production of new cells and proteins. The requirement of exogenous energy by the cell, may serve as an important factor influencing neo-tissue development where local limitation in the energy may reduce the replicative capacity of progenitor cells and affect the rate of healing process at the site of the prosthetic vascular grafts. In contrast, ECM material undergoes biodegradation and remodeling which provide energy, biochemical essential structural units and components necessary for protein synthesis and remodeling. All these factors contribute to cell growth, their metabolic activity and development of neo-tissue.

5. Vascular tissue Functionality and Homeostasis Maintenance

5.1. Biomechanical Properties of Graft Materials and Their Importance in Sufficient Reconstruction of Vascular Tree

Mechanical factors are recognized as important parameters which affect short and long-term graft patencies [4,5,16,173]. Researchers have identified that one of the factors limiting the success of prosthetic vascular grafts is material mismatch with the host vessel in terms of strength, stiffness, compliance and elasticity. Salacinski *et al*., have shown that mechanical properties including compliance mismatch, diameter mismatch and Young's modulus all greatly affect the graft performance and failure rate [173] and support the idea that an ideal vascular graft must have similar viscoelasticity to the native vessel [174]. Data for compliance and elasticity of native vessels and various small-diameter grafts made from different materials is tabulated in Table 3.

Table 3. Compliance and Modulus of Elasticity of native blood vessel and various graft materials.

Vessel type	Compliance	Modulus of Elasticity (E)	Reference
Carotid (man)	14.7%	0.4 × 106 dynes/cm^2	[175]
Carotid (man)	-	6.07 × 106 dynes/cm^2	[176]
Asc. A (man)	-	0.76 × 106 dynes/cm^2	[176]
SIS, 3-layer (pig)	4.6- 8.7%	8.03 × 106 dynes/cm^2	[177]
Saphenous Vein	1.96 - 0.64%	5.5 × 106 dynes/cm^2	[178,179]
Dacron®	0.76%	56.49 × 106 dynes/cm^2	[178,180]
ePTFE	0.2%	39.07 × 106 dynes/cm^2	[180,181]

The compliance of 3-layered small diameter SIS grafts was shown to be 4.6% (d = 5 mm) and 8.7% (d = 8 mm) [177], only slightly less than those of carotid and femoral arteries, about four times more compliant than a typical vein graft and an order of magnitude more compliant than modern synthetic vascular grafts of expanded ePTFE and Dacron®. The influence of these particular parameters on flow pattern and hence the cellular healing process will be highlighted in Section 5.2.

Mechanical properties of ECM material vary depending on the animal species, age, organ, physiological and mechanical functions of the organ, size of the organ, species-specific localisation of structural components, protein-homology and protein identity within the tissue and degree of ECM cross-linking [177,182,183]. For example, the modulus of elasticity for canine jejunum is

8.5 MPa [183] compared to that from porcine sources at 7 MPa [177]. Manufacturing and processing parameters such as dehydration time, technique, sterilisation methods and storage conditions are important parameters which could potentially affect the mechanical properties of ECM devices and should be taken into consideration when engineering tissue constructs [182]. The effect of varying the number of layers on the biaxial strength is illustrated in Table 4.

Table 4. Biaxial failure load of multi-laminated bioscaffolds [182].

	SIS UBM	
2-layer	42 ± 9 N	19 ± 7 N
4-layer	130 ± 29 N	35 ± 2 N
8-layer	325 ± 53 N	

For example, sterilisation by ETO has been shown to have the least detrimental effect upon the mechanical properties of UBM. Gamma and e-beam irradiation decrease the uniaxial and biaxial strength and maximum tangential stiffness. However, ETO had no effect on strength or energy dissipated, indicative of unchanged viscoelasticity. All methods significantly decreased material stiffness, when compared to non-sterilised controls (48–60%) [184].

In addition, the mechanical properties of ECM material are more dynamic than those of synthetic materials due to the susceptibility of ECM material to degradation and remodeling *in vitro* and *in vivo*. *In vitro* studies have shown that material undergoes ultrastructural changes during incubation with Human Umbilical Vein Endothelial Cells (HUVECs) seeded onto the substrates. UBM weight losses up to 2.5% over a 5 day period were recorded. ECM weight loss correlated to an increased production of metalloproteases MMP-1 and MMP-9, both of which are known contributors to ECM degradation, angiogenesis and vessel remodeling [185]. *In vivo* studies provided complementary results and showed that during graft healing and remodeling, the compliance, modulus of elasticity and burst pressure of ECM graft approached the corresponded mechanical properties of native vessel [186]. Sterilisation of ECM material has been shown to influence on the rate of ECM degradation. An extensive *in vitro* degradation study of SIS over a 49 day period found that e-beam irradiation almost doubled the rate of hydrolytic degradation compared with unsterile SIS, gamma irradiation and ETO (42% versus 23–27%) [187]. These changes are a result of collagen backbone degradation and the difference between the radiation methods could be attributed to the dose and form. Hence, the choice of sterilisation technique should be carefully considered and tailored to the intended application, load bearing requirements and degree of degradability.

In order to engineer a graft which mimics the native soft tissue, manipulation of certain variables such as the origin of the ECM, the number of layers [42,182], the decellularisation method (physical, enzymatic or chemical treatment) [18] and sterilisation techniques (ETO, gamma irradiation, electron beam irradiation) must be determined and elucidiated in order to form a stable reproducable protocol for graft development in each size and substitute location (vein, artery).

The principal strategy being developed to prevent hemodynamic disturbance within the region of the anastomosis is based on the design and fabrication of more compliant ECM–based grafts with viscoelastic properties which mimic those of the human artery. Methods have been introduced to

characterize flow structure and wall shear stress (WSS), which may be used in order to provide quantitative comparison of different haemodynamic environments associated with various vascular geometries. Computational fluid dynamics (CFD) and finite element analysis (FEA) softwares may be applied in studies to visualise the flow pattern using velocity vectors, velocity contours and shear stress distribution within the vascular tree or graft replacement region. As these parameters are very difficult to measure *in vivo*, computational modeling can become a nessesary and essential tool of analysis the effect of geometry and shape of the graft placement site on flow pattern and severity of flow alteration [188,189]. Indeed, CFD and FEA offer much more repeatability and resolution than *in vitro* and *in vivo* methods, however, computations must be carefully validated against experimental and clinical data. Preliminary evaluations of graft design have utilised CFD to characterise wall shear stress on tubular ECM grafts and FEA has been used to evaluate stress distributions during mechanical testing of ECM materials; both of these computational methods show good prospects for utilisation in the evaluation of ECM materials as a graft material [190]. The major development of clinical imaging, such as magnetic resonance imaging (MRI) or computed tomography (CT), opens new avenues for detailed patient-specific information on the actual hemodynamics and structural behavior of living tissues. The coupling of CFD/FEA with clinical biomedical imaging technologies may provide an efficient standard evaluation of material performance as a part of clinical practice in the surgical planning and design of graft materials for specific location in the vascular tree.

5.2. Mechanotransduction Pathways in the Healing Process of Vascular Graft

It is desirable that the compliance of the graft matches that of the native vessel to avoid potential stagnant regions [181] or disturbances to the local haemodynamics around the anastomosed site. This interruption establishes abnormal pulsatile mechanical stresses at the anastomosis. These stresses can result in suture-line disruption, formation of a false aneurysm, and development of subintimal hyperplasia [3]. These events can either result in thrombosis and increased pannus ingrowth at the anastomosis, thus threatening the patency of the implanted vascular graft. The vascular endothelium is a vital organ, whose healthy physiology and function are essential for normal vascular vessel physiology. The dysfunction of vascular endothelium can be a critical factor in the pathogenesis of vascular disease. ECs lining the blood vessels are transducers of various physiological stimuli which are actively involved in many physiological processes such as regulation of selective permeability, blood coagulation and homing of immune cells to specific sites of the body. Activation of mechanotransductory intracellular pathways is pivotal to shear stress adaptation and is regulated via integrin–mediated connections and cells within the sub-endothelial substrate. These pathways, which are influenced by shear stress, are known to modulate gene expression, cell migration and proliferation. Relationships between hemodynamic parameters [191–199], such as wall shear stress and intra-luminal healing, show that a molecular and cellular cascade is triggered by the various flow patterns created at the anastomosis site which reflects the compliance differences between the material and native vessel. The latter results in turbulent flow, which due to its action on vascular endothelium induces pro-inflammatory and pro-thrombotic expression pathways. Molecular determinants of these cellular pathways stimulated within anastomosis sites of synthetic (PFTE) graft are summarised in Table 5.

Table 5. Regulation of the molecular cascade in the area of turbulent flow.

Graft Material	Location	Biological Response in anastomosis site			Reference
		Methodology	**Up-Regulated Biomarkers**	**Down-Regulated Biomarkers**	
PTFE	Carotid artery (Dog)	Microarray, RT-PCR and immunohisto-chemistry.	(α1) collagen -I, (α2) collagen-I, 80K-L protein (MARCKS), osteopontin, NAP-22, VESPR.	Smoothelin-B, tropomyosin 2 (β), calcium/calmodulin-dependent protein kinase II, RBP-MS types 4 and 5, cysteinerich motor neuron 1	[200]
	Aorta (monkey)	Immunohisto-chemistry	Osteoblast-specific factor-2 (OSF2)/Cbfα1, (α2)collagen-I, (α1)collagen-III, versican, (α3)collagen-VI, (α2)collagen-V, (α1) collagen-V.	SPARClike-1 (SPARCL1)/hevin, RGS5.	[201]

As can be seen from the data, molecular determinants of osteogenesisis and vascular bed remodelling are present in the vascular tissue in the area of turbulent flow, where the molecular marker of SMC contractility (like smoothelin) is down regulated demonstrating that blood vessel function and structure are pathologically altered.

It was shown in a previous study by Orr *et al*. [202] that flow-induced activation of the atherogenic transcription factor NF-κβ occurs in a matrix-specific manner. In a study conducted by Jalali *et al*. [203], it was found that EC mechanotransduction in response to shear stresses requires the activation of integrins by their specific ligands which are supported, controlled and influenced by formation of new integrin-ligand connections. Through integrin mechanotransduction, shear stress produced by blood flow upregulates genes involved in regulation of apoptosis, cell cycle arrest, morphological remodelling and nitrogen oxide production; which contribute to atheroprotective effects [204]. Integrins are glycoproteins within the membrane, composed of α and β subunits. To date, 18α and 8β subunits have been identified in mammalian cells [204], with each of these subunits spanning the extracellular and cytoplasmic domain. The major ECM proteins that interact with vascular ECs include collagen, laminin, fibronectin, vitronectin, and fibrinogen [205]. Various ECM proteins have been shown to bind to different integrins, and in turn activate different signalling molecules. For example, collagen type I matrix binds to α2β1 and α1β1 integrins in the endothelium [206–208]. Laminin tends to bind with α6β1 integrin in ECs [209]. Fibronectin mainly binds to α5β1 and αvβ3 integrins. Vitronectin and fibrinogen also bind to αvβ3 integrin [205]. The density and distribution of ECM proteins are known to be controlling factors in the level of integrin-ECM adhesive interaction and play an important role in regulating cell migration [205]. The cytoplasmic domains of both the α and β subunits interact with signalling molecules and cytoskeletal proteins to regulate cellular events (such as signal transduction, cytoskeletal organisation) as well as regulating cell motility via the modulation of integrin affinity and/or avidity.

The integrin-ligand connection acts as a source of communication, transmitting signals from the ECs to the ECM and *vice versa*, coordinating cellular activity. As previously mentioned, the

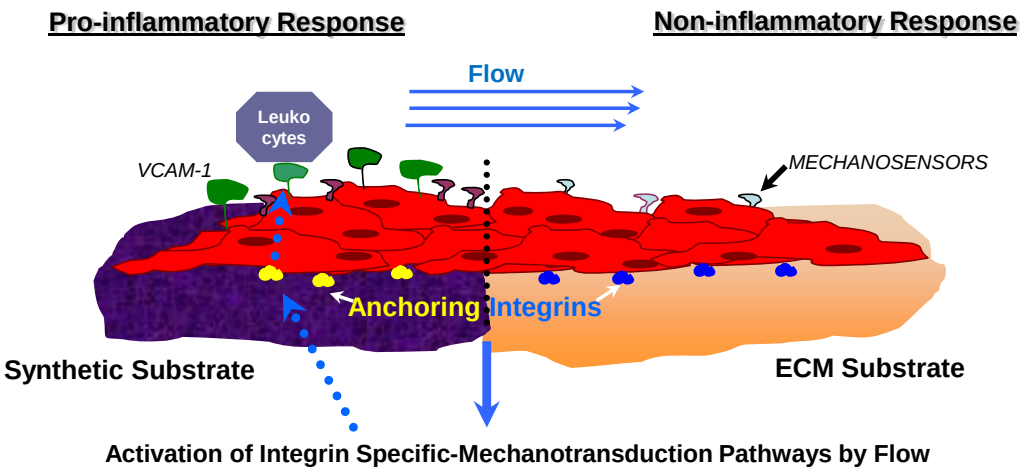
predominant structural component of ECM matrices is collagen; EC attachment to this type of matrix occurs via α2β1 integrins. This interaction inhibits activation and nuclear translocation of NF-κβ and the pro-infammatory molecular cascade under pathological flow conditions. This effect may be beneficial at the early stage of cell repopulation and migration through an anastomosis site, allowing successful tissue reconstruction of the graft without thrombosis developing. Integrin mediated mechanotransduction involves multiple kinases (FAK, c-Src, and Fyn), adaptor molecules (CAS and Shc), guanine nucleotide exchange factors (C3G and SOS) as well as small GTPases (Rap1 and Ras) responsible for activating mitogen-activated protein kinases (MAPKs) such as ERK. In static conditions, the integrins are inactive and signalling does not occur. Shear stress is required to activate the integrins. Through specific interactions of the α and β subunits, the FAK/c-Src and Cav-1/Fyn pathways are activated. Activation pattern is directly associated with members of the Rho small GTPase family, including RhoA, Cdc42, and Rac. RhoA, Cdc42 and Rac each have particular functions in regulating the actin-based cytoskeletal structure. RhoA increases cell contractility, focal adhesions and actin stress fiber formation; Cdc42 regulates filopodia formation; and Rac regulates membrane ruffling [210]. The importance of the β2-integrin family in lipopolysaccharide (LPS) stimulation was highlighted by Monick *et al*. [211]. LPS stimulation plays an important role in regulating the inflammatory process, thus the link between this stimulation and the role of *β2*-integrins is important in terms of tissue remodelling. It has also been found that laminar shear stress suppresses the G1- to S-phase transition in ECs [212,213]. This leads to an increased expression of p21 which inhibits cyclin-dependent kinases, thus inhibiting cell proliferation and remodelling. The regulation of transcription factor expression was compared under disturbed flow conditions and uniform laminar shear stress conditions by Nagel *et al*. [214]. The ECs subjected to disturbed flow, similar to that found in atherosclerosis-prone areas, showed increased levels of nuclear localized NF-κβ, Egr-1, c-Jun and c-Fos compared with those exposed to uniform laminar shear stress or under static conditions. NF-κB induces the transcription of a large range of genes implicated in inflammatory response [215]. It also plays a fundamental role in protecting vascular SMCs against apoptosis and weakening of vascular wall. This transcription factor is stimulated by flow through the integrin and Rac dependent production of reactive oxygen species. It has been previously shown that uniform laminar shear stress plays an inhibitory role in the pro-inflammatory gene expression in ECs located in close proximity to SMC [214,215].

As the specific activation of inflammatory cascades is complex, further studies into the gene expression of various scaffold materials are needed to predict *in vivo* performance. Intuitively it would be expected that the performance of synthetic grafts would be impeded due to their nature and the inability of integrins to bind to corresponding ECM ligands and thus inhibiting of initiation of "healthy" mechanotransduction within the vascular cell. From this point of view, naturally derived scaffolds have a distinct advantage. However, certain ECM components trigger more favourable responses than others. Gene expression in response to physiological fluid flow has yet to be fully characterised for all ECM materials.

In a study conducted by Cenni *et al*. [216], integrin expression was evaluated for ECs alone and ECs in contact with polyethylene terephthalate (PET) woven Dacron. The following integrins were evaluated under both conditions by flow cytometry: VLA-2 (α2β1-CD49b/CD29), VLA-5 (α5β1-CD49e/CD29), VLA-6 (α6β1-CD49f/CD29) and αVβ3-CD51/CD61). The isolated ECs in

contact with woven Dacron showed a significant decrease in the expression of CD29 and CD49e and the other integrins were not modified by contact with the material. CD29 and CD49e are the α5β1 integrin types which are known to have affinity to fibronectin ligands and are important for cell adhesion. The decrease in this integrin type may suggest that adhesion chemistry between vascular cell and synthetic material differs from that of cell adhesion to natural ECM components. Strength of adhesion and retention under the flow shear stress and rate of EC migration on this type of substrate may lead to incomplete endothelial lining which may result in thrombogenicity [216]. To combat these issues, synthetic materials such as PET and PTFE are often coated in fibronectin. Plasma treated PET and PTFE have also shown improved adhesion and growth of ECs [217]. Depending on the nature and origin of ECM materials, different integrins are expressed. Activation of certain integrins suppresses the activation of other specific integrins, maintaining a balance which aims to promote healthy tissue remodelling. Manipulation of integrin activation could eliminate adverse remodelling events, for example, by blocking the inhibition of integrin α2β1 (activated on fibronectin through protein kinase Cα) then collagen signaling can occur via this integrin and inhibit the flow induced activation of the atherogenic transcription factor NF-κβ [218]. The state of EC surface thrombogenicity is under substrate control, and is also related to the cellular differentiation status (as shown in Figure 3).

Figure 3. The effect of sub-endothelial substrate on the activation pattern of pro-inflammatory cellular mechanisms of mechanotransduction. This figure illustrates the biochemical processes induced by fluid shear stress for both a synthetic material and ECM scaffold material. As fluid flows across the EC layer (depicted in red), the mechanosensors at the endothelium surface sense the stress and react by transmitting signals through the transmembrane integrins (illustrated in red and blue). Specific integrin mechanotransduction pathways are thus activated, sending messages from 'inside-out' through specific integrins, triggering certain responses. Depending on which type of integrin is activated, various responses occur. Synthetic materials are prone to stimulate a pro-inflammatory response of adhered cell [217] and exposed to the flow, in which presentation on the surface of vascular endothelium of adhesion molecules (for example VCAM-1) induce a subsequent attraction, rolling and adhesion and subsequent attachment of leukocytes to the site.



These cellular processes demonstrate the potential of the underlying vascular material to affect the long-term cellular functionality of the prosthesis. *Ex vivo* evaluation of the material properties in order to support functionality of the EC and their mechanotransduction capacities require optimization. *In vitro* studies under static conditions have been popular for characterization of EC thrombogenicity and shear resistance due to their logistical simplicity, but are not necessarily reflective of the surface thrombogenicity under flow conditions where mechanotransduction activation in a fashion similar to the vascular tree *in vivo* are necessary and its modulation by substrates may be analysed and determined. A biorheological conditioning protocol proposed by O'Keeffe *et al.* [219] can provide a efficient informative *in vitro* screening method which would allow determination of vascular cell behaviour on surface graft material under pathological shear stress, elucidate an alteration pattern of the molecular cascade of endothelial cell mechanotransduction, investigate the ability of materials to support a polarization and EC cytoskeleton reorganisation under various flow patterns (which may be recreated in the anastomosis site of a graft vessel). The undestanding of molecular mechanisms of graft failure will lead to the possibility of further modification of the vascular material in order to enhance clinical performance of prosthetic and ECM grafts.

5.3. Restoration of Innervation and Blood Vessel Homeostasis

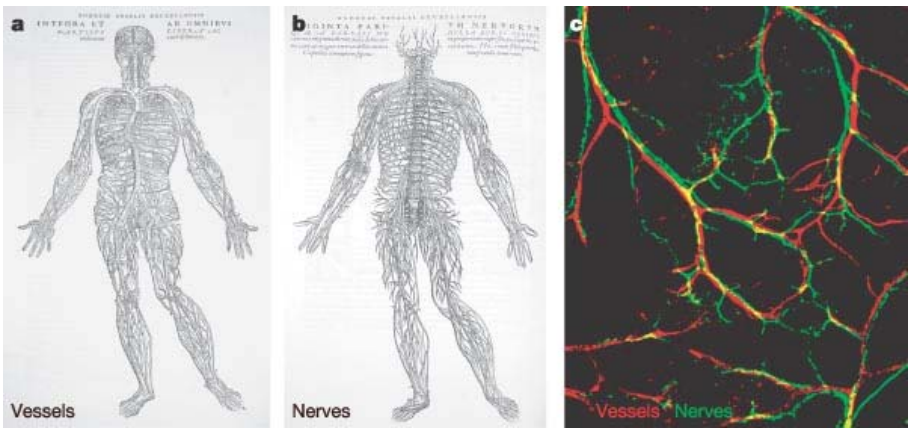
In recent years, biomedical research has clarified the involvement of neuromodulation in human tissue processes which occur during healing [220,221]. However, limited data exists on the re-innervation pattern of vascular graft materials during the healing process due to the complexity of the neuron detection and analysis [222,223]. However even limited findings have demonstrated the role of innervation and its pattern may play a part in the development of fully functional tissue during the healing of vascular graft [224,225].

Anatomical investigations reveal that blood vessels and nerve fibres run throughout the body alongside one another and the mechanisms involved in wiring both networks are proposed to be similar (Figure 4) [226–228]. Recent morphological and pharmacological findings support the hypothesis of active communication between vascular and neural networks and their interactions may contribute to the health and homeostasis of vascular vessels [229–231].

The blood vessels are innervated by the autonomic nervous system. Sympathetic adrenergic nerves, which travel along arteries and nerves, are found in the adventitia (outer wall of a blood vessel). The sympathetic fibres mediate a vasoconstrictive action in the vascular bed as well as providing secretomotor activity. Activation of vascular sympathetic nerves cause vasoconstriction of arteries and veins mediated by α-adrenoreceptors [232,233]. Neurogenic control of vascular tone and vascular innervations of the blood vessel adventitia have been well documented [230,231]. The release of neurotransmitter and chemical signalling occurs in small enlargements along the nerve fibres. Nerve stimulation can elicit different responses, in terms of type and amplitude, at different areas of the vascular system [234,235]. Neurogenic vasocontrol can thus follow different patterns depending on which molecules are released and what local reactions they trigger. Active molecules released locally from adventitial nerves may diffuse and act directly on the adventitia and the media or act on the endothelium which in turn will release molecular signals (like nitrogen oxide) which then influences the media [229]. The complexity of neurochemically defined autonomic nerves stimulating the vessel

baroreceptor and chemoreceptor regions suggests functionally separate, independently regulated pathways. Auger *et al.* [230] summarised previous literature and concluded that vascular autonomic and various types of sensory nerves inclusive of cholinergic, adrenergic, peptidergic or nitrergic are found in different proportions and density depending on the specific anatomical site. One of the findings of this study was that the variety of nerves which can be found in the adventitia is directly related to the presence of many neuron-related peptides and molecules (such as acetylcholine, noradrenaline, neuropeptide Y, substance P(SP), calcitonin gene-related peptide (CGRP), neurotensin and vasoactive intestinal peptides (VIP)) in different quantities at various anatomical regions, although their complete physiological roles are not yet known.

Figure 4. Illustration by the Belgian anatomist Andreas Vesalius, highlighting the similarities in the arborisation of the vascular and nervous networks. Vessels (red) and nerves (green). [227], *Copyright, Reprinted with permission from the Nature Publishing Group.*



Modern surgical procedures utilized for implantation of vascular grafts have been shown to cause extensive damage to the sympathetic nerves which supply and accompany blood vessels [237,238]. Some procedures may cause extensive degeneration of adrenergic nerves and the extent of denervation may vary with vessel type with regard to their anatomical characteristics and structure (elastic or muscular). Comparative studies were able to determine that rate of nerve re-growth in muscular vessels is faster than that of elastic vessel. Re-growth of injured fibers can be altered and lead to hyper or denervation along the graft reconstruction or only at certain parts. Preliminary analysis of data indicates that a non-matching to the original pattern of nerve re-growth may lead to a lack or alteration of vessel tone autoregulation in the graft region and its exclusion from the baroreflex modulation of blood flow. This growth pattern is potentially regulated by a number of factors such as chemical affinity of the material surface, cytokine and growth factor gradient along the grafted site, the type of ECM molecule deposition, adsorption to the material, the presence and distribution of required chemical ligand to the surface and within the scaffold, inflammatory sites and infection.

In newly developed vascular tissue, neuromodulation activity or its complete absence appears to greatly affect the functionality of the vessel itself, the healing process of the vessel and its homeostasis. Instability, due to focal unbalancing of constrictive forces and regulated, molecular signaling may serve as a pathophysiological basis for the well-established phenomenon of vascular SMC hypertrophy

and hyperplasia after grafting [239], occlusion of the vascular graft [240] or its dilation (pseudo aneurysms) [241].

Recent studies have reported successful re-innervation of ECM reconstructed organs [242–244], and the capacity of ECM materials to support nerve conduits and promote growth of the Schwann cell (SC) [244–248]. During biocompatibility studies *in vitro* [248], when co-cultured with SCs, SIS-ECM showed good ability to support SCs adhesion, survival, migration and proliferation on its surface. Observation of the ultrastructure of SCs by TEM demonstrated that SCs adhered tightly and grew productively on the surface of SIS. MTT assay also showed that SIS did not have a cytotoxic effect on SCs. Quantitative analysis of nerve growth factor-β (NGF-β) and brain-derived neurotrophic factor (BDNF) by ELISA, as well as semi-quantitative analysis of NGF-β mRNA and BDNF mRNA by RT–PCR, showed that SCs seeded on SIS had more productive function of secretion than the normal cultured SCs. NGF-β and BDNF are the main growth factors secreted by SCs, which are known to have neurotrophic effects on nerve regeneration. Adhesion and growth of the nerve cells is guided by specific structural components of ECM laminins [249–253]. There is a significant lack of research focusing on the analysis of innervation fibre density, their localization in the adventia and media of the synthetic and ECM grafts. This issue needs to be elucidated and determined in future studies, but the authors hypothesize that ECM graft material may provide a better support for the re-innervation of the newly developed vascular tissue and an enhanced structural and chemical microenvironment for the reconstruction of a balanced interactive network between the nervous system and remodeled vascular tissue. ECM material has the potential to provide a homeostatic environment based on the regulation of vasoactivity function, thus increasing its ability to regulate blood flow and function in a similar manner to the native non-injured vessel compared with vessels substituted by synthetic materials.

6. Future Perspectives for Cardiovascular Implants Based on ECM

With the enhanced healing properties previously discussed, biologically derived ECM materials have been shown to be diverse and inconsistent in both structure and morphology [41], and affected by a number of factors such as the manufacturing process (*i.e.*, mechanical decellularisation vs. chemical decellularisation) [18] and the age and health status of the animal at harvest. Numerous limitations and problems are associated with decellularising techniques and procedures, as described previously in detail [18,254–256], may have great influence on ECM product quality, mechanical and biochemical properties, biocompatibility and clinical performance [257–259]. Mechanical methods of acellularization, including repeated freeze-thawing, sonication, or other physical means of disrupting cells' plasma membranes, provide a direct, mild and rapid tissue decellularisation, but used alone, such methods are not capable of completely removing cellular material, which has been shown to prevent complete recellularisation of this material by host cells [257–259]. It remains a concern for the biomedical community that trace amounts of potentially antigenic compounds of animal origins (lipids, DNA, glycosilation products) have been reported to be present for certain types of ECM material and may provoke an inflammatory response at the placement site [260,261]. Complete removal of these antigenic compounds from the material is important for improving the biocompatibility of ECM material; however, such a goal seems to be quite challenging and difficult to achieve with the application of standard biochemical extraction methods, due to the high degree of chemical complexity

and variability of the contaminants. The degradation and damage of structural components due to the absence of a long-active protease inhibitors, multiple incubation and rinsing steps during the long decellularisation procedures may unintentionally remove desirable ECM components and lead to an alteration of mechanical properties of the ECM material [262]. The ability of a decellularisation method to sufficiently remove of lipid moeities from the tissue has been shown to have a dramatic impact on the rate of graft calcification and substantially decrease patency time *in vitro* [263,264]. Minimally invasive tissue-specific decellularisation techniques with detailed manufacturing protocols where *in vivo* performance will be supported by enhanced cell repopulation, minimal infiltration of inflammatory cell and calcification still need to be developed in the near future.

Suitability of materials derived from various organs for clinical application in the vascular area are still under investigation as the biochemical and biophysical properties are not always tailored to the potential tissue characteristics desirable for the application [17,18]. Modification, remodelling and ECM matrix deposition that can be performed *in vitro* utilising cellular machinery able to perform the most complex synthesis reactions and cleavage of others with high specificity and efficiency, presents a potential method to improve the biological properties of ECM material obtained by decellularisation of non-vascular organs (SIS) for vascular application [265]. SIS-ECM material was pre-conditioned with human endothelial cells *in vitro* and during the conditioning process, remodelling of the matrix and synthesis of novel components as well as deposition of sub-endothelial matrix (basement membrane) known to be absent in the original SIS material, was shown to occur. Following decellularisation of the cell-seeded scaffold, neo-ECM was shown to have improved biological activity and the vascular endothelial cells seeded on the neo-matrix had enhanced organization of the cell junction, an increased metabolic activity and released a lower amount of pro-inflammatory prostaglandin PG1 compared to the cells incubated on the control SIS. Neo-ECMs were also shown to have a lower degree of human platelet adhesion and improved thrombogenic potential.

In this state-of-the-art era, with strong development in genetic engineering methods [266] and the multitude of recombinant vectors [267], gene delivery systems [268–280], the variety of cell lines which are able to express recombinant ECM molecules, enzymes and growth factors [281–283] all show great promise for ECM material modification. A more complete understanding has emerged of the native molecular regulation of the ECM remodelling process by the cells under chemical and/or mechanical stimulation (flow [284], stretch [285], pressure [286]), providing an optimised physiological environment within an engineered bioreactor. This may facilitate a more physiological remodelling process, ultimately leading to a more manufacturable tissue-specific ECM material. Advanced bioreactor design and application will be an essential part of conditioning the ECM material and ECM- material based constructs with further advances in the technology making the engineering of more complex tissues and organs (multi-functional, multi-layered, bio-chemical, bio-properties) a reality in the clinical environment.

ECM material has been shown to a very attractive material as a base or one of the structural components for a composite repair material as part of the continuing challenge to find ways to translate the mechanical properties and clinical performance of ECM biomaterials to vascular clinical applications. In order to increase the mechanical strength of ECM, cross-linking structural components with chemicals such as glutaraldehyde, 1-Ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride (EDC or EDAC) and hexamethylene-diisocyanate is applied; however, modification by

this type of method has been shown to have a lower degradation rate *in vivo*, promote early calcifications and changes the host tissue response from an anti-inflammatory, constructive remodelling response to a pro-inflammatory, foreign body response.

Decellularised ECM materials have been incorporated with synthetic scaffolds successfully to date through a number of approaches. A multilayered poly(styrene sulfonate)/poly(allylamine hydrochloride) (PSS/PAH) have recently been used as luminal coatings onto human umbilical arteries, demonstrating a high graft patency post 3 months rabbit implantation and restoring initial compliance of the tissue [287]. Stankus *et al*. developed a composite scaffold containing poly (ester urethane) urea elastomer (PEUU) and UBM [288,289]. As the water-soluble electrospun UBM was a fragile and brittle material, it was blended with PEUU and dissolved in hexafluoroisopropanol and then electrospun. The scaffold was also more resistant to degradation compared to electrospun UBM alone and had improved mechanical properties. The scaffold was both strong and distensible with a tensile strength of 4.9 ± 1.6 MPa and a breaking strain of 85 ± 28%, compared to lyophilized sheets of UBM (0.3–0.4 MPa and 47–67% strain, respectively) [288,290]. After 28 days implantation in a rat subcutaneous model, there was an increase in scaffold degradation and cellular infiltration with increasing UBM proportions. *In vitro* seeding with SMCs displayed enhanced adherence and proliferation with increasing UBM proportions. Most likely, this is due to increased cell adhesion sites retained from the biological component (*e.g.*, collagen, fibronectin, laminin) and growth factors, which survived the enzymatic digestion and acidic conditions during initial processing and electrospinning solvent conditions. Despite the fact that the harsh fluoroalcohols typically employed to electrospin collagen/ECM material effectively denature collagen to gelatin [291], with losses of more than 90% of triple-helical structure, the gelatinous structures with retained growth factors do confer an enhanced bioactivity. The synthetic portion comprising of bioresorbable or non-resorbable meshes such as Prolene™, Vicryl™, Mersilene™, PDS II™, Panacryl™, and Monocryl™ can be introduced by preparation of laminated structures of ECM sheets presenting a new method of manufacturing hybrid-ECM material with enhanced properties. Hence, a synthetic scaffold enhanced with an ECM component may possess more consistent mechanical properties, such as failure strengths, compliance and degree of shrinkage [292], whilst eliminating the need to cross-link or laminate the structures. Incorporation of ECM components into the synthetic material adds several desirable characteristics which are absent even from the most advanced textured synthetic scaffolds and forms a 'smarter' biomaterial [293], and introduces new functions of the material with near-physiological multifunctionality of the natural ECM, complex signalling, improved control of cell-matrix interactions [294] and cell-specific matrix response.

Specific ECM components have been commonly used (*e.g.*, collagens, fibronectins, laminins) in cell culture for many years and have been shown to have strong effects on cell attachment and growth. The intricate, ordered nature of the ECM, combined with the complex combination of biomolecular cues, is highly difficult to reproduce with synthetic scaffolds. At best, common synthetic ECMs exploit one or two biomolecular classes. A recent study elegantly demonstrated that the tissue-specific matrix components cause significant differences in adhesion efficiencies, growth rates, morphology and phenotypes of skin, muscle and liver cells, suggesting the need for more appropriate, tissue-specific matrices for *in vitro* cell culture [296]. As mentioned previously, the major disadvantage of synthetic vascular materials is their lack of a confluent endothelium and that they are prone to thrombus

induction, embolism and occlusion. They are also less durable than autologous material and are associated with poor healing and lack of compliance and often require extensive use of anticoagulant or antithrombotic agents [297]. Therefore, the importance of creating a suitable endothelium on the luminal surface of any diameter synthetic vessel substitute is paramount. Coatings of proteins, decellularised matrices are being pursued to increase the bioactivity of the prostheses in order to render then more suitable for EC seeding. Common approaches to treat vascular graft surfaces include autologous fibrin coating [298,299] or heparin [300,301] and have been met with mixed success. On the whole, these linings do not provide vital vascular functions such as vascular responsiveness or other biological secretory functions seen with normal blood vessels [302]. A mixture of collagen type I, elastin and poly (D, L-lactide-coglycolide) (PLGA) to impart increased mechanical strength was electrospun to form a non-cytoxic tubular construct with similar compliance to native arteries and minimal inflammatory response [303]. Tillman *et al.* electrospun a collagen type I - PCL tubular scaffold, pre-seeded with ECs and SMCs under bioreactor conditioning flow [304]. The grafts used had a caliber of 5 mm and were able to support EC and SMC growth under pulsatile flow conditions. Although smaller diameters are associated with a higher degree of thrombotic occlusion most remained patent at 1 month, even without the presence of anti-thrombogenic ECs. For example, the Hemashield™ vascular graft is a woven double-velour polyester graft impregnated with weakly cross-linked purified bovine collagen, softened by exposure to glycerol. This confers anti-thrombogenicity, an improved healing response and eliminates the need for pre-clotting, which is patient-specific, time-consuming and troublesome.

Replacement of the vessel, in major surgical cases, may serve as a symptomatic treatment of atherosclerotic lesions or aneurisms that have developed in the vessel wall altering its structure and function but does not target the cause of disease known to include molecular and biochemical processes in the blood and the blood vessel wall, and their interface such as deposition of plaques, cholesterol, platelets and other related molecules within the arterial walls. Due to this factor, long–term performance of the ECM material and functionality of the new vessel tissue depends on the origin of the disease, genetic predisposition, specific diet, age, hormone status and many other risk factors. ECM as a protein–based material may be further modified and activated as a potential delivery method of therapeutic agents (drugs, enzymes, inhibitors) which can be released after incorporation of the material into the body. This approach may only provide a short-term treatment due to quick exhaustion of quantity and activity of the loaded functional protein or drug. Incorporation of the specific DNA molecules with coding sequence of the disease-related gene, its uptake by the host cell during repopulation of the ECM vessel following development of the stable/induced subpopulation of the vascular cell may potentially provide a new resistant to arteriosclerosis development vascular tissue due to continuous or inducible synthesis appropriate enzyme, cellular receptor or ECM components coded by delivered DNA molecules.

The future perspectives for the application of ECM technology to vascular applications still have many obstacles to its success and development, with decellularisation, material properties and component modification processing still at the development stages. The advancement of these technologies should ensure a highly improved bioscaffold for the treatment in cardiovascular applications. Furthermore with the application of new research and approaches to ECM materials may allow many of the outlined shortfalls in the current treatment approaches to be eliminated.

7. Conclusions

With our expanding knowledge of molecular cascades during natural healing and their inter-relationship, it remains very challenging to develop a material which may avoid the natural recognition system of our body. The creation of a prosthetic vascular graft material for clinical use which will be able to achieve an excellent treatment regime and eliminate many of the current complications requires considerable further scientific investigation.

The long-term patency of the vascular graft is a challenging goal for the vascular surgeon. After the early stages of graft acceptance, the degree of functionality of the developing grafted vessel is regulated by physical and biorheological forces (shear stress, wall pressure, particle deposition). Reconstruction of the active dynamic and complex inter-communication with another system of the human body (neural) has influence on modulation of the cellular and molecular events that underlie regulation of vascular tissue adaptation and final healing. The success of a vascular graft is shown to depend upon the intrinsic properties of the graft material and the hemodynamic environment recreated at the grafting site. The degree to which the homeostatic mechanisms are perturbed, the extent of pathophysiologic responses and their resolution are scales of the host reactions to the biomaterial determine the ultimate success of the graft.

Biological material composed of decellularised tissue matrices has been shown to have the potential to stimulate and augment healing processes via multiple biological activities during symptomatic treatment of atherosclerotic lesions or aneurisms. A range of ECMs have been shown to provide an excellent microenvironment for the many processes that occur in the early stages of healing and allow a long-term maintenance of balanced homeostasis and functional neo-tissue development. Applications of this type of biomaterial in clinical use may lead to successful regeneration therapies for the patient. Further development of techniques to improve the degree of biostability, biocompatibility and calcification potential of a decellularized matrices should be considered in future studies.

Acknowledgements

The authors would like to acknowledge the support of Enterprise Ireland Technical Development Fund CFTD 2007/131 and the Irish Research Council for Science, Engineering and Technology (IRCSET).

References and notes

1. *Vascular Surgery: Principals and Practice*; Hobson, R.W., Wilson, S.E., Veith, F.J., Eds.; McGraw-Hill: New York, NY, USA, 2003.
2. *Vascular Graft Update, ASTM STP 898*; Kambic, H.E., Kantrowitz, A., Sung, P., Eds.; American Society for Testing and Materials International: Philadelphia, PA, USA, 1986.
3. Bezuidenhout, D.; Zilla, P. Vascular grafts. In *Encyclopedia of Biomaterials and Biomedical Engineering*; Wnek, G.E., Bowlin, G.L., Eds.; Informa Health Care: New York, NY, USA, 2008.

4. Davis, L.; Dower, T.; Zilla, P. The lack of healing in conventional vascular grafts. In *Tissue Engineering of Vascular Prosthetic Grafts*; Zilla, P., Greisler, H.P., Eds.; Landes Company: Austin, TX, USA, 1999; pp. 3–44.
5. Greisler, H.P. Characteristics and healing of vascular grafts. In *Vascular Surgery: Theory and Practice*; Callow, A.D., Ernst, C.B., Eds.; Appleton & Lange: Stamford (Conn), New York, NY, USA, 1995; pp. 1181–1212.
6. Anderson, M. Procedures in the retrieval and evaluation of vascular grafts. In *Vascular Graft Update: Safety and Performance*; Kambic, H.E., Kantrowitz, A., Sung, P., Eds.; American Society for Testing and Materials: Philadelphia, Pennsylvania, USA, 1986; pp. 156–165.
7. Clowes, W.; Gown, A.M.; Hanson, S.R.; Reidy, M.A. Mechanisms of arterial graft failure. 1. Role of cellular proliferation in early healing of PTFE prostheses. *Amer. J. Pathol.* **1985**, *118*, 43–54.
8. Clowes, A.W.; Kinkman, T.R.; Reidy, M.A. Mechanisms of arterial graft healing. A rapid transmural capillary ingrowth provides a source of intimal endothelium and smooth muscle in porous PTFE prostheses. *Amer. J. Pathol.* **1986**, *123*, 220–230.
9. Burkel, W.E. The development of cellular linings in artificial vascular prostheses. In *Biocompatible Polymers, Metals and Composites*; Szycher, M., Ed.; Technomic Publ. Co., Inc.: Lancaster, PA, USA, 1983; pp. 165–178.
10. *Nanotechnology and Tissue Engineering: The scaffold*; Laurencin, C.T., Nair, L., Eds.; CRC Press: New York, NY, USA, 2008.
11. Ratner, B.D.; Hoffman, A.S.; Schoen, F.J.; Lemons, J.E. *Biomaterials Science: An Introduction to Materials and Medicine*, 2nd ed.; Elsevier: Oxford, UK, 2004.
12. *Biomaterials Engineering and Devices: Fundamentals and Vascular and Carrier Applications*; Wise, D.L., Ed.; Humana Press: Totowa, NJ, USA, 2000.
13. *Functional Materials and Biomaterials*; Liu, X.D., Ed.; Springer: Berlin, Germany, 2007.
14. Szycher, M. Blood compatibility and vascular prostheses. In *High Performance Biomaterials: A Complete Guide to Medical and Pharmceutical Applications*; Szycher, M., Ed.; CRC Press LLC: Boca Raton, FL, USA, 1991.
15. Inayat-Hussain, S. and Rajab, N.F. *In vitro* testing of biomaterial toxicity and biocompatibility. In *Cellular Response to Biomaterials*; Di Silvio, L., Ed.; Woodhead Publishing Ltd: Cambridge, UK, 2008.
16. Fortunato, J.E.; Glagov, S.; Bassiouny, H.S. Biomechanical factors as regulators of biological responses to vascular grafts. *Semin. Vasc. Surg.* **1999**, *12*, 27–37.
17. Badylak, S.F.; Freytes, D.O.; Gilbert, T.W. Extracellular matrix as a biological scaffold material: Structure and function. *Acta Biomater.* **2009**, *5*, 1–13.
18. Gilbert, T.W.; Sellaro, T.L.; Badylak, S.F. Decellularisation of tissues and organs. *Biomaterials* **2006**, *27*, 3675–3683.
19. Sandusky, G.E.; Lantz, G.C.; Badylak, S.F. Healing comparison of small intestine submucosa and ePTFE grafts in the canine carotid artery. *J. Surg. Res.* **1995**, *58*, 415–420.
20. Badylak, S.F.; Coffey, A.C.; Lantz, G.C.; Tacker, W.A.; Geddes, L.A. Comparison of the resistance to infection of intestinal submucosa arterial autografts versus polytetrafluoroethylene arterial prostheses in a dog model. *J. Vasc. Surg.* **1994**, *19*, 465–472.

21. Prevel, C.D.; Eppley, B.L.; McCarty, M.; Jackson, J.R.; Voytik, S.L.; Hiles, M.C.; Badylak, S.F. Experimental evaluation of small intestinal submucosa as a microvascular graft material. *Microsurgery* **1994**, *15*, 586–591.
22. Lantz, G.C.; Badylak, S.F.; Hiles, M.C.; Coffey, A.C.; Geddes, L.A.; Kokini, K.; Sandusky, G.E.; Morff, R.J. Small intestinal submucosa as a vascular graft: A review. *J. Invest. Surg.* **1993**, *6*, 297–310.
23. Hiles, M.C.; Badylak, S.F.; Geddes, L.A.; Kokini, K.; Morff, R.J. Porosity of porcine small-intestinal submucosa for use as a vascular graft. *J. Biomed. Mater. Res.* **1993**, *27*, 139–144.
24. Lantz, G.C.; Badylak, S.F.; Coffey, A.C.; Geddes, L.A.; Sandusky, G.E. Small intestinal submucosa as a superior vena cava graft in the dog. *J. Surg. Res.* **1992**, *53*, 175–181.
25. Badylak, S.F.; Lantz, G.C.; Coffey, A.; Geddes, L.A. Small intestinal submucosa as a large diameter vascular graft in the dog. *J. Surg. Res.* **1989**, *47*, 74–80.
26. Prasertsung, I.; Kanokpanont, S.; Bunaprasert, T.; Thanakit, V.; Damrongsakkul, S. Development of acellular dermis from porcine skin using periodic pressurized technique. *J Biomed. Mater. Res. B Appl. Biomater.* **2008**, *85*, 210–219.
27. Mirsch, M.W., II; Schroeder, R.F.B.; Illingworth B.; Borner, W.H.; Montoya, S.I. Use of microorganisms for decellularizing bioprosthetic tissue. 2000, *US Patent 6121041*.
28. Rashid, S.T.; Salacinski, H.J.; Hamilton, G.; Seifalian, A.M. The use of animal models in developing the discipline of cardiovascular tissue engineering: A review. *Biomaterials* **2004**, *25*, 1627–1637.
29. Schmidt, C.E.; Baier, J.M. Acellular vascular tissues: natural biomaterials for tissue repair and tissue engineering. *Biomaterials* **2000**, *21*, 2215–2231.
30. Lü, W.D.; Zhang, M.; Wu, Z.S.; Hu, T.H. Decellularized and photooxidatively crosslinked bovine jugular veins as potential tissue engineering scaffolds. *Interact. CardioVasc. Thorac. Surg.* **2009**, *8*, 301–305.
31. Derham, C.; Yow, H.; Ingram, J.; Fisher, J.; Ingham, E.; Korrosis, S.A.; Homer-Vanniasinkam, S. Tissue engineering small-diameter vascular grafts: Preparation of a biocompatible porcine ureteric scaffold. *Tissue Eng. Part A* **2008**, *14*, 1871–1882.
32. Wilshaw, S.P.; Kearney, J.; Fisher, J.; Ingham, E. Biocompatibility and potential of acellular human amniotic membrane to support the attachment and proliferation of allogeneic cells. *Tissue Eng. Part A* **2008**, *14*, 463–472.
33. Nyland, J.; Larsen, N.; Burden, R.; Chang, H.; Caborn, D.N. Biomechanical and tissue handling property comparison of decellularized and cryopreserved tibialis anterior tendons following extreme incubation and rehydration. *Knee Surg. Sports Traumatol. Arthrosc.* **2009**, *17*, 83–91.
34. Weadock, K.; Olson, R.M.; Silver, F.H. Evaluation of collagen crosslinking techniques. *Biomater. Med. Devices Artif. Organs* **1983**, *11*, 293–318.
35. Sacks, M.S.; Hamamoto, H.; Connolly, J.M.; Gorman, R.C.; Gorman, J.H., III; Levy, R.J. *In vivo* biomechanical assessment of triglycidylamine crosslinked pericardium. *Biomaterials* **2007**, *28*, 5390–5398.
36. Garcia, Y.; Hemantkumar, N.; Collighan, R.; Griffin, M.; Rodriguez-Cabello, J.C.; Pandit, A. *In vitro* characterization of a collagen scaffold enzymatically cross-linked with a tailored elastin-like polymer. *Tissue Eng. Part A* **2009**, *15*, 887–899.

37. Somers, P.; De Somer, F.; Cornelissen, M.; Bouchez, S.; Gasthuys, F.; Narine, K.; Cox, E.; van Nooten, G. Genipin blues: An alternative non-toxic crosslinker for heart valves? *J. Heart Valve Dis.* **2008**, *17*, 682–688.
38. Freytes, D.O.; Martin, J.; Velankar, S.S.; Lee, A.S.; Badylak, S.F. Preparation and rheological characterization of a gel form of the porcine urinary bladder matrix. *Biomaterials* **2008**, *29*, 1630–1637.
39. Brockbank, K.G.; MacLellan, W.R. Optimized preservation of extracellular matrix in cardiac tissues: Implications for long-term graft durability. *Ann. Thorac. Surg.* **2007**, *83*, 1641–1650.
40. Freytes, D.O.; Tullius, R.S.; Valentinm, J.E.; Stewart-Akers, A.M.; Badylak, S.F. Hydrated versus lyophilized forms of porcine extracellular matrix derived from the urinary bladder. *J Biomed. Mater. Res. A.* **2008**, *87*, 862–872.
41. Piterina, A.V.; Davis, L.M; Meaney, C.L; Walsh, M.T.; Badylak, S.F.; McGloughlin, T.M. Characterisation of structural features a full-thickness acellular matrices deriving from animal organs. In *Proceedings of Bioengineering in Ireland 15*, Jan 30–31, Limerick, Ireland, 2009.
42. Piterina, A.V.; Callanan, A.; Davis, L.M; Meaney, C.L; Walsh, M.T.; McGloughlin, T.M. ECM matrices as an advanced scaffold for vascular tissue engineering. *Bio.—Med. Mater. Eng*. **2009**, in press.
43. Piterina, A.V.; Davis, L.M.; Meaney, C.L.; Cloonan, A.J.; Walsh, M.T.; McGloughlin, T.M.; Cell-seeded decellularised extracellular matrices as an advanced approach for tissue engineering. In *Proceedings of International Conference on Tissue Engineering ICTE*, Leiria, Portugal, July 9–11, 2009
44. Brown, B.; Lindberg, K.; Reing, J.; Stolz, D.B.; Badylak, S.F. The basement membrane component of biologic scaffolds derived from extracellular matrix. *Tissue Eng.* **2006**, *12*, 519–526.
45. Hodde, J.; Record, R.; Tullius, R.; Badylak, S. Fibronectin peptides mediate HMEC adhesion to porcine-derived extracellular matrix. *Biomaterials* **2002**, *23*, 1841–1848.
46. Hodde, J.P.; Record, R.D.; Liang, H.A.; Badylak, S.F. Vascular endothelial growth factor in porcine-derived extracellular matrix. *Endothelium* **2001**, *8*, 11–24.
47. Helton, W.S.; Fisichella, P.M.; Berger, R.; Horgan, S.; Espat, N.J.; Abcarian, H. Short-term outcomes with small intestinal submucosa for ventral abdominal hernia. *Arch. Surg.* **2005**, *140*, 549–562.
48. Badylak, S.F.; Vorp, D.A.; Spievack, A.R.; Simmons-Byrd, A.; Hanke, J.; Freytes, D.O.; Thapa, A.; Gilbert, T.W.; Nieponice, A. Esophageal reconstruction with ECM and muscle tissue in a dog model. *J. Surg. Res*. **2005**, *128*, 87–97.
49. Rosalia, M.; Mark, P.C.; Anthony, J.C.; Martin, K.; Kirstan, K.M.; Richard, C.R. Small intestinal submucosa bladder neck slings for incontinence associated with neuropathic bladder. *J. Urology* **2005**, *174*, 1680–1682.
50. Malcarney, H.L.; Bonar, F.; Murrell, G.A.C. Early Inflammatory reaction after rotator cuff repair with a porcine small intestine submucosal implant. *Am. J. Sport Med.* **2005**, *33*, 907–911.
51. El-Assmy, A.; Hafez, A.T.; El-Sherbiny, M.T.; El-Hamid, M.A.; Mohsen, T.; Nour, E.M.; Bazeed, M. Use of single layer small intestinal submucosa for long segment ureteral replacement: A pilot study. *J. Urology* **2004**, *171*, 1939–1942.

52. De Ugarte, D.A.; Choi, E.; Weitzbuch, H.; Wulur, I.; Caulkins, C.; Wu, B.; Fonkalsrud, E.W.; Atkinson, J.B.; Dunn, J.C.Y. Mucosal regeneration of a duodenal defect using small intestine submucosa. *Am. Surgeon* **2004**, *70*, 49–51.
53. Jones, J.S.; Rackley, R.R.; Berglund, R.; Abdelmalak, J.B.; Deorco, G.; Vasavada, S.P. Porcine small intestinal submucosa as a percutaneous mid-urethral sling: 2-year results. *BJU Int.* **2005**, *96*, 103–106.
54. Ziats, N.P.; Miller, K.M.; Anderson, J.M. *In vitro* and *in vivo* interactions of cells with biomaterials. *Biomaterials* **1988**, *9*, 5–13.
55. Tang, L.; Ugarova, T.P.; Plow, E.F.; Eaton, J.W. Molecular determinants of acute inflammatory responses to biomaterials. *J. Clin. Invest.* **1996**, *97*, 1329–1334.
56. Anderson, J.M.; Rodriguez, A.; Chang, D.T. Foreign body reaction to biomaterials. *Semin. Immunol.* **2008**, *20*, 86–100.
57. Janatova, J. Activation and control of complement, inflammation, and infection associated with the use of biomedical polymers. *ASAIO J.* **2000**, *46*, 53–62.
58. Xia, Z.; Triffitt, J.T. A review on macrophage responses to biomaterials. *Biomed. Mater.* **2006**, *1*, 1–9.
59. Anderson, J.M.; Miller, K.M. Biomaterial biocompatibility and the macrophage. *Biomaterials* **1984**, *5*, 5–10.
60. Valentin, J.E.; Stewart-Akers, A.M.; Gilbert, T.W.; Badylak, S.F. Macrophage participation in the degradation and remodeling of ECM scaffolds. *Tissue Eng. Part A* **2009**, *15*, in press.
61. Mensik, A.; Brouwer, A.; van den Burg, E.H.; Geurts, S.; Jongen, W.M.F.; Lakemond, C.M.M.; Meijerman, I.; van der Wijk, T. Modulation of intercellular communication between smooth muscle cells by growth factors and cytokines. *Eur. J. Pharmacol.* **1996**, *310*, 73–81.
62. Mills, D.; Kincaid, K.; Alt, J.M.; Heilman, M.J.; Hill, A.M. M-1/M-2 macrophages and the Th1/Th2 paradigm. *J. Immunol*. **2000**, *164*, 6166–6173.
63. Badylak, S.F.; Gilbert, T.W. Immune response to biologic scaffold materials. *Semin. Immunol.* **2008**, *20*, 109–116.
64. Rehman, J.; Li, J.; Orschell, C.M.; March, K.L. Peripheral blood 'endothelial progenitor cells' are derived from monocyte/ macrophages and secrete angiogenic growth factors. *Circulation* **2003**, *107*, 1164–1169.
65. Palmer, E.M.; Beilfuss, B.A.; Nagai, T.; Semnani, R.T.; Badylak, S.F.; van Seventer, G.A. Human helper T cell activation and differentiation is suppressed by porcine small intestinal submucosa. *Tissue Eng.* **2002**, *8*, 893–900.
66. Allman, A.J.; McPherson, T.B.; Merrill, L.C.; Badylak, S.F.; Metzger, D.W. The Th2-restricted immune response to xenogeneic small intestinal submucosa does not influence systemic protective immunity to viral and bacterial pathogens. *Tissue Eng.* **2002**, *8*, 53–62.
67. Brodbeck, W.G.; Voskerician, G.; Ziats, N.P.; Nakayama, Y.; Matsuda, T.; Anderson, J.M. *In vivo* leukocyte cytokine mRNA responses to biomaterials are dependent on surface chemistry. *J. Biomed. Mater. Res. A* **2003**, *64*, 320–329.
68. Zetrenne, E.; McIntosh, B.C.; McRae, M.H.; Gusberg, R.; Evans, G.R.; Narayan, D. Prosthetic vascular graft infection: A multi-center review of surgical management. *Yale J. Biol. Med.* **2007**, *80*, 113–121.

69. Chiesa, R.; Astore, D.; Frigerio, S.; Garriboli, L.; Piccolo, G.; Castellano, R.; Scalamogna, M.; Odero, A.; Pirrelli, S.; Biasi, G.; Mingazzini, P.; Biglioli, P.; Polvani, G.; Guarino, A.; Agrifoglio, G.; Tori, A.; Spina, G. Vascular prosthetic graft infection: Epidemiology, bacteriology, pathogenesis and treatment. *Acta Chir. Belg.* **2002**, *102*, 238–247.
70. Mertens, R.A.; O'Hara, P.J.; Hertzer, N.R.; Krajewski, L.P.; Beven, E.G. Surgical management of infrainguinal arterial prosthetic graft infections: Review of a 35-year experience. *J. Vasc. Surg*. **1995**, *21*, 782–791.
71. Bunt, T.J. Vascular graft infections: An update. *Cardiovasc. Surg.* **2001**, *9*, 225–233.
72. Mermel, L.A.; Farr, B.M.; Sheretz, R.J.; Raad, I.I.; O'Grady, N.; Harris, J.S.; Craven, D.E. Guidelines for the management of intravascular catheter-related infections. *Clin. Infect. Dis*. **2001**, *32*, 1249–1272.
73. Perera, G.B.; Fujitani, R.M.; Kubaska, S.M. Aortic graft infection: Update on management and treatment options. *Vasc. Endovasc. Surg.* **2006**, *40*, 1–10.
74. Sharp, W.J.; Hoballah, J.J.; Mohan, C.R.; Kresowik, T.F.; Martinasevic, M.; Chalmers, R.T.A.; Corson, J.D. The management of the infected aortic prosthesis: A current decade of experience. *J. Vasc. Surg*. **1994**, *19*, 844–850.
75. Swain, T.W., III; Calligaro, K.D.; Dougherty, M.D. Management of infected aortic prosthetic grafts. *Vasc. Endovasc. Surg.* **2004**, *38*, 75–82.
76. Padberg, F.T., Jr.; Calligaro, K.D.; Sidawy, A.N. Complications of arteriovenous hemodialysis access: Recognition and management. *J. Vasc. Surg.* **2008**, *48*, S55–S80.
77. Holland, F.W.; Darling, R.C., III; Chang, B.B.; Shah, D.M.; Leather, R.P. Clostridial aortic graft infection. *Ann. Vasc. Surg.* **1994**, *8*, 387–389.
78. Upchurch, G.R., Jr.; Clair, D.G.; Whittemore, A.D.; Mannick, J.A. Clostridium septicum bacteremia associated with aortic graft infection. *J. Vasc. Surg.* **1995**, *22*, 493–495.
79. Lephart, P.; Ferrieri, P.; van Burik, J.A. Reservoir of Candida albicans infection in a vascular bypass graft demonstrates a stable karyotype over six months. *Med. Mycol*. **2004**, *42*, 255–260.
80. van Dijk, J.; Herkströter, F.; Busscher, H.; Weerkamp, A.; Jansen, H.; Arends, J. Surface-free energy and bacterial adhesion. An *in vivo* study in beagle dogs. *J. Clin. Periodontol.* **1987**, *14*, 300–304.
81. Wadström, T. Molecular aspects of bacterial adhesion, colonization, and development of infections associated with biomaterials. *J. Invest. Surg.* **1989**, *2*, 353–360.
82. Fleer, A.; Verhoef, J. An evaluation of the role of surface hydrophobicity and extracellular slime in the pathogenesis of foreign-body-related infections due to coagulase-negative staphylococci. *J. Invest. Surg.* **1989**, *2*, 391–396.
83. Jansen, B.; Schumacher-Perdreau, F.; Peters, G.; Pulverer, G. New aspects in the pathogenesis and prevention of polymer-associated foreign-body infections caused by coagulase-negative staphylococci. *J. Invest. Surg.* **1989**, *2*, 361–380.
84. Hussain, M.; Wilcox, M.H.; White, P.J. The slime of coagulase-negative staphylococci: Biochemistry and relation to adherence. *FEMS Microbiol. Rev*. **1993**, *10*, 191–207.
85. Baselga, R.; Albizu, I.; De La Cruz, M.; Del Cacho, E.; Barberan, M.; Amorena, B. Phase variation of slime production in Staphylococcus aureus: Implications in colonization and virulence. *Infect. Immun.* **1993**, *61*, 4857–4862.

86. Christensen, G.D.; Simpson, W.A.; Bisno, A.L.; Beachey, E.H. Adherence of slime-producing strains of Staphylococcus epidermidis to smooth surfaces. *Infect. Immun.* **1982**, *37*, 318–326.
87. Kristinsson, K.G.; Spencer, R.C. Slime production as a marker for clinically significant infections with coagulase-negative staphylococci. *J. Infect. Dis.* **1986**, *154*, 728–729.
88. Gross, M.; Cramton, S.E.; Gotz, F.; Peschel, A. Key role of teichoic acid net charge in *Staphylococcus aureus* colonization of artificial surfaces. *Infect. Immun.* **2001**, *69*, 3423–3426.
89. Treiman, G.S.; Copland, S.; Yellin, A.E.; Lawrence, P.F.; McNamara, R.M.; Treiman, R.L. Wound infections involving infrainguinal autogenous vein grafts: A current evaluation of factors determining successful graft preservation. *J. Vasc. Surg.* **2001**, *33*, 948–954.
90. Donlan, R.M.; Costerton, J.W. Biofilms: Survival mechanisms of clinically relevant microorganisms. *Clin. Microbiol. Rev.* **2002**, *15*, 167–193.
91. Gilbert, P.; Maira-Litran, T.; McBain, A.J.; Rickard, A.H.; Whyte, F.W. The physiology and collective recalcitrance of microbial biofilm communities. *Adv. Microb. Physiol.* **2002**, *46*, 202–256.
92. Ito, A.; Taniuchi, A.; May, T.; Kawata, K.; Okabe, S. Increased antibiotic resistance of *Escherichia coli* in mature biofilms. *Appl. Environ. Microbiol.* **2009**, *75*, 4093–4100.
93. Aslam, S. Effect of antibacterials on biofilms. *Am. J. Infect. Control.* **2008**, *36*, S175e9–175e11.
94. Simões, M.; Simões, L.C.; Vieira, M.J. Species association increases biofilm resistance to chemical and mechanical treatments. *Water Res.* **2009**, *43*, 229–237.
95. Anderson, G.G.; O'Toole, G.A. Innate and induced resistance mechanisms of bacterial biofilms. *Curr. Top. Microbiol. Immunol*. **2008**, *322*, 85–105.
96. Lewis, K. Multidrug tolerance of biofilms and persister cells. *Curr. Top. Microbiol. Immunol.* **2008**, *322*, 107–131.
97. Dofferhoff, A.S.; Nijland, J.H.; de Vries-Hospers, H.G.; Mulder, P.O.; Weits, J.; Bom, V.J. Effects of different types and combinations of antimicrobial agents on endotoxin release from gram-negative bacteria: An *in-vitro* and *in-vivo* study. *Scand. J. Infect. Dis.* **1991**, *23*, 745–754.
98. Prins, J.M.; van Deventer, S.J.; Kuijper, E.J.; Speelman, P. Clinical relevance of antibiotic-induced endotoxin release. *Antimicrob. Agents Ch.* **1994**, *38*, 1211–1218.
99. Kirikae, T.; Nakano, M.; Morrison, D.C. Antibiotic-induced endotoxin release from bacteria and its clinical significance. *Microbiol. Immunol.* **1997**, *41*, 285–294.
100. Hurley, J.C. Antibiotic-induced release of endotoxin: A reappraisal. *Clin. Infect. Dis.* **1992**, *15*, 840–854.
101. Nau, R.; Eiffert, H. Minimizing the release of proinflammatory and toxic bacterial products within the host: A promising approach to improve outcome in life-threatening infections. *FEMS Immunol. Med. Microbiol.* **2005**, *44*, 1–16.
102. Nagase, H.; Woessner, F. Matrix metalloproteinases. *J. Biol. Chem.* **1999**, *274*, 21491–21494.
103. Young, R.M.; Cherry, K.J., Jr.; Davis, P.M.; Gloviczki, P.; Bower, T.C.; Panneton, J.M.; Hallett, J.W., Jr. The results of *in situ* prosthetic replacement for infected aortic grafts. *Am. J. Surg.* **1999**, *178*, 136–140.
104. Wilson, S.E. New alternatives in management of the infected vascular prosthesis. *Surg. Infect.* **2001**, *2*, 171–177.

105. Greco, R.S.; Harvey, R.A.; Smilow, P.C.; Tesoriero, J.V. Prevention of vascular prosthetic infection by a benzalkonium-oxacillin bonded polytetrafluoroethylene graft. *Surg. Gyn. Obstet.* **1982**, *155*, 28–32.
106. Sobinsky, K.R.; Flanigan, P. Antibiotic binding to polytetrafluoroethylene via glucosaminoglycan-keratin luminal coating. *Surgery* **1986**, *100*, 629–633.
107. Shenk, J.S.; Ney, A.L.; Tsukayama, D.T.; Olson, M.E.; Bubrick, M.P. Tobramycin-adhesive in preventing and treating PTFE vascular graft infections. *J. Surg. Res.* **1989**, *47*, 487–492.
108. Ney, A.L.; Kelly, P.H.; Tsukayama, D.T.; Bubrick, M.P. Fibrin glue-antibiotic suspension in the prevention of prosthetic graft infection. *J. Trauma* **1990**, *30*, 1000–1006.
109. Haverich, A.; Hirt, S.; Karck, M.; Siclari, F.; Wahlig, H. Prevention of graft infection by bonding of gentamycin to Dacron prostheses. *J. Vasc. Surg.* **1992**, *15*, 187–193.
110. Gahtan, V.; Esses, G.E.; Bandyk, D.F.; Nelson, R.T.; Dupont, E.; Mills, J. Antistaphylococcal activity of rifampin-bonded gelatin-impregnated Dacron grafts. *J. Surg. Res.* **1995**, *58*, 105–110.
111. Sago, T.; Mori, Y.; Takagi, H.; Iwata, H.; Murase, K.; Kawamura, Y.; Hirose, H. Local treatment of Dacron patch graft contaminated with *Staphylococcus aureus* with antibiotic-releasing porous apatite ceramic: An experimental study in the rabbit. *J. Vasc. Surg.* **2003**, *37*, 169–174.
112. Darouiche, R.O.; Mansouri, M.D. *In vitro* activity and *in vivo* efficacy of antimicrobial-coated vascular grafts. *Ann. Vasc. Surg.* **2004**, *18*, 497–501.
113. Kinney, E.V.; Bandyk, D.F.; Seabrook, G.A.; Kelly, H.M.; Towne, J.B. Antibiotic-bonded PTFE vascular grafts: The effect of silver antibiotic on bioactivity following implantation. *J. Surg. Res.* **1991**, *50*, 430–435.
114. Hernandez-Richter, T.; Schardey, H.M.; Löhlein, F.; Heiss, M.M.; Redondo-Müller, M.; Hammer, C.; Schildberg, F.W. The prevention and treatment of vascular graft infection with a triclosan (Irgasan)-bonded Dacron graft: An experimental study in the pig. *Eur. J. Vasc. Endovasc. Surg.* **2000**, *20*, 413–418.
115. Ghiselli, R.; Giacometti, A.; Cirioni, O.; Mocchegiani, F.; Orlando, F.; Kamysz, W.; Del Prete, M.S.; Lukasiak, J.; Scalise, G.; Saba, V. Temporin A as a prophylactic agent against methicillin sodium susceptible and methicillin sodium resistant *Staphylococcus epidermidis* vascular graft infection. *J. Vasc. Surg.* **2002**, *36*, 1027–1030.
116. Ginalska, G.; Kowalczuk, D.; Osinska, M. A chemical method of gentamicin bonding to gelatine-sealed prosthetic vascular grafts. *Int. J. Pharm.* **2005**, *288*, 131–140.
117. Ginalska, G.; Osinska, M.; Uryniak, A.; Urbanik-Sypniewska, T.; Belcarz, A.; Rzeski, W.; Wolski, A. Antibacterial activity of gentamicin-bonded gelatin-sealed polyethylene terephtalate vascular prostheses. *Eur. J. Vasc. Endovasc. Surg.* **2005**, *29*, 419–424.
118. Sacar, M.; Scar, S.; Kaleli, I.; Onem, G.; Turgut, H.; Goksin, I.; Ozcan, V.; Inan, B.K.; Duver, H.; Baltalari, A. Linezolid alone and in combination with rifampicin prevents experimental vascular graft infection due to methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis*. *J. Surg. Res.* **2007**, *139*, 170–175.
119. Schmacht, D.; Armstrong, P.; Johnson, B.; Pierre, K.; Back, M.; Honeyman, A.; Cuthbertson, D.; Bandyk, D. Graft infectivity of rifampin and silver-bonded polyester grafts to MRSA contamination. *Vasc. Endo Surg.* **2005**, *39*, 411–420.

120. Hirose, K.; Marui, A.; Arai, Y.; Nomura, T.; Inoue, S.; Kaneda, K.; Kamitani, T.; Fujita, M.; Mitsuyama, M.; Tabata, Y.; Komeda, M. Sustained-release vancomycin sheet may help to prevent prosthetic graft methicillin-resistant *Staphylococcus aureus* infection. *J. Vasc. Surg.* **2006**, *44*, 377–382.
121. Hardman, S.; Cope, A.; Swann, A.; Bell, P.R.F.; Naylor, A.R.; Hayes, P.D. An *in vitro* model to compare the antimicrobial activity of silver-coated versus rifampicin-soaked vascular grafts. *Ann. Vasc. Surg.* **2004**, *18*, 308–313.
122. Batt, M.; Magne, J.L.; Alric, P.; Muzj, A.; Ruotolo, C.; Ljungstrom, K.G.; Garcia-Casas, R.; Simms, M. *In situ* revascularization with silver-coated polyester grafts to treat aortic infection: Early and midterm results. *J. Vasc. Surg.* **2003**, *38*, 983–989.
123. Ueberrueck, T.; Zippel, R.; Tautenhahn, J.; Gastinger, I.; Lippert, H.; Wahlers, T. Vascular graft infections: *In vitro* and *in vivo* investigations of a new vascular graft with long-term protection. *J. Biomed. Mater. Res. B Appl. Biomat.* **2005**, *74*, 601–607.
124. Hernandez-Richter, T.; Schardey, H.M.; Wittmann, F.; Mayr, S.; Schmitt-Sody, M.; Blasenbreu, S.; Heiss, M.M.; Gabka, C.; Angele, M.K. Rifampin and triclosan but not silver is effective in preventing bacterial infection of vascular Dacron graft material. *Eur. J. Vasc. Endovasc. Surg*. **2003**, *26*, 550–557.
125. Gomez-Lus, R. Evolution of bacterial resistance to antibiotics during the last three decades. *Int. Microbiol.* **1998**, *1*, 279–284.
126. Brennan, E.P.; Reing, J.; Chew, D.; Myers-Irvin, J.M.; Young, E.J.; Badylak, S.F. Antibacterial activity within degradation products of biological scaffolds composed of extracellular matrix. *Tissue Eng.* **2006**, *12*, 2949–2955.
127. Sarikaya, A.; Record, R.; Wu, C.C.; Tullius, B.; Badylak, S.; Ladisch, M. Antimicrobial activity associated with extracellular matrices. *Tissue Eng.* **2002**, *8*, 63–71.
128. Badylak, S.F.; Coffey, A.C.; Lantz, G.C.; Tacker, W.A.; Geddes, L.A. Comparison of the resistance to infection of intestinal submucosa arterial autografts versus polytetrafluoroethylene arterial prostheses in a dog model. *J. Vasc. Surg.* **1994**, *19*, 465–472.
129. Badylak, S.F.; Wu, C.C.; Bible, M.; McPherson, E. Host protection against deliberate bacterial contamination of an extracellular matrix bioscaffold versus Dacron mesh in a dog model of orthopedic soft tissue repair. *J. Biomed. Mater. Res. B Appl. Biomater.* **2003**, *67*, 648–654.
130. Steinstraesser, L.; Koehler, T.; Jacobsen, F.; Daigeler, A.; Goertz, O.; Langer, S.; Kesting, M.;Steinau, H.; Eriksson, E.; Hirsch, T. Host defense peptides in wound healing. *Mol. Med.* **2008**, *14*, 528–537.
131. Hirsch, T.; Metzig, M.; Niederbichler, A.; Steinau, H.U.; Eriksson, E.; Steinstraesser, L. Role of host defense peptides of the innate immune response in sepsis. *Shock* **2008**, *30*, 117–126.
132. Nuding, S.; Zabel, L.T.; Enders, C.; Porter, E.; Fellermann, K.; Wehkamp, J.; Mueller, H.A.; Stange, E.F. Antibacterial activity of human defensins on anaerobic intestinal bacterial species: A major role of HBD-3. *Microbes Infect.* **2009**, *11*, 384–393.
133. Brown, K.L.; Hancock, R.E. Cationic host defense (antimicrobial) peptides. *Curr. Opin. Immunol.* **2006**, *18*, 24–30.
134. Gallo, R.L.; Murakami, M.; Ohtake, T.; Zaiou, M. Biology and clinical relevance of naturally occurring antimicrobial peptides. *J. Allergy Clin. Immunol.* **2002**, *110*, 823–831.

135. Alobaid, N.; Alnaeb, M.E.; Sales, K.M.; Seifalian, A.M.; Mikhailidis, D.P.; Hamilton, G. Endothelial progenitor cells and their potential clinical applications in peripheral arterial disease. *Endothelium* **2005**, *12*, 243–250.
136. Miller-Kasprzak, E.; Jagodziński, P.P. Endothelial progenitor cells as a new agent contributing to vascular repair. *Arch. Immunol. Ther. Exp.* **2007**, *55*, 247–259.
137. Hristov, M.; Weber, C. Endothelial progenitor cells: Characterization, pathophysiology, and possible clinical relevance. *J. Cell Mol. Med.* **2004**, *8*, 498–508
138. Hristov, M.; Erl, W.; Weber, P.C. Endothelial progenitor cells: Mobilization, differentiation, and homing. *Arterioscler Thromb. Vasc. Biol*. **2003**, *23*, 1185–1189.
139. Yasu, T. Differentiation of endothelial progenitor cells. *Circ. J.* **2009**, *73*, 1199–1200.
140. Pelliccia, F.; Pasceri, V.; Cianfrocca, C.; Vitale, C.; Pristipino, C.; Speciale, G.; Mercuro, G.; Rosano, G. Endothelial progenitor cells in patients with coronary artery disease and left ventricular dysfunction. *Coron. Artery Dis.* **2009**, in press.
141. Zilla, P.; Bezuidenhout, D.; Human P. Prosthetic vascular grafts: Wrong models, wrong questions and no healing. *Biomaterial* **2007**, *28*, 5009–5027.
142. Bordenave, L.; Fernandez, P.; Rémy-Zolghadri, M.; Villars, S.; Daculsi, R.; Midy, D. *In vitro* endothelialized ePTFE prostheses: Clinical update 20 years after the first realization. *Clin .Hemorheol. Microcirc.* **2005**, *33*, 227–234.
143. Bhat, V.D.; Klitzman, B.; Koger, K.; Truskey, G.A.; Reichert, W.M. Improving endothelial cell adhesion to vascular graft surfaces: Clinical need and strategies. *J. Biomater. Sci. Polym. Ed.* **1998**, *9*, 1117–1135.
144. Xiao, L.; Shi, D. Role of precoating in artificial vessel endothelialization. *Chin. J. Traumatol.* **2004**, *7*, 312–316.
145. Salacinski, H.J.; Tiwari, A.; Hamilton, G.; Seifalian, A.M. Cellular engineering of vascular bypass grafts: Role of chemical coatings for enhancing endothelial cell attachment. *Med. Biol. Eng. Comput*. **2001**, *39*, 609–618.
146. Shaikh, F.M.; Callanan, A.; Kavanagh, E.G.; Burke, P.E.; Grace, P.A.; McGloughlin, T.M. Fibrin: A natural biodegradable scaffold in vascular tissue engineering. *Cells Tissues Organs* **2008**, *188*, 333–346.
147. Alobaid, N.; Salacinski, H.J.; Sales, K.M.; Hamilton, G.; Seifalian, A.M. Single stage cell seeding of small diameter prosthetic cardiovascular grafts. *Clin. Hemorheol. Microcirc.* **2005**, *33*, 209–226.
148. Walluscheck, K.P.; Steinhoff, G.; Haverich, A. Endothelial cell seeding of de-endothelialised human arteries: Improvement by adhesion molecule induction and flow-seeding technology. *Eur. J. Vasc. Endovasc. Surg.* **1996**, *12*, 46–53.
149. Walluscheck, K.P.; Steinhoff, G.; Haverich, A. Endothelial cell seeding of native vascular surfaces. *Eur. J. Vasc. Endovasc. Surg.* **1996**, *11*, 290–303.
150. Bordenave, L.; Rémy-Zolghadri, M.; Fernandez, P.; Bareille, R.; Midy, D. Clinical performance of vascular grafts lined with endothelial cells. *Endothelium* **1999**, *6*, 267–275.
151. Falk, J.; Townsend, L.E.; Vogel, L.M.; Boyer, M.; Olt, S.; Wease, G.L.; Trevor, K.T.; Seymour, M.; Glover, J.L.; Bendick, P.J. Improved adherence of genetically modified endothelial cells to

small-diameter expanded polytetrafluoroethylene grafts in a canine model. *J. Vasc. Surg.* **1998**, *27*, 902–908.

152. Rotmans, J.I.; Heyligers, J.M.; Stroes, E.S.; Pasterkamp, G. Endothelial progenitor cell-seeded grafts: Rash and risky. *Can. J. Cardiol.* **2006**, *22*, 1113–1116.
153. Reing, J.E.; Zhang, L.; Myers-Irvin, J.; Cordero, K.E.; Freytes, D.O.; Heber-Katz, E.; Bedelbaeva, K.; McIntosh, D.; Dewilde, A.; Braunhut, S.J.; Badylak, S.F. Degradation products of extracellular matrix affect cell migration and proliferation. *Tissue Eng. Part A* **2009**, *15*, 605–614.
154. Brennan, E.P.; Tang, X.H.; Stewart-Akers, A.M.; Gudas, L.J.; Badylak, S.F. Chemoattractant activity of degradation products of fetal and adult skin extracellular matrix for keratinocyte progenitor cells. *J. Tissue Eng. Regen Med*. **2008**, *2*, 491–498.
155. de Mel, A.; Jell, G.; Stevens, M.M.; Seifalian, A.M. Biofunctionalization of biomaterials for accelerated *in situ* endothelialization: A review. *Biomacromolecules* **2008**, *9*, 2969–2979.
156. Prasad, C.K.; Krishnan, L.K. Regulation of endothelial cell phenotype by biomimetic matrix coated on biomaterials for cardiovascular tissue engineering. *Acta Biomater.* **2008**, *4*, 182–191.
157. Alobaid, N.; Salacinski, H.J.; Sales, K.M.; Ramesh, B.; Kannan, R.Y.; Hamilton,G.; Seifalian, A.M. Nanocomposite containing bioactive peptides promote endothelialisation by circulating progenitor cells: An *in vitro* evaluation. *Eur. J. Vasc. Endovasc. Surg.* **2006**, *32*, 76–83.
158. Wijelath, E.; Rahman, S.; Murray, J.; Patel, Y.; Savidge, G.; Sobel, M. Fibronectin promotes VEGF-induced CD34 cell differentiation into endothelial cells. *J. Vasc. Surg*. **2004**, *39*, 655–660.
159. Schneider, A.; Chandra, M.; Lazarovici, G.; Vlodavsky, I.; Merin, G.; Uretzky, G.; Borman,J.B.; Schwalb, H. Naturally produced extracellular matrix is an excellent substrate for canine endothelial cell proliferation and resistance to shear stress on PTFE vascular grafts. *Thromb. Haemost*. **1997**, *78*, 1392–1398.
160. Pollara, P., Alessandri, G., Bonardelli, S., Simonini, A., Cabibbo, E., Portolani, N., Tiberio, G.A., Giulini, S.M., Turano, A. Complete *in vitro* prosthesis endothelialization induced by artificial extracellular matrix. *J. Invest. Surg*. **1999**, *12*, 81–88.
161. Temple, W.J.; Voitk, A.J.; Snelling, C.F.; Crispin, J.S. Effect of nutrition, diet and suture material on long term wound healing. *Ann. Surg.* **1975**, *182*, 93–97.
162. Say, J. The metabolic changes associated with trauma and sepsis. *Nurs. Crit. Care* **1997**, *2*, 83–87.
163. Wilmore, D.W. Metabolic response to severe surgical illness: Overview. *World J. Surg.* **2000**, *24*, 705–711.
164. Williams, J.; Barbul, A. Nutrition and wound healing. *Surg. Clin. North Am.* **2003**, *83*, 71–96.
165. Demling, R. Anticatabolic and anabolic strategies in critical illness. *Shock* **1998**, *10*, 155–160.
166. MacKay, P.; Miller, J. Nutritional support for wound healing. *Altern. Med. Rev.* **2003**, *8*, 359–362.
167. Demling, R. H. Nutrition, anabolism, and the wound healing process: An overview. *Eplasty* **2009**, e*9*, 65–94.
168. Trujillo, E.B. Effects of nutritional status on wound healing. *J. Vasc. Nurs.* **1993**, *11*, 12–18.
169. Kiyama, T.; Witte, M.B.; Thornton, F.J.; Barbul, A. The route of nutrition support affects the early phase of wound healing. *J. Parenter. Enter. Nutr.* **1998**, *22*, 276–279.

170. Stotts, N.A.; Washington, D.F. Nutrition: A critical component of wound healing. *AACN Clin. Issues Crit. Care Nurs.* **1990**, *1*, 585–594.
171. Wray, C.; Mammen, J.; Hasselgren, P. Catabolic response to stress and potential benefits of nutritional support. *Nutrition* **2002**, *18*, 971–977.
172. Swinburn, B.A.; Ravussin, E. Energy and macronutrient metabolism. *Clin. Endocrinol. Metab.* **1994**, *8*, 527–548.
173. Salacinski, H.J.; Goldner, S.; Giudiceandrea, A.; Hamilton, G.; Seifalian, A.M.; Edwards, A, Carson, R.J. The Mechanical Behaviour of Vascular Grafts: A Review. *J. Biomater. Appl*. **2001**, *15*, 241–278.
174. Haruguchi, H.; Teraoka, S. Intimal hyperplasia and hemodynamic factors in arterial bypass and arteriovenous grafts: A review. *J. Artif. Organs.* **2003**, *6*, 227–235.
175. Arndt, J.O.; Klauski, J.; Hersch, F. The diameter of the intact carotid artery in man. *Pfluegers Arch*. **1968**, *301*, 230–240.
176. Patel, D.F.; Greenfield, J.C.; Fry, D.L. *In vitro* pressure-length-radius relationships of certain blood vessels in man and dog. In *Pulsatile Blood Flow*; Attinger, E.O., Ed.; Blahiston-McGraw Hill: New York, NY, USA, 1963, pp. 293–305.
177. Roeder, R.; Wolfe, J.; Lianakis, N.; Hinson, T.; Geddes, L.A.; Obermiller, J. Compliance, elastic modulus and burst pressure of small-intestine submucosa (SIS), small-diameter vascular grafts. *J. Biomed. Mater. Res*. **1999**, *47*, 65–70.
178. Jacot, J.G.; Abdullah, I.; Belkin, M.; Gerhard-Herman, M.; Gaccione, P.; Polak, J.F.; Donaldson, M.C.; Whittemore, A.D.; Conte, M.S. Early adaptation of human lower extremity vein grafts: Wall stiffness changes accompany geometric remodeling. *J. Vasc. Surg.* 2**004**, *39*, 547–555.
179. Sawyer, P.N. *Modern Vascular Grafts*; McGraw-Hill, Inc.: New York, NY, USA, 1987; p. 326.
180. Hasegawa, M.; Azuma, T. Mechanical properties of synthetic arterial grafts. *J. Biomech.* **1979**, *12*, 509–517.
181. Stewart, S.F.C.; Lyman, D.J. Essential physical characteristics of vascular grafts. In *Modern Vascular Grafts*; Sawyer, P.N., Ed.; McGraw-Hill, Inc.: New York, NY, USA, 1987; pp. 117–121.
182. Freytes, D.O.; Badylak, S.F.; Webster, T.J.; Geddes, L.A.; Rundell, A.E. Biaxial strength of multilaminated extracellular matrix scaffolds. *Biomaterials* **2004**, *25*, 2353–2361.
183. Herbert, S.T.; Badylak, S.F.; Geddes, L.A.; Hillberry, B.; Lantz, G.C.; Kokini, K. Elastic modulus of prepared canine jejenum, a new vascular graft material. *Ann. Biomed. Eng.* **1993**, *21*, 727–733.
184. Freytes, D.O.; Stoner, R.M.; Badylak, S.F. Uniaxial and biaxial properties of terminally sterilized porcine urinary bladder matrix scaffolds. *Mater. Res. Part B: Appl. Biomater.* **2008**, *84B*, 408–414.
185. Callanan, A.; Biggins, E.M.; Badylak, S.F.; McGloughlin, T.M. The influence of endothelial cell attachment to UBM extracellular matrix on the regulation of matrix metalloproteinase's (MMP's) and degradation. In *Proceedings of Biologic Scaffolds for Regenerative Medicine*; - Arizona Symposium February 15–16th, Phoenix, AZ, USA, 2008.

186. Roeder, R.A.; Lantz G.C.; Geddes L.A. Mechanical remodeling of small-intestine submicosa small–diameter vascular graft—A preliminary report. *Biomed. Instrum. Technol.* **2001**, *35*, 110–120.
187. Grimes, M.; Pembroke, J.T.; McGloughlin, T.M. The effect of choice of sterilisation method on the biocompatibility and biodegradability of SIS (Small Intestinal Submucosa). *Bio.—Med. Mater. Eng.* **2005**, *15*, 65–71.
188. O'Brien, TP.; Grace, P.; Walsh, M.; Burke, P.; McGloughlin, T. Computational investigations of a new prosthetic femoral-popliteal bypass graft design. *J. Vasc. Surg.* **2005**, *42*, 1169–1175.
189. Rickard, R.F.; Meyer, C.; Hudson, D.A. Computational modeling of microarterial anastomoses with size discrepancy (small-to-large). *J. Surg. Res.* **2009**, *153*, 1–11.
190. Callanan, A.; Morris, L.; Badylak, S.F.; McGloughlin, T.M. MMP and VEGF regulation in endothelial cell-seeded UBM extracellular matrix in a bioreactor. In *Proceeding of European Society of Biomechanics (ESB)*, Lucerne, Switzerland, 6–9 July, 2008.
191. Mitsuoka, H.; Kitamura, S.; Kuwahara, K.; Unno, N. Impact of *in vivo* ranges of the variances in the flow velocity waveforms and flow split ratio on the hemodynamic effects of the anastomotic cuff at distal end-to-side anastomosis. *Surg. Today* **2006**, *36*, 769–774.
192. Longest, P.W.; Kleinstreuer, C. Numerical simulation of wall shear stress conditions and platelet localization in realistic end-to-side arterial anastomoses. *J .Biomech. Eng.* **2003**, *125*, 671–681.
193. Noori, N.; Scherer, R.; Perktold, K.; Czerny, M.; Karner, G.; Trubel, M.; Polterauer, P.; Schima, H. Blood flow in distal end-to-side anastomoses with PTFE and a venous patch: Results of an *in vitro* flow visualisation study. *Eur. J. Vasc. Endovasc. Surg.* **1999**, *18*, 191–200.
194. Lei, M.; Archie, J.P.; Kleinstreuer, C. Computational design of a bypass graft that minimizes wall shear stress gradients in the region of the distal anastomosis. *J. Vasc. Surg.* **1997**, *25*, 637–646.
195. Hofer, M.; Rappitsch, G.; Perktold, K.; Trubel, W.; Schima, H. Numerical study of wall mechanics and fluid dynamics in end-to-side anastomoses and correlation to intimal hyperplasia. *J. Biomech.* **1996**, *29*, 1297–1308.
196. Zhang, L.; Moskovitz, M.; Piscatelli, S.; Longaker, M.T.; Siebert, J.W. Hemodynamic study of different angled end-to-side anastomoses. *Microsurgery* **1995**, *16*, 114–117.
197. Migliavacca, F.; Dubini, G. Computational modeling of vascular anastomoses. *Biomech. Model. Mechanobiol.* **2005**, *3*, 235–250.
198. Jackson, M.J.; Bicknell, C.D.; Zervas, V.; Cheshire, N.J.; Sherwin, S.J.; Giordana, S.; Peiró, J.; Papaharilaou, Y.; Doorly, D.J.; Caro, C.G. Three-dimensional reconstruction of autologous vein bypass graft distal anastomoses imaged with magnetic resonance: Clinical and research applications. *J. Vasc. Surg.* **2003**, *38*, 621–625.
199. Rickard, R.F.; Meyer, C.; Hudson, D.A. Computational modeling of microarterial anastomoses with size discrepancy (small-to-large). *J. Surg. Res.* **2009**, *153*, 1–11.
200. Willis, D.J.; Kalish, J.A.; Li, C.; Deutsch, E.R.; Contreras, M.A.; LoGerfo, F.W.; Quist, W.C. Temporal gene expression following prosthetic arterial grafting, *J. Surg. Res.* **2004**, 120, 27–36.
201. Geary, R.L.; Wong, J.M.; Rossini, A.; Schwartz, S.M.; Adams, L.D. Expression profiling identifies 147 genes contributing to a unique primate neointimal smooth muscle cell phenotype. *Arterioscler. Thromb. Vasc. Biol.* **2002**, *22*, 2010–2016.

202. Orr, A.W.; Ginsberg, M.H.; Shattil, S.J.; Deckmyn, H.; Schwartz, M.A. Matrix-specific suppression of integrin activation in shear stress signaling. *Mol. Biol. Cell* **2006**, *17*, 4686–4697.
203. Jalali, S.; del Pozo, M.A.; Chen, K.D.; Miao, H.; Li, Y.S.; Schwartz, M.A.; Shyy, J.Y.; Chien, S. Integrin-mediated mechanotransduction requires its dynamic interaction with specific extracellular matrix (ECM) ligands. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 1042–1046.
204. Shyy, J.Y.J.; Chien, S. Role of integrins in endothelial mechanosensing of shear stress. *Circ. Res*. **2002**, *91*, 769–775.
205. Li, S.; Huang, N.F.; Hsu, S. Mechanotransduction in endothelial cell migration. *J. Cell Biochem.* **2005**, *96*, 1110–1126.
206. Senger, D.R.; Claffey, K.P.; Benes, J.E.; Perruzzi, C.A.; Sergiou, A.P.; Detmar, M. Angiogenesis promoted by vascular endothelial growth factor: Regulation through α1β1 and α2β1 integrins. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 13612–13617.
207. Davis, G.; Black, S.; Bayless, K. Capillary morphogenesis during human endothelial cell invasion of three-dimensional collagen matrices. *In vitro Cell Dev. Biol. An.* **2000**, *36*, 513–519.
208. Davis, G.E.; Bayless, K.J.; Mavila, A. Molecular basis of endothelial cell morphogenesis in three-dimensional extracellular matrices. *Anat. Record* **2002**, *268*, 252–275.
209. Sonnenberg, A.; Modderman, P.W.; Hogervorst, F. Laminin receptor on platelets is the integrin VLA-6. *Nature* **1988**, *336*, 487–489.
210. Lim, L.; Manser, E.; Leung, T.; Hall, C. Regulation of phosphorylation pathways by p21 GTPases: The p21 Ras-related Rho subfamily and its role in phosphorylation signaling pathways. *Eur. J. Biochem*. **1996**, *242*, 171–185.
211. Monick, M.M.; Powers, L.; Butler, N.; Yarovinsky, T.; Hunninghake, G.W. Interaction of matrix with integrin receptors is required for optimal LPS-induced MAP kinase activation. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2002**, *283*, 390–402.
212. Akimoto, S.; Mitsumata, M.; Sasaguri, T.; Yoshida, Y. Laminar shear stress inhibits vascular endothelial cell proliferation by inducing cyclin-dependent kinase inhibitor p21Sdi1/Cip1/Waf1. *Circ. Res.* **2000**, *86*, 185–190.
213. Lin, K.; Hsu, P.P.; Chen, B.P.; Yuan, S.; Usami, S.; Shyy, J.Y.J.; Li, Y.S.; Chien, S. Molecular mechanism of endothelial growth arrest by laminar shear stress. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 9385–9389.
214. Nagel, T.; Resnick, N.; Dewey, C.F.; Jr.; Gimbrone, M.A., Jr. Vascular endothelial cells respond to spatial gradients in fluid shear stress by enhanced activation of transcription factors. *Arterioscler. Thromb. Vasc. Biol.* **1999**, *19*, 1825–1834.
215. Chiu, J.J.; Chen, L.J.; Chang, S.F.; Lee, P.L.; Lee, C.I.; Tsai, M.C.; Lee, D.Y.; Hsieh, H.P.; Usami, S.; Chien, S. Shear stress inhibits smooth muscle cell-induced inflammatory gene expression in endothelial cells: Role of NF-{kappa}B. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 963–969.
216. Cenni, E.; Granchi, D.; Verri, E.; Remiddi, G.; Cavedagna, D.; Di Leo, A. Evaluation of endothelial cell integrins after *in vitro* contact with polyethylene terephthalate. *J. Mater. Sci.—Mater. M.* **2001**, *12*, 345–349.

217. Pu, F.R.; Williams, R.L.; Markkula, T.K.; Hunt, J.A. Effects of plasma treated PET and PTFE on expression of adhesion molecules by human endothelial cells *in vitro*. *Biomaterials* **2002**, *23*, 2411–2428.
218. van der Zijpp, Y.J.; Poot, A.A.; Feijen, J. ICAM-1 and VCAM-1 expression by endothelial cells grown on fibronectin-coated TCPS and PS. *J. Biomed. Mater. Res. A* **2003**, *65*, 51–59.
219. O'Keeffe, L.M.; Muir, G.; Piterina, A.V.; McGloughlin, T.M. Vascular cell adhesion molecule-1 expression in endothelial cells exposed to physiological coronary wall shear stresses. *J. Biomech. Eng.—T. ASME* **2009**, *131*, 081003–081009.
220. Aro, H. Effect of nerve injury on fracture healing. Callus formation studied in the rat. *Acta Orthop. Scand*. **1985**, *56*, 233–237.
221. Lambiase, A.; Manni, L.; Bonini, S.; Rama, P.; Micera, A.; Aloe, L. Nerve growth factor promotes corneal healing: Structural, biochemical, and molecular analyses of rat and human corneas. *Invest. Ophthalmol. Vis. Sci*. **2000**, *41*, 1063–1069.
222. Cowen, T.; Burnstock, G. Quantitative analysis of the density and pattern of adrenergic innervation of blood vessels. A new method. *Histochemistry* **1980**, *66*, 19–34.
223. Crick, S.J.; Wharton, J.; Sheppard, M.N.; Royston, D.; Yacoub, M.H.; Anderson, R.H.; Polak, J.M. Innervation of the human cardiac conduction system. A quantitative immunohistochemical and histochemical study. *Circulation* **1994**, *89*, 1697–1670.
224. Cowen, T.; MacCormick, D.E.M.; Toff, W.D.; Burnstock, G.; Lumley, J.S.P. The effect of surgical procedures on blood vessel innervation a fluorescence histochemical study of degeneration and regrowth of perivascular adrenergic nerves. *Blood Vessels* **1982**, *19*, 65–78.
225. Head, R.J. Hypernoradrenergic innervation and vascular smooth muscle hyperplastic change. *Blood Vessels* **1991**, *28*, 173–178.
226. Autiero, M.; De Smet, F.; Claes, F.; Carmeliet, P. Role of neural guidance signals in blood vessel navigation. *Cardiovasc. Res*. **2005**, *65*, 629–638.
227. Carmeliet, P.; Tessier-Lavigne, M. Common mechanisms of nerve and blood vessel wiring. *Nature* **2005**, *436*, 193–200.
228. Raab, S.; Plate, K.H. Different networks, common growth factors: Shared growth factors and receptors of the vascular and the nervous system. *Acta Neuropathol.* **2007**, *113*, 607–626.
229. Yoshida, K.; Okamura, T.; Kimura, H.; Bredt, D.S.; Snyder, S.H.; Toda, N. Nitric oxide synthase-immunoreactive nerve fibers in dog cerebral and peripheral arteries. *Brain Res.* **1993**, *629*, 67–72.
230. Auger, F.A.; D'Orléans-Juste, P.; Germain, L. Adventitia contribution to vascular contraction: Hints provided by tissue-engineered substitutes. *Cardiovasc. Res*. **2007**, *75*, 669–678.
231. Gutterman, D.D. Adventitia-dependent influences on vascular function. *Am. J. Physiol.* **1999**, *277*, 1265–1272.
232. van Brummelen, P.; Jie, K.; van Zwieten, P.A. Alpha-adrenergic receptors in human blood vessels. *Br. J. Clin. Pharmacol*. **1986**, *21*, 33–39.
233. Vanhoutte, P.M. Endothelial adrenoceptors. *J. Cardiovasc. Pharm*. **2001**, *38*, 796–808.
234. Tsuru, H.; Tanimitsu, N.; Hirai, T. Role of perivascular sympathetic nerves and regional differences in the features of sympathetic innervation of the vascular system. *Jpn. J. Pharmacol*. **2002**, *88*, 9–13.

235. Tsuru, H. The diversity of autonomic innervation in the vascular system. *Autonomic Nervous System* **1999**, *36*, 119–125.
236. Bevan, J.A. Some bases of differences in vascular response to sympathetic activity. *Circ. Res.* **1979**, *45*, 161–171.
237. Bevan, R.D.; Clementson, A.; Joyce, E.; Bevan, J.A. Sympathetic denervation of resistance arteries increases contraction and decreases relaxation to flow. *Am. J. Physiol. Heart Circ. Physiol.* **1993**, *264*, 490–494.
238. Meagher, S.; McGeachie, J.; Prendergast, F. Vein to artery grafts. An experimental study of reinnervation of the graft wall. *Ann. Surg.* **1984**, *200*, 153–158.
239. Hoch, J.R.; Stark, V.K.; Turnipseed, W.D. The temporal relationship between the development of vein graft intimal hyperplasia and growth factor gene expression. *J. Vasc. Surg.* **1995**, *22*, 51–58.
240. Reuthebuch, O.T.; Kadner, A.; Lachat, M.L.; Turina, M.I. Graft occlusion after deployment of the symmetry bypass system. *Ann. Thorac. Surg*. **2003**, *75*, 1626–1629.
241. Alimi, Y.; Juhan, C.; Morati, N.; Girard, N.; Cohen, S. Dilation of woven and knitted aortic prosthetic grafts: CT scan evaluation. *Ann. Vasc. Surg.* **1994**, *8*, 238–242.
242. Kropp, B.P.; Sawyer, B.D.; Shannon, H.E.; Rippy, M.K.; Badylak, S.F.; Adams, M.C.; Keating, M.A.; Rink, R.C.; Thor, K.B. Characterization of small intestinal submucosa regenerated canine detrusor: assessment of reinnervation, *in vitro* compliance and contractility. *J. Urol.* **1996**, *156*, 599–607.
243. Kropp, B.P.; Rippy, M.K.; Badylak, S.F.; Adams, M.C.; Keating, M.A.; Rink, R.C.; Thor, K.B. Regenerative urinary bladder augmentation using small intestinal submucosa: Urodynamic and histopathologic assessment in long-term canine bladder augmentations. *J. Urol.* **1996**, *155*, 2098–2104.
244. Vaught, J.D.; Kropp, B.P.; Sawyer, B.D.; Rippy, M.K.; Badylak, S.F.; Shannon, H.E.; Thor, K.B. Detrusor regeneration in the rat using porcine small intestinal submucosal grafts: Functional innervation and receptor expression. *J. Urol.* **1996**, *155*, 374–378.
245. Ciardelli, G.; Chiono, V. Materials for peripheral nerve regeneration. *Macromol. Biosci.* **2006**, *6*, 13–26.
246. Crouzier, T.; McClendon, T.; Tosun, Z.; McFetridge, P.S. Inverted human umbilical arteries with tunable wall thicknesses for nerve regeneration. *J. Biomed. Mater. Res. A* **2009**, *89*, 818–828.
247. Hadlock, T.A.; Sundback, C.A.; Hunter, D.A.; Vacanti, J.P.; Cheney, M.L. A new artificial nerve graft containing rolled Schwann cell monolayers. *Microsurgery* **2001**, *21*, 96–101.
248. Su, Y.; Zeng, B.F.; Zhang, C.Q.; Zhang, K.G.; Xie, X.T. Study of biocompatibility of small intestinal submucosa (SIS) with Schwann cells *in vitro*. *Brain Res.* **2007**, *11*, 41–47.
249. Aumailley, M.; El Khal, A.; Knöss, N.; Tunggal, L. Laminin 5 processing and its integration into the ECM. *Matrix Biol.* **2003**, *22*, 49–54.
250. Armstrong, S.J.; Wiberg, M.; Terenghi, G.; Kingham, P.J. ECM molecules mediate both Schwann cell proliferation and activation to enhance neurite outgrowth. *Tissue Eng.* **2007**, *13*, 2863–2870.

251. Matesz, C.; Modis, L.; Halasi, G.; Szigeti, Z.M.; Felszeghy, S.; Bacskai, T.; Szekely, G. Extracellular matrix molecules and their possible roles in the regeneration of frog nervous system. *Brain Res. Bull.* **2005**, *66*, 526–531.
252. Ranieri, J.P.; Bellamkonda, R.; Bekos, E.J.; Gardella, J.A., Jr.; Mathieu, H.J.; Ruiz, L.; Aebischer, P. Spatial control of neuronal cell attachment and differentiation on covalently patterned laminin oligopeptide substrates. *Int. J. Dev. Neurosci.* **1994**, *12*, 725–735.
253. Reichardt, L.F.; Tomaselli, K.J. Extracellular matrix molecules and their receptors: Functions in neural development. *Annu. Rev. Neurosci.* **1991**, *14*, 531–570.
254. McFetridge, P.S.; Daniel, J.W.; Bodamyali, T.; Horrocks, M.; Chaudhuri, J.B. Preparation of porcine carotid arteries for vascular tissue engineering applications. *J. Biomed. Mater. Res. A* **2004**, *70*, 224–234.
255. Grauss, R.W.; Hazekamp, M.G.; Oppenhuizen, F.; van Munsteren, C.J.; Gittenberger-de Groot, A.C.; DeRuiter, M.C. Histological evaluation of decellularised porcine aortic valves: Matrix changes due to different decellularisation methods. *Eur. J. Cardiothorac Surg.* **2005**, *27*, 566–571.
256. Schenke-Layland, K.; Vasilevski, O.; Opitz, F.; König, K.; Riemann, I.; Halbhuber, K.J.; Wahlers, T.H.; Stock, U.A. Impact of decellularisation of xenogenetic tissue on extracellular matrix integrity for tissue engineering of heart valves. *J. Struct. Biol.* **2003**, *143*, 201–208.
257. Spark, J.I.; Yeluri, S.; Derham, C.; Wong, Y.T.; Leitch, D. Incomplete cellular depopulation may explain the high failure rate of bovine ureteric grafts. *Br. J. Surg*. **2008**, *95*, 582–585.
258. Gratzer, P.F.; Harrison, R.D.; Woods, T. Matrix alteration and not residual sodium dodecyl sulfate cytotoxicity affects the cellular repopulation of a decellularized matrix. *Tissue Eng.* **2006**, *12*, 2975–2983.
259. Korossis, S.A.; Wilcox, H.E.; Watterson, K.G.; Kearney, J.N.; Ingham, E.; Fisher, J. *In-vitro* assessment of the functional performance of the decellularized intact porcineaortic root. *J. Heart Valve Dis.* **2005**, *14*, 408–421.
260. Gilbert, T.W.; Freund, J.M.; Badylak, S.F. Quantification of DNA in biologic scaffold materials. *J. Surg. Res*. **2008**, *152*, 135–139.
261. Daly, K.; Stewart-Akers, A.; Hara, H.; Ezzelarab, M.; Long, C.; Cordero, K.; Johnson, S.; Ayares, D.; Cooper, D.; Badylak, S.F. Effect of the αGal epitope on the response to small intestinal submucosa extracellular matrix in a nonhuman primate model. *Tissue Eng. Part A* **2009**, in press.
262. Seebacher, G.; Grasl, C.; Stoiber, M.; Rieder, E.; Kasimir, M.T.; Dunkler, D.; Simon, P.; Weigel, G.; Schima, H. Biomechanical properties of decellularized porcine pulmonary valve conduits. *Artif. Organs* **2008**, *32*, 28–35.
263. Herijgers, P.; Ozaki, S.; Verbeken, E.; van Lommel, A.; Ràcz, R.; Zietkiewicz, M.; Perek, .B; Flameng, W. Calcification characteristics of porcine stentless valves injuvenile sheep. *Eur. J. Cardiothorac Surg*. **1999**, *15*, 134–142.
264. Hopkins, R.A.; Jones, A.L.; Wolfinbarger, L.; Moore, M.A.; Bert, A.A.; Lofland, G.K. Decellularization reduces calcification while improving both durability and 1-year functional results of pulmonary homograft valves in juvenile sheep. *J. Thorac. Cardiovasc. Surg*. **2009**, *137*, 907–913.

265. Woods, A.M.; Rodenberg, E.J.; Hiles, M.C.; Pavalko, F.M. Improved biocompatibility of small intestinal submucosa (SIS) following conditioning by human endothelial cells. *Biomaterials* **2004**, *25*, 515–525.
266. Ball, P. Natural strategies for the molecular engineer. *Nanotechnology* **2002**, *13*, 15–28.
267. Hu, L.; Hu, Z.; Wang, S. Progress in genetic modification of vascular prostheses and its significance in molecular reconstruction. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi.* **2008**, *22*, 1501–1504.
268. Baker, A.H. Designing gene delivery vectors for cardiovascular gene therapy. *Prog. Biophys. Mol. Biol.* **2004**, *84*, 279–299.
269. Hay, C.M.; De Leon, H.; Jafari, J.D.; Jakubczak, J.L.; Mech, C.A.; Hallenbeck, P.L.; Powell, S.K.; Liau, G.; Stevenson, S.C. Enhanced gene transfer to rabbit jugular veins by an adenovirus containing a cyclic RGD motif in the HI loop of the fiber knob. *J. Vasc. Res.* **2001**, *38*, 315–323.
270. Tiera, M.J.; Winnik, F.O.; Fernandes, J.C. Synthetic and natural polycations for gene therapy: State of the art and new perspectives. *Curr. Gene. Ther.* **2006**, *6*, 59–71.
271. Li, J.M.; Collins, L.; Zhang, X.; Gustafsson, K.; Fabre, J.W. Efficient gene delivery to vascular smooth muscle cells using a nontoxic, synthetic peptide vector system targeted to membrane integrins: A first step toward the gene therapy of chronic rejection. *Transplantation* **2000**, *70*, 1616–1624.
272. Corchero, J.L.; Villaverde, A. Biomedical applications of distally controlled magnetic nanoparticles. *Trends Biotechnol.* **2009**, *8*, 468–476.
273. Zhao, X.; Pan, F.; Holt, C.M.; Lewis, A.L.; Lu, J.R. Controlled delivery of antisense oligonucleotides: A brief review of current strategies. *Expert Opin. Drug Deliv.* **2009**, *6*, 673–686.
274. Xu, G.; Zhang, N. Nanoparticles for gene delivery: A brief patent review. *Recent Pat. Drug Deliv. Formul.* **2009**, *3*, 125–136.
275. Nam, H.Y.; Park, J.H.; Kim, K.; Kwon, I.C.; Jeong, S.Y. Lipid-based emulsion system as non-viral gene carriers. *Arch. Pharm. Res.* **2009**, *32*, 639–646.
276. Singh, R.; Kostarelos, K. Designer adenoviruses for nanomedicine and nanodiagnostics. *Trends Biotechnol*. **2009**, *27*, 220–229.
277. Paleos, C.M.; Tziveleka, L.A.; Sideratou, Z.; Tsiourvas, D. Gene delivery using functional dendritic polymers. *Expert Opin. Drug Deliv.* **2009**, *6*, 27–38.
278. Glickson, J.D.; Lund-Katz, S.; Zhou, R.; Choi, H.; Chen, I.W.; Li, H.; Corbin, I.; Popov, A.V.; Cao, W.; Song, L.; Qi, C.; Marotta, D.; Nelson, D.S.; Chen, J.; Chance, B.; Zheng, G. Lipoprotein nanoplatform for targeted delivery of diagnostic and therapeutic agents. *Adv. Exp. Med. Biol.* **2009**, *645*, 227–239.
279. Wang, V.; Wu, W. MicroRNA-based therapeutics for cancer. *BioDrugs* **2009**, *23*, 15–23.
280. Mykhaylyk, O.; Zelphati, O.; Hammerschmid, E.; Anton, M.; Rosenecker, J.; Plank, C. Recent advances in magnetofection and its potential to deliver siRNAs *in vitro*. *Methods Mol. Biol.* **2009**, *487*, 111–146.
281. Stone, P.J.; Morris, S.M.; Griffin, S.; Mithieux, S.; Weiss, A.S. Building Elastin. Incorporation of recombinant human tropoelastin into extracellular matrices using nonelastogenic rat-1 fibroblasts as a source for lysyl oxidase. *Am. J. Respir. Cell Mol. Biol.* **2001**, *24*, 733–739.

282. Kallenbach, K.; Salcher, R.; Heim, A.; Karck, M.; Mignatti, P.; Haverich, A. Inhibition of smooth muscle cell migration and neointima formation in vein grafts by overexpression of matrix metalloproteinase-3. *J. Vasc. Surg.* **2009**, *49*, 750–758.
283. Li, S.F.; Meng, Q.H.; Yao, W.C.; Hu, G.J.; Li, G.L.; Li, Z.J.; Wei, J.J.; Bo, Y.L.; Zhang, Z.H.; Wang, R.Z. Recombinant AAV1 mediated vascular endothelial growth factor gene expression promotes angiogenesis and improves neural function: Experiment with rats. *Zhonghua Yi Xue Za Zhi* **2009**, *89*, 167–170.
284. Callanan, A.; Morris, L.; McGIoughlin, T.M.; Gilbert, T.W.; Badylak, S.F. Regulation of MMP‘s in endothelial cell-seeded UBM extracellular matrix under shear. In *Proceedings of the Tissue Engineering Regenerative Medicine International Society (TERMIS) EU Chapter Meeting*, London, UK, September 4–7, 2007.
285. Gilbert, T.W.; Stewart-Akers, A.M.; Sydeski, J.; Nguyen, T.D.; Badylak, S.F.; Woo, S.L.Y. Gene expression by fibroblasts seeded on small intestinal submucosa and subjected to cyclic stretching. *Tissue Eng.* **2007**, *13*, 1313–1323.
286. Shaikh, F.M.; O'Brien, T.P.; Callanan, A.; Kavanagh, E.G.; Burke, P.E.; Grace, P.A.; McGloughlin, T.M. New pulsatile hydrostatic pressure bioreactor for vascular tissue-engineered constructs. *Artif. Organs* **2009**, in press.
287. Isenberg, B.C.; Williams, C.; Tranquillo, R.T. Small-diameter Artificial arteries engineered *in vitro*. *Circ. Res.* **2006**, *98*, 25–35.
288. Stankus, J.J.; Freytes, D.O.; Badylak, S.F.; Wagner, W.R. Hybrid nanofibrous scaffolds from electrospinning of a synthetic biodegradable elastomer and urinary bladder matrix. *J. Biomater.Sci. Polym. Ed.* **2008**, *19*, 635–652.
289. Courtney, T.; Sacks, M.S.; Stankus, J.; Guan, J.; Wagner, W.R. Design and analysis of tissue engineering scaffolds that mimic soft tissue mechanical anisotropy. *Biomaterials* **2006**, *27*, 3631–3638.
290. Freytes, D.O.; Rundell, A.E.; vande Geest, J.; Vorp, D.A.; Webster, T.J.; Badylak, S.F. Analytically derived material properties of multilaminated extracellular matrix devices using the ball-burst test. *Biomaterials* **2005**, *26*, 5518–5531.
291. Zeugolis, D.I.; Khew, S.T.; Yew, E.S.Y.; Ekaputra, A.K.; Tong, Y.W.; Yung, L.-Y.L.; Hutmacher, D.W.; Sheppard, C.; Raghunath, M. Electro-spinning of pure collagen nano-fibres—Just an expensive way to make gelatin. *Biomaterials* **2008**, *29*, 2293–2305.
292. Min, L.; Paul, C.Y.C.; James, C.Y.D. Evaluation of small intestinal submucosa as scaffoldsfor intestinal tissue engineering. *J. Surg. Res.* **2008**, *147*, 168–171.
293. Lutolf, M.P.; Hubbell, J.A. Synthetic biomaterials as cell-responsive artificial extracellular matrices. In *Advances in Tissue Engineering*, 2nd ed.; Polak, J., Mantalaris, S., Harding, S.E., Eds.; Imperial College Press: London, UK, 2007, pp. 154–196.
294. Ruoslahti, E.; Reed, J. Cell adhesion: New way to activate caspases. *Nature* **1999**, *397*, 479–480.
295. Lauer-Fields, J.; Nagase, H.; Fields, G. Selective hydrolysis of triple-helical peptides by matrix metalloproteinases. In *Peptides for the New Millennium*; Kluwer Academic Publisher, Springer: New York, NY, USA, 2000; pp. 342–343.

296. Zhang, Y.; He, Y.; Bharadwaj, S.; Hammam, N.; Carnagey, K.; Myers, R.; Atala, A.; van Dyke, M. Tissue-specific extracellular matrix coatings for the promotion of cell proliferation and maintenance of cell phenotype. *Biomaterials* **2009**, *30*, 4021–4028.
297. Thomas, A.C.; Campbell, G.R; Campbell, J.H. Advances in vascular tissue engineering. *Cardiovasc. Pathol.* **2003**, *12*, 271–276.
298. Swartz, D.D.; Russell, J.A.; Andreadis, S.T. Engineering of fibrin-based functional and implantable small-diameter blood vessels. *Am. J. Physiol. Heart Circ. Physiol.* **2005**, *288*, 1451–1460.
299. Lamm, P.; Adelhard, K.; Juchem, G.; Weitkunatb, R.; Milzc, S.; Kilgerd, E.; Gotzd, A.; Reicharta, B. Fibrin glue in coronary artery bypass grafting operations: Casting out the Devil with Beelzebub? *Eur. J. Cardiothorac Surg.* **2007**, *32*, 567–572.
300. Aldenhoff, Y.B.; van Der Veen, F.H.; ter Woorst, J. Performance of a polyurethane vascular prosthesis carrying a dipyridamole (Persantin) coating on its lumenal surface. *J. Biomed. Mater. Res.* **2001**, *54*, 224–233.
301. Walpoth, B.H.; Rogulenko, R.; Tikhvinskaia, E.; Gogolewski, S., Schaffner, T.; Hess, O.M.; Althaus, U. Improvement of patency rate in heparin-coated small synthetic vascular grafts. *Circulation* **1998**, *98*, 319–323.
302. Nerem, R.M.; Seliktar, D. Vascular tissue engineering. *Annu. Rev. Biomed. Eng*. **2001**, *3*, 225–243.
303. Stitzel, J.; Liu, J.; Lee, S.J.; Komura, M.; Berry, J.; Soker, S.; Lim, G.; van Dyke, M.; Czerw, R.; Yoo, J.J.; Atala, A. Controlled fabrication of a biological vascular substitute. *Biomaterials* **2006**, *27*, 1088–1094.
304. Tillman, B.W.; Yazdani, S.K.; Lee, S.J.; Geary, R.L.; Atala, A.; Yoo, J.J. The *in vivo* stability of electrospun polycaprolactone-collagen scaffolds in vascular reconstruction. *Biomaterials* **2009**, *30*, 583–588.

© 2009 by the authors; licensee Molecular Diversity Preservation International, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).