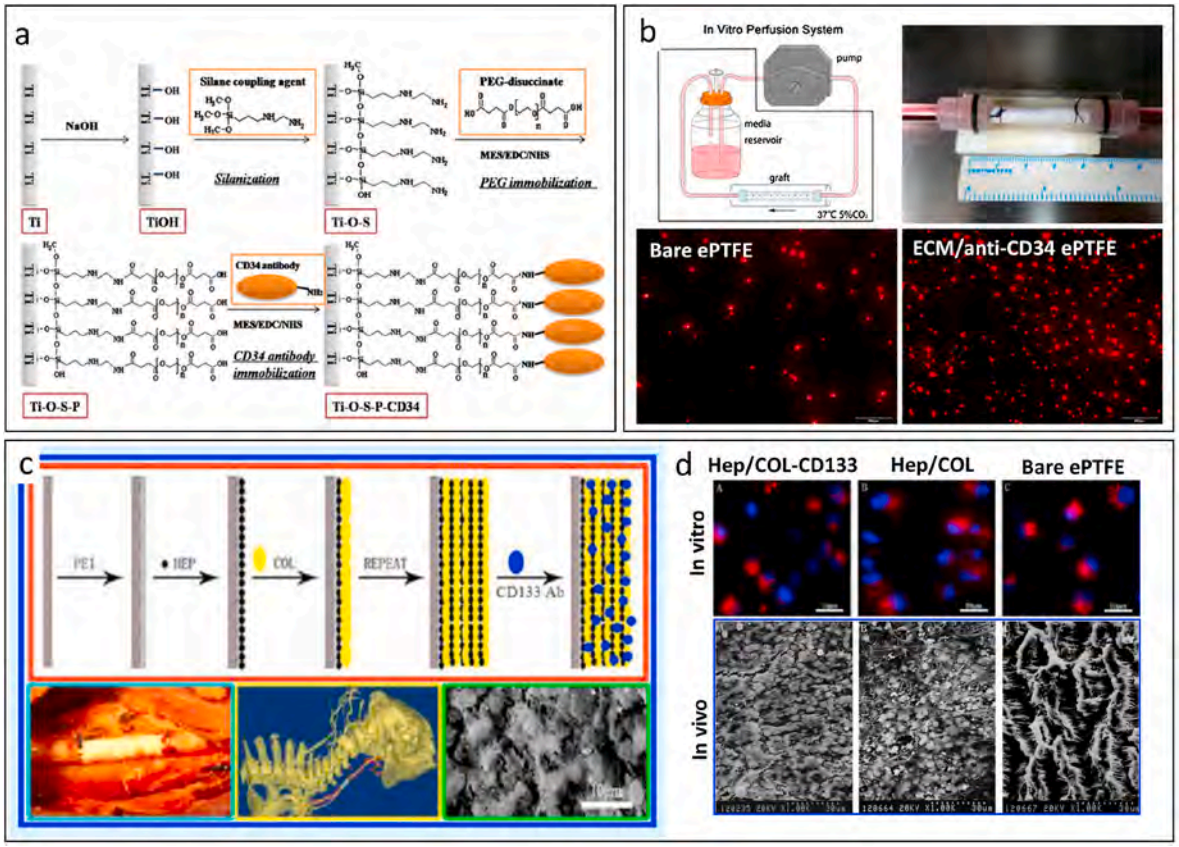

Fig. 6. **(a)** Schematic representation of a multi-step functionalization procedure of titanium surfaces using a PEG/anti-CD34 antibody coating. The hemocompatibility and endothelial cell adhesion of Ti surfaces were studied and compared with untreated Ti substrates. A long-chain PEG_{4000} grafted on the surface provided superior antifouling and thromboresistant properties compared with PEG_{600} coated surfaces. In addition, the anti-CD34 antibody provided affinity to EPC, however cell spreading, and the formation of a confluent endothelial layer was not observed on PEG/anti-CD34 functionalized Ti surfaces. Reproduced with permission from Ref. [158]. Copyright 2012 Elsevier. **(b)** HUVEC adhesion on untreated and ECM/anti-CD34 treated ePTFE grafts was investigated in an *in vitro* perfusion system. The blood circulation sheer stress was mimicked in the *in vitro* perfusion setting. After 24 h of flow, the number of adherent HUVECs was significantly higher on ECM/anti-CD34 treated ePTFE surfaces than that of untreated ePTFE grafts. Adapted from Ref. [44] with permission from Springer Nature. **(c–d)** ePTFE surfaces were modified with an anit-CD133 antibody functionalized heparin/collagen (Hep/COL-CD133) multilayer using a layer-by-layer technique and biocompatibility and endothelial cell adhesion were investigated both *in vitro* and *in vivo*. From the fluorescence images obtained from the *in vitro* experiments, Hep/COL-CD133 modified ePTFE grafts had significantly higher HUVEC adhesion compared with bare ePTFE and Hep-COL modified grafts. From the SEM images obtained from the *in vivo* experiments, HEP/COL-CD133 modified ePTFE grafts exhibited a luminal lining of cells with characteristics typical of the endothelium. No thrombus formation was seen on these surfaces. HEP/COL-modified grafts exhibited incomplete endothelialization and the deposition of platelets, fibrin, and red blood cells was observed on these surfaces. The bare ePTFE grafts showed no evidence of endothelialization. Panels c and d reproduced with permission from Ref. [46]. Copyright 2013 American Chemical Society. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the two main components of lubricant-infused systems. These components work in concert to create a stable yet dynamic liquid interface. Most importantly, the underlying flat or porous/rough solid substrate must have high chemical affinity for the infiltrating lubricant layer and a relatively low affinity for the contaminating liquid. This can be achieved by either exploiting the innate chemical properties of the solid surface (Fig. 7b and c) [249,254] or by chemically modifying the flat/porous solid surface with an appropriate functional layer that is compatible with the desired lubricant (Fig. 7*d, e, f and g*) [250,252,261,262]. Once the appropriate conditions are met, the solid substrate "locks in" the liquid layer through a combination of van der Waals and capillary forces, thereby creating a stable, highly repellent and homogenous lubricant-infused interface. Thus, the chemical affinity and physical properties of the underlying substrate creates a platform that is more energetically favorable for the lubricant layer than for the contaminating liquid to infiltrate and wet the solid substrate [263].

2.5.2. Platforms and modification techniques

LIS have shown to be compatible with numerous solid substrates used in medical applications such as polyurethane [264], glass [260,265], stainless steel [248,266], gold [256], aluminum [59,267], polyether amide [252], ePTFE [248,249,254], PET, polycarbonate, poly (methyl methacrylate) (PMMA) [248] and polydimethylsiloxane (PDMS) [253]. The first reported slippery lubricant infused porous surfaces (SLIPS), inspired by *Nepenthes* pitcher plants were created using epoxy-resin-based nanostructured substrates and Teflon nanofibrous membranes infiltrated with low surface energy perfluorinated lubricants [254]. Because the surface chemistry of porous epoxy-resin-based substrates does not match the chemical nature of the perfluorinated lubricants, they were chemically modified with a fluorosilane monolayer prior to adding the lubricant layer. In contrast to epoxy surfaces, Teflon membranes are synthesized from a synthetic fluorocarbon-based polymer [130] and do not require further chemical modification because they are porous and have the appropriate surface chemical composition to interact with the perfluorinated lubricant layer [254,255]. SLIPS created using both these surfaces had low contact angle hysteresis ($<2.5°$), repelled various aqueous and organic liquids as well as complex solutions such as blood and were able to function under high pressures. In a different study, Chen et al. investigated the bacterial repellency properties of lubricant-infused ePTFE substrates and their ability to prevent medical device associated infection [249]. ePTFE-SLIPS were created by infiltrating the ePTFE membranes with three different fluorinated lubricants: perfluoropolyether, perfluoroperhydrophenanthrene and perfluorodecalin. Lubricant-infused ePTFE surfaces were highly resistant to biofilm formation and exhibited a 99% reduction in *S. aureus* adhesion *in vitro* and no significant difference was seen between the different lubricants. In addition, upon implantation *in vivo*, lubricant-infused ePTFE implants limited bacterial adhesion and largely reduces local inflammation [249]. If the surface chemical properties of the underlying substrate are unsuitable for stable LIS formation, the substrate can be modified with compatible functional groups such as fluorosilanes. Silanization is one of the most popular and straightforward modification techniques used to enhance the surface chemical properties of the substrate and can be easily preformed using techniques such as liquid phase deposition (LPD) [248,252,268] or chemical vapour deposition (CVD) [250,252,258]. In our recent study we used CVD and LPD modification techniques to develop slippery lubricant-infused coronary catheters by creating self-assembled monolayers (SAMs) of tridecafluoro-1,1,2,2-tetrahydrooctyl trichlorosilane (TPFS) and investigated the antithrombotic properties of the modified catheters (Fig. 8*a* and *b*) [252]. Although LPD is a well-known technique for producing SAMs of silanes [269], our results suggest that CVD is a more efficient and effective method than LPD for creating LIS and rendering medical grade polymeric catheters less thrombogenic. One of the main drawbacks of the LPD method is that the treated surfaces are directly exposed to the side products released in the liquid phase (*e.g.* hydrochloric acid), which can damage the treated surfaces [269]. This concept was supported by the results of SEM analysis; catheters treated with LPD exhibited surface roughness, etching and exposure of inner layers, whereas CVD treated samples remained intact [252].

In addition to chemical properties, creating porosity and adding roughness to flat surfaces (*e.g.* incorporating micro or nano features) are effective techniques for stabilizing the lubricant layer and increasing the repellency and omniphobic properties of the LIS [263]. Such surface properties can be achieved with surface modification techniques including layer-by-layer deposition of particles, organic and synthetic charged polymers [250,251,270–272], surface wrinkling [256,273] and UV initiated polymerization [265]. LIS generated using these techniques

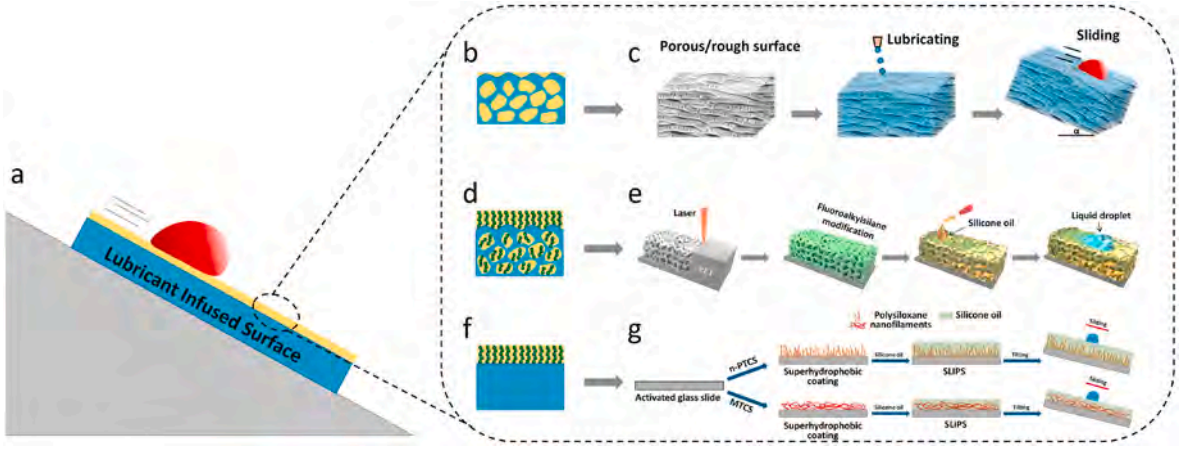

Fig. 7. **(a)** Schematic representation of lubricant-infused surfaces**. (b–c)** A lubricant-infused layer can be generated using a porous/rough surface with appropriate innate chemical properties that will interact with the lubricant layer. **(c)** Lubricant-infused PTFE/ePTFE nanofibrous membranes were created by infiltrating the membranes with low-surface-tension perfluorinated lubricants. No further chemical modification was performed on Teflon membranes prior to adding the lubricant layer [249,254]. Lubricant-infused surfaces can be generated by chemically modifying porous/rough **(d–e)** or flat **(f–g)** substrates with appropriate chemical molecules to create surfaces that possess suitable chemical properties for stabilizing the lubricant layer. **(e)** Schematic representation of creating lubricant-infused porous PET surfaces by femtosecond laser direct writing. After creating the porous structure, the PET substrates were chemically functionalized with fluoroalkylsilane and further lubricated with silicone oil. Adapted with permission from Ref. [261]. Copyright 2018 John Wiley & Sons. **(g)** Oxygen plasma treated, flat glass substrates were silanized with n-Propyltrichlorosilane (n-PTCS) or methyltrichlorosilane (MTCS) and infiltrated with silicone oil to create lubricant-infused polysiloxane nanofilament coatings. Adapted with permission from Ref. [262]. Copyright 2019 Elsevier.

prevent infection [274], protein [272,274], bacterial [251,265,275] and platelet adhesion [274] and attenuate thrombus formation [256,270,274]. When creating porous structures, Kratochvil et al. took an interesting approach and created a dynamic LIS by incorporated anti-virulence agents against *Pseudomonas aeruginosa* in their multilayer structure and studied the gradual release of these molecules and their ability to attenuate virulent phenotypes through non-biocidal pathways (Fig. 8c) [251]. The anti-biofilm quorum sensing inhibitor (QSI) or 5, 6-dimethyl-2-aminobenzimidazole (DMABI, a potent biofilm inhibitor that indirectly modulates QS in *P. aeruginosa*) agents loaded in the lubricant-infused layer did not compromise the slippery and repellency properties of the surface and remained biologically active after the modification process, enabling the loaded LIS to both prevent bacterial adhesion and biofilm formation (through the slippery lubricant-infused coating) and reduce the production of key virulence factors in planktonic cultures of this bacterium (Fig. 8d, e and f).

2.5.3. Stability of the lubricant layer

The stability of the lubricant-infused layer is one of the important factors that needs to be considered when designing LIS for medical applications. The dynamic liquid layer on the surface of medical implants and instruments needs to remain stable under physiological flow conditions, withstand the mechanical forces that may be applied when implanting or inserting/extracting the device and resist evaporation when placed in open environments. In addition, the designed surfaces need to withstand sterilization procedures such as ethylene oxide treatment and/or UV exposure [243]. To investigate the stability of the lubricant layer, Howell et al. studied the stability of different immobilized lubricant layers under various flow conditions, both in closed and open systems (Fig. 8g) [276]. Krytox 103 perfluoropolyether and perfluorodecalin (PFD) were the two types of lubricants tested in the experiments, with the first one being favorable for industrially relevant applications [277] and the latter being a suitable candidate for medical applications [248]. Medical-grade polyvinyl chloride (PVC) tubing was used as the base substrate and lubricant loss was quantified on structured PVC surfaces functionalized with perfluoroalkyl phosphate surfactant and flat substrates functionalized with a SAM of TPFS using LPD. Both structured and flat LIS-PVC surfaces treated with either of the lubricant types were highly stable under physiological flow conditions in a closed environment but in an open environment, there was a significant lubricant loss [276]. When comparing the flow results between the flat and structured surfaces treated with the two different lubricants, flat substrates showed a greater lubricant loss, specially when treated with the volatile PFD lubricant, however these differences were not significant. PFD is a less viscous lubricant compared with Krytox, therefore less energy is required to remove this lubricant from the surface. However, this was less evident on structured substrates since it is expected that the capillary action of the nanoscale topography of the structured surface will retain more of the lubricants under flow conditions (Fig. 8h and i) [278].

In another study, the stability and thrombogenicity of LIS-acrylic surfaces coated with TPFS were tested under physiological shear stresses using human whole blood and the results obtained from this study confirmed that these surfaces remain functional and continue to effectively repel blood and prevent clot formation even after being exposed to a constant shear strain rate (1000 s^{-1}) for up to 16 h [248]. Although these results are promising for short-term applications, the long-term stability of LIS under more complex physiological conditions needs to be investigated.

Evaporation of the lubricant layer may be a concern depending on the type of lubricant applied on the substrate and the storage conditions. In a study preformed with lubricant-infused ePTFE surfaces, perfluoropolyether (PFPE), perfluoroperhydrophenanthrene (PFPH), and PFD lubricants with different chemical properties and vapour pressures were tested and the stability of the lubricant layer was investigated when surfaces were stored in PBS buffer or were exposed to air [249]. All three lubricants were stable in PBS for up to 1 week. In contrast, there was a significant loss of surface lubricant after 30 min of exposure to air with PFD treated samples (the lubricant used in medical applications and the most volatile lubricant), and less loss with PFPE and PFPH lubricants with more than 75% retention after 120 min of exposure to air [249]. These results suggest that the high evaporation rate of medical-grade lubricants such as PFD could be attenuated by storing the surfaces in a sterilized aqueous buffer such as PBS, prior to their use. Moreover, designing a surface with vasculature features, inspired by natural self-replenishing surfaces, has shown to be an effective technique to create self-lubricating systems, capable of retaining the lubricant layer for longer periods of time [279].

2.5.4. LIS surfaces for blood-contacting medical devices

Due to the good performance of LIS and their excellent repellency properties, these surfaces have gained attention in biomedical applications where preventing non-specific adhesion is crucial. Device associated infection and clot formation are two of the main concerns and challenges that surface engineers need to address when designing platforms for biomedical purposes. LIS have shown to be a promising candidate to mitigate these issues by effectively preventing the adhesion and proliferation of different cell types and significantly reducing bacterial biofilm formation and thrombosis [248,251,252,264,270]. Moreover, these surfaces have shown to outperform conventional surface blocking techniques such as PEGylated or bovine serum albumin (BSA) coated surfaces [258–260]. PTFE-based LIS, infiltrated with perfluoropolyether (Krytox-103) was associated with a 35-fold reduction in biofilm formation compared with a PEG-coated surface [259]. In our studies, we compared the repellency properties of our lubricant infused surfaces with conventional surface blocking coatings such as BSA or PEG. We developed LIS using mixed silanes and investigated the protein and blood cell repellency properties of our surfaces. To further demonstrate superior blocking properties of LIS, cell adhesion and repellency of different blocking agents were compared with our developed surfaces. Samples blocked using LIS, BSA and poly(L-lysine)-PEG were incubated with cells for 24 h, and cell adhesion and growth were monitored. We demonstrated fewer adherent cells on LIS compared with BSA or PEG [260]. This was also observed in a later study with biofunctional lubricant-infused surfaces patterned with anti-CD34 antibodies. Such surfaces exhibited enhanced adhesion and controlled localized binding of CD34 positive cells (e.g. HUVECs) and outperformed conventional BSA and PEG blocking methods in buffer and in human whole blood [258].

Taking into account the design flexibility and surface material compatibility offered by LIS, they can be applied in a variety of medical related applications such as, implants [249], surgical equipment [280,281], point-of-care diagnostics [256] and medical catheters and tubing [248,252,264]. Medical catheters and tubing modified with a lubricant-infused layer are capable of supressing thrombin generation, fibrinogen and platelet adhesion [248,252] and biofilm formation [248,249,264] *in vitro*.

Although most of the studies performed on LIS to date, have been *in vitro*, initial *in vivo* studies are promising. For example, lubricant-infused PVC cardiopulmonary perfusion tubing remained patent for up to 8 h without systemic heparin anticoagulation in a porcine arteriovenous shunt model [248]. In another study, lubricant-infused ePTFE implants effectively resisted bacterial infection and were associated with a reduced local inflammatory response when implanted subcutaneously in rats, even after exposure to high levels of *S. aureus*. Further, ePTFE-SLIPS were biocompatible and reduced the thickness of the collagen connective tissue formed around the implant by about 50% compared with unmodified ePTFE implants [249].

Despite the promising results with LIS, these surfaces suffer from the lack of biofunctionality because they inhibit all bio-interactions with the surface. This is troublesome for permanent implants such as vascular grafts, where tissue integration and endothelial cell capture play a

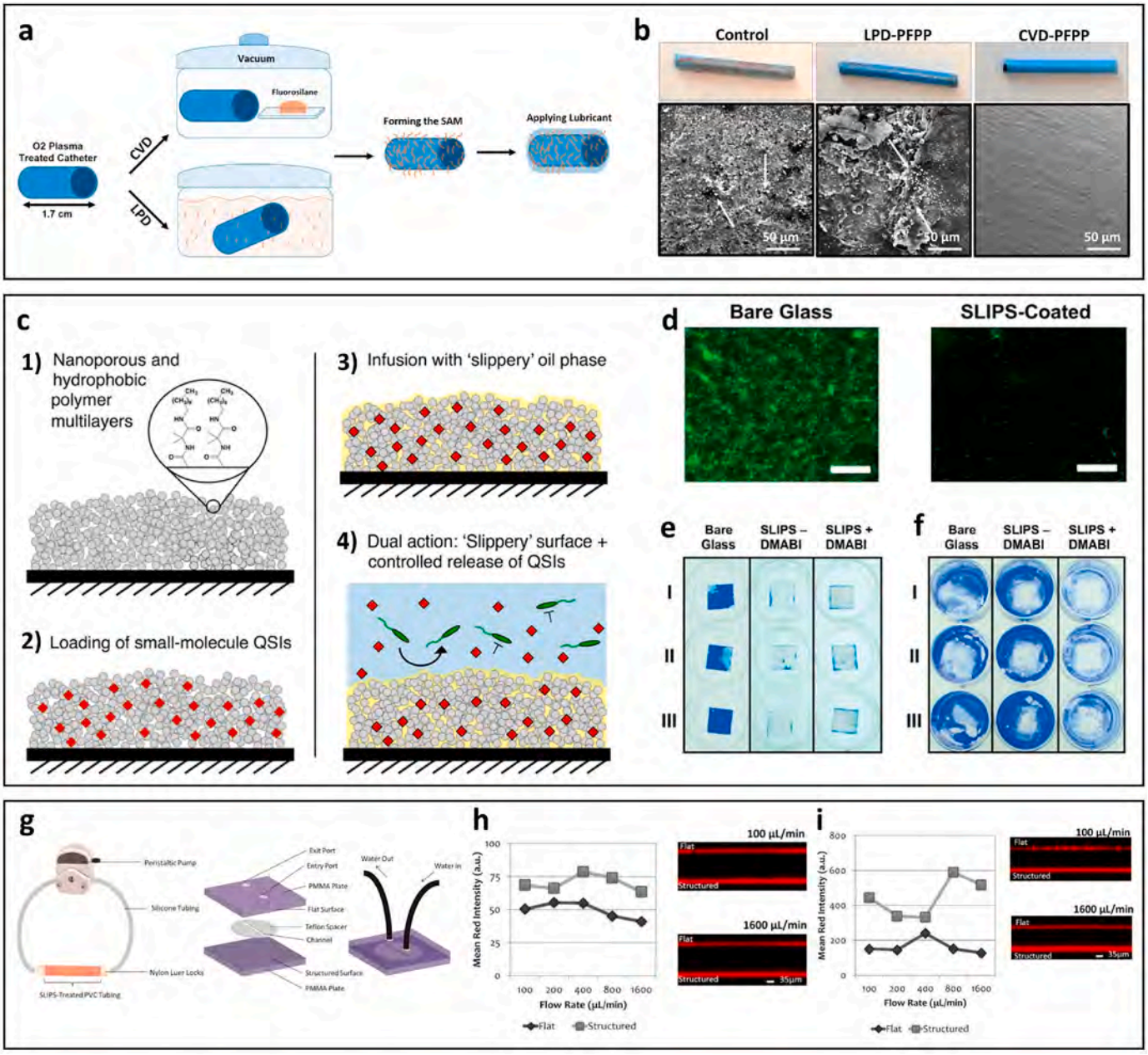

Fig. 8. Examples of different LIS prepared on different substrates. **(a)** The flat surfaces of medical grade catheters were functionalized with a fluorosilane SAM, using CVD or LPD modification techniques and infiltrated with fluorine-based lubricants in order to create LIS. **(b)** SEM images and photographs of catheters incubated with whole blood. Lubricant infused catheters treated with CVD-PFPP significantly prevented blood clot formation compared with LPD-PFPP treated catheters and untreated control catheters. In addition, platelet adhesion (shown with white arrows) was evident on control and LPD-PFPP treated catheters, while no platelets or protein adhesion was seen on CVD-PFPP treated catheters. Panels a and b reproduced with permission from Ref. [252] under a Creative Commons license. **(c)** Schematic representation of QSI-loaded lubricant infused surfaces. Nanoporous polymer multilayers are functionalized with n-decylamine to make them hydrophobic (1). Small-molecule QSI or DMABIs are loaded into the polymer multilayers using a solvent-evaporation technique (2). The small molecule-loaded polymeric multilayers are infused with silicone oil to created QSI-loaded lubricant infused surfaces (3). The lubricant-infused QSI-loaded surfaces gradually release QSIs into aqueous solutions and prevent bacterial adhesion and biofilm formation (4). **(d)** Representative fluorescence microscopy images of a *P. aeruginosa* biofilm formed on glass or SLIP-coated substrates. **(e)** Representative image of crystal violet-stained biofilms attached to bare glass substrates, SLIPS coated substrates without DMABI, or SLIPS loaded with DMABI. Little to no crystal violet-staining was seen on the DMABI loaded and unloaded SLIPS surfaces. **(f)** Representative image of crystal violet-staining of the bottoms of the wells of the 12-well plate, after the removal of the control and treated substrates shown in panel (e). In addition to preventing surface biofilm formation, DMABI-loaded SLIPS reduce biofilm formation on the surrounding uncoated wells as well. Panels c–f adapted with permission from Ref. [251]. Copyright 2016 American Chemical Society. **(g)** Schematic representation of the macroscale and mesoscale peristaltic flow experimental setup used to investigate the stability of the lubricant layer in SLIPS-treated PVC tubing. **(h)** Mean red intensity of the flat (diamonds) and structured (squares) surfaces lubricated with the dyed fluorescent Krytox 13 at varying flow rates are shown. Representative confocal cross-sections of the channels with the flat and structured surfaces at the flow rate of 100 µL/min and 1600 µL/min are presented. **(i)** Mean red intensity of the flat (diamonds) and structured (squares) surfaces lubricated with the dyed fluorescent PFD at varying flow rates. Representative confocal cross-sections of the channels with the flat and structured surfaces at the flow rate of 100 µL/min and 1600 µL/min are shown. Panels g–i reproduced with permission from Ref. [276]. Copyright 2013 American Chemical Society. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

significant role in the performance and patency of the device. To tackle this problem, we synthesized a new class of LIS where biofunctionality and targeted binding were incorporated in the lubricant-infused platform without compromising the repellency and blocking properties of the surface (Fig. 9*a*) [260]. Biofunctional lubricant-infused surfaces (BLIS) were generated by creating SAMs of a 3-aminopropyltriethoxysilane (APTES)-TPFS mixture using CVD and utilizing APTES coupling agents for biomarker immobilization. APTES was chosen as the silane coupling agent because it has a track record for the synthesis of stable biofunctional interfaces [282–285]. We investigated the repellency properties of our surfaces by performing blood and plasma clotting assays and the biofunctionality and targeted-binding features were investigated by immobilizing endothelial cell specific biomarkers (*e.g.* anti-CD34 antibody) on the BLIS and studying targeted endothelial cell-capture from human whole blood. The BLIS surfaces exhibited excellent blocking and prevented clot formation and non-specific

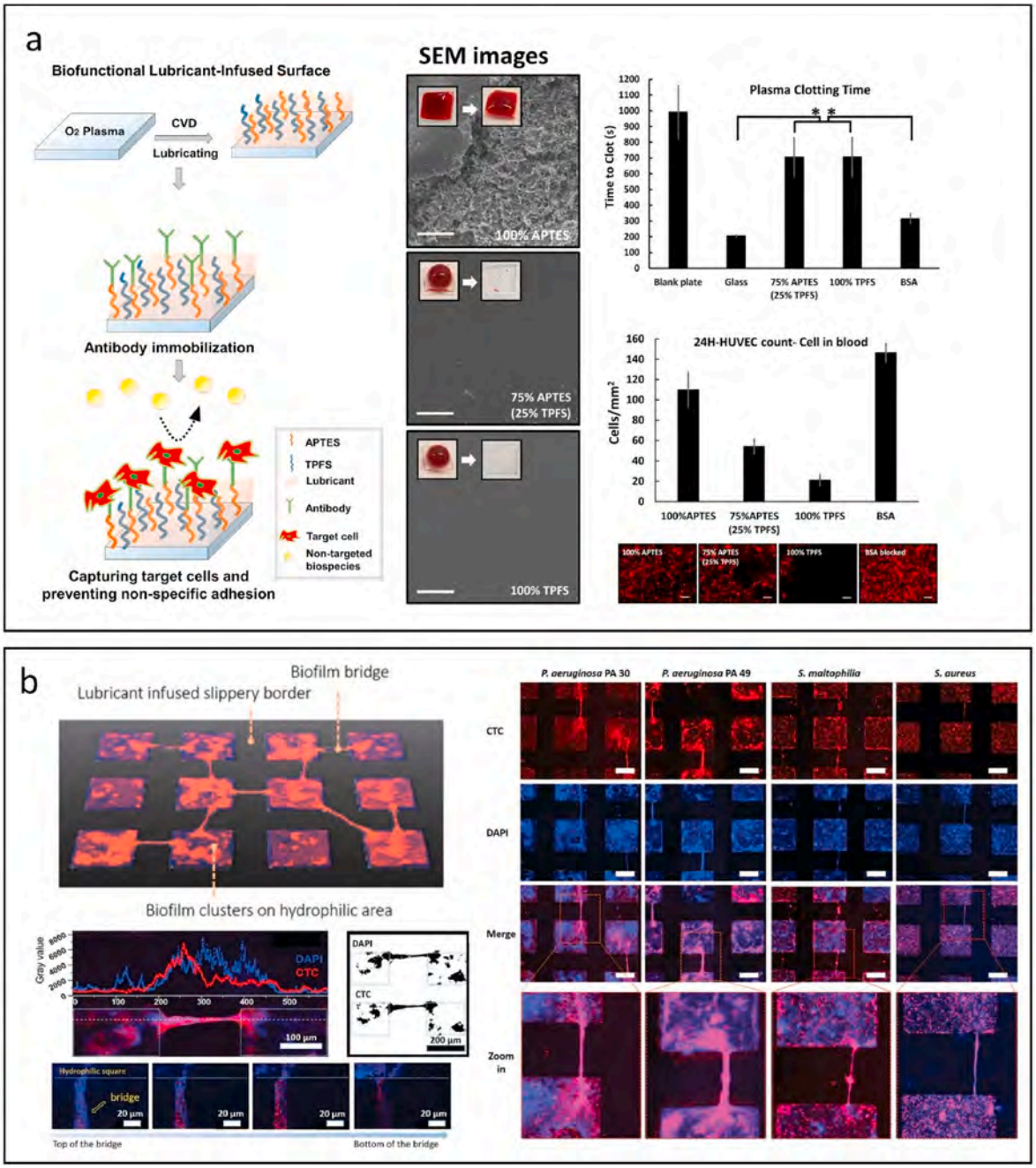

Fig. 9. Lubricant-infused surfaces with biofunctional features. (a) Schematic representation of creating biofunctional lubricant-infused surfaces (BLIS) using CVD of mixed silanes. SEM images obtained from the human whole blood clotting assay experiments performed on APTES treated, BLIS and LIS. Similar to LIS, BLIS were able to prevent clot formation and blood cell adhesion on their surfaces. Plasma clotting assay experiments performed on treated surfaces indicate that BLIS surfaces outperform conventional blocking techniques such as BSA, by significantly attenuate plasma clot formation. In addition to preventing non-specific adhesion, BLIS coated with anti-CD34 antibody were able to promote specific binding of endothelial cells. Reproduced with permission from Ref. [260]. Copyright 2018 American Chemical Society. **(b)** Patterned lubricant-infused surfaces were created and the biofilm structure and spreading of *Pseudomonas aeruginosa*, Stenotrophomonas maltophilia, and *Staphylococcus aureus* were investigated. Looking at the fluorescence images obtained from the bacterial adhesion studies it was concluded that bacteria are able to spread and communicate over bacteria-repellent lubricant-infused regions and form biofilm bridges. Reproduced with permission from Ref. [286]. Copyright 2019 John Wiley & Sons.

adhesion of cells and proteins. In addition, BLIS remained biofunctional and promoted targeted binding of ECs [260]. In a different approach, Lei et al., created patterned biofunctional LIS and investigated biofilm formation and bacteria spreading (Fig. 9*b*) [286]. These studies demonstrated that bacteria could communicate, and form interconnected networks over the repellent slippery islands. The results obtained from this study could help researchers better understand the complex structure, interrelationship, and dynamics of biofilms in hospital settings and as a result decrease the rate of hospital-associated infection.

In our further studies, we developed a novel method and aimed to create BLIS on medical grade ePTFE and PET vascular grafts using silanized bio-inks [255,257]. Preserving the surface chemical properties of the base ePTFE substrate is critical in order to further infiltrate the surface with perfluorocarbon-based lubricants and to create functional and stable LIS without the need for chemically modifying the surface with appropriate functional groups. In order to do so, a novel method

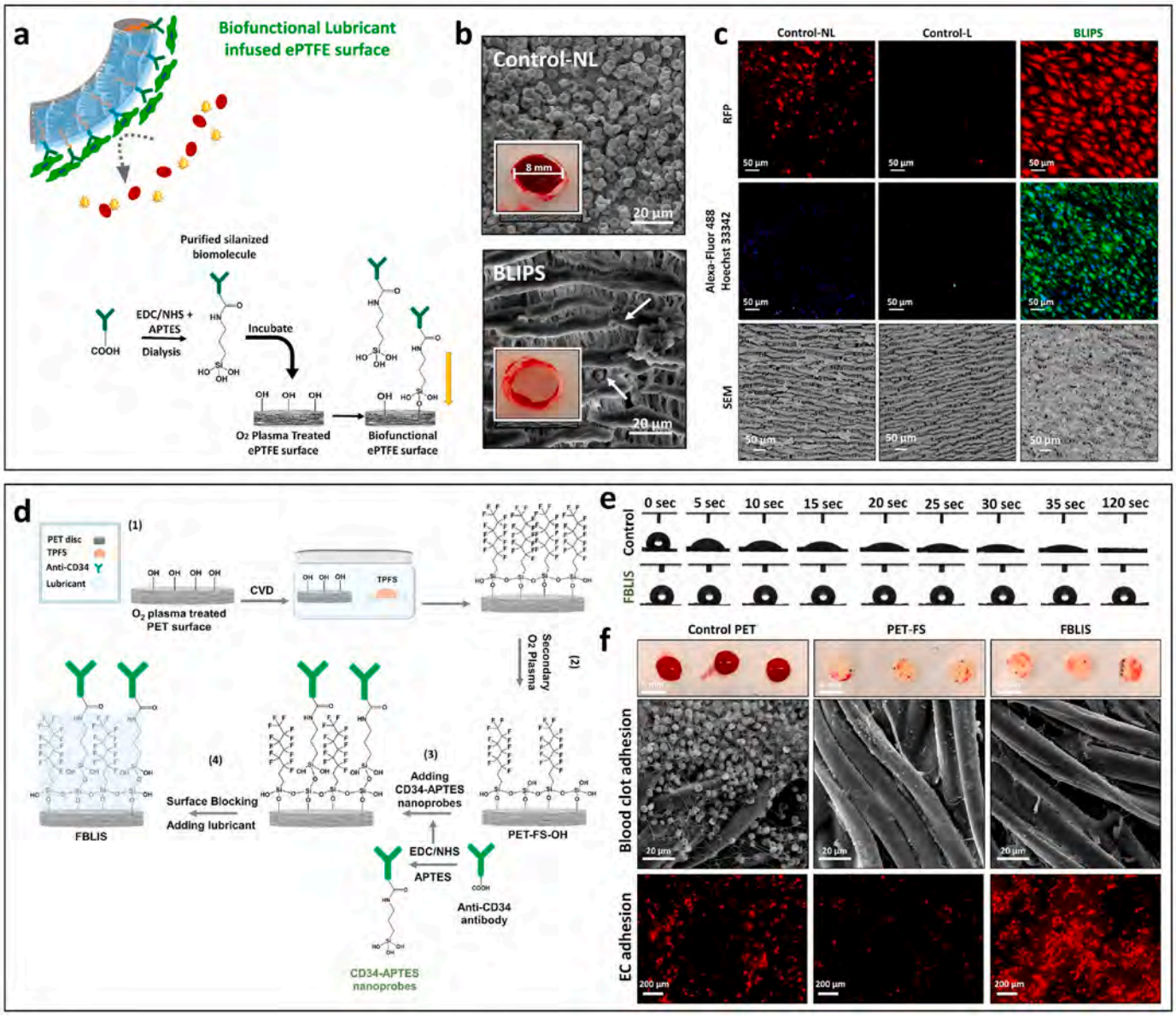

Fig. 10. Creating biofunctional lubricant infused surfaces on ePTFE and PET vascular grafts. (a) A new generation of BLIS were created using silanized bio-inks. ePTFE surfaces were biofunctionalized with CD34-APTES antibodies and infiltrated with a perfluorocarbon lubricant. **(b)** SEM images obtained from whole blood clotting assay performed on BLIPS and control ePTFE vascular grafts. BLIPS were antithrombotic and significantly prevented blood clot adhesion when compared with non-lubricated control ePTFE grafts. **(c)** Representative fluorescence and SEM images of ePTFE grafts incubated with a blood/EC mixture for four days. When compared to non-lubricated control ePTFE grafts (control-NL), BLIPS promoted EC adhesion, spreading and proliferation and a confluent endothelial layer was formed on these surfaces. Lubricated ePTFE (control-L) surfaces blocked EC attachment and minimum cell adhesion was observed on these surfaces. Panels a–c adapted with permission from Ref. [255]. Copyright 2019 American Chemical Society. **(d)** Schematic representation of creating fluorosilanized, biofunctionalized lubricant-infused PET surfaces (FBLIS) using silanized CD34–APTES nanoprobes. PET surfaces are initially oxygen plasma treated and functionalized with TPFS through CVD (1). The fluorosilanized PET grafts are then briefly exposed to a secondary plasma treatment in order to partially etch the fluorosilane layer (2). The hydroxyl-fluorine functionalized PET grafts are biofunctionalized with CD34-APTES nanoprobes (3) and lubricated with PFPP lubricant (4). **(e)** Images of the water droplet were taken at different time points. In contrast to the untreated control PET surfaces, the water droplet was not absorbed onto the surfaces FBLIS substrates even after 120 s. **(f)** The hemocompatibility and biofunctionality of the modified FBLIS was investigated. FBLIS prevented blood clot adhesion and promoted EC adhesion when compared to untreated control PET surfaces. Lubricant-infused PET grafts with no biofunctionality (PET-FS) prevented specific and non-specific adhesion and endothelial and blood cells respectively. Panels d–f were adapted with permission from Ref. [257]. Copyright 2019 John Wiley & Sons.

was developed where APTES silanized anti-CD34 antibodies were produced and directly immobilized on oxygen plasma treated ePTFE substrates (Fig. 10a). The biofunctionalized surfaces were then infiltrated with perfluoroperhydrophenanthren lubricant and biofunctional lubricant-infused ePTFE surfaces (BLIPS) were created.

BLIPS significantly prevented thrombin generation and blood clot adhesion when compared with control ePTFE vascular grafts (Fig. 10b). Further, BLIPS were incubated with a blood/EC mixture for four days and EC capture, and the formation of a confluent endothelial layer was investigated. In addition to preventing clot formation and non-specific adhesion of blood proteins and cells, BLIPS were able to promote targeted binding by capturing ECs from a blood/cell mixture. The positive staining for VE-cadherin shown in the representative fluorescence images (Fig. 10c) confirmed the EC phenotype of adherent cells and provided evidence of tight junctions between cells consistent with the formation of a confluent endothelial layer [255].

In contrast to ePTFE vascular grafts, PET vascular grafts do not possess the innate chemical properties suitable for creating non-chemically modified LIS. Therefore, these surfaces should initially be modified with an appropriate chemical layer to be able to stabilize the lubricant layer and create functional LIS. In our recent study, a novel method was developed to create fluorinated lubricant-infused PET surfaces (FBLIS) using plasma etching and silanized nanoprobes [257]. Hydroxyl-activated PET vascular grafts were initially covered with a SAM of TPFS using CVD. Later, the fluorinated PET vascular grafts were briefly exposed to a secondary oxygen plasma treatment to partially etch the fluorine layer and create excess hydroxyl groups for immobilizing the APTES silanized anti-CD34 nanoprobes (Fig. 10d). This method simplifies the modification procedure for creating BLIS and eliminates the need of using a mixture of silanes when creating the SAM. PET vascular grafts are highly porous. Although the porosity is necessary for cell adhesion and tissue integration, it leads to blood leakage after implantation [287]. PET surfaces coated with the proposed biofunctional lubricant-infused layer, significantly reduced leakage when compared to uncoated grafts, without tampering the physical porous properties required for promoting cell adhesion and proliferation (Fig. 10e). In addition, compared with control PET grafts, the modified FBILS significantly reduced thrombin generation and blood clot adhesion and at the same time promoted targeted binding of ECs (Fig. 10f). The proposed method could be applied to other medical implants and different plasma gases and cell specific biomarkers could be used to activate and biofunctionalize the surface of the device.

3. Future directions

Creating stable and biocompatible surface coatings for blood-contacting interfaces is critical in order to prevent device-associated complications such as clot formation, fouling and device failure. The durability, stability and efficiency of the coating are important factors that need to be considered when developing such interfaces for short and long-term applications. Several surface coatings with different mechanisms of action, including coating the surface with bioinert polymeric coatings, immobilizing antithrombotic and anticoagulant agents, altering the hydrophilicity/hydrophobicity and chemical and physical properties of the biomaterial and immobilizing EC specific biomarkers to promote endothelialization and postoperative tissue integration have been explored and have shown varying degrees of success. Among these, lubricant-infused surfaces (LIS) have yielded promising results in creating functional surfaces with superior repellency and antifouling properties. The simplicity and high performance of these coatings have made them a promising new candidate for designing antifouling surfaces for medical implants. Although these surface coatings will continue to be explored for different biomedical related platforms, several challenges need to be addressed when designing the future generations of these surfaces. Most importantly, the stability of the lubricant-layer needs to be optimized, aiming to design self-lubricating surfaces or surfaces that retain the lubricant-layer for longer time periods and prevent it from evaporating, particularly when the blood-contacting device is placed in open air conditions prior to or during the real-life application. Another approach for overcoming this limitation is to design lubricant-infused surfaces with high affinity for non-volatile lubricants that can operate with other biocompatible and stable liquid lubricants.

In addition to biocompatibility, surface biofunctionality and the ability of the coating to promote targeted binding of cells is a critical requirement when designing surfaces for permanent medical implants such as synthetic vascular grafts, stents, and mechanical heart valves. However, designing surfaces that effectively integrate both these features on a single platform remains challenging. For example, ePTFE grafts coated with a anti-CD133 antibody functionalized heparin/collagen multilayer using a layer-by-layer technique have shown promising results in preventing clot formation and promoting endothelial cell adhesion [46], however; the amount of collagen used in the modification procedure is critical and needs to be precisely controlled because excess amounts of this ECM protein negatively affect the anticoagulant properties of the surface and could compromise the device performance [83,152]. In addition, the bioactivity of the agents after immobilization and stability and durability of the coating play an important part in the long-term performance and patency of the device and these factors need to be further investigated and optimized in future studies.

4. Conclusion

Device-associated thrombosis and poor tissue integration remain critical challenges whose complications could result in device failure and increased rates of patient morbidity and mortality. Newly developed surface coatings and modification techniques that integrate various physical, chemical, and biological approaches have exhibited promising results in enhancing the hemocompatibility and cell integration of various biomaterials. Although researchers have come a long way, there are still challenges and questions that need to be addressed. Long-term studies in animal models and in humans are needed to evaluate the performance, stability and bioactivity of surface coatings.

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.

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