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Periadventitial Drug Delivery for the Prevention of Intimal Hyperplasia Following Open Surgery

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Abstract

Background—Intimal hyperplasia (IH) remains a major cause of poor patient outcomes after surgical revascularization to treat atherosclerosis. A multitude of drugs have been shown to prevent the development of IH. Moreover, endovascular drug delivery following angioplasty and stenting has been achieved with a marked diminution in the incidence of restenosis. Despite advances in endovascular drug delivery, there is currently no clinically available method of periadventitial drug delivery suitable for open vascular reconstructions. Herein we provide an overview of the recent literature regarding innovative polymer platforms for periadventitial drug delivery in preclinical models of IH as well as insights about barriers to clinical translation.

Methods—A comprehensive PubMed search confined to the past 15 years was performed for studies of periadventitial drug delivery. Additional searches were performed for relevant clinical trials, patents, meeting abstracts, and awards of NIH funding.

Results—Most of the research involving direct periadventitial delivery without a drug carrier was published prior to 2000. Over the past 15 years there have been a surge of reports utilizing periadventitial drug-releasing polymer platforms, most commonly bioresorbable hydrogels and wraps. These methods proved to be effective for the inhibition of IH in various animal models (e.g. balloon angioplasty, wire injury, and vein graft), but very few have advanced to clinical trials.

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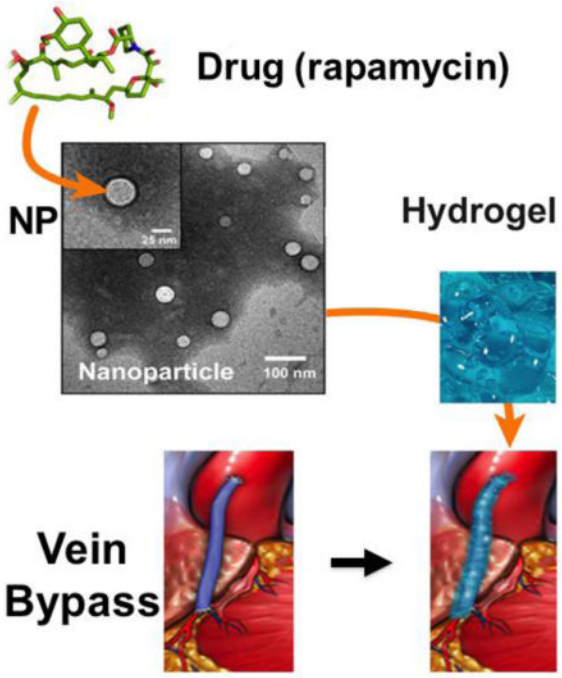
There are a number of barriers that may account for this lack of translation. Promising new approaches including the use of nanoparticles will be described.

Conclusions—No periadventitial drug delivery system has reached clinical application. For periadventitial delivery, polymer hydrogels, wraps, and nanoparticles exhibit overlapping and complementary properties. The ideal periadventitial delivery platform would allow for sustained drug release yet exert minimal mechanical and inflammatory stresses to the vessel wall. A clinically applicable strategy for periadventital drug delivery would benefit thousands of patients undergoing open vascular reconstruction each year.

Graphic abstract

Periadventitial Drug Delivery — schematic depicting a periadventitial drug delivery platform of nanoparticles carried in a hydrogel. Based on Shi et al, PLoS One, 9 (2014) e89227.



Keywords

Open surgery; periadventitial drug delivery; intimal hyperplasia; hydrogel; wrap; nanoparticles

Each year over a million patients in the US are treated with vascular surgical procedures for flow-limiting atherosclerosis or for hemodialysis access[1]. Although initially successful, a large proportion of these reconstructions eventually fail due to intimal hyperplasia (IH)[2]. IH can result from injury that occurs at the time of arterial reconstruction, for example, manipulation of a vein being prepared for bypass[3]. Alterations of hemodynamics can provide a more persistent stimulus for IH. An example of this is the exposure of a vein graft to arterial pressures and subsequent arteriolization of the vein[4]. The development of recurrent disease leads to the narrowing of the new conduit with the eventual development of stenosis or occlusion. Recently, significant progress has been made in the development of

endovascular drug eluting stents (DESs) and balloons (DEBs), which have significantly reduced the incidence of restenosis [5, 6]. However, limitations of these technologies are quickly becoming evident. For example, drugs (rapamycin analogs or paclitaxel) released directly into the luminal vessel wall can impair reendothelialization, thereby increasing the risk of thrombosis[7]. Most importantly, drug delivery methods designed for stents or balloons are not applicable for the patients undergoing open vascular surgery. To date, there are no clinically available methods for drug delivery to prevent IH in patients undergoing open vascular reconstruction.

With a host of new biocompatible drug-carrying materials developed over the past decade, there is a refreshed interest in periadventitial drug delivery. It is somewhat surprising that the technology for endovascular drug delivery is well developed whereas a periadventitial approach for open vascular reconstructions, which is at least theoretically less challenging, has not yet reached clinical use. Endovascular delivery requires attachment of a drug to a balloon or stent and remote application. Release kinetics can be altered by the hemodynamics of blood flow. Alternatively, for open surgery, the drug carrier can be conveniently applied to the periadventitial surface of an artery or vein at the time of reconstruction and is unaffected by adverse flow or hemodynamics. Moreover, since the drug does not directly enter the circulation, there is improved bioavailability to the vessel wall while minimizing systemic toxicity. Since the drug is applied to the adventitia, away from the endothelial layer, there is diminished impairment of endothelial healing. The ideal periadventitial drug delivery system for effective prevention of IH would be one that allows for sustained and steady release of drug considering that the stimuli for IH following arterial reconstruction is often persistent. The ideal strategy would also produce minimal periadventitial inflammation as inflammation of the adventitia can stimulate myofibroblast migration into the subintimal space thereby enhancing IH or producing unfavorable constrictive remodeling[8]. Lastly, the ideal drug carrier would be one that is not bulky and has minimal effect on the hemodynamics of the treated arterial wall. Herewith we review the current options for periadventitial delivery and the associated benefits and disadvantages with regard to potential clinical use. Our focus is primarily on the literature published over the past 15 years and approaches that have at minimum been applied in preclinical models.

Direct Application

Until the beginning of this century, the most commonly used periadventitial delivery technique was the direct application of an anti-restenotic agent without a carrier. Using this approach, a number of therapeutic agents including small molecules, DNA, viral vectors, proteins and antibodies have been tested for their efficacy in preventing IH[9]. These agents have been directly applied to the arterial wall in either a powder form or in solution. Alternatively, a drug in-solution can be administered into the vessel wall of an *ex-vivo* vein (prior to grafting) using a pressure-mediated delivery system[10]. These studies show that direct application of anti-restenotic agents is somewhat effective in reducing IH in short-term animal models. While the greatest advantage of this approach is its simplicity, there are obvious limitations. Without a carrier, the therapeutic agent quickly diffuses into the capillary bed and into surrounding tissues making it necessary to use high concentrations of drug[11]. As such, there is potential toxicity to adjacent tissues and there is little ability to

provide uniform drug administration. For these reasons, direct periadventitial application of drug has been replaced with carriers or platforms that allow more controlled and directed drug release.

Hydrogels

Hydrogels have become the most widely utilized platform for the periadventitial delivery of drugs to prevent IH in animal models. Examples of synthetic hydrogels used for periadventitial delivery include block copolymers of polyethylene glycol (PEG) such as PEG-polypropylene glycol (PPG)-PEG (e.g., Pluronic gel), poly(lactic-co-glycolic acid) (PLGA)-PEG-PLGA (e.g., ReGel gel) as well as gels derived from Sodium Alginate[12–15]. There are a number of reports where hydrogels have been used to deliver small molecules, DNA plasmids, siRNAs, viruses, as well as proteins/peptides into the perivascular space[16–18] Much of the enthusiasm surrounding this approach centers around its ease of use and its customizability.

The properties of hydrogels can be readily adjusted by controlling the polymer concentration, structure and molecular weight[19]. Many of the widely studied hydrogels used for biomedical applications are thermoreversible gels including Pluronic gel and ReGel [20, 21]. Thermoreversible gels typically remain in a liquid form at relatively low temperatures, convenient for mixing with various therapeutic agents; however, they can rapidly form gels at body temperature creating a drug reservoir localized at the treatment site. A prominent feature of thermoreversible hydrogels is their ability to mold into any shape, in this case forming an attached layer surrounding the vessel. This formability is particularly advantageous for periadventitial drug delivery since the artery is circumferential and the anatomy around bifurcations and anastomoses is even more complex. In addition, also showing excellent formability, a self-assembling nanofiber gel capable of nitric oxide release effectively reduced IH after periadevtitial application in a rat carotid injury model [22].

Although hydrogels are the most commonly used approach for perivascular drug delivery, they have inherent limitations. First, many studies including our own, reveal that hydrogels often produce an initial burst of drug release immediately after the drug-laden hydrogel is applied to the arterial wall[13, 23]. Although there are some advantages of the early release of a bolus of drug for the prevention of IH, this early loss of large quantities of drug leaves less available for long-term delivery to the arterial wall. After an initial burst, drug is then released quite slowly from the hydrogel until the hydrogel itself dissolves[24]. With this dissolution, there is often the rapid release of a second large bolus of drug causing similar issues. The timing of the second bolus is related to the kinetics of dissolution of the hydrogel[25]. For example, Pluronic gel F127 dissolves over 3 days and as such the second bolus is almost immediate. Alternatively, a hydrogel made in our laboratory, comprised of PLGA-PEG-PLGA block copolymer (referred to as Triblock gel), dissolves at 6 weeks so the second large bolus occurs around 6 weeks after application of the hydrogel (Kent et al, unpublished data). Thus drug release from hydrogels is typically bimodal, with a large bolus at the time of initial application and a second large bolus when the gel dissolves. Although a

bimodal bolus of drug may be effective in preventing IH, theoretically a steady and sustainable release of drug would be more desirable.

The duration of drug delivery required to prevent IH has not been well established and may vary with the type of reconstruction. For example with angioplasty, there is an acute injury to the arterial wall and drug may be required for only a short period during which the injury resolves and the artery heals. That said, it is not clear how short is short, and even with acute arterial injury healing is not immediate and drug may be required for 6 weeks or more following injury. To this end, recently published data using a rat carotid angioplasty model suggest that delivery of rapamycin through Pluronic gel produces only temporary inhibition of IH at two weeks with recurrence of disease by four weeks[13]. Alternatively following a vein bypass, exposure of the vein which is accustomed to a low pressure system, now to arterial pressures (arterialization), produces a stimulus for IH that continues throughout the life span of the vein graft. Therefore, prevention of IH following bypass grafting with an autogenous vein may require prolonged release of the drug. Thus use of a hydrogel such as Pluronic gel for drug delivery, which dissolves over three days, may be an ineffective approach to IH.

There are additional disadvantages of hydrogels. Hydrogels may not be homogenous. Moreover, the quantity of drug that can be loaded into a hydrogel is limited compared to other deliver methods[19]. In addition, it is difficult to control hydrogel elasticity and degradability[26]. Hydrogels can also produce an inflammatory response due to decomposition. Reid et al. demonstrated that implantation of a hydrogel into adipose tissue in rats increased macrophage and neutrophil infiltration[27]. Zhu et al echoed these findings with significant increases in T cell and macrophage infiltration after intramuscular injection of the PNIPAM hydrogel[28].

It is worth noting that considerable efforts have been devoted to circumvent the foregoing limitations of hydrogels. A PLGA-PEG-PLGA triblock hydrogel exhibits improved properties over Pluronic gel. This hydrogel has a life-span of 60 days with continuous release of rapamycin throughout[29]. By adding a second layer that covers the hydrogel and directionally “caps” drug diffusion, Sanders et al. was able to significantly reduce drug loss to the surrounding tissues[30]. In order to prevent the initial drug loss due to burst release, Chun et al covalently crosslinked paclitaxel to the hydrogel resulting in markedly prolonged drug release[31]. This technique has not been attempted with periadventitial drug delivery for the prevention of IH. Moreover, natural hydrogels have also been used for periadventitial drug delivery, examples being hyaluronic acid (HA), collagen and others[32, 33]. Although these materials elicit a minimal inflammatory response, they have a relatively short life span because of their susceptibility to biodegradation. As new materials are being discovered, more opportunities will emerge for producing hydrogels with improved properties to achieve the goal of steady prolonged periadventitial release with minimal mechanical and inflammatory stress to the vessel wall.

Wraps

Another important platform for periadventitial drug delivery is polymer wraps. Wraps share a few favorable characteristics with hydrogels. For example, they can be easily produced. Following evaporation of an organic solvent used to dissolve the drug/polymer mixture, a drug-loaded polymer film (or wrap) can be formed. The thickness of the film and drug loading capacity are readily adjustable by controlling the amount of the various polymer(s) [34]. A number of FDA-approved biocompatible and biodegradable polymers including aliphatic polyesters such as polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLLA), and poly(ε-caprolactone) (PCL) can be used to create polymer wraps. Such polymers have been used for a variety of clinical applications particularly in orthopedics[35]. Moreover, a number of different versions, such as polymer cuffs, meshes, films, or sheaths, collectively termed “wraps” for purposes of this review, have been used for periadventitial drug delivery in animal models of intimal hyperplasia.

Like hydrogels, polymer wraps possess distinct properties desirable for periadventitial drug delivery. 1) Polymer wraps provide the mechanical strength and rigidity to allow for relatively easy deployment and immobilization around a blood vessel. 2) The hydrophobic environment inside the polymer matrix confers a relatively high loading capacity for hydrophobic drugs while protecting the drug from early hydrolysis. For example, in a PCL film of 0.5 cm^2 size and 50 μm thickness, at least 100 μg of rapamycin can be loaded[34]. 3) Polymer wraps can persist for longer periods, leading to more prolonged drug release than with hydrogels. For example, a PCL wrap provides a steady rapamycin release for at least 2 months[34]. 4) An initial loss of the drug due to burst release is less of a problem with polymer wraps than with hydrogels, likely due to the polymer wraps having a more condensed structure or greater hydrophobicity, or both. 5) In addition, polymers with different drug release properties can be conveniently mixed to produce co-polymers attaining desirable “customized” release profiles[34]

A number of polymer wraps have been tested for their effectness in preventing neointimal hyperplasia in various animal models. Pires et al reported that paclitaxel- and rapamycin-eluting PCL cuffs placed around the mouse femoral artery reduced IH by ~75% at 21 days, compared to drug-free control[36]. Using a rabbit vein graft model, Skalsky et al found that a sirolimus-releasing polyester mesh wrapped around the graft reduced the intima-media thickness by 60% and 30% after 3 and 6 weeks, respectively [37]. Yu et al showed that a periadventitial PCL sheath steadily releasing rapamycin, greatly reduced (by 85%) IH compared to a drug-free sheath two weeks after balloon angioplasty of the rat common carotid artery[34]. Most recently, Gregory et al used a citrate-based polyester membrane for periadventitial delivery of all trans retinoic acid to balloon injured rat carotid arteries and observed a 50% reduction of restenosis two weeks after surgery[38].

While various drug-loaded polymer wraps have been shown to be effective in mitigating IH, it is important to note that these wraps have also exhibited various limitations. A common problem is the mechanical stress imposed on the vessel due to the rigidity of the wrap. For example, while the PCL cuff serves as a drug-releasing device, the cuff itself (without drug) can induce IH in the mouse artery[36]. In studies by Yu et al, PLGA and PLLA wraps were

soft when initially applied around the vessel wall, but became stiff and rigid *in vivo* and produced thrombosis of arteries surrounded by the hardened structure[34]. To circumvent this problem, when using a PCL sheath the authors created a modification such that the shealth was not placed in a fully circumferential manner thus leaving the wrap open at the top (Figure 1). Since this provided flexibility allowing normal hemodynamics, thrombosis was prevented. Alternatively, to alleviate the issue of arterial constriction produced by more traditional wraps, Serrano et al employed elastomers, which provided enhanced elasticity[39].

Although periadventitial wraps, much like hydorgels, deliver drug to the vessel wall, they inevitably release drug into the surrounding tissues with the potential of local toxicity. Sanders et al elegantly addressed this issue with a bilayer polymer wrap employing a drug-free non-porous outer barrier laminated onto a drug-loaded porous inner layer which is in direct contact with the vessel wall [30]. Using Sunitinib as the drug in a pig model of arteriovenous (AV) hemodialysis graft access, they found this bilayer PLGA wrap was able to provide unidirectional drug delivery to the vessel with minimal drug loss to extravascular tissues. While multilayer drug delivery systems are conceptually ideal to produce directed drug delivery, they are bulky and complex to produce. These issues in turn can affect arterial hemodynamics and degradation products can promote inflammation leading to constrictive vessel remodeling. With this in mind, some investigators have explored naturally occuring materials such as hyaluronic acid and collagens as drug carriers[40, 41]. A recent example is the evaluation of a sirolimus-eluting collagen wrap in humans. Patients undergoing AVG placement received the collagen membrane (Coll-R) around the site of the venous and PTFE anastamosis. Unfortunately, the lack of appropriate controls prohibited any definitive conclusions regarding the efficacy of the collagen wrap. Although associated with minimal inflammation, natural materials are generally not able to provide the same amount of mechanical strength (for wrapping) or durability compared to synthetic polymers. These disadvantages are also shared by hydrogels as previously discussed. Interestingly, progress has been made in the development of “hybrids” that reconcile the properties of synthetic polymer wraps and hydrogels formed by natural materials. For example, a prototypical design is a bilayer wrap recently produced by Sanders et al, in which the PCL outer layer provides durable mechanical support while the natural HA hydrogel infused into the porous inner layer produces prolonged drug release in vitro [30]. To date, the *in vivo* efficacy of this hybrid wrap for inhibiting neointima remains to be assessed. Nevertheless, continued research is required for the invention of next-generation periadventitial wraps that are 1) durable, 2) bioresorbable, 3) non-inflammatory, 4) not disruptive to the vessel, and 5) can directionally release drug in a controlled and sustained manner. Ultimately, a wrap with all of these characteristics would be highly effective in preventing IH.

Nanoparticles

The latest development in periadventitial drug delivery is the use of nanoparticles (NP) as a drug-releasing platform, which echoes the recent surge of research in nanomedicine. Compared to traditional platforms, such as hydrogels and polymer wraps, NPs possess a number of properties favorable for periadventitial delivery. (1) Their small size (typically 10–200 nm) allows for efficient infiltration of NPs into the arterial wall with drug release or

endocytosis of cells[42]. (2) Due to their minute mass, their degradation products are less likely to produce an inflammatory response as compared to bulky hydrogels or wraps[43–45]. In addition, NPs are less likely impose mechanical stress on the vessel wall. (3) NPs are highly customizable and can be readily tailored for controlled and sustained drug release[46]. (4) NPs can be produced with hydrophobic cores to harbor a hydrophobic drug, while a hydrophilic outer surface renders the drug-loaded NPs highly soluble[47]. (5) NPs can be fluorescently labeled, facilitating *in vitro* and *in vivo* imaging and localization[47]. (6) For targeting a specific tissue or cell population, the surface of the NP can be conjugated with targeting ligands[48, 49]. As such targeted delivery using NPs could provide high local drug concentrations to pathogenic cells with minimal collateral damage to normal cells, a unique strength of NPs that cannot be achieved with traditional platforms (e.g. hydrogels or wraps) [50].

NPs have been widely applied in various disease models particularly in cancer[49]. While considerable attention has been given to the endovascular delivery of NPs via systemic injection[51], research on NPs for periadventitial drug delivery is just emerging In a study of periadventitial application, Rajathurai et al utilized rapamycin-loaded microspheres in Pluronic gel to treat IH in a pig vein graft model[52]. While low doses of rapamycin did not inhibit IH, high doses were associated with toxicity as manifested by graft rupture and the paradoxical acceleration of vein graft stenosis. Nonetheless, they demonstrated a 63% reduction in neointimal growth after 4 weeks of treatment with a rapamycin dose of 60 ug/cm^2. Although microspheres (or microbeads) share similarities with NPs, they are of a larger size and possess different release kinetics. The first study using NPs for periadventitial delivery was reported by Li et al in 2010[53]. These investigators used a lysine-based NP incorporating the siRNA of NOX2 (an enzyme generating reactive oxygen species) to inhibit IH after balloon angioplasty. Two weeks after periadventitial application of these NPs, IH was reduced by 83% compared to control NPs without NOX2 siRNA. Efficient siRNA delivery was demonstrated by penetration of fluorescent-labeled NPs into the artery wall and an 85% knockdown of NOX2. In another study Gasper et al used a unique approach to deliver NPs formed by conjugating albumin and rapamycin (termed Nab-rapamycin), by injecting these particles into the adventitia via an intraluminally inserted microinfusion balloon catheter with needles that transgress the arterial wall[54]. Although this periadventitial delivery method is intrusive to the vessel, the treatment proved safe and reduced IH following balloon angioplasty. More recently, Shi et al used periadventitial NPs to deliver rapamycin for inhibition of restenosis in a rat carotid balloon injury model[13]. Almost all the drug carriers including hydrogels, wraps, microspheres and NPs are associated with an initial burst release at the time of application. Thus a prominent question arises, i.e. to produce sustained inhibition of IH, is the initial burst release sufficient or is continued release over some period of time required? To address this question, Shi et al compared the inhibitory effect (on IH) of rapamycin mixed in Pluronic gel, which dissolves over 3 days thus only providing early burst release, and rapamycin loaded in PLGA NPs (suspended in Pluronic gel), which produces release of rapamycin over two weeks. These investigators found that rapamycin loaded in Pluronic gel inhibited smooth muscle cell proliferation (Ki-67 staining) and IH at 2 weeks after periadventitial application, but with recurrence of both by 4 weeks. Alternatively, rapamycin-loaded NPs produced durable

inhibition of smooth muscle cell proliferation and IH at two as well as four weeks. These studies strongly support the notion that prolonged drug delivery facilitated by NPs promotes lasting inhibition of IH.

Depending on the required functionality, an array of NPs, e.g., solid polymer nanoparticles, polymer micelles, and solid lipid nanoparticles have been produced and tested in a variety of *in vitro* and *in vivo* experimental systems [55, 56]. The “payload” that can be delivered ranges from small molecules, proteins/peptides, to nucleic acid (e.g., siRNAs and DNA). Recently, unimolecular micelle NPs, formed by individual/single multi-arm star amphiphilic block copolymer molecules, have gained more attention due to their excellent *in vitro* and *in vivo* stability, and chemical versatility including the ability of conjugating various types of targeting ligands [47, 57–59]. NPs conjugated with a specific type of targeting ligand can recognize its cognate receptor highly expressed on the surface of a specific population of cells allowing for preferential cellular uptake of targeted NPs. In a recent study, Chan et al synthesized paclitaxel-containing NPs that target Collagen IV. After systemical delivery following balloon injury[60], they observed greater efficacy of the targeted NPs versus non-targeted NPs 14 days after application. However, there have been no reports of periadventitial application using NPs targeting specific pathogenic smooth muscle cell populations or collagen in the vessel wall, underscoring a need for research in this area.

Though a highly promising tool for periadventitial drug delivery, NPs are not without drawbacks. Because of their small size and high solubility, periadventitially applied NPs may quickly diffuse into the surrounding tissues and the capillary bed, or be cleared by immune cells such as macrophages[61]. These issues could be resolved by specific tailoring, e.g. crosslinking NPs to the adventitia, or via combined use of NPs together with traditional platforms such as hydrogels[13]. While NPs embedded in a hydrogel can be effectively sequestered around the adventitia, evidence also indicates that coating with PEG and polylactic acid (PLA) copolymers can reduce the loss of NP to the immune system [62–64]. It is clear that the combination of hydrogels and NPs offers another layer of manipulation to generate optimal drug release kinetics.

Clinical Trials

A variety of polymer platforms have been used for periadventitial drug delivery and many of these have proven efficacious for inhibition of IH in preclinical models. However, none of these have advanced to clinical application. In fact, only a few clinical trials have been carried out to evaluate periadventitial drug delivery. The trials that have been performed are generally for patients receiving hemodialysis access. A rapamycin-impregnated polymer mesh was recently tested for safety and efficacy for hemodialysis access. Unfortunately this clinical trial (NCT01033357) was terminated due to an increase in the rate of graft infection in the experimental group. Another clinical trial (NCT00895479) which involved the periadventitial application of a VEGF-D-expressing adenovirus injected into a reservoir formed by collagen collars entered Phase III but was terminated for ‘strategic reasons’. In addition, the V-Health Phase I/II trials by Conte et al tested periadventitially applied endothelial cells in a gelfoam matrix in an effort to reduce neointimal hyperplasia formation in patients undergoing placement of dialysis access [65]. Unfortunately, the investigators

were unable to demonstrate a significant difference in primary or secondary patency by using this approach. Most recently, a phase I/II trial of periadventitial application of recombinant human pancreatic elastase I dissolved in phosphate buffered saline administered to patients undergoing dialysis access was completed (NCT01001351)[66, 67]. The overall 30-day outcomes were not significantly different for drug-treated patients. The subgroup of patients undergoing placement of a radiocephalic fistula and treated with elastase did demonstrate a statistically significant increase in primary patency at 3-years. Encouraged by these results, Proteon Therapeutics has begun to enroll this group of patients in a Phase III trial (NCT02110901) (NCT02414841). The PREVENT trial was a major investigation of the use of an oligonucleotide decoy of the transcription factor E2F (edifoligide) applied intraluminally to vein grafts at the time of arterial bypass. It is important to note that in this trial, the transcription factor was not delivered periadventially but through a pressurized intaluminal technique [68–70]. Unfortunately, the Phase III/IV trials indicated that the decoy was not more effective than placebo in preventing vein graft failure. In summary, to date there have been no successful clinical trials proving benefit to periadvential drug delivery in the prevention of intimal hyperplasia. This is surprising considering the great success achieved to date in preclinical studies. This realization underscores the need for further investigation into strategies to translate these various approaches to drug delivery into the clinical arena.

Conclusion

Over the past 15 years, in contrast to a rapid advancement in endovascular drug delivery technologies including drug-eluting stents and dru-eluting balloons, there remains a conspicuous lack of a clinically available approach to perivascular drug delivery for open vascular reconstructive surgery. As open surgeries including coronary artery bypass, peripheral bypass, as well as renal hemodialysis access remain common interventions, there is no doubt that a clinically applicable periadventitial drug delivery system is an urgent medical need. During the past decade, encouraging progress has been made in evaluating a variety of polymer materials and formats for periadventitial delivery, some of which have shown substantial efficacy for inhibiting IH in various preclinical models. Of particular note, nanoparticles open a new frontier for this endeavor. However, human clinical trials to translate these preclinical outcomes have severely lagged. Continued research to identify innovative periadventitial delivery methods to prevent recurrent vascular disease followed by properly designed clinical trials will ultimately benefit thousands of patients undergoing vascular reconstruction each year.

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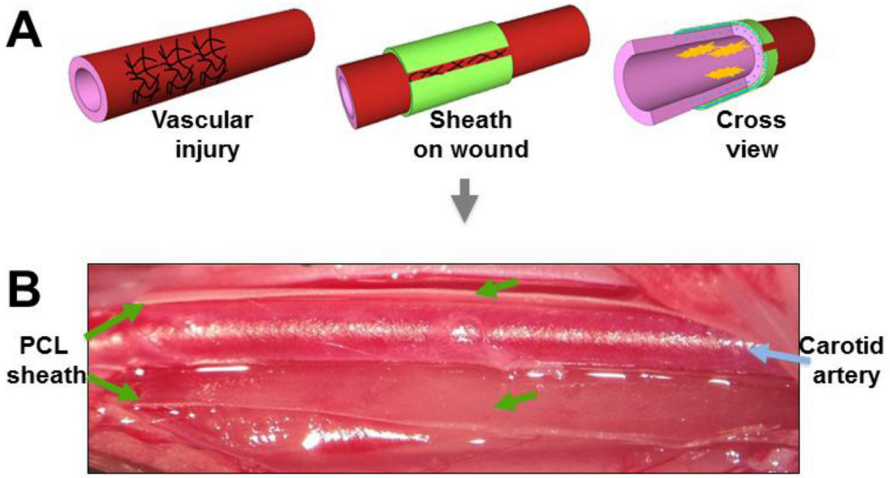

Figure 1. Non-constrictive periadventitial sheath

Diagram (A) and picture (B) showing a PCL sheath wrapped around a balloon-injured segment of rat carotid artery with an open slot, which generates flexibility and reduces constriction. (Reproduced from Yu et al (JCR) with permission).

Table 1

Comparison of periadventitial drug delivery methods

Methods	Advantages		Disadvantages	
Direct Application	**1**	Simplicity	**1**	Quick loss of drug
	2	Low cost (depending on the drug)	**2**	High doses necessary
			3	Toxicity to surrounding tissues
			4	No control of release kinetics
			5	Lack of uniformity
Hydrogels	**1**	Simplicity of application	**1**	Large initial burst of drug release
	2	Customizability	**2**	Toxicity concern
	3	Thermo-sensitivity	**3**	Bulkiness and inflammation concern of degradation products
	4	Adaptability to irregular shapes	**4**	Low adjustability of release kinetics
	5	Biocompatible and biodegradable	**5**	Limited control in material properties such as elasticity and degradability
	6	FDA-approved polymers available		
	7	Low cost		
Wraps	**1**	Ease of production and application	**1**	Mechanical stress to vessel
	2	Mechanical strength	**2**	Toxicity to surrounding tissues
	3	Durability	**3**	Bulkiness and inflammation concern of degradation products
	4	High drug loading capacity	**4**	Low adaptability to irregular vessel shapes
	5	Adjustability for prolonged release		
	6	Low burst release		
	7	Customizability for directional release		
Nanoparticles	**1**	Ability to infiltrate into the vessel	**1**	Need of a carrier (e.g. hydrogel) for immobilization
	2	High drug-loading capacity	**2**	Clearance by immune cells
	3	Minor inflammation concern of degradation products	**3**	Relatively high cost at present
	4	Minor concern of mechanical stress	**4**	New NPs yet to be FDA approved
	5	Adjustability of initial burst release		
	6	Durability and prolonged release		
	7	Versatility for ligand and/or imaging probe conjugation		
	8	Customizability for targeted delivery		