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## Nanomaterials for small diameter vascular grafts: overview and outlook

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Small-diameter vascular grafts (SDVGs) cannot meet current clinical demands owing to their suboptimal long-term patency rate. Various materials have been employed to address this issue, including nanomaterials (NMs), which have demonstrated exceptional capabilities and promising application potentials. In this review, the utilization of NMs in different forms, including nanoparticles, nanofibers, and nanofilms, in the SDVG field is discussed, and future perspectives for the development of NM-loading SDVGs are highlighted. It is expected that this review will provide helpful information to scholars in the innovative interdisciplinary of cardiovascular disease treatment and NM.

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### Introduction

The fast-developing era has witnessed the prevalence of cardiovascular diseases (CVDs), mostly originating from unhealthy lifestyles. CVDs have become the leading cause of global mortality and morbidity, heavily burdening society and patient families.<sup>1</sup> A consensus has been reached that maintaining a healthy lifestyle greatly benefits the prevention and control of the onset and progression of CVDs, while appropriate medical measures should be taken for people based on the progressive stages of diseases, including drug medication, interventional therapy, and vascular replacement.<sup>1,2</sup> In the suffering populations, one that should be of special concern is those who urgently need small-diameter vascular grafts (SDVGs) with an inner diameter of less than or equal to 6 mm to save their lives because this kind of graft on demand is still considerably insufficient in quantity.<sup>3</sup>

Every year, more than 1 million people urgently need SDVG surgeries globally to cure severe CVDs, such as coronary/carotid

artery diseases, critical limb ischemia, and vascular trauma.<sup>4</sup> The current gold standard for the treatment is grafting autologous vessels in which the great saphenous veins, internal mammary arteries, and radial arteries are mostly used.<sup>4</sup> However, over 30% of these people cannot obtain their arteries/veins because of old age, existing diseases (*e.g.*, diabetes mellitus), vascular injuries, secondary vascular acquisition, and other reasons. In this context, pioneers have employed VGs as substitutions for natural blood vessels. Unlike large diameter VGs with an inner diameter larger than 6 mm used to replace large vessels (*e.g.*, aorta) prepared by materials, such as ePTFE or PET, their small diameter counterparts with the same materials tend to have stenosis or occlusion.<sup>3,4</sup> This is mainly attributed to the fact that slow blood flow in small vessels makes thrombogenic chemicals and cells more prone to aggregate on the lumen. Additionally, SDVGs experience complex biochemical and biomechanical environments under a blood flowing physiological condition, further increasing their challenges in maintaining long-term patency.

To date, substantial advances have been made in the development of an eligible SDVG.<sup>5</sup> Nonetheless, the venue for success is rather slushy, and only few have crossed pre-clinical stages to enter clinical trials, yet none of them have hit the market so far.<sup>5</sup> The main reasons are ascribed to thrombus formation, intimal hyperplasia (IH), and mechanical mismatches.<sup>6</sup> Intensive strategies have been adopted to resolve or mitigate these issues, such as surface modification, cell coverage, and new substrate material usage.<sup>7</sup> With the advancement of nanotechnology, NMs have entered the horizons of SDVG researchers and have exhibited enormous potential to improve SDVG performance.<sup>8</sup> NMs are a set of materials with a scale ranging from one to several hundred nanometers in at least one dimension. They represent a cutting-edge direction of materials whose attractive properties include a high surface-to-volume ratio, high

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adsorption, and high reactive/catalytic activity, basically stemming from their ultra-small scale.<sup>9</sup> NMs with various forms in shape, such as particles, fibers, and films, can be distinct in derivations from the inorganically synthetic to the organically synthetic and to the biological, such as AuNPs, PLGA NPs, and EVs. Various NMs have enhanced the performance of SDVGs by their beneficial functions,<sup>8</sup> which include improving EC adhesion, regulating inflammation, mimicking vascular ECM, controllably releasing vasoactive drugs, and refining mechanical properties. Although the application of NMs in SDVGs is generally underexplored, they have shown great promise in boosting the development of SDVGs. In this review, we summarize the state-of-the-art applications of NMs in SDVGs and discuss future perspectives of this new field.

## Application of nanomaterials in SDVGs

To date, various types of NMs have been employed to improve the performance of SDVGs (Fig. 1 and Table 1).<sup>8</sup> Grossly classified by the nano-scale dimensions that the materials possess, they include nanoparticles (NPs), nanofibers, and nanofilms. NPs, also called zero dimensional (0D) NMs, have three dimensions (anterior-posterior, left-right, up-down directions) in a nano scale; nanofibers, also called one dimensional (1D) NMs, have two dimensions in a nano scale but the third in a micro/macro scale, which typically form interconnected mats or matrices; nanofilms,

also called two dimensional (2D) NMs, have only one dimension in a nano scale yet the other two in micro/macro. In this section, we summarize the progress of representative NMs that have been applied to fabricate SDVGs (vascular patches with similar application scenarios are also included).

### Nanoparticles

NPs used in SDVGs can be synthetic or biological in origin and are inorganic or organic in composition. The inorganically synthetic ones include metallic NPs (*e.g.*, AuNPs), metallic oxide NPs (*e.g.*, Fe<sub>3</sub>O<sub>4</sub> NPs, ZnO NPs, and BaTiO<sub>3</sub> NPs), and inorganic nonmetal NPs (*e.g.* carbon nanotubes (CNTs)). The organically synthetic ones mainly contain polymeric NPs (*e.g.*, PLGA NPs and poly(propylacrylic acid) NPs) and micelles (*e.g.*, L-lactic acid oligomer (Lo)-grafted gelatin micelles). The biological ones used in SDVGs are specifically referred to as EVs in this review.

### Gold NPs

Gold NPs (AuNPs), usually existing stably in the form of colloidal suspension in aqueous solutions, are a kind of noble metallic NM that may be prepared using various methods, including sodium citrate reduction, crystal seed growth, and electrochemistry. Owing to their unique physicochemical properties, they have been extensively used in biomedicine.<sup>10,11</sup> In tissue engineering (TE), AuNPs are typically incorporated

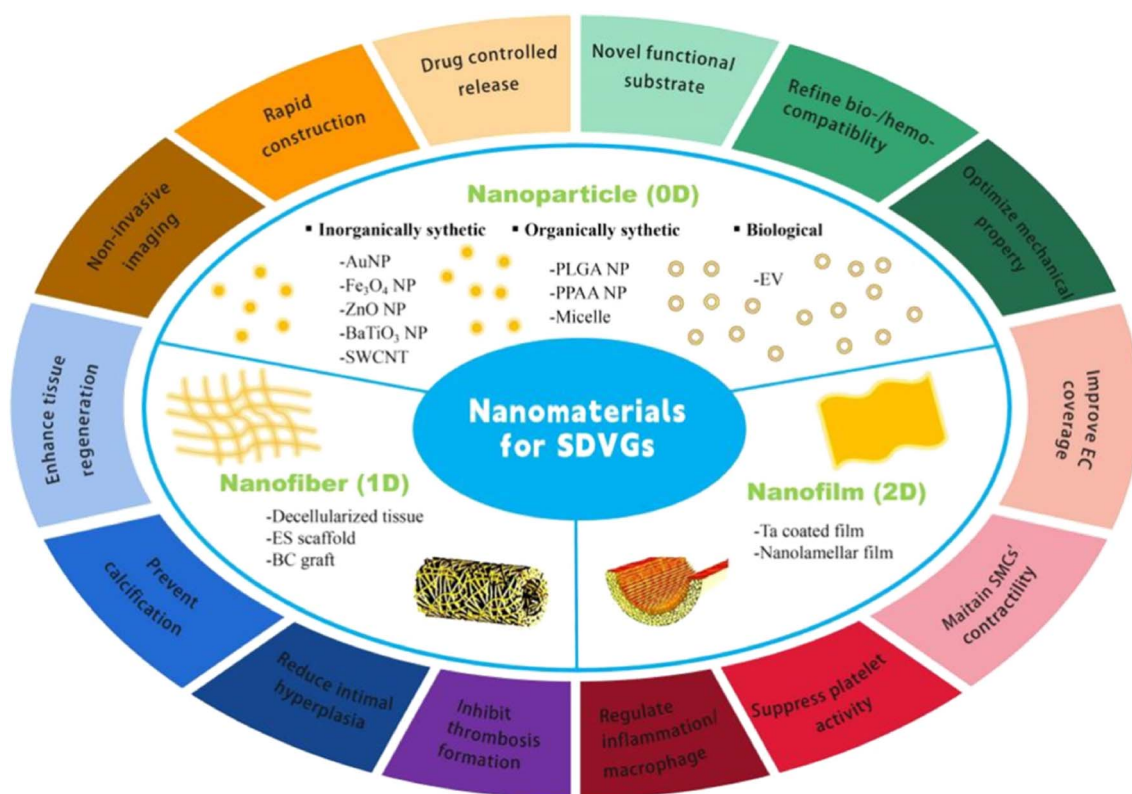


Fig. 1 NMs for SDVGs. The figure shows major examples of representative NMs employed in SDVGs and their beneficial functions. According to the nano-scale dimensions that the materials possess, they can be categorized into NPs, nanofibers, and nanofilms. NPs have all three dimensions in nano scales, called 0D NMs. Nanofibers have two dimensions in nano scales but the third in micro/macro called 1D NMs. Nanofilms have only one dimension on a nano scale, yet the other two in micro/macro, called 2D NMs.





Table 1 NMs in SDVG applications

VG No.	NM-bearing VG constitution	VG assessment stage	Merits of NMs	Flaws or needed improvement of NMs	Ref.
1	AuNP bearing decellularized porcine aorta	Longitudinal arteriotomy model of pig for 2 to 6 months	<ul style="list-style-type: none"> <li>● AuNP</li> <li>- Minor inflammation</li> <li>- Enhanced EC and SMC regeneration</li> <li>● Decellularized tissue nanofiber</li> <li>- Biomimetic and high biocompatibility</li> <li>- Easy-to-fabricate</li> <li>- Abundant-in-source</li> <li>- Off-the-shelf and non-invasive acquisition of xenogenous VGs</li> <li>- Mildly invasive for autologous VGs</li> <li>● Fe<sub>3</sub>O<sub>4</sub> NP</li> <li>- Superparamagnetic</li> <li>- Homogeneous and rapid cell layer formation and biomimetic multi-layer VG construction</li> <li>- Noninvasive imaging of cell distribution</li> <li>● ZnO NP</li> <li>- Economic- and biomedical-friendly</li> <li>- Promoted HUVEC adhesion and proliferation</li> <li>- Enhanced subcutaneous angiogenesis</li> <li>- ROS production</li> <li>● ES P(VDF-TrFE) nanofiber</li> <li>- Low cost, controllable parameter, simple equipment, and scalable</li> <li>- ECM-like substrates</li> <li>- Piezoelectric</li> <li>● BaTiO<sub>3</sub> NP</li> <li>- High biocompatibility, non-linear optical property, piezoelectric property, drug loading capacity, and elasticity</li> <li>- Refined mechanical property of VG</li> </ul>	<ul style="list-style-type: none"> <li>● AuNPs</li> <li>- Uncertain long-term metabolism behavior and safe concentration range</li> <li>- Photothermal/electronic, drug delivering and anti-bacterial ability need exploitation in VGs</li> <li>- NP size, shape and surface modification on tissue reaction need evaluation</li> <li>● Decellularized tissue nanofiber</li> <li>- Remove more immunogenic substances</li> <li>- Add pro-regenerative coatings</li> <li>- Optimize fabrication approach</li> <li>● Fe<sub>3</sub>O<sub>4</sub> NP</li> <li>- <i>In vivo</i> performance of participant VGs</li> <li>- Long-term and <i>in vivo</i> safety</li> <li>- Measures to lower the risk of toxicity</li> <li>● ZnO NP</li> <li>- Measures to lower the risk of toxicity</li> <li>- Evaluate <i>in vivo</i> reactivity related to their sizes, concentrations, and surface modifications</li> <li>● ES P(VDF-TrFE) nanofiber</li> <li>- Optimize fiber size and orientation</li> <li>- Decorate proper coatings and/or seeding cells</li> <li>- Elongated <i>in vivo</i> test</li> <li>● BaTiO<sub>3</sub> NP</li> <li>- <i>In vivo</i> performance of participant VGs</li> <li>- Exploit optical property and drug loading capacity in VGs</li> </ul>	12 and 13
2	Fe <sub>3</sub> O <sub>4</sub> NP loading HUVECs seeded on PTFE VG	<i>In vitro</i>			19
3	LbL assembles Fe <sub>3</sub> O <sub>4</sub> NPs loading vascular cell sheets	<i>In vitro</i>			20
4	Construct Fe <sub>3</sub> O <sub>4</sub> NPs loaded with vascular cell spheroids, form cell sheets, and then LbL constructs VGs	<i>In vitro</i>			21
5	ZnO NP coated P(VDF-TrFE) ES VGs	<i>In vitro</i> and subcutaneous implantation			24
6	BaTiO <sub>3</sub> NP doped PU-PDMS VGs	<i>In vitro</i>			26



Table 1 (Contd.)

VG No.	NM-bearing VG constitution	VG assessment stage	Merits of NMs	Flaws or needed improvement of NMs	Ref.
7	RSV-carrying SWCNTs coated onto the surface of rat-decellularized carotid	Rat common carotid artery replacement model for 90 days	<ul style="list-style-type: none"> <li>● SWCNT</li> <li>- Outstanding mechanical, thermal, electrical, and adsorptive properties</li> <li>- Stable coating and controlled drug release-Stabilize</li> <li>- SMCs in a contractile state</li> <li>- Transit macrophages to the M2 state</li> <li>● Decellularized tissue nanofiber</li> <li>- Idem VG No. 1</li> <li>● PLGA NP</li> </ul>	<ul style="list-style-type: none"> <li>● SWCNT</li> <li>- <i>In vivo</i> toxicity</li> <li>- Exploit mechanical, thermal, and electrical properties in VGs</li> <li>● Decellularized tissue nanofiber</li> <li>- Idem VG No. 1</li> </ul>	29
8	Covalently immobilize FD-loaded PLGA NPs on ePTFE VGs	<i>In vitro</i>	<ul style="list-style-type: none"> <li>- FDA-approved</li> <li>- Excellent biocompatibility, biodegradability, non-immunogenicity, and drug-loading ability</li> <li>- Stable immobilization on VGs</li> </ul>	<ul style="list-style-type: none"> <li>● PLGA NP</li> <li>- Elongated <i>in vivo</i> test</li> <li>- Improve drug loading efficiency</li> </ul>	32
9	Coat miR-145 loading PLGA NPs on rabbit jugular veins	Rabbit carotid artery replacement model for 2 weeks	<ul style="list-style-type: none"> <li>● PLGA NP</li> <li>- Idem VG No. 8</li> <li>- Controlled release of miR-145</li> <li>- Stabilize SMCs' contractile phenotype-inhibit IH</li> <li>● Decellularized tissue nanofiber</li> <li>- Idem VG No. 1</li> <li>● PPAA NP</li> </ul>	<ul style="list-style-type: none"> <li>● PLGA NP</li> <li>- Idem VG No. 8</li> <li>● Decellularized tissue nanofiber</li> <li>- Idem VG No. 1</li> </ul>	33 and 34
10	MK2i loading PPAA NPs coated on fresh rabbit external jugular veins	Rabbit common carotid artery replacement model for 4 weeks	<ul style="list-style-type: none"> <li>- Superior biocompatibility and drug carrying ability</li> <li>- pH-dependent membrane disruptive activity</li> <li>- Increase MK2i cellular uptake</li> <li>- Loaded MK2i peptides have anti-inflammatory, anti-migratory, and anti-proliferating properties</li> <li>- Triggered the signalling of inflammation and proliferation inhibition</li> <li>- Strong reduction in IH</li> </ul>	<ul style="list-style-type: none"> <li>● PPAA NP</li> <li>- Reduced EC coverage</li> <li>- Undesirable hemolysis</li> <li>- Establish-optimized concentration in VGs</li> <li>- Broaden pH-responsive range by molecular structure design</li> </ul>	36



Table 1 (Contd.)

VG No.	NM-bearing VG constitution	VG assessment stage	Merits of NMs	Flaws or needed improvement of NMs	Ref.
11	Bilayered vascular patch; outer layer: SF/gelatin hydrogel; inner layer: SMV-loaded micelles in gelatin hydrogel	Rat carotid artery replacement model for 2 weeks	<ul style="list-style-type: none"> <li>● Micelle</li> <li>- Excellent drug carriers</li> <li>- Lower blood lipids, promote EPC adhesion and proliferation</li> <li>- Inhibit SMC migration and proliferation</li> <li>- Rapid endothelialization</li> <li>● EV</li> </ul>	<ul style="list-style-type: none"> <li>● Micelle</li> <li>- Elongated <i>in vivo</i> test</li> <li>- Optimize application conditions for each kind of micelle NP based on its carried drug and formulation</li> <li>● EV</li> </ul>	39
12	Human placental MSC-derived EV and heparin-modified ES PCL VGs	Rat abdominal artery replacement model in hyperlipidemia conditions for 3 months	<ul style="list-style-type: none"> <li>- Abundant sources, easy acquisition, ultralow immunity, high para-secretion and immunomodulation, and low ethical risk</li> <li>- Off-the-shelf</li> <li>- Improve VG patency</li> <li>- Inhibit thrombosis and calcification, enhance regeneration, and transit macrophages to the M2 state</li> <li>● ES PCL nanofiber</li> <li>- Idem VG No. 5 (except for "piezoelectric")</li> <li>● EV</li> <li>- Idem VG No. 12</li> <li>● Decellularized tissue nanofiber</li> <li>- Idem VG No. 1</li> <li>● ES PCL nanofiber</li> <li>- Idem VG No. 12</li> <li>- CNP loading showed higher EC coverage, NO production, VEGF secretion, M2-type macrophage polarization, contractile SMC transition, and ECM deposition</li> <li>- 100% patency rate</li> </ul>	<ul style="list-style-type: none"> <li>- Long-term implantation in VG</li> <li>- Detailed the therapeutic mechanism</li> <li>● ES PCL nanofiber</li> <li>- Idem VG No. 5</li> <li>- Slow degradation of PCL polymers may cause calcification and degeneration of neotissues</li> <li>● EV</li> <li>- Idem VG No. 12</li> <li>● Decellularized tissue nanofiber</li> <li>- Idem VG No. 1</li> <li>● ES PCL nanofiber</li> <li>- Idem VG No. 12</li> </ul>	42
13	Human adipose MSC-derived EV-seeded silk-based VGs	Rat aortic replacement model for 8 weeks			43
14	Decellularized fibrotic conduits with heparin coating	Carotid artery replacement model of rats for 6 months and that of mini-pigs for 1 month			49
15	CNP loaded with ES PCL VGs	Rabbit AV-shunt model for 1.5 hours and rat abdominal aorta replacement model for 1 month			56



Table 1 (Contd.)

VG No.	NM-bearing VG constitution	VG assessment stage	Merits of NMs	Flaws or needed improvement of NMs	Ref.
16	20% NaOH treatment of tubular BC hydrogel	Rat abdominal aorta replacement model for 5 months	<ul style="list-style-type: none"> <li>● BC nanofiber</li> <li>- ECM-like and high biocompatibility</li> <li>- Convenient fabrication</li> <li>- NaOH treatment improved the mechanical property, lessened platelet adhesion and activation, and promoted EC proliferation</li> <li>- Low immunity and high patency rate</li> <li>● Ta nanofilm</li> <li>- Abundant lightweight metal with considerable material strength, corrosion resistance, and biocompatibility</li> <li>- Refine hydrophobicity of the VG surface</li> <li>- Improve EC coverage, and suppress platelet adhesion/activation</li> <li>● Lamellar nanofilms</li> </ul>	<ul style="list-style-type: none"> <li>● BC nanofiber</li> <li>- Long degradation term <i>in vivo</i></li> <li>- Proper surface modification to improve its performance in VGs</li> <li>● Ta nanofilm</li> <li>- Improve rigidity, abrasive resistance, and reactivity with other metals</li> <li>● Lamellar nanofilms</li> <li>- Precise manufacturing techniques</li> <li>● ES PCL nanofiber</li> <li>- Idem VG No. 12</li> </ul>	62
17	Nano-thick Ta film on ePTFE VGs	Canine aortic replacement model for 4 weeks	<ul style="list-style-type: none"> <li>● Lamellar nanofilms</li> </ul>	<ul style="list-style-type: none"> <li>- Refine the VG surface by physical method without changing the property of materials</li> <li>- Guide EC alignment, inhibit platelet adhesion, reduce blood flow disturbance, and induce a high patency rate</li> <li>- Computer-aided design</li> <li>● ES PCL nanofiber</li> <li>- Idem VG No. 12</li> <li>- Reinforce the VG</li> </ul>	67
18	A bilayer VG, inner layer: freeze-casting SF/gelatin to form high aspect ratio lamellar nanofilms; outer layer: ES PCL	Rabbit carotid artery replacement model for 3 months	<ul style="list-style-type: none"> <li>● Lamellar nanofilms</li> </ul>	<ul style="list-style-type: none"> <li>- Refine the VG surface by physical method without changing the property of materials</li> <li>- Guide EC alignment, inhibit platelet adhesion, reduce blood flow disturbance, and induce a high patency rate</li> <li>- Computer-aided design</li> <li>● ES PCL nanofiber</li> <li>- Idem VG No. 12</li> <li>- Reinforce the VG</li> </ul>	70

into scaffold matrices to uprate scaffold performance. For VGs, it has been reported that vascular patches made of decellularized porcine aorta conjugated with mercaptoethylamine-functionalized AuNPs showed fine patency in longitudinal arteriotomy models of pigs. The AuNPs enhanced the tissue integration and EC and SMC regeneration, as well as decreased inflammation and scaffold degradation, compared with the commercially available bovine pericardium material control after the patches were implanted in carotis<sup>12</sup> or thoracic aorta<sup>13</sup> from 2 to 6 months. This is partially because AuNPs hinder collagenase binding sites.<sup>11,14,15</sup> The possible disadvantage of AuNPs in VGs may arise from their undetermined long-term metabolism behavior and safe concentration range, which needs to be determined. The utilization of AuNPs in VGs is in a very early stage because important properties, such as anti-bacteria, photothermal/electronic effect, and drug delivery of AuNPs, are still unexploited. Furthermore, AuNP sizes, shapes (e.g., nanospheres, nanorods, and nanostars), and surface modifying groups highly affect their tissue reactions, which should therefore be carefully evaluated in VG applications.

### Fe<sub>3</sub>O<sub>4</sub> NPs

Pure Fe<sub>3</sub>O<sub>4</sub> NPs, appearing as black powders, are complex ionic crystals bonded by Fe<sup>2+</sup>, Fe<sup>3+</sup>, and O<sup>2-</sup> ions. Owing to their special crystal structure, ultrasmall size, and the characteristic feature of transition metal Fe, Fe<sub>3</sub>O<sub>4</sub> NPs are famous because of their superparamagnetic properties and thus have been widely used in magnetic control and imaging in biomedicine.<sup>16–18</sup> These advantages have also shown benefits in the SDVG field. For instance, human umbilical vein endothelial cells (HUVECs) were incubated with carboxydextran-coated Fe<sub>3</sub>O<sub>4</sub> NPs and then seeded on a polytetrafluorethylene (PTFE) VG lumen homogeneously under the guidance of an annular magnetic field. In addition to the rapidness of construction, cell arrangements of the cell-seeded VG could be sensed non-invasively using magnetic resonance imaging (MRI).<sup>19</sup> In another study, vascular ECs, SMCs, and fibroblasts (FBs) were separately incubated with Fe<sub>3</sub>O<sub>4</sub> NPs encapsulated in cationic liposomes to form cell sheets on flat magnets, and then the sheets were rolled layer-by-layer around a cylindrical magnet to construct a cell distribution mimicking multilayered VG.<sup>20</sup> This method can rapidly and conveniently prepare structurally mimetic VGs. In a third study, researchers first established magnetic tissue spheroid units around 200 μm in diameter, each of which contained two coterminal domains: one was cell aggregates assembled by one type of vascular cells (ECs, SMCs, or FBs), while the other was collagen gel encapsulating Fe<sub>3</sub>O<sub>4</sub> NPs.<sup>21</sup> To rapidly complete a biomimetic VG, the magnetic units first formed flat rectangle stripes under the guidance of flat magnets, and the stripes were then wrapped layer by layer around cylinder magnets. However, all the three VGs were proof of concept models, and their *in vivo* performances had not been validated. In addition, the long-term and *in vivo* safety of Fe<sub>3</sub>O<sub>4</sub> NPs in these VGs were still questionable although a safe dose range of 10–200 μg mL<sup>-1</sup> was identified by short-time cell tests and measures; for example, separating cell and NP containing domains were used to lower the risk of toxicity in the above cases.

### ZnO NPs

ZnO NPs are nanosized hexagonal crystals with white powders, which are mainly fabricated using solid, liquid, or vapor phase methods. ZnO NPs are considered a novel type of economic- and biomedical friendly inorganic NM with broad application potentials.<sup>22,23</sup> Researchers have fabricated ZnO NP-decorated VGs rapidly using the electrospinning (ES) method when ZnO NPs are dispersed into ES solutions constituted by a piezoelectric polymer poly(vinylidene fluoridetrifluoroethylene) P(VDF-TrFE).<sup>24</sup> Below 2% concentration, ZnO NP-decorated ES VGs promote HUVEC proliferation in *in vitro* tests, and subcutaneous implantation further demonstrated that they increased microvessel formation compared to undecorated ones. The mechanism was attributed to ZnO NP-induced moderate H<sub>2</sub>O<sub>2</sub> molecule release and piezoelectric properties (the ability to transform energies between mechanical stress and electrical potential) of P(VDF-TrFE). These results demonstrate the biocompatibility and preliminary feasibility of ZnO ES VGs. However, the *in vivo* performance of VGs in vascular replacement models has not been tested. Moreover, the biochemical activity and *in vivo* reaction of ZnO NPs are highly related to their sizes, concentrations, and surface modifications, which should therefore be carefully evaluated.

### BaTiO<sub>3</sub> NPs

BaTiO<sub>3</sub> NPs, originating from a perovskite-like oxide-based elastomeric ceramic, can be prepared using coprecipitation, sol-gel, or emulsion methods. BaTiO<sub>3</sub> NPs are very promising NMs in biomedical applications owing to their high biocompatibility, non-linear optical property, piezoelectric property, drug loading capacity, and elasticity.<sup>25</sup> Hence, BaTiO<sub>3</sub> NPs are favorable for incorporating materials into VGs although currently the application of these NPs is limited. Researchers have doped glycol chitosan (GC)-coated BaTiO<sub>3</sub> NPs into VGs. Porous VGs were fabricated by phase inversion spraying of polyurethane (PU)/polydimethylsiloxane (PDMS) solutions when the NPs were dissolved in spray solutions before being doped into the microfibers that were sprayed out. Owing to the elasticity of the NPs, the mechanical property of the VGs was greatly refined.<sup>26</sup> After NP doping, the burst strength of VGs increased greatly from ~800 kPa to ~1100 kPa; the cytocompatibility with human fibroblasts was greatly improved, and the VGs acquired piezoelectric properties. These *in vitro* tests exhibited excellent potential for doped VGs, and further *in vivo* tests were warranted. In addition, the powerful advantages of BaTiO<sub>3</sub> NPs, such as their unique optical property and drug loading ability, are still underused.

### Carbon nanotubes

Single-walled carbon nanotubes (SWCNTs) are tubular nanosized graphite crystals formed by a single graphite sheet curled around the central axis at a definitive spiral angle. Their particular structure endows SWCNTs with outstanding mechanical, thermal, electrical, and adsorptive properties, making them a multifaceted material in biomedical



applications.<sup>27,28</sup> In a novel VG design, resveratrol (RSV), a star natural small molecular drug, was conjugated to SWCNTs, and the drug-carrying SWCNTs were then coated as irregular mesh onto the surface of decellularized rat carotids (Fig. 2).<sup>29</sup> During 90 days of assessment in a rat common carotid artery replacement model, the SWCNTs showed a well-controlled drug release profile and potent resistance to physiological blood flow shear. The released drug prohibited the proliferating state but stabilized the contractile state of the SMCs to reduce IH formation and sustain VG elasticity. In addition, SWCNTs engulfed by macrophages together with resveratrol released inside cells shifted the macrophage state from M1 pro-inflammatory to M2 anti-inflammatory. These overall benefits enhanced the VG patency and regeneration compared to the group without coating RSV-carrying SWCNTs, the group coated with SWCNTs without RSV carrying, and the group carrying RSV but without SWCNTs. However, as far as we know, the toxicity of SWCNTs to cells and organisms remains an unresolved issue. Additionally, valuable features of SWCNTs, including their mechanical, thermal, and electrical properties, should be developed in VG applications.

### PLGA NPs

PLGA NPs are nanoscale aggregates of PLGA polymers. They are considered the most widely applied type of organic NPs in the biomedical field and have been approved by the FDA owing to their biocompatibility, biodegradability, non-immunogenicity, and drug-loading ability.<sup>30,31</sup> PLGA NPs have shown promise in VGs. For instance, researchers covalently immobilized PLGA NPs loaded with a model molecule, fluorescein isothiocyanate-dextran (FD), on ePTFE VGs using wet chemistry.<sup>32</sup> The mobilization was blood flow resistant and promoted L929 cell adhesion and growth. This approach provided a model of drug loading PLGA for improving VG patency. To propel the application of the model, researchers further loaded microRNA-145 (miR-145) into PLGA NPs (Fig. 3), which were then coated on the jugular veins of male Japanese white rabbits to construct a new VG.<sup>33,34</sup> The miR-145 enabled the alteration of the phenotype of SMCs from proliferative states to contractile states. After the VGs were implanted into the carotid arteries of rabbits for 2 weeks, the controlled release of miR-145 from PLGA NPs stabilized the SMC contractile phenotype and suppressed SMC proliferation and inflammation, resulting in

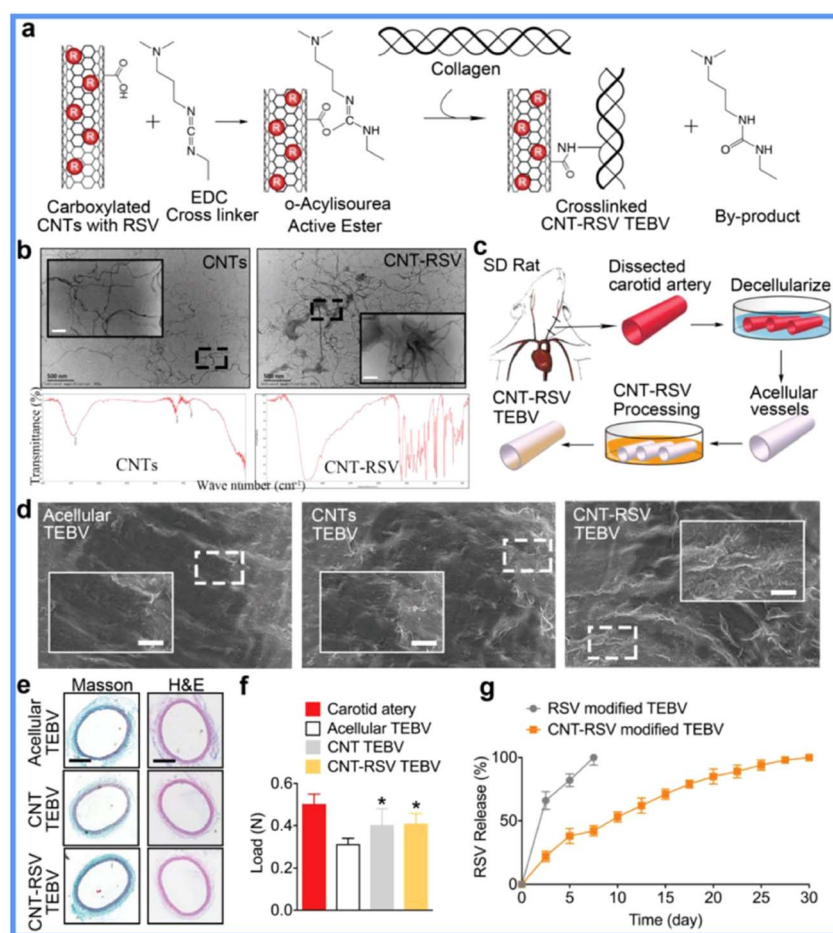


Fig. 2 Application of CNTs in SDVGs. (a) Scheme of surface modification of SDVGs with collagen and CNTs. (b) Transmission electron microscopy and infrared spectrum detection of CNTs. (c) Procedure for preparing SDVGs. (d) Scanning electron microscopy images showing the lumen of SDVGs. (e) H&E and Masson staining of SDVGs. (f) Tension test for SDVGs. (g) *In vitro* release profiles of RSV from SDVG. Reprinted with permission from ref. 29. Copyright 2018, WILEY-VCH Verlag GmbH & Co. KGaA.





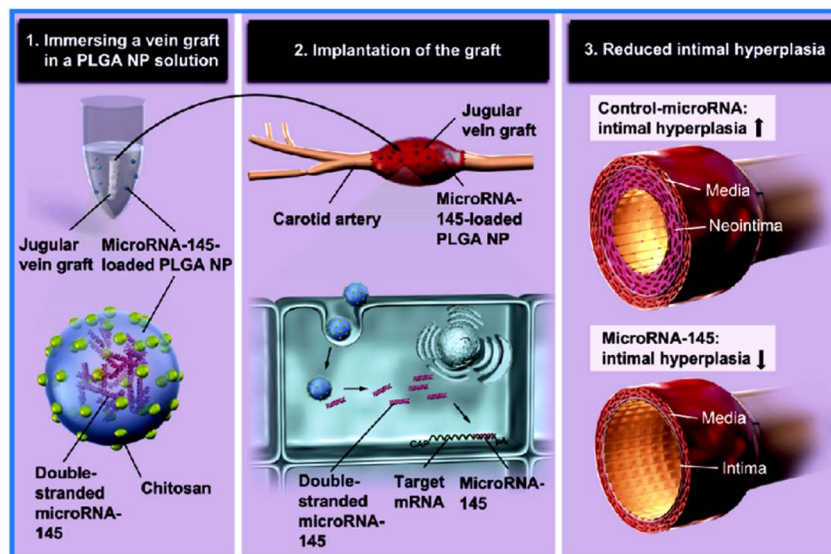


Fig. 3 Application of PLGA NPs in SDVGs. SDVGs modified by PLGA NP loading miR-145 showed significantly reduced IH. Reprinted with permission from ref. 33. Copyright 2019, Elsevier.

reduced IH formation. A follow-up mechanism study indicated that these NPs could act on SMCs by regulating the CD40 and NF- $\kappa$ B signals. Despite the large potentials of PLGA NPs in VGs, relevant reports are still rare, and the *in vivo* implantation period of the VGs should be further elongated. Scientists are also working on improving PLGA NP drug loading efficiency and reducing burst release and the influence of their degradation products on *in vivo* circulation.

### Poly(propylacrylic acid) NPs

Poly(propylacrylic acid) (PPAA) NPs are novel anionic polymer NPs with pH-responsive features. They have superior biocompatibility, drug carrying ability, and, particularly, membrane destabilizing ability at pH  $\sim$ 6.7, rendering them a quite useful material in biomedicine.<sup>35</sup> In VGs, researchers have fabricated vasoactive drug-loading PPAA NPs by mixing PPAA homopolymers and MAPK-activated protein kinase 2 inhibitor (MK2i) peptides *via* electrostatic complexation.<sup>36</sup> The external jugular veins were then coated with PPAA NPs that delivered MK2i peptides possessing anti-inflammatory, anti-migratory, and anti-proliferating properties into vascular cells. When the VGs were implanted into rabbit common carotid arteries for 28 days, they showed high patency and potent IH suppression, increased MK2i peptide cellular uptake, endosomal escape, and intracellular stability induced by PPAA encapsulation. The mechanism could be explained by MK2i-PPAA NPs depressing phosphorylation of the transcription factor cAMP element-binding protein, the chaperone heat shock protein 27, and the gene regulator heterogeneous nuclear ribonucleoprotein A0, triggering signaling on the inhibition of inflammation and proliferation.<sup>36</sup> However, the reduced EC coverage linked to MK2i-PPAA NPs may be a hurdle in VG applications. Although PPAA NPs have shown promise as an easy-fabricated drug-loading environmentally responsive nano vehicle, they may cause

undesirable hemolysis, their optimized concentration has not been established, and their pH-responsive range can be broadened by designing molecular structures and functional groups to expand their applications.

### Micelles

Micelles are nanoscale spheroids self-assembled by amphiphilic block copolymers, with a hydrophobic core and hydrophilic shell. They are excellent drug carriers that increase the solubility of indissoluble drugs and well protect the inner contents.<sup>37,38</sup> The micelles have been widely used in other biomedical fields but are still rarely reported in VGs. Researchers have constructed a micelle-containing double-layered vascular patch, whose outer layer comprises Thai silk fibroin/gelatin, and inner layer comprises gelatin hydrogel incorporating L-lactic acid oligomer (Lo)-grafted gelatin micelles loaded with simvastatin (SM). The controlledly released SM played roles that included lowering blood lipids, promoting the adhesion and proliferation of endothelial progenitor cells (EPCs), and inhibiting the migration and proliferation of SMCs. After the vascular patches were implanted in rat carotid arteries for 2 weeks, they achieved complete endothelialization and were well regenerated. However, the long-term performance of the design in real tissue-engineered VGs should be evaluated in the future. Additionally, the drug and formulation-specific therapeutic effects should be evaluated for each kind of micelle NP.

### Extracellular vesicles

Extracellular vesicles (EVs) secreted by cells are nanoscale disk-like vesicles containing complex RNAs and proteins, which are widely distributed within the cell micro-environment and body liquids. EVs are regarded to possess the same regulatory functions as corresponding cells yet with off-the-shelf properties.<sup>40,41</sup>



With the development of cellular therapy, accompanying EV therapy has demonstrated great application potential. In a recent study, heparin-modified ES polycaprolactone (PCL) tubular scaffolds were decorated by human placental MSC-derived EVs to construct VGs, which were then evaluated in a rat abdominal artery replacement model of hyperlipidemia for 3 months (Fig. 4A).<sup>42</sup> The patency of the graft was great because the MSC-derived EVs effectively inhibited thrombosis and calcification, enhanced the regeneration of ECs and SMCs, and switched the phenotype of macrophages from pro-inflammatory M1 to anti-inflammatory M2c. Further mechanism studies illustrated that this partially contributed to the indigenous presence of bioactive factors in EVs, such as miR-145, miR-126, and VEGF. It is noteworthy that even in a high-cholesterol pathological state, the MSC-derived EVs still exhibited powerful regenerative capacities in VGs. More recently, EVs derived from human adipose MSCs were loaded into porous silk-based tubular scaffolds by vacuum seeding to

establish a new VG (Fig. 4B).<sup>43</sup> After implantation in a rat aortic replacement model for 8 weeks, high patency of the VGs was observed. The EV-loading VGs showed higher endothelialization and smooth muscle regeneration but reduced macrophage numbers compared to the non-loading ones. The merits of these EVs for VGs include the basic properties of placental and adipose MSCs, such as abundant sources, easy acquisition, ultralow immunity, high para-secretion and immunomodulation, as well as low ethical risk. However, long-term implantation should be performed continuously to accelerate the translational process, and the detailed therapeutic mechanism of EVs should be elucidated.

### Nanofibers

Nanofibers are the second form of NMs used in VGs. The fibers are usually interconnected to form 3D tubular matrices or 2D films (which can then be rolled up to form 3D tubular

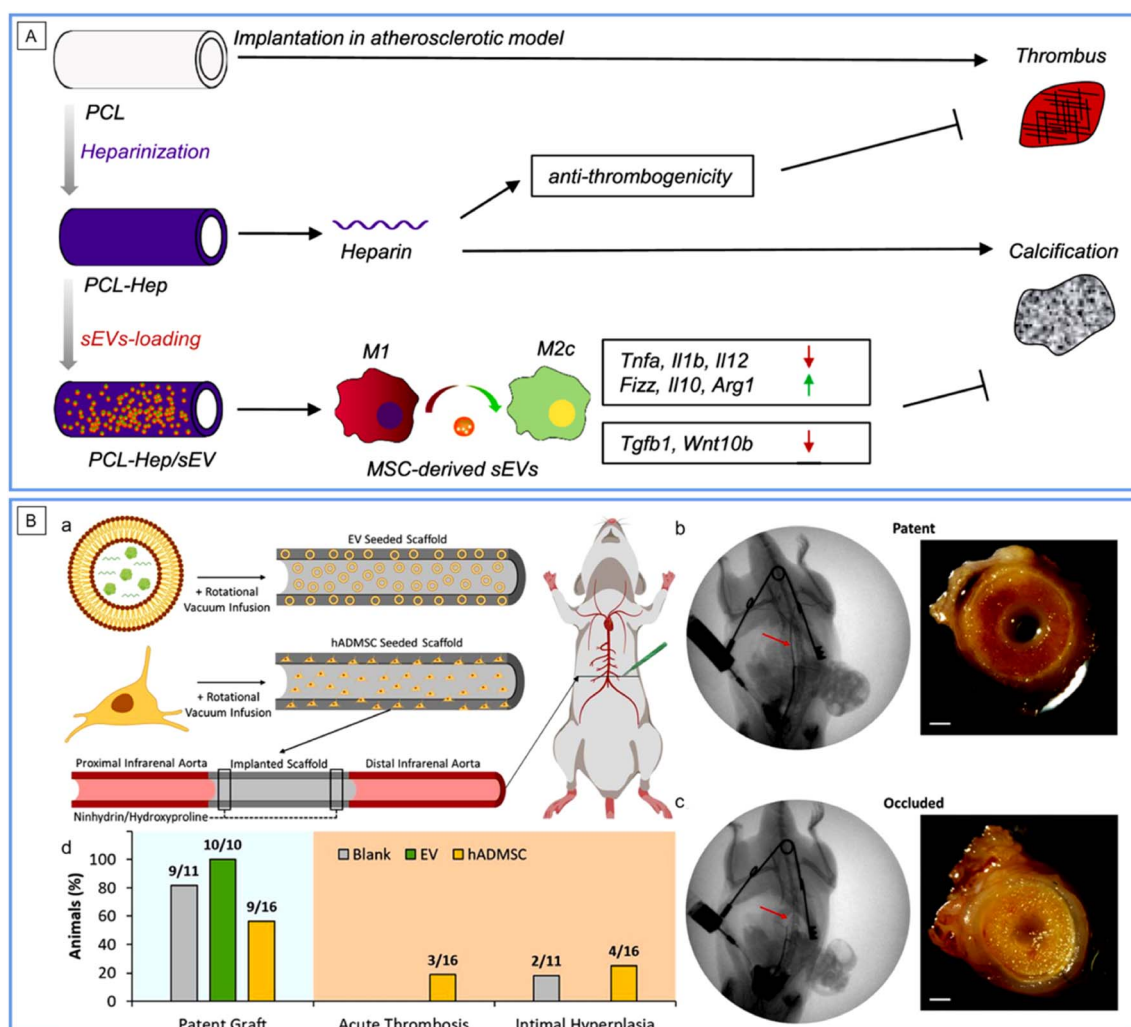


Fig. 4 Application of EVs in SDVGs. (A) Schematic mechanism of the improved performance of PCL SDVGs loaded with human placenta-derived MSC EVs in a rat model of hyperlipidemia. Reprinted with permission from ref. 42. Copyright 2019, Elsevier. (B) Graft patency of silk SDVGs loaded with human adipose-derived MSC EVs in a rat model. (a) Schematic representation of scaffold seeding and implantation. (b and c) Angioplasty and gross imaging of a representative patent (b) and occluded (c) explant. Scale bar: 500  $\mu$ m. (d) Patency rates of SDVGs and manner of graft occlusion. Reprinted with permission from ref. 43. Copyright 2020, American Chemical Society.

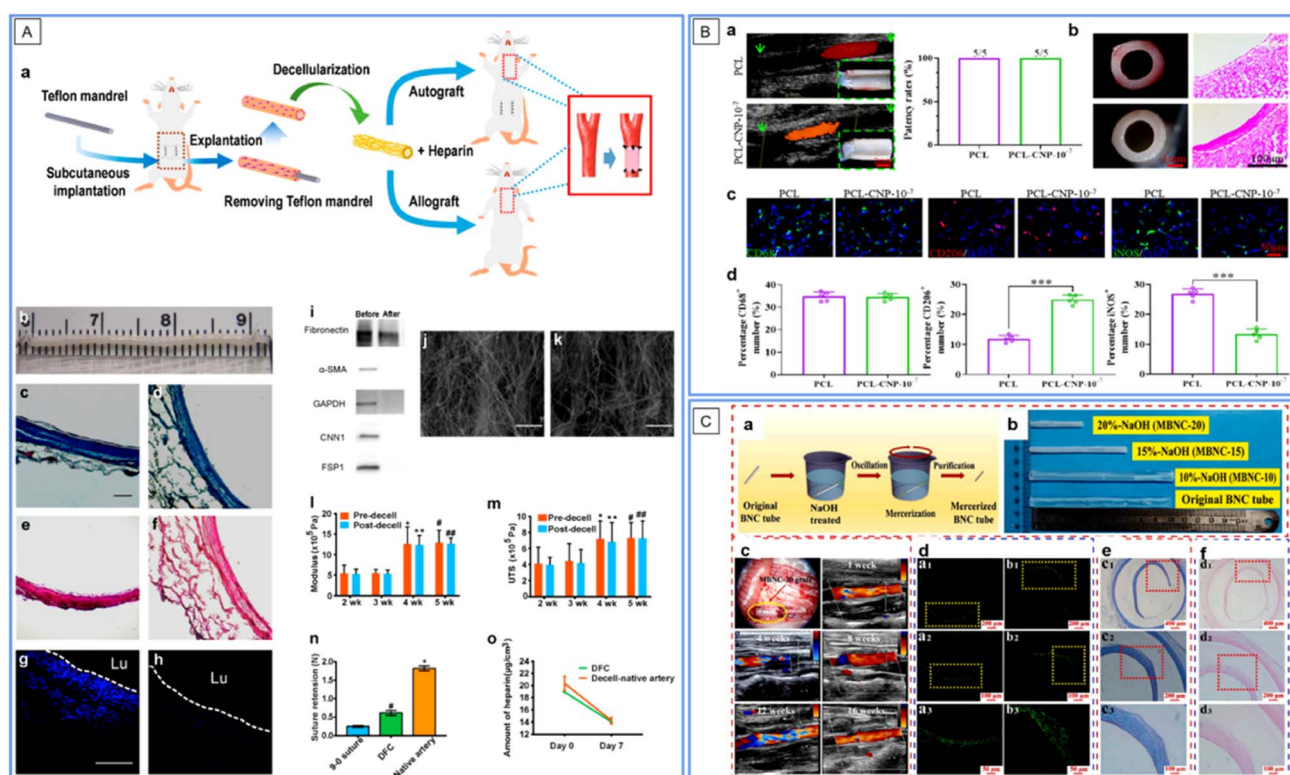


structures), which are then used as scaffold materials for VGs. There are three main kinds of widely used nanofiber interlaced materials in VGs: decellularized tissue matrices, electrospinning scaffolds, and bacterial cellulose scaffolds.

### Decellularized tissue matrices

When tissues are decellularized, the remnant parts are their extracellular matrix (ECM) mainly constituted by nano/micro-scale extracellular protein fibers, which provide a very biomimetic (both constitutively and mechanically) substrate for cell in-growth. Many decellularized tissues, such as blood vessels, ureters, small intestinal submucosas, and amnions, have been introduced into VG applications, and excellent reviews have been proposed on this topic (see ref. 44–48). In the above-mentioned VG examples in this review, some adopted decellularized tissues, e.g., vascular patches by AuNP conjugated decellularized porcine aorta<sup>12,13</sup> and VGs by resveratrol-carrying

SWCNT-coated rat decellularized carotid.<sup>29</sup> Here, we highlight one more of the latest developments in interest. In this study, researchers first subcutaneously implanted the ePTFE mandrel into the abdominal wall of rats for 4 weeks, and fibrotic tissue tubes were formed around the mandrel. The VGs were then developed by decellularizing the fibrotic tubes with an anti-thrombogenic heparin coating (Fig. 5A).<sup>49</sup> After evaluation in a carotid artery replacement model of rats for 6 months and in that of mini-pigs for 1 month, the researchers found that the decellularization greatly improved the patency and regenerative performance, compared to non-decellularized fibrotic tubes made using the same method. Furthermore, the decellularized autologous grafts exhibited an even higher patency rate compared to the decellularized allogeneic fibrotic tubes, indicating that a foreign body reaction still exists. The decellularized tissue matrix-based VGs represent an easy-to-fabricate and abundant-in-source kind of VG approach, showing off-the-shelf and non-invasive features for allogeneic VGs and mildly



**Fig. 5** Application of nanofibers in SDVGs. (A) Fabrication and characterization of decellularized fibrotic tissue-based VGs (DFC in the figure). (a) Schematic showing the fabrication, modification and implantation of the VG. (b) Gross appearance of the VG before implantation. (c and d) Masson's trichrome staining of VGs before (c) and after (d) decellularization. (e and f) Verhoeff's staining of VGs before (e) and after (f) decellularization. (g and h) DAPI staining of cross sections of VGs before (g) and after (h) decellularization. (i) Western blotting analysis of major cellular proteins before and after decellularization. (j and k) SEM images of the inner (j) and outer (k) surfaces of VGs. Scale bars: 50  $\mu\text{m}$ . (l and m) Young's modulus (l) and ultimate tensile strength (UTS) (m) before and at 2–5 weeks after decellularization. (n) Suture retention of VGs at 4 weeks after decellularization. (o) Content of heparin conjugated on VG and the decellularized native artery on days 0 and 7 under *in vitro* flow conditions. Reprinted with permission from ref. 49. Copyright 2021. Elsevier. (B) Evaluation of the patency and macrophage polarization of the explanted grafts 1 month after implantation. (a) Patency of VGs. (b) Representative stereomicroscope and HE images of cross sections of VGs. (c) Distribution of total M2 and M1 macrophages. (d) Quantitative analysis of the number of macrophages per field. Reprinted with permission from ref. 56. Copyright 2022, Elsevier. (C) Preparation and implantation of mercerized BC VGs. (a) Schematic illustration of the alkaline treatment process. (b) Tuning the morphology of VGs using various NaOH concentrations. (c) VGs during transplantation and ultrasonic analysis after implantation for 1–16 weeks. (d–f) Analysis of VGs by fluorescence staining of ECs (d), HE staining (e), and Masson's staining (f) after implantation for 5 months. Reprinted with permission from ref. 62. Copyright 2022, Elsevier.



invasive features for autologous ones. However, to further improve the VG quality and fabrication for allogeneic/xenogenic ones, measures such as removing immunogenic substances and coating immuno-suppressive/regeneration promoting molecules should be taken; meanwhile, for autologous ones, the period for fibrotic tube formation should be reduced.

### Electrospinning scaffolds

Electrospinning (ES) is an electrical field-controlled, useful technology for fabricating ECM-like nano/micro-diameter fibers with various synthetic or natural polymers. It is well known in biomedical and other fields owing to its low cost, process controllability, simple equipment, diversiform spinnable substances, and scalability. By tuning the working conditions, ES can well control the fiber size and orientation, scaffold configuration (2D films or 3D geometry in designated shapes) and surface thickness. ES substrates are typically versatile scaffold materials in VGs, which can load drugs and control cell behaviors.<sup>50,51</sup> There have been several examples of ES-based VGs in the previous texts in this review, *e.g.*, VGs by ZnO NP-coated P(VDF-TrFE) ES conduits<sup>24</sup> and by human placental MSC-derived EV-modified ES PCL conduits.<sup>42</sup> Intensive and comprehensive reviews on this topic have been published (see ref. 52–55). Herein, we provide another latest example of interest. The VG was fabricated by decorating a C-type natriuretic peptide (CNP), a vasodilator, on PCL ES tubular scaffolds (Fig. 5B).<sup>56</sup> The VG showed great blood compatibility in a rabbit arterial venous (AV)-shunt model for 1.5 hours of the test. One month post-implantation in a rat abdominal aorta replacement model, compared to its counterpart without CNPs, the CNP loaded with VGs showed significantly more EC coverage, NO production, VEGF secretion, M2 type macrophage polarization, contractile SMC transition, and ECM deposition, along with a parallel yet also 100% patency rate. Therefore, the CNP decoration further improved the regenerative capacity of the VG, which may play an important role in long-term VG patency. However, the *in vivo* test should be performed at an elongated time. In addition, the slow degradation of PCL polymers may cause the calcification and degeneration of vascular neotissues. To achieve ideal VGs, it is a critical issue for ES-based VGs to select the proper polymer material, construct the proper fiber size and orientation, and decorate proper seeding cells and/or coatings.

### Bacterial nanocellulose scaffolds

Bacterial nanocellulose (BC) is another kind of nanofiber material for VG applications. It is a natural polysaccharide produced by several bacteria, such as *Acetobacter xylinum* and *Gluconacetobacter sucrofermentans*, within a short period of around 10 days.<sup>57</sup> The nanofibrous networks of BC are similar to those of ECM cells, thus providing superior biocompatibility. BC can be conveniently fabricated into 2D films, hollow tubes, and other 3D shapes. Numerous reviews on the application of BCs in VGs have been presented (see ref. 58–61). Herein, we also underline one of the latest examples of interest. The tubular BC hydrogel was treated with 20% NaOH to construct a novel VG

(Fig. 5C).<sup>62</sup> The treatment greatly increased the smoothness, burst strength, and compliance of the VGs. Compared with untreated BC VGs, the treated ones showed lessened platelet adhesion and activation and promoted EC proliferation *in vitro*. After the subcutaneous implantation of the VGs in a rat for 6 months, both the treated and untreated BC showed low inflammation and good tissue growth, indicating their superior biocompatibility. After 5 months of implantation in a rat abdominal aorta replacement model, the treated BC VG showed normal blood circulation and satisfactory patency. By treating NaOH with different concentrations, the length, diameter, and wall thickness of the VG could become tunable, which may fit multiple applications. However, the long degradation term *in vivo* may be a limitation of BC's application in VGs. Moreover, more surface modification of BC could be attempted to improve its performance in VGs.

### Nano-films

Nanoscale films, the third type of NMs used in VGs, are a novel but effective strategy to enhance the performance of VGs as well. Nano-films can be formed by surface coating to construct uniform nano-thick films (*e.g.*, tantalum-coated films), or surface patterning to construct films with designated nanoscale geometries (*e.g.*, nanolamellar films). Reports on nano-film bearing VGs are rare to date. Here, we provide two representative cases.

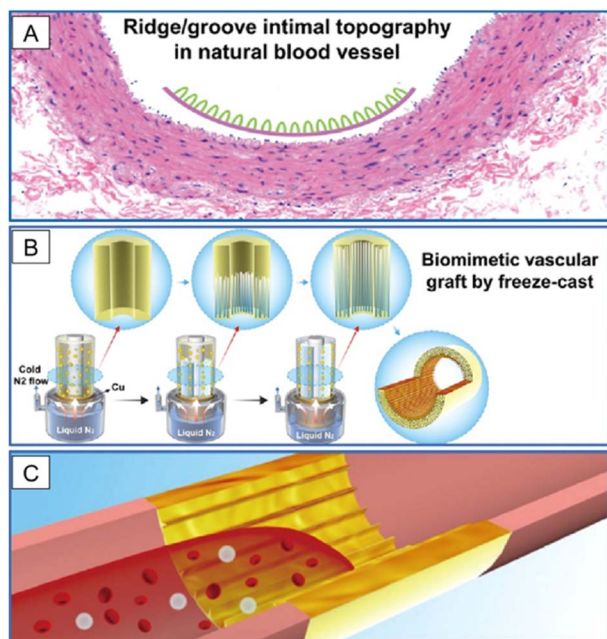
#### Tantalum nanofilms

Tantalum (Ta) is an abundant lightweight metal with considerable material strength, corrosion resistance, and biocompatibility; thus, it is one of the major metals for biomedical use. Ta and its alloys have played important roles in surface and structural modification in current clinical devices, including cardiovascular ones.<sup>63–66</sup> Recently, nano-thick Ta surface coatings have been employed in VGs. Commercially available ePTFE vascular scaffolds were coated with a nano-thick Ta layer *via* a sputtering-based plasma immersion ion implantation technique within 1 min.<sup>67</sup> The Ta coating was found to refine the hydrophobicity of ePTFE, improve EC growth, and suppress platelet adhesion and activation, thereby rendering the graft more biocompatible and anti-thrombogenic. Assessing a canine aortic replacement model for 4 weeks demonstrated thrombosis suppression and rapid EC layer formation of the VG. Although Ta films have shown great merits in VGs, they are mainly limited by their low rigidity, abrasive resistance, and reactivity with other metals.

#### Nanolamellar films

The second strategy for obtaining nanofilms is to design nanoscale topographic cues for device surfaces. This strategy does not need to introduce new materials to the devices but only needs to fabricate the device surface using physical methods without changing the properties of the materials. It has been reported that the nano topographic lumen plays pivotal roles in tuning cell fate, device integrity, and tissue remodeling fate.<sup>68,69</sup> In VG application, researchers have fabricated a double-layered





**Fig. 6** Application of nanolamellar films in SDVGs. (A) Natural blood vessel shows a ridge/groove nanotopography on the intimal surface. (B) SDVG with a biomimetic structure is prepared by applying a freeze-cast technique with lamellar nanotopography on the inner surface. (C) VG is used to replace the injured vessel to promote fast endothelialization and to maintain long-term patency. Reprinted with permission from ref. 70. Copyright 2019, American Chemical Society.

graft, whose inner layer was fabricated by freeze-casting silk fibroin and gelatin solutions on a cylinder template with pre-designed nano patterns to eventually form longitudinally aligned high aspect ratio lamellar nanotopography on the lumen, and whose outer layer was reinforced by ES PCL (Fig. 6).<sup>70</sup> The nanolamellar surface, mimicking the groove-valley topography of the native vascular inner layer, guided EC alignment, inhibited platelet adhesion, and reduced blood flow disturbance, thereby maintaining a high patency rate of the VG after 3 months in a rabbit carotid artery replacement model. It is noteworthy that in this VG, numerical simulation was successfully employed to predict the performance of its surface nanopatterns. Therefore, more efficient nanopatterns can be designed through computers. The major difficulty of this strategy arises from precise manufacturing techniques.

## Summary and outlook

The major efforts of SDVGs are to reverse the dilemma that surgeons clearly know the gold treatment to cure diseases but lack available grafts to save more lives. NMs have opened a new door for enhancing the performance of vascular grafts although the application of NMs in SDVGs is still in its infancy. As listed in Table 1, NMs in the forms of nanoparticles, nanofibers, nanofilms, or some of these in combination have been utilized for SDVG patency improvement, regeneration promotion, rapid construction, non-invasive imaging, and so forth. Each kind of material has its advantages and disadvantages. Thus, it is

important to rationally use a specific material according to the target goal. Because all these NMs have represented a certain effectiveness in VGs, safety is the fundamental issue to be considered in the VG application. In this context, the Ta nanofilms, nanopatterns, and distinct nanofibers tested practically or experimentally perform well. For NPs, in general, the safest ones are biologically derived EVs with the highest biocompatibility; the safety of organically synthetic ones takes second place, which should be further identified; and the safety of inorganically synthetic ones is even lower, which should be carefully evaluated for further applications, although combining inorganic NPs and organic substrates demonstrates a new direction that improves VG performance. High safety means high translational potential. However, the effectiveness of the NMs in VGs could be continuously improved by structural redesign, surface modification, chemical treatment, a combination of various NMs, and so forth. Moreover, it is worth noting that the aforementioned VGs include not only the fabrication or refinement of newly designed synthetic VGs (the major efforts in the SDVG field currently) but also the amelioration of gold-standard and traditional material-based ones.

By scanning the huge NM pool, many NMs potentially applicable to SDVGs are to be discovered. For example, silver NPs were linked to porous PCL films, which showed potent effects in inhibiting platelet adhesion and aggregation *in vitro*, simultaneously retaining the inherent antimicrobial properties of the NPs.<sup>72–74</sup> An alternative nanomaterial, plasma-modified TiO<sub>2</sub> nanotube coating, has been widely used in cardiovascular stents and other biomedical devices. Researchers have found that the coating can enhance endothelial coverage but reduce platelet adhesion and unfavorable SMC propagation. Interestingly, the coating also exhibited good anti-infective capacity.<sup>75</sup> Although they have not been directly applied, NMs have shown powerful potential in improving SDVG patency.<sup>76</sup> It is noteworthy that owing to the shared targeting organ systems and disease mechanisms with small diameter vascular diseases, NMs used in the management of atherosclerosis and other cardiovascular diseases (*e.g.*, NMs in vascular or heart stents) could enhance the utilization of NMs in SDVGs (see several excellent reviews on this topic<sup>77–80</sup>).

In our opinion, there are several future studies on improving NM-bearing SDVGs. First, as aforementioned, only very few NMs have been tested in the SDVGs in the context of the exploding development of thousands of NMs.<sup>71</sup> An item that could be immediately executed is the discovery of more currently available NMs that can be used in SDVGs. Second, owing to the strong designability of NMs, we can construct new NMs for SDVG based on our particular goal. It is suggested that in the design, the target should be considered systematically because the reasons for the low patency are closely interconnected. Multi-cargo carrying and precisely targeting NMs may be helpful. Third, the long-term and systematic impact of NMs on SDVGs should be evaluated to obtain more reliable conclusions to promote clinical translation. NM functions, distributions, and toxicities are all essential parts of the safety and efficacy of the NM-bearing VG. In the meantime, intrinsic limitations on each material should be overcome with the development of science and technology. Finally, we noticed that



computer-based numerical stimulation has been applied in the design and evaluation of the efficacy of NMs in nanolamellar surface bearing VGs.<sup>70</sup> Therefore, NMs in conjugation with other advanced technologies may significantly accelerate the development of SDVGs, and the fabrication and application of NMs are a collection of advanced technologies. Although the incorporation of NMs into SDVGs may not be dominant, we believe that the outstanding particularity and utilization potential of NMs will illuminate the way ahead for achieving commercially available SDVGs and directing the SDVG into a new era.

## Abbreviations

CVD	Cardiovascular disease
VG	Vascular graft
SDVG	Small diameter vascular graft
NP	Nanoparticle
AuNP	Gold nanoparticle
EC	Endothelial cell
SMC	Smooth muscle cell
HUVEC	Human umbilical cord vascular EC
PTFE	Polytetrafluoroethylene
ePTFE	Expanded polytetrafluoroethylene
LbL	Layer by layer
P(VDF-TrFE)	Poly(vinylidene fluoridetrifluoroethylene)
ES	Electrospinning
PU	Polyurethane
PDMS	Polydimethylsiloxane
RSV	Resveratrol
SWCNT	Single walled carbon nanotube
FD	Fluorescein isothiocyanate-dextran
miR	microRNA
PLGA	Poly(lactic-co-glycolic acid)
PPAA	Poly(propylacrylic acid);
MK2i	MAPK-activated protein kinase 2 inhibitor peptide
IH	Intimal hyperplasia
SF	Silk fibroin
SMV	Simvastatin
MSC	Mesenchymal stem cell
EV	Extracellular vesicle
CNP	C-Type natriuretic peptide
PCL	Polycaprolactone
AV	Arterial venous
BC	Bacterial nanocellulose
Ta	Tantalum
0D/1D/2D/3D	zero/one/two/three dimensional, respectively
Lo	L-Lactic acid oligomer
TE	Tissue engineering
GC	Glycol chitosan

## Author contributions

Conceptualization, N. W. & Z. H.; resources, N. W., H. W. & D. W.; data curation, N. W. & H. W.; writing – original draft

preparation, N. W.; writing – review & editing, D. W., L. Y., Y. W., H. W., F. W., T. Z., J. L. & Z. H.; visualization, N. W., H. W. & D. W.; supervision, Z. H.; project administration, N. W. & Z. H.; funding acquisition, F. W., N. W. & Z. H.

## Conflicts of interest

The authors declare no conflict of interest.

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