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Quickening: Translational Design of Resorbable Synthetic Vascular Grafts

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Abstract

Traditional tissue-engineered vascular grafts have yet to gain wide clinical use. The difficulty of scaling production of these cell- or biologic-based products has hindered commercialization. *In situ* tissue engineering bypasses such logistical challenges by using acellular resorbable scaffolds. Upon implant, the scaffolds become remodeled by host cells. This review describes the scientific and translational advantages of acellular, synthetic vascular grafts. It surveys *in vivo* results obtained with acellular synthetics over their fifty years of technological development. Finally, it discusses emerging principles, highlights strategic considerations for designers, and identifies questions needing additional research.

Keywords

degradable vascular graft; biodegradable; in situ tissue engineering; host remodeling

Introduction

Several of the most costly and morbid cardiovascular diseases are treated by vascular grafting. 16.5 million Americans live with coronary heart disease, which will cost the U.S. economy \$400 billion by 2030. (1) Another 8.5 million in the U.S. and 202 million worldwide live with peripheral artery disease. (1) Despite advances in medical management and transcatheter treatments, some patients still require surgical bypass. 400,000 coronary artery bypasses and 460,000 peripheral artery bypasses are performed each year in the U.S. (1,2) At least another 80,000 Americans receive arteriovenous fistulae or grafts for hemodialysis vascular access. (3,4) These procedures save lives or limbs.

Surgeons prefer autologous grafts for small-diameter (<6 mm) applications. (5–7) Autograft sources include the great saphenous vein, the internal mammary artery, and the radial artery. (5,7) For vascular access, the autograft analog is the arteriovenous fistula. The strong performance of autografts arises from several traits. Autografts possess a confluent endothelium which can counteract coagulation and suppress SMC proliferation. (8) They have mechanical properties that resemble the recipient vessel's more than synthetic grafts'

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do, which reduces neointimal hyperplasia. (9) Lastly, as living structures, they can battle infection and grow with the host. (10,11)

However, in a substantial portion of patients, anatomy, disease, or previous utilization preclude autografting. (12,13) Then surgeons resort to prosthetics. The invention of prosthetic grafts in the 1950s was a critical innovation that has saved countless lives and furthered the development of vascular surgery. (14) Today, the prosthetic graft market is dominated by products made of ePTFE and PET. (12) Prosthetic grafts have the advantage of convenience. They are relatively inexpensive to produce, have long shelf lives, and can be used in almost any patient at a moment's notice. Unfortunately, they also perform poorly in small-diameter applications. Failure modes include thrombosis, stenosis, and infection. (7,10,15,16) These problems are thought to stem from their supraphysiologic stiffness and artificial composition. (9) Though incremental advances have somewhat improved performance (17), no disruptive innovations have taken hold in the vascular graft market for the last forty years.

This review will address the strategic design and developmental status of resorbable synthetic vascular grafts: polymeric prosthetics that spur host cells to build up neotissue as they degrade. These prosthetics transform *in situ* from a polymeric tube to a living, vessel-like structure. [Fig. 1] Resorbable synthetic grafts could combine the convenience of prosthetics with the functionality of autografts, producing a broadly available therapy for patients without autologous alternatives. For reviews on cell-based and decellularized grafts, two alternative strategies for tissue-engineered graft production, see these recent publications. (18,19)

Strategic Advantages of Resorbable Synthetic Grafts

All vascular grafts share a core set of design objectives. The functional objectives are:

- implantable in all required configurations,
- available at the time of need,
- low complication rates, and
- high patency.

Those designing for low-resource communities or the battlefield might add “off-the-shelf availability” and “stable under ambient conditions”.

Translational objectives are:

- acceptable to regulators, payers, and other translational gatekeepers,
- profitable, and
- applicable in some target population.

It should be noted that the ultimate design objective is profitability. Ethical bioengineers should still design a graft that meets the other objectives as best they can – and the graft will not be profitable for long if they do not. However, as the case of current prosthetic grafts

demonstrates, a fair-performing graft can still improve the lives of millions of patients if paired with low price and broad availability.

Of course, it would be better to have strong performance with low price and broad availability. That has been the mission of tissue engineers, who have been working to make living grafts for the last fifty years. The diversity of their efforts illustrates the myriad ways to achieve these objectives.

The first robust tissue-engineered graft was produced by Sparks in the late 1960s. (20,21) The “Sparks mandrel” graft was a fibrotic tube encapsulating a Dacron graft, formed after the Dacron had been implanted along the rib cage several weeks prior. Unfortunately, the Sparks graft was difficult to reproduce, and its long-term patency was even worse than prosthetics. (22–24) Weinberg and Bell introduced the first *in vitro* tissue-engineered graft in the 1980s. (25) Sequential layers of collagen gel had been compacted by SMCs, reinforced by Dacron, and seeded with ECs. This technology was taken up by Organogenesis, Inc. (26), but failed to exit R&D. The next commercial prospect arose from the first strong biologic graft produced *in vitro*. (27,28) L’Heureux and colleagues cultured human fibroblasts and SMCs past confluence until the ECM they produced could be detached from the culture dish. These cell/ECM sheets were rolled into tubes, matured *in vitro*, endothelialized, and implanted. This “tissue engineering by self-assembly” technique underlaid Cytograft Tissue Engineering, Inc. Cytograft reported its first clinical data in 2007. (29) But business problems caused the company to fail. Soon after L’Heureux’s report, Niklason et al. described the graft that has advanced furthest to date. (30) They cultured SMCs on a tubular PGA scaffold in a bioreactor until the scaffold had been replaced by ECM. Optionally, the muscular grafts could then be seeded with ECs. This technology spawned Humacyte, Inc., in 2004, which has progressed to phase III trials. (31) A more material-centric strategy was introduced by Breuer and Shinoka, a pair of surgeons interested in repair of congenital great vessel defects. Shinoka was the first surgeon to implant a tissue-engineered vascular graft – a synthetic scaffold that had been seeded with autologous vascular cells 10 d before. (32) Later, freshly harvested BM-MNCs were substituted for the vascular cells, and a centrifugal separation and vacuum seeding method shortened the production lead time from days to hours. Though use has been restricted to low-pressure systems, the clinical outcomes are heartening. (33,34) More recently, a proprietary synthetic graft from Xeltis reached first-in-human. (35) Nakayama et al.’s devitalized “biotube,” grown similarly to the Sparks mandrel, has also achieved clinical use. (36)

Economic Factors

Despite these remarkable achievements, none of these designs have yet translated into a commercial success. In our view, this is not due to poor performance. Traditional tissue-engineered grafts face daunting obstacles to translation. If an acellular synthetic graft were to perform well, it would have a simpler path to the bedside. [Table 1]

On the technical side, synthetics have the advantages of consistency and flexibility. Polymer stock can be synthesized reproducibly using existing industrial infrastructure. Furthermore, the graft structure can be finely controlled in manufacturing. This precision allows for batch-to-batch consistency and the delicate tuning of mechanical and topographical cues. By

contrast, the properties of biologic batches tend to vary. Cell-based products pose even greater challenges. Immunogenicity, sterility, and phenotypes must be monitored. As more of the biology underlying tissue engineering is elucidated, these barriers may shrink. But cell-based products are unlikely to ever match synthetics' convenience.

From a translational perspective, synthetics have lower production costs and potentially simpler adoption pathways. Polymers are typically inexpensive to synthesize and process, and the unit cost decreases as production scales. (Of course, the simpler the manufacturing, the better.) Biologic products tend to be expensive and difficult to produce at scale. (37) Synthetics also might be regulated as medical devices. In many regulatory systems, medical devices do not need as elaborate an approval process as biologics do. Biologics and living grafts thus may face more ambiguous and expensive regulatory pathways. Ordering, shipping, and storage logistics are also simpler for off-the-shelf synthetics than for custom-produced or perishable biologics.

Recall that the primary objective of a translational product is to be profitable. If a graft is expensive to bring to market, the manufacturer will charge high prices to recoup their costs. To justify the increased price, payers will demand better outcomes. Performance expectations will thus rise with the cost of commercialization – perhaps outstripping the graft's capabilities.

The lesson is that tissue engineering the perfect graft, while a valid strategy, is not a guarantee of translation. [Fig. 2] There are many ways to make a graft that helps patients.

Scientific Factors

Low cost is not the only draw of resorbable synthetics. There is evidence that traditionally tissue-engineered grafts may not need to be as elaborately seeded and cultured as was once assumed. Resorbable synthetics may thus be capable of strong performance.

One hint came from the fate of seeded cells. The ostensible purpose of seeding cells is to populate the scaffold. The idea that the seeded cells eventually formed the living conduit was backed up by consistent observations that a graft seeded with cells did better than the same graft without them. For example, Nieponice et al. implanted spongy PEUU scaffolds with or without muscle-derived stem cells into the rat IAA. (38) Seeding improved patency at 8 wks. from 10% (1/10) to 65% (11/17). Failed grafts showed thrombus suggestive of early occlusion. In another study, Hibino et al. implanted nonwoven PGA grafts into the mouse IVC with or without BM-MNCs. (39) Within 2 wks., 80% (8/10) of the unseeded grafts were stenosed. Seeding reduced stenosis to 20% (2/10).

That cell seeding can reduce thrombosis and stenosis is uncontested. Yet for a time, many investigators assumed that the cells enacted these effects by, or at least while, repopulating the graft. Then, Roh et al. implanted SCID/bg mice with a miniaturized Breuer/Shinoka graft: a fast-degrading PGA scaffold acutely seeded with human BM-MNCs. (40) Surprisingly, the human RNA vanished after a few days – but the seeded grafts still were more cellular at 7 d than the unseeded ones. A prior study had also noted this effect. (41) Loading the scaffold with MCP-1 recaptured much of the benefit of cell seeding. The

authors surmised the main role of the seeded cells was paracrine signaling to host monocytes.

Of course, the seeded cells may persist in other graft designs. Progenitor cells are famously finicky about their living conditions. It is conceivable that differentiated cells, protectively encased in ECM from extended culture, would survive better. But this cannot be assumed. Robust lineage tracing is challenging (42), and few studies have included tracing at all.

Regeneration without cell seeding may also be model-dependent. Rodents heal more robustly than humans. (43) But if it is true that a large portion of the seeded cells' effect can be paracrine, and the graft can still be as successful clinically as the Breuer/Shinoka one has been, biochemical and material cues might recapitulate the benefits of cell seeding.

Clinical results have also suggested that even leading tissue-engineered designs may not strictly require seeding. In 2011, during their clinical trial in hemodialysis access, Cytograft fabricated an autologous graft for a patient whose condition unexpectedly improved. (44) Cytograft air-dried the graft and froze it for later bench testing. Later, the patient's accesses began failing. Even a devitalized graft was deemed ethically acceptable as a life-prolonging measure. Cytograft endothelialized and implanted it. The graft remained patent and functioning well to the time of the report at 8 wks. Cytograft then fabricated grafts with banked cells, devitalized them, and implanted them without endothelium into three patients. (45) No immune reaction was seen, and the grafts maintained secondary patency for months. In the same year, Humacyte reported allogeneic grafts cultured *in vitro*, decellularized, and implanted in large animals. (46) 88% (7/8) of grafts implanted as arteriovenous shunts in baboons were patent at timepoints ranging up to 6 mo. 83% (5/6) of grafts implanted as endothelialized carotid bypasses in dogs were patent at timepoints ranging up to 1 yr. Explanted grafts were found to be slowly cellularizing, with cells migrating from the anastomoses and the adventitia. Humacyte's clinical trials have utilized similar decellularized vessels without endothelium as arteriovenous shunts and achieved 89% secondary patency at 1 yr. (31) A midgraft segment was removed from one patient at 44 wks. The segment showed CD31+ cells and α -SMA+ cells surrounding healing cannulation tracts. The acellular grafts appear to function in humans – at least, in the low-pressure, high-flow setting of arteriovenous shunts.

It is not certain that cell-free grafts will ever perform on par with cellular grafts. Almost any scaffold seems to perform better when seeded. However, given the difficulties of producing cellular grafts at scale, research into cell-free synthetics is merited. At worst, these designs allow the basic science exploration of the material and chemical cues driving host remodeling. At the best, they could provide a high-performance graft free of the costs and complications of cell seeding. Again, there are many ways to make a graft that helps patients.

Designs and Progress

The degradable vascular graft arose naturally from work in traditional prosthetics. The concept was not a giant leap from gelatin-impregnated Dacron or endothelialized ePTFE; in

fact, it had been proposed as early as 1919. (47) In 1971, Marinescu et al. found that when dogs lived years with polyurethane prosthetics, the graft degraded, and a neovessel formed. (48) This then-unseen result spawned ten years of research into polyurethane grafts. (49–54) However, further study found the grafts were not degrading, but eroding. (55) The prospect of biostable particles accumulating within patients brought that research avenue to an end. Since then, the progress of vascular tissue engineering has closely tracked the materials available. Table 2 shows properties of commonly chosen polymers.

Many groups have fabricated synthetic grafts. This review will focus only on grafts that are primarily synthetic, fully degradable, designed for arterial use, intended to be cell-free, and that have been tested chronically in an orthotopic model.

Strong and Tunable: Poly(lactic acid) and Poly(glycolic acid)

The poly(lactic acid)/poly(glycolic acid) (PLA/PGA) family of polyesters is a popular choice for any biomaterials work. PLA and PGA can be synthesized alone or copolymerized into poly(lactic acid-*co*-glycolic acid) (PLGA). Varying the lactide:glycolide ratio in the copolymer or the *D:L* ratio in the lactide monomer tunes strength, hydrophilicity, and degradation rate. (56) The fast degradation of PGA/PLGA and the slow of PLA make them useful for extreme degradation rate strategies. The materials are clinically accepted as resorbable sutures and orthopedic implants. (56,57) Concerns with this polymer family include their acidic degradation products, moderate cytocompatibility, and supraphysiologic stiffness.

Poly(glycolic acid) and poly(lactic acid-*co*-glycolic acid).—The first resorbable synthetic grafts were made from the PGA/PLA family. In the late 1970s, Bowald et al. fabricated tubular meshes from PG910 (PLGA with 90% glycolide: 10% lactide) and implanted them in pigs as aortic wall patches. (58) By 40 d, the PG910 had visibly lost mass. Spindle-shaped cells populated the graft wall, and the lumen was lined with cobblestone-shaped cells. The authors then placed full-circumference grafts in the aortic arch. (59) 100% (6/6) of pigs with grafts longer than 15 cm died of ruptures at approximately 21 d, which corresponds with the degradation timeframe of PG910. Ruptured grafts demonstrated incomplete cell infiltration. However, 100% (7/7) of shorter grafts showed similar histological changes to the aortic patch.

Subsequently, Greisler and colleagues implanted tubes of woven PGA into the rabbit IAA. (60) 76% (34/45) showed no change in diameter out to as long as 7.5 mo. Full-length stenosis and dilation were seen in 13% (6/45) and 11% (5/45), respectively. By 3 wks., a smooth intima was grossly visible, and the PGA had begun to lose mass on histology. Staining revealed a sporadic subintimal layer of SMC-like cells, surrounded by more peripheral myofibroblasts and collagen. Both layers formed luminal to the graft wall. The neovessels withstood three to five times systolic pressure *ex vivo*. At later timepoints, cartilaginous metaplastic sites and early atherosclerotic lesions were observed. (61) Woven PLGA gave similar results. (62,63)

Though these studies rightly excited the young field of tissue engineering, the high incidence of early dilation caused concern. So, investigators composited PGA or PLGA with slower-

degrading materials. One method wove together PG910 and PDO strands at a 74:26 ratio. (64) 97% (36/37) of rabbits with these aortic grafts underwent no diametric change from 2 wks. to 12 mo. The grafts evolved at a rate intermediate to pure PG910 and pure PDO grafts. Phagocytic macrophages appeared to mediate degradation, with inflammation peaking at 2 wks. The resolution of neotissue thickening coincided with full PG910 mass loss at 2 mo. Another effort coated woven PG910 with a blend of P(*D,L*)-LA and poly(2,3-butylene fumarate). (65) This coating overly retarded degradation in the dog IAA; polymer was still visible at 12 wks. A poly(2,3-butylene succinate) coating degraded more quickly, allowing external capillaries to infiltrate the graft and seed vascular cells. (84)

A substantial body of work has examined PGA/PLCL grafts in the great vessels, but its low-pressure application places it outside the scope of this review. For a summary, see Drews et al. (85)

PGA and PLGA can provide strength to a graft early on. But they may degrade too quickly to be the only load-bearing components. Biochemical interventions might recoup some of the rapid remodeling seen with cell-seeded grafts. (85) Still, PGA and PLGA may always require compositing with some longer-lasting material.

Poly(lactic acid).—In contrast to PGA and PLGA, PLA degrades slowly. When a nanofibrous PLA graft was implanted in the mouse IAA, most material was still present at 12 mo. (86) A confluent layer of ECs and some smooth muscle had formed. But few cells had penetrated the wall, and microcalcifications had nucleated. In another study, electrospun PLLA was reinforced with blended fibers of PCL and poly(*L*-lactide-*co*-caprolactone-*co*-glycolide). (87) Mucin was covalently attached to improve thrombogenicity. These grafts showed 100% (8/8) patency at 1 mo. in the athymic rat carotid. They endothelialized fully and maintained their original mechanics. Still, few cells infiltrated the graft wall.

To accelerate remodeling, some groups blend PLA with other materials. Grafts electrospun from PLLA and low molecular weight PCL endothelialized and developed an adventitial muscle layer after 4 wks. in the rat carotid. (88) But growth was slow, and the neotissue was thin. Patency was also low at 56% (5/9). Releasing heparin-bound SDF-1 α from these grafts increased the rates of endothelial coverage and adventitial tissue formation. Patency rose to 89% (8/9). SDF-1 α is believed to attract circulating EPCs, and indeed, several of the midgraft ECs were CD31+/CD34+. However, the impenetrability of the small-pored and slow-degrading PLLA/PCL graft barred the luminal ECs from contacting the adventitial SMCs until the graft developed transmural defects, which took between 3 and 6 mo.

Some groups use PLA as a failsafe component of an otherwise fast-degrading graft. PGA mesh, coated with PLCL and reinforced with PLA nanofibers, demonstrated good diametral stability to 8 wks. in the mouse IAA. (89) PLLA spun into yarn with PGA, woven into a graft, and coated with a collagen sponge showed good stability and tissue formation in the dog carotid. (90) A similar study in the pig thoracic aorta used the collagen-PGA weave reinforced with a film of PCL and a weave of PLA. Grafts showed 100% (15/15) patency out to 12 mo. with full endothelialization and some muscle function. (91)

Though progress has been made, PLA grafts still struggle with slow remodeling and degenerative changes. Biochemical modifications or compositing may remediate remodeling.

Tough, Ductile, and Slower-Degrading: Poly(ϵ -caprolactone) and Poly(p -dioxanone)

Poly(ϵ -caprolactone) (PCL) and poly(p -dioxanone) (PDO) both offer softer, more ductile, more moderately degrading alternatives to the PGA/PLA family. Otherwise, they are quite different. PCL is hydrophobic, but PDO is strongly hydrophilic. PCL is an order of magnitude softer than PDO. PCL degrades within a few years, whereas PDO lasts several months. Both are familiar as sutures, resorbable implants, and scaffolding materials. Concerns with them include their still suprphysiologic moduli and impaired cell adhesion on PCL.

Poly(p -dioxanone).—PDO first garnered interest as a slower-degrading alternative to the PGA grafts then in development. In 1987, Greisler et al. implanted rabbits with woven PDO. (92) 96% (27/28) had unchanged diameters at up to 12 mo., and 4% (1/28) were stenotic. In an improvement over similarly constructed PGA grafts, no aneurysm or dilation was seen. The neointima took longer to develop than with PGA, and its thickness stabilized at less than the overly thick PGA-derived neovessel. Cessation of neotissue formation again coincided with full material loss. In another improvement, little lipid or calcium deposition was seen at 12 mo. (63)

Since then, PDO has rarely been used alone. Degradation rate seems dependent on microstructure. In contrast to the stability observed by Greisler, Pan et al. saw that microfibrinous PDO grafts developed aneurysms in the rat aorta by 3 mo. (93)

Poly(ϵ -caprolactone).—PCL has been more popular. In 2008, Walpoth's group implanted microfibrinous PCL grafts into the rat IAA. (94,95) No stenosis or dilation was observed in any of the 15 rats out to 24 wks. Within 12 wks., the grafts had endothelialized, been infiltrated by capillaries, and developed a thin neointima of spindle-shaped cells. Neointimal thickness stabilized past 12 wks. Unfortunately, chondroid metaplasia was observed at 6 wks. These areas gradually diminished to leave behind focal neointimal calcifications.

One question was the long-term stability of the neointima, which had formed luminal to the graft wall. This layer could be akin to Greisler's productive "inner capsule", which had fused with the outer layer after the graft degraded fully. It could also be the beginnings of stenosis. Another set of rats were taken to 18 mo. with microfibrinous PCL grafts. (96) Patency was 100% (15/15). Full endothelial coverage was obtained by 6 mo. The α -SMA+ neointimal layer stabilized at 6 mo. at a reasonable thickness of 40–70 μ m. Then, it slowly remodeled from a cellular layer into a lightly populated collagenous one. The neointimal cell loss correlated with the regression of capillaries and a loss of cells in the graft wall. Unfortunately, this was occurring just when the scaffold was losing strength. The PCL molecular weight fell to 50% by 12 mo., and fiber fragmentation was visible at 18 mo. The neointimal chondroid metaplasia noted at earlier timepoints grew, progressed into endochondral ossification, and spread to the wall. By 18 mo., 15% of the total graft volume

was calcified. However, the by then advanced age of the rats may have encouraged this dysfunctional remodeling.

It is not certain how tightly quasi-osteochondral phenotypes and calcification are linked to PCL. Kuwabara et al. did not observe chondroid metaplasia or calcification in microfibrinous PCL grafts taken to 48 wks. in the rat carotid. (97) Neither did Ye et al. at 4 wks. in the canine femoral (98), or Wang et al. at 100 d in the rat IAA. (99)

Several creative approaches have sought to stabilize cellularity. Pan et al. simultaneously electrospun PCL and PDO fibers. (93) The PDO/PCL grafts demonstrated faster endothelialization, more matrix synthesis, and deeper smooth muscle penetration than pure PCL grafts. De Valence et al. increased the hydrophilicity of PCL with plasma treatment. They saw increased cell infiltration and capillary invasion in the rat IAA; in fact, there were more cells and capillaries at 3 wks. in the hydrophilic PCL than at any time up to 18 mo. in the untreated. (100) Other authors have attached cell-adhesive peptides (101–105) or added cell-friendly biochemicals (102,103,105–107) to entice engraftment.

Of course, these problems were all seen in rodents, which mimic human physiology poorly. PCL was eventually evaluated in the pig carotid. (108) 8 cm microfibrinous grafts were implanted as interpositions and followed for 1 mo. with aspirin and clopidogrel. The grafts had a patency rate of 78% (7/9), vs. 67% (4/6) in control ePTFE. No diametral or flowrate changes were seen. Endothelialization was extensive at 86%, though misaligned cells suggested some dysfunction. Whether longer-term implants would reveal the regression seen in the rats was unknown. (96)

Another group implanted nanofibrous PCL in the sheep carotid. (109) The grafts were electrospun from a 20:1 blend of PCL and chitosan. These grafts lost 50% of their ultimate tensile strength *in vitro* in 2 wks. They also matched native compliance (14%/100 mmHg). Despite this distensibility, they held stable diameters out to 6 mo. Patency was 67% (4/6). Histology revealed a confluent endothelium and the presence of α -SMA+, calponin+, and MHC+ cells in the media. The graft had stiffened to twice its original modulus. By 6 mo., only 10% of the original graft material was detectable. No calcification was found. The grafts' 1.5 cm length prevents much extrapolation to clinical outcomes, but the PCL/chitosan blend is apparently supportive of more rapid degradation and better remodeling than some PCL designs.

PCL has been a widely popular material. Its predictable, slow degradation and its moderate strength make it a solid choice. Yet cell infiltration and chronic inflammation are recurring challenges. Low-porosity PCL seems to act as a barrier. Researchers pursuing a transmural infiltration strategy will likely need to increase its cytocompatibility.

Softer and Elastic: Poly(ester urethane urea), Poly(glycerol sebacate), and Chain-Extended UPy-poly(L-lactide-co-caprolactone)

An elastomer can sustain repeated high strain without plastic deformation. To be an elastomer, a material must operate above its glass transition temperature, be only slightly crystalline, and be lightly crosslinked. (110) Chemically crosslinked elastomers are held

together by covalent bonds. These bonds are strong, but forming them may require toxic crosslinkers or harsh conditions. Physically crosslinked elastomers contain phase-separated domains where intermolecular forces bind the chains into tight crystalline phases. These bonds are often easier to produce but may not be as durable. Elastomers are attractive for vascular prosthetics because an elastomeric graft might match native compliance without suffering dilation.

Poly(ester urethane)urea.—A classic elastomer toolkit is the polyurethane. The strong hydrogen bonds between the urethane linkages cause the “hard blocks” (the crosslinkers and chain extenders) to phase-separate into a crystalline domain. The “soft blocks” (often polyesters or polyethers) remain amorphous and rubbery, giving the polymer chain the slack needed to sustain large deformations and the entropic drive to recoil when the load is released. (110) The modular design of polyurethanes makes them a versatile platform. This also means that the term “polyurethane” communicates little about the material. Properties must be categorized individually for each polymer.

Hong et al. synthesized a polyurethane from 2 kD PCL, putrescine, and diisocyanate. (111) This material was a poly(ester urethane)urea, or PEUU. It had a modulus of approximately 80 MPa and had lost half its molecular weight by 56 d *in vitro*. It supported cell proliferation, though initial adhesion was somewhat impaired. (112) The authors electrospun it into a nanofibrous graft. (111) Compliance was reasonable at 3–5%/100 mmHg. But the grafts had a 40% (10/25) patency at 8 wks. in the rat IAA, even with antiplatelet therapy. *In vitro* testing indicated high platelet adhesion. So, the authors fabricated a second set of grafts made of an 85:15 (g/g) PEUU/phospholipid polymer blend. The phospholipid polymer did not substantially affect graft mechanics or microstructure. It did improve platelet adhesion *in vitro* and increase 8 wk. patency to 67% (6/9). However, the vWF+ and α -SMA+ layers were thin and did not penetrate the dense graft wall. *In vitro* cytocompatibility assays suggested the addition of the phospholipid polymer decreased cell adhesion on the scaffolds.

The PEUU grafts were reformulated for a second study. (113) This time, the grafts were spun from pure PEUU and coated with covalently bound phospholipid polymer. The phospholipid coating again reduced platelet adhesion *in vitro*. The grafts were implanted into the rat IAA and followed for 24 wks. with aspirin. Coated grafts showed 92% (11/12) patency at 8 wks., with full endothelialization and correct EC alignment to flow. A thin layer of collagen and α -SMA+ cells underlaid the endothelial lining. Compliance rose from an initial 5%/100 mmHg to match native aorta at 14%/100 mmHg at 8 wks., and then fell again to ~7%/100 mmHg at 24 wks. These shifts are suggestive of early material degradation and later collagen deposition. Still, there was no infiltration into the graft wall out to 24 wks.

This PEUU is strong and can support productive remodeling. Incorporation of phospholipid polymer substantially improves its thrombogenicity. However, longer studies must assess degradation timeframe and determine whether inner and outer tissue capsules developing on either side of the dense wall will eventually produce an organized neovessel.

Poly(glycerol sebacate).—Poly(glycerol sebacate) (PGS) is a soft (~300 kPa) thermoset elastomer. (73) Hydrolytic enzymes and likely free radical species affect its rapid and

surface-mediated degradation in vivo. (74,114) PGS is thought to support constructive remodeling through both the micromechanical cues conveyed by its low stiffness and the resolution of inflammation brought about by its rapid resorption.

In 2012, a spongy PGS tubular core reinforced with a thin layer of electrospun PCL was implanted into the rat IAA. (115) Three months later, the PGS was no longer detectable. The grafts displayed complete endothelialization with ECs aligned to flow. A media had formed within the former PGS core that stained for α -SMA and MHC. A follow-up study with rats survived to 12 mo. maintained a patency of 80%, with all failures being acute postoperative occlusion. (116) The neoarteries demonstrated native compliance. Perivascular innervation was observed, as well as limited responses to vasoactive agents. Importantly, the amount of insoluble elastin was equivalent to native artery. Elastin is difficult to quantify, and not all studies have attempted to do so. Still, this was the largest amount of elastin reported in a tissue-engineered vascular graft to date. Though loose ECM organization, residual adventitial macrophage presence, and impaired vasoactivity still clearly distinguished them from native aorta, the neoarteries had substantially approached native properties from 3 to 12 mo.

PGS grafts have demonstrated potential. However, as Greisler learned in the 1980s, a rapid remodeling strategy places special demands on the host's regenerative capacity. Ongoing work is examining PGS grafts in rodent disease models and large animals.

Chain-extended UPy-poly(L-lactide-co-caprolactone).—Unlike traditional polymers, in which monomers are joined by covalent bonds, supramolecular polymers are held together by directional noncovalent interactions. These interactions are strong enough that the molecular aggregate behaves more like a single macromolecule than a set of transiently associated monomers. Because the noncovalent bonds are reversible, the properties of supramolecular polymers differ from traditional polymers. In supramolecular elastomers, the self-assembling regions act as physical crosslinks. For a description, see Lehn. (117)

Muylaert et al. extended low molecular weight PLCL with UPy moieties, then electrospun it into grafts. (118) Some grafts were spun from pure PLCL-UPy, whereas some had UPy-conjugated fragments of SDF-1 α added. UPy dimerizes with a free energy of 44–50 kJ/mol. (119) This dimerization both bound the SDF-1 α peptides to the PLCL chains and bound the PLCL chains to each other, driving the self-assembly. The grafts were implanted in the rat IAA for 7 d. Peptide-loaded grafts showed greater cell and macrophage infiltration than the unloaded grafts.

More work is ongoing in industry. Xeltis, a European startup based on this technology, is in clinical trials for pediatric congenital heart defect repair. As of 2016, five modified Fontan patients had borne grafts for 2 yrs. with no graft-related complications. (35) As more information becomes available, the learnings should be exciting.

Unanswered Questions in Design

Work on resorbable grafts has traditionally focused on clinical outcomes. But some have begun to examine the design inputs of remodeling.

What graft cues control the remodeling response?

As is the theme in tissue engineering, nearly every scaffold property likely influences remodeling somehow. Still, a few factors deserve special attention.

Degradation rate.—There is no consensus on how quickly the graft should degrade. Though it may seem that a slower-degrading graft would give more time for neotissue to mature, the rate of tissue formation seems to positively correlate with that of material degradation. (92,115,120) The foundational design requirement is that at any given moment, the material and neotissue combined must bear arterial pressure stably. [Fig. 3] Both fast- and slow-degrading tactics have produced stable, patent grafts – at least, in animals.

Of course, some degradation rates will outstrip the host's regenerative capacity, leading to aneurysm. Yet opting for as slow a degradation rate as possible may cause other problems. This was first hinted at in the late 1980s. Researchers were investigating hybrid degradable/stable grafts, searching for a combination that would provide both mechanical integrity and regeneration. Interestingly, simply providing more biostable polymer did not always improve long-term mechanics. The presence of the biostable material impaired regeneration. If the biostable material inhibited regeneration more than the resorbable promoted it, the aneurysm rate could actually increase upon biostable material addition. (121) Chronic inflammation, chondrogenesis, and osteogenesis were also observed near the biostable material. (122) As discussed previously, slowly resorbing graft materials like PCL or PLA can face similar challenges. (123,96,120)

It seems the chronic presence of foreign materials biases the neovessel towards degenerative changes. However, arterial regeneration is a complex process. It is likely each design will have its own optimum degradation timeframe. Also, even if there exists some degradation rate that produces the highest-quality neotissue, some investigators may still choose to risk long-term degeneration to preclude any chance of short-term failure.

Degradation timeline is one of the most challenging variables to investigate. The degradation rate cannot always be varied independently of other important graft properties, and the experiments are time-consuming. Computational tools may soon reduce this empirical search space. Arterial growth and remodeling models were originally developed to predict mechanical changes in disease. (125) Some groups are now adapting them to predict the dimensions and mechanics of a remodeling graft. (114,126) Both more data and more model development are required before researchers will be able to optimize a graft design *a priori*, but work is ongoing.

Pore size.—There has been more targeted investigation into the effect of pore size.

The ostensible impact of porosity is to allow cellular infiltration. Interconnected pores permit transmural regeneration and anchor neotissue in the graft. (127) Roughly, cells need 10 μm gaps to traverse a scaffold. (128) One might then assume the larger the pore, the better. But grafts with large pores might experience transmural blood seepage during implant. This can sometimes be managed surgically, but it adds time and frustration to the operation.

Pore size can even affect the remodeling outcome. Macrophages modulate their phenotype according to the scaffold pore size. (131) In general, pores of the size range 25–40 μm promote a more pro-healing phenotype than larger pores. Pores are harder to define in fibrous structures, but a similar trend has been observed in electrospun fabrics. (99)

Pore size may be more critical for materials that degrade slowly or have poor cell adhesion. Kong's group reported that if electrospun PCL fibers were too thin (meaning the spaces between the fibers were small), cells could not infiltrate the graft, and no neotissue formed at all. (99) Thicker fibers produced more robust macrophage infiltration, capillary invasion, and neotissue production. (132) Similarly, Wang et al. were able to substantially increase early macrophage infiltration in the rabbit carotid by including a loosely packed subluminal layer in an otherwise dense electrospun PCL graft. (133) The increased macrophage infiltration, and subsequent increased staining for VEGF and MCP-1, were thought to have increased the rate of endothelialization and smooth muscle formation. The smooth muscle layer was also observed to form within the graft wall instead of on the luminal face, as was often observed in Walpoth's PCL grafts.

Still, not all designs intend cells to cross the graft wall. High quality regeneration has been obtained from fusion of the adventitial and luminal neotissue forming around a degrading, nonporous graft. (129) Why this graft regenerated well, while other grafts cells could not penetrate did not, is unknown.

One challenge in investigating pore size is controlling it. Many synthetic grafts are electrospun, a process which typically yields small pores. But process modifications can increase pore size. (134) Increasing fabrication platform versatility will allow more study.

Mechanics.—Mechanics has been the highest-prioritized factor in graft design. Of course, a graft must bear arterial pressure without creep or fatigue. Yet mechanics also impacts patency and remodeling. These effects can be described on the scale of the graft or the cell.

A focus on graft-scale mechanics presented early in the field's development. Biomechanics researchers noted a nonlinear relationship between pressure and diameter in an internally pressurized artery. As pressure increased, diameter increased more and more slowly, producing a J-shaped curve. (135) [Fig. 4] The nonlinearity is due to the arterial ECM architecture. Fibrillar collagen is laid down adventitially in undulating and variably aligned paths, whereas sheets of elastin are located more luminal. As the luminal pressure rises and the artery expands, a small amount of energy goes to straightening the collagen fibers. But most of the load is borne by the soft and distensible elastin. As the artery continues to stretch, the now-straight collagen fibers begin to engage with their large tensile moduli.

Subsequent fiber recruitment progressively stiffens the vessel. This allows the artery to both be compliant in the physiologic pressure range and to lock in a stable diameter under spikes in load.

Current prosthetic grafts are orders of magnitude stiffer than native arteries. The mechanical mismatch at the anastomoses disrupts the normal levels of shear stresses at the intima and transmural stresses in the wall. (136) Both ECs and SMCs can become pathological. The results are thrombosis, from turbulent flow and EC dysfunction, and anastomotic or neointimal hyperplasia, from excessive SMC proliferation. (137)

If non-native compliance can cue destructive remodeling, it is reasonable to think that native compliance would cue constructive remodeling. Compliance does appear to affect SMC proliferation in degradable grafts. In otherwise identical composite degradable/stable grafts, the softer graft version had a thicker neointima and a lower patency rate. (138) However, in slow-degrading grafts, the stiffer ones developed thicker neointimas. (127) More research is required here.

Another question is whether mechanics can cue elastin synthesis. Functional elastin provides long-term mechanical stability and healthy biochemical signaling. Yet few tissue-engineered grafts have contained it. (140) A mechanical influence on elastin production was suspected early in the development of the field. (53) Elastin was observed on Orcein staining of distensible polyurethane/PLA grafts in 1983, in contrast to none in the stiff PGA grafts in concurrent development. (49,141) When the distensible grafts were wrapped in stiff ePTFE, elastin staining decreased. (142,143) This result could mean that pulsatile strain is necessary for elastin synthesis, as some evidence indicates – but the story is not clear. (144)

Regardless of its influences on elastin production, the benefits of native compliance on patency are undisputed. Unfortunately, few materials are both as strong and distensible as native arteries. Increasing graft compliance with this limited material set often requires clever microstructural design.

One method to make a material more resilient is to alter the graft microstructure. A fibrous graft accommodates small deformations by fiber bending, and many small fibers require less force to bend than a single large fiber. Therefore, fibrous materials tend to be more distensible than the same material fabricated some other way, to the same porosity. (145) If the alignment and tortuosity of the fibers can be controlled, structural deformation becomes programmable. Hence one reason for the popularity of fibrous grafts.

Another option is to layer softer and stronger materials together coaxially. By setting the unpressurized inner diameter of the inner, softer tube smaller than that of the outer, stiffer tube, one can design a graft that is soft in low pressure and stiff in high. For example, Sonoda et al. set their graft to switch from soft to stiff at 100 mmHg. (146)

Native compliance is possible with many materials. (146–149) The challenge is achieving the necessary manufacturing precision. Also, in grafts intended to remodel quickly, the effort may not be justified. The more important goal is to approach native compliance during

remodeling. (115,116) After all, though native compliance clearly benefits the outcomes of biostable grafts, we do not know what mechanics produce optimal regeneration.

Of course, all mechanical phenomena at the graft scale are sensed at the cell scale. Forces and stiffnesses affect several important cellular decisions. (150,151) Designers should remember that graft-scale mechanics and cell-scale mechanics are partially uncoupled in nonhomogeneous or thick-walled designs. For example, imagine a cell adhered to Walpoth's "no-barrier" microfibrinous PCL graft. (152) When the cell exerts traction on the material through its focal adhesions, it will presumably sense the bulk stiffness of the PCL fiber – approximately 340 MPa. (67) But because of the graft's fibrous structure, its graft-scale modulus will be approximately 7 MPa. As the graft deforms under arterial pressure, the cell will experience the same strain it would feel in a homogenous 7 MPa graft. The point is that a graft designer can use microstructure to present diverse cues to cells, offering another level of influence.

What cells infiltrate the graft, and how do they affect remodeling?

The invading cells are believed to serve two basic functions: orchestration of remodeling and scaffold repopulation.

Leukocytes: the orchestrators.—The now broadly accepted idea that macrophages coordinate the host response to a biomaterial was suggested even by early graft researchers. (153,154) A series of publications in the early 2010s further elaborated on the theory. In mice, Breuer and Shinoka demonstrated that much of the functional improvement from seeding BM-MNCs could be recaptured by loading MCP-1. (40) Another study examined MCP-1 in microfibrinous PCL grafts in rats. (155) Burst release increased the number of CD34+ cells at 90 d.

It is still not clear which cues influence macrophage behavior. Macrophages definitely respond to pore size and material type. (131,154) But the sensing and integrating mechanisms, as well as any other inputs, are poorly understood.

Additionally, it now appears that other immune cells play a role. Over several studies, Breuer and Shinoka implanted PGA/PLCL grafts into the IVC of C57BL/6 or SCID/bg mice. 100% of SCID/bg grafts were patent at 6 wks. (156) But in the C57BL/6, 80% of grafts were half occluded by neointima within 2 wks. The stenosis worsened out to the 10 wk. endpoint. (39) The development of stenosis corresponded to the peak of macrophage infiltration and, counterintuitively, to an M1-to-M2 phenotype switch. BM-MNC-seeded grafts did not develop such extensive stenosis. Furthermore, fewer macrophages infiltrated them, and no M1-to-M2 switch was observed. The authors next ablated all macrophages using clodronate liposomes and saw decreased stenosis in the unseeded grafts. (39) However, neotissue formation also halted. Apparently, some portion of macrophage activity is necessary for regeneration.

A second study set out to identify the difference between the responses in SCID/bg and wild-type mice. (157) Grafts were implanted into SCID/bg, SCID, and background mice. SCID mice and background mice both showed high stenosis rates. However, both SCID/bg

and background mice given an NK cell-neutralizing antibody or an aspirin/clopidogrel regimen displayed minimal to moderate stenosis. SCID/bg mice also had less macrophage infiltration. The authors explained that NK cells and platelets (which are both affected by the bg mutation) could be responsible for attracting macrophages to the graft. If too many macrophages enter, the neotissue overgrows. If too few macrophages enter, the neotissue does not form. Alternatively, the NK cells and platelets may directly cooperate with the infiltrating mononuclear phagocytes to orchestrate remodeling.

Lending credence to a role for platelets, a correlation between thrombus formation and stenosis has been observed across multiple groups. (41,158) Furthermore, the anti-stenotic effect of mesenchymal stem cell seeding might partially explained. (40,41,157) Platelet deposition decreased on seeded grafts. (41) If platelets attract macrophages, then controlling platelet adhesion could influence not just thrombosis incidence, but also remodeling outcome.

No conclusive evidence has yet been demonstrated for this hypothesis. However, administration of the platelet inhibitor cilostazol did reduce stenosis in wild-type mice. (159) Similarly, inhibiting TGF β 1R1 simultaneously reduced stenosis and macrophage iNOS expression. (160) TGF- β 1 inhibition reduced stenosis rates comparably to seeding with BM-MNCs. (161) *In vitro*, monocytes pre-activated with LPS and IFN- γ expressed even higher levels of inflammatory markers when also given TGF- β 1. One may thus conclude that macrophages promote stenosis by secreting TGF- β 1, but recall that proinflammatory macrophages were associated with less stenosis *in vivo*. (39) The role of TGF- β 1 may be more complex. More research is needed here.

Neutrophils also may influence remodeling in response to material cues. (162) As the first responders to an implant, they are well positioned to set the tone for later events.

Resorbable grafts apparently can't live with leukocytes or without them. Tissue will not regenerate without leukocyte involvement, but including them risks occlusion. To appreciate these subtle cells, researchers must move beyond simplistic M1/M2 categorizations and the macrophage-exclusive focus. (163) High-resolution techniques like flow cytometry or RNA-seq may enable distinction of these various cell phenotypes and perhaps identify new regulators of remodeling.

Progenitor (?) cells: the repopulators.—Perhaps the most burning question surrounding any acellular graft is the identity and source of the cells that repopulate it. Three theories have been advanced. [Fig. 5]

Trans-anastomotic migration is when the vascular cells in the adjacent arterial stumps proliferate and spread into the graft. This form of ingrowth usually is thought to only reach a cm or so in humans, as demonstrated from pannus ingrowth on traditional prosthetics. (43) Therefore, graft designers have sought not to rely on it. Unfortunately, transanastomotic regeneration may dominate remodeling of short grafts, including almost all grafts tested in small animals. This length-dependent effect inherently limits the utility of small animals in vascular tissue engineering.

Fall-out healing is when circulating progenitor cells attach to the graft. The idea is theoretically attractive, in that grafts of any length could be repopulated, but practically challenging, in that circulating progenitors are rare. Bone marrow mesenchymal stem cells were once widely thought to contribute to smooth muscle in the neotissue. (164) But as stem cell researchers began to suspect studies showing engraftment might be mistaken (42), focus on them decreased. They are today more commonly envisioned acting paracrinely. More researchers now suspect EPCs play a leading role. EPCs may even contribute to smooth muscle formation through a process similar to endoMT. (165)

Transmural infiltration is when adventitial progenitor cells and capillaries invade a porous graft from the outside in. The capillaries seed the graft lumen with ECs, and the adventitial progenitors differentiate into smooth muscle. Transmural infiltration would likely have the greatest capacity for regenerating long grafts. However, the invasion of external capillaries and the proliferation of smooth muscle are also hallmarks of atherosclerotic plaque development or stenosis. To be effective, transmural remodeling thus must self-limit. Also, the nature and possible pathological tendencies of these adventitial progenitors are still being discussed. (166)

The involvement of stem cells in remodeling is especially controversial. Some studies, especially those using attractive chemokines or capture antibodies on the graft, have found ECs that express EPC markers like CD34 (88,167) or CD133 (168). Others have not seen such markers. (164) The local controversy around whether a given stem cell can populate a graft has its roots in broader controversies about stem cell definitions, differentiation, and tracking methods within the applicable areas of stem cell biology. While the biologists resolve their differences, a few studies have ventured graft-specific questions.

Talacua et al. sought to isolate each healing mechanism in a rat model. (155) They implanted PCL microfibrinous grafts into the rat IAA, then flanked them with GoreTex cuffs attached to segments of sex-mismatched rat aorta. The GoreTex barred transanastomotic migration from the sex-mismatched aorta, and the sex-mismatching allowed identification of any cells that managed to traverse the barrier anyways. The grafts were also sometimes wrapped externally with GoreTex to prevent transmural infiltration. The presence of the GoreTex cuffs cut the proportion of sex-mismatched cells observed in the neoartery from 40% to 10%. Furthermore, while immune cells permeated the entire graft in all cases, the adventitial wrap decreased early cellularity. Nevertheless, normal remodeling proceeded, with full endothelial confluence by 3 mo. This suggests that at least in the rat, fall-out healing can support remodeling. The source of the SMCs was not identified. The authors observed only one vWF+/ α -SMA+ cell, suggesting endoMT was infrequent.

Fall-out healing appears rarer in humans. (130) Circulating progenitors are sparse, and their numbers decrease further with cardiovascular disease. (169) Therefore, Pennel et al. asked whether transmural infiltration could also support remodeling. (130) 1 cm high-porosity polyurethane test grafts were anastomosed to two 4.5 cm impermeable ePTFE grafts. These composite grafts were implanted as loops in the rat IAA. In this way, transanastomotically migrating cells would have to traverse nearly 5 cm to reach the test graft. Some test grafts were additionally wrapped in porous but cell-impermeable ePTFE jackets, and some were

sealed with a nonporous abluminal film. Patency in unwrapped grafts was 75% (9/12), with 80% endothelial coverage by 12 wks. But film-sealed grafts had 0% (0/6) patency. The wrapped grafts exhibited 83% (10/12) patency, but only 16% endothelial coverage. Furthermore, capillary ostia were found on the unwrapped graft lumen, with ECs streaming outwards from the opening. The authors concluded that although fall-out healing can contribute some cells, the bulk of remodeling relies on transmural infiltration via capillary invasion.

Another effort was made in sheep. (170) Row et al. formed grafts from small intestinal submucosal sheets, sealed them with fibrin glue, and seeded them with allogeneic ECs. Some grafts were also seeded with allogeneic stem cell-derived SMCs. The grafts were implanted into immunosuppressed sheep and explanted at 1, 4, and 12 wks. These grafts were 5 mm in diameter and 4–5 cm long. Yet at even 1 wk., the cell density was even along the graft length. Cells were densest at the lumen and ablumen. As the grafts matured, the cell density became radially uniform. The speed of midgraft infiltration and the radial cell gradient at 1 wk. suggests long grafts can be populated by both fall-out and transmural healing. This would support the observations of Bowald and colleagues, who saw that pigs survived degradation of fast-degrading aortic grafts up to 15 cm in length. (59) But because the authors did not distinguish cell type in their counts, it is unclear whether some of the infiltrating cells were inflammatory. Those would presumably not contribute to repopulation, unless transdifferentiation takes place – which would be as difficult to demonstrate as stem cell participation.

An obstacle to determining the mode of graft healing is that the healing mode may depend on the graft. Though investigators can speak of major and minor healing modes as trends, each graft should be studied individually.

How will remodeling proceed in elderly and comorbid patients?

Most grafts have been tested in healthy, young animals. Yet vascular pathologies overwhelmingly occur in older patients, whose age and disease have impaired their regenerative ability. Few studies have examined graft remodeling under these conditions.

The effects of hypercholesterolemia were investigated with the early PG910 grafts. (171) Hypercholesterolemic rabbits were more likely to develop aneurysms, hematomas, and calcific nodules. Their arterial neotissue was about 25% as thick as that in healthy animals and contained lipid-laden, poorly aligned myofibroblasts. Infiltrating macrophages also became full of cholesterol, and they remained present after material degradation. Still, these sobering results were observed with an aggressively atherogenic diet. Over 50% of the rabbits died during disease induction, and another 30% died within days of surgery. Moderate illness may have more moderate impact.

Diabetes has also been studied. In rats with streptozotocin-induced diabetes, microfibrillar PCL grafts showed heavy inflammation, heavy platelet adhesion, and some calcification by even 1 mo. (105) These results correlated with slower endothelialization and smooth muscle infiltration. Coating the grafts with RGD gave no measurable benefit.

Age has been less frequently evaluated. Aging elicits changes in vascular biology, including progressive stiffening and endothelial dysfunction. (175) It also reduces progenitor cell proliferative capacity and function, slowing healing. (176) Senescent models have been explored in biostable graft research (43,172), but most studies in vascular tissue engineering have used young animals. (28,46,173,174) Our work with PGS/PCL grafts in aged rats confirms that regeneration is altered [unpublished data]. The effect of age is a significant unanswered question for the field.

The potential consequences of disease and age on acellular grafts are concerning. *In vitro* tissue-engineered graft designers can select for healthy, allogeneic cells (though this may also introduce immunogenicity). Acellular graft designers are restricted to whichever cells happen to be within the patient. Advances in stem cell rejuvenation can inform graft designs and, if necessary, concurrent treatments to encourage endogenous tissue restoration. (177)

Though aged or diseased animals are more difficult to obtain and work with, they are undeniably more clinically relevant. The earlier in development that a graft's failure modes can be identified, the earlier they can be solved – and the less costly it will be to do so.

Conclusion

Understanding of resorbable vascular grafts has progressed dramatically since Guthrie proposed the concept in 1919. Some designs have ventured into the clinic, and more will follow in coming years.

Yet the ideal design is nowhere near clear. Bioengineers are needed to investigate the effects of material composition, mechanics, microstructures, and degradation rates, as well as other scaffold parameters that may not yet be appreciated. Experts in developmental biology, stem cells, vascular biology, and immunology are needed to study the infiltrating cells and identify ways to control their functionality. Finally, biomedical researchers are needed to assess these grafts in aged and diseased animals.

Should these grafts prove safe and efficacious, they will likely reach more patients than traditionally tissue-engineered grafts. The translational benefits and scientific insights possible with resorbable grafts merit their further development.

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Abbreviations

α-SMA	α -smooth muscle actin
BM-MNC	bone marrow mononuclear cell
CD31	cluster of differentiation 31

EC	(vascular) endothelial cell
EndoMT	endothelial-to-mesenchymal transition
EPC	endothelial progenitor cell
ePTFE	expanded polytetrafluoroethylene, a.k.a. Teflon or Gore-Tex
H&E	hematoxylin and eosin
IAA	infrarenal abdominal aorta
IFN-γ	interferon- γ
iNOS	inducible nitric oxide synthase
IVC	inferior vena cava
LPS	lipopolysaccharide
MCP-1	monocyte chemoattractant protein-1
MIF	macrophage migration inhibitory factor
PCL	poly(ϵ -caprolactone)
PDO	poly(<i>p</i> -dioxanone), also abbreviated PDS
PEG	poly(ethylene glycol), a.k.a. poly(ethylene oxide) (PEO)
PET	poly(ethylene terephthalate), a.k.a. Dacron
PEUU	poly(ester urethane urea)
PG910	polyglactin 910
PGA	poly(glycolic acid), a.k.a. polyglycolide
PLA	poly(lactic acid), a.k.a. polylactide
PLCL	poly(lactide- <i>co</i> -caprolactone), also abbreviated PCLA
PLGA	poly(lactic acid- <i>co</i> -glycolic acid), a.k.a. polyglactin
SCID/bg	severe combined immunodeficiency/beige mutations
SDF-1α	stromal cell-derived factor-1 α
SMC	(vascular) smooth muscle cell
SM-MHC	smooth muscle myosin heavy chain
Sox10	(sex-determining region Y)-box 10
TGF-β1	transforming growth factor- β 1
TGFβ1R1	transforming growth factor- β 1 receptor-1

UPy	2-ureido-[1H]-pyrimidin-4-one
VEGF	vascular endothelial growth factor

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics—2017 update: A report from the American Heart Association. *Circulation*. 2017;135:00–00.
2. Kim LK, Swaminathan RV, Minutello RM, Gade CL, Yang DC, Charitakis K, et al. Trends in hospital treatments for peripheral arterial disease in the United States and association between payer status and quality of care/outcomes, 2007–2011. *Catheter Cardiovasc Interv*. 2015;86(5):864–72. [PubMed: 26446891]
3. USRDS. Chapter 4: Vascular access. In: 2015 Annual Data Report. 2015 p. 197–210.
4. USRDS. Chapter 1: Incidence, prevalence, patient characteristics, and treatment modalities. In: 2015 Annual Data Report. 2015 p. 139–58.
5. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. *J Am Coll Cardiol* [Internet]. 2011;58(24):e123–210. Available from: 10.1016/j.jacc.2011.08.009
6. Sidawy AN, Spergel LM, Besarab A, Allon M, Jennings WC, Padberg FT, et al. The Society for Vascular Surgery: Clinical practice guidelines for the surgical placement and maintenance of arteriovenous hemodialysis access. *J Vasc Surg*. 2008;48(5):2S–25S. [PubMed: 19000589]
7. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). *Circulation* [Internet]. 2006;113(11):e463–654. Available from: <http://circ.ahajournals.org/cgi/doi/10.1161/CIRCULATIONAHA.106.174526>
8. Rajendran P, Rengarajan T, Thangavel J, Nishigaki Y, Sakthisekaran D, Sethi G, et al. The vascular endothelium and human diseases. *Int J Biol Sci*. 2013;9(10):1057–69. [PubMed: 24250251]
9. Collins MJ, Li X, Lv W, Yang C, Protack CD, Muto A, et al. Therapeutic strategies to combat neointimal hyperplasia in vascular grafts. *Expert Rev Cardiovasc Ther*. 2012;10(5):635–47. [PubMed: 22651839]
10. Wilson WR, Bower TC, Creager MA, Amin-Hanjani S, O’Gara PT, Lockhart PB, et al. Vascular graft infections, mycotic aneurysms, and endovascular infections: A scientific statement from the American Heart Association. *Circulation*. 2016;134(20):e412–60. [PubMed: 27737955]
11. Patterson JT, Gilliland T, Maxfield MW, Church S, Shinoka T, Breuer CK. Tissue-engineered vascular grafts for use in the treatment of congenital heart disease: From the bench to the clinic and back again. *Regen Med*. 2013;7(3):409–19.
12. Desai M, Seifalian AM, Hamilton G. Role of prosthetic conduits in coronary artery bypass grafting. *Eur J Cardio-thoracic Surg*. 2011;40(2):394–8.
13. Markar SR, Kutty R, Edmonds L, Sadat U, Nair S. A meta-analysis of minimally invasive versus traditional open vein harvest technique for coronary artery bypass graft surgery. *Interact Cardiovasc Thorac Surg*. 2010;10:266–70. [PubMed: 19942633]
14. Gotto AM. Profiles in cardiology: Michael E. DeBakey. *Clin Cardiol*. 1991;14:1007–10. [PubMed: 1841017]
15. USRDS. Clinical indicators & preventive care. In: 2012 USRDS Annual Data Report. 2012 p. 229–36.
16. Schwab SJ. Vascular access for hemodialysis. *Kidney Int*. 1999;55:2078–90. [PubMed: 10231476]
17. Lin PH, Chen C, Bush RL, Yao Q, Lumsden AB, Hanson SR. Small-caliber heparin-coated ePTFE grafts reduce platelet deposition and neointimal hyperplasia in a baboon model. *J Vasc Surg*. 2004;39(6):1322–8. [PubMed: 15192575]
18. Chang WG, Niklason LE. A short discourse on vascular tissue engineering. *NPJ Regen Med*. 2017;2:7. [PubMed: 29057097]

19. Seifu DG, Purnama A, Mequanint K, Mantovani D. Small diameter vascular tissue engineering. *Nat Rev Cardiol*. 2013;10:410–21. [PubMed: 23689702]
20. Sparks CH. Autogenous grafts made to order. *Ann Thorac Surg* [Internet]. 1969;8(2):104–13. Available from: <http://www.scopus.com/inward/record.url?eid=2-s2.0-0014561934&partnerID=40&md5=a820c47d83e112adcd31373532877f53>
21. Sparks CH. Silicone mandril method for growing reinforced autogenous femoro-popliteal artery grafts in situ. *Ann Surg*. 1973;177(3):293–300. [PubMed: 4266308]
22. Hallin RW, Sweetman WR. A seven-year follow-up of mandril grafts placed by Charles H. Sparks and his associates. *Am J Surg*. 1976;132(2):221–3. [PubMed: 133619]
23. Guidoin R, Noel HP, Marois M, Martin L, Laroche F, Beland L, et al. Another look at the Sparks-Mandril arterial graft precursor for vascular repair: Pathology by scanning electron microscopy. *Biomater Med Devices Artif Organs*. 1980;8(2):145–67. [PubMed: 6446943]
24. Christenson JT, Eklof B. Sparks mandril, velour Dacron and autogenous saphenous vein grafts in femoropopliteal bypass. *Br J Surg*. 1979;66(7):514–7. [PubMed: 157181]
25. Weinberg CB, Bell E. A blood vessel model constructed from collagen and cultured vascular cells. *Science* (80-). 1986;231(4736):397–400.
26. Lilly cuts aid to researcher. *The New York Times* [Internet]. 1992 11 5; Available from: <http://www.nytimes.com/1992/11/05/business/lilly-cuts-aid-to-researcher.html>
27. L'Heureux N, Pâquet S, Labbé R, Germain L, Auger FA. A completely biological tissue-engineered human blood vessel. *FASEB* [Internet]. 1998;12(1):47–56. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9438410>
28. L'Heureux N, Dusserre N, König G, Victor B, Keire P, Wight TN, et al. Human tissue-engineered blood vessels for adult arterial revascularization. *Nat Med* [Internet]. 2006;12(3):361–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16491087%5Chttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1513140>
29. L'Heureux N, McAllister TN, de la Fuente LM. Tissue-engineered blood vessel for adult arterial revascularization. *N Engl J Med* [Internet]. 2007;357(14):1451–3. Available from: <http://www.nejm.org/doi/full/10.1056/NEJMc071536%5Chttp://www.ncbi.nlm.nih.gov/pubmed/17914054>
30. Niklason LE, Gao J, Abbott WM, Hirschi KK, Houser S, Marini R, et al. Functional arteries grown in vitro. *Science* (80-). 1999;284(5413):489–93.
31. Lawson JH, Glickman MH, Ilzecki M, Jakimowicz T, Jaroszynski A, Peden EK, et al. Bioengineered human acellular vessels for dialysis access in patients with end-stage renal disease: two phase 2 single-arm trials. *Lancet* [Internet]. 2016;387(10032):2026–34. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0140673616005572>
32. Shin'oka T, Ikada Y. Transplantation of a tissue-engineered pulmonary artery. *N Engl J Med*. 2001;344(7):532–3. [PubMed: 11221621]
33. Shin'oka T, Matsumura G, Hibino N, Naito Y, Watanabe M, Konuma T, et al. Midterm clinical result of tissue-engineered vascular autografts seeded with autologous bone marrow cells. *J Thorac Cardiovasc Surg*. 2005;129(6):1330–6. [PubMed: 15942574]
34. Hibino N, McGillicuddy E, Matsumura G, Ichihara Y, Naito Y, Breuer C, et al. Late-term results of tissue-engineered vascular grafts in humans. *J Thorac Cardiovasc Surg* [Internet]. 2010 2 [cited 2014 Nov 5];139(2):431–6, 436–2. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20106404>
35. Xeltis. A novel bioabsorbable vascular graft in modified Fontan procedure - mid-term results [Internet]. 2016 Available from: <http://www.xeltis.com/technology/>
36. Nakayama Y, Furukoshi M, Terazawa T, Tatsumi E. In body tissue architecture (IBTA) for autologous 3D tissue fabrication. *Tissue Eng Part A*. 2017;23(S1):S72.
37. Archer R, Williams DJ. Why tissue engineering needs process engineering. *Nat Biotechnol*. 2005;23(11):1353–5. [PubMed: 16273058]
38. Nieponice A, Soletti L, Guan J, Hong Y, Gharaibeh B, Maul TM, et al. In vivo assessment of a tissue-engineered vascular graft combining a biodegradable elastomeric scaffold and muscle-derived stem cells in a rat model. *Tissue Eng Part A*. 2010;16(4):1215–23. [PubMed: 19895206]

39. Hibino N, Yi T, Duncan DR, Rathore A, Dean E, Naito Y, et al. A critical role for macrophages in neovessel formation and the development of stenosis in tissue-engineered vascular grafts. *FASEB J* [Internet]. 2011 12 [cited 2014 Nov 10];25(12):4253–63. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3236622&tool=pmcentrez&rendertype=abstract>
40. Roh JD, Sawh-Martinez R, Brennan MP, Jay SM, Devine L, Rao DA, et al. Tissue-engineered vascular grafts transform into mature blood vessels via an inflammation-mediated process of vascular remodeling. *Proc Natl Acad Sci U S A* [Internet]. 2010 3 9 [cited 2014 Nov 10];107(10):4669–74. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2842056&tool=pmcentrez&rendertype=abstract>
41. Hashi CK, Zhu Y, Yang G-Y, Young WL, Hsiao BS, Wang K, et al. Antithrombogenic property of bone marrow mesenchymal stem cells in nanofibrous vascular grafts. *Proc Natl Acad Sci* [Internet]. 2007;104(29):11915–20. Available from: <http://www.pnas.org/content/104/29/11915%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/17615237%5Cnhttp://www.pnas.org/content/104/29/11915.full%5Cnhttp://www.pnas.org/content/104/29/11915.full.pdf>
42. Terada N, Hamazaki T, Oka M, Hoki M, Mastalerz DM, Nakano Y, et al. Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. *Nature* [Internet]. 2002;416(6880):542–5. Available from: <http://www.nature.com/doifinder/10.1038/nature730>
43. Zilla P, Bezuidenhout D, Human P. Prosthetic vascular grafts: Wrong models, wrong questions and no healing. *Biomaterials* [Internet]. 2007 12 [cited 2014 Oct 16];28(34):5009–27. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17688939>
44. Wystrychowski W, Cierpka L, Zagalski K, Garrido S, Dusserre N, Radochonski S, et al. Case study: First implantation of a frozen, devitalized tissue- engineered vascular graft for urgent hemodialysis access. *J Vasc Access*. 2011;12(1):67–70. [PubMed: 21360466]
45. Wystrychowski W, McAllister TN, Zagalski K, Dusserre N, Cierpka L, L'Heureux N. First human use of an allogeneic tissue-engineered vascular graft for hemodialysis access. *J Vasc Surg* [Internet]. 2014;60(5):1353–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24103406>
46. Dahl SLM, Kypson AP, Lawson JH, Blum JL, Strader JT, Li Y, et al. Readily available tissue-engineered vascular grafts. *Sci Transl Med*. 2011;3(68):68ra9.
47. Guthrie CC. End-results of arterial restitution with devitalized tissue. *J Am Med Assoc*. 1919;73(3):186–7.
48. Marinescu V, Pulescu E, Crnaru S. Long-term biological fate of polyurethane aortic prostheses. *Thorax* [Internet]. 1971;26(1):108–11. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/5543818>
49. Lommen E, Gogolewski S, Pennings AJ, Wildevuur CRH, Nieuwenhuis P. Development of a neo-artery induced by a biodegradable polymeric vascular prosthesis. *ASAIO Trans*. 1983;29:255–9.
50. van der Lei B, Darius H, Schror K, Nieuwenhuis P, Molenaar I, Wildevuur CRH. Arterial wall regeneration in small-caliber vascular grafts in rats: Neoendothelial healing and prostacyclin production. *J Thorac Cardiovasc Surg*. 1985;90(3):378–86. [PubMed: 3897723]
51. van der Lei B, Wildevuur CRH, Nieuwenhuis P, Blaauw EH, Dijk F, Hulstaert CE, et al. Regeneration of the arterial wall in microporous, compliant, biodegradable vascular grafts after implantation into the rat abdominal aorta - Ultrastructural observations. *Cell Tissue Res*. 1985;242(3):569–78. [PubMed: 4075377]
52. van der Lei B, Nieuwenhuis P, Molenaar I, Wildevuur CRH. Long-term biologic fate of neoarteries regenerated in microporous, compliant, biodegradable, small-caliber vascular grafts in rats. *Surgery*. 1987;101(4):459–67. [PubMed: 3563893]
53. Robinson PH, van der Lei B, Knol KE, Pennings AJ. Patency and long-term biological fate of a two-ply biodegradable microarterial prosthesis in the rat. *Br J Plast Surg*. 1989;42(5):544–9. [PubMed: 2804520]
54. Lei B v. d., Bartels HL, Dijk F, Wildevuur CRH. Insufficient reduction of the thrombogenic characteristics of small caliber polyurethane vascular prostheses after heparin bonding. *ASAIO Trans*. 1985;31:107–10.
55. Hinrichs WLJ, Kuit J, Feil H, Wildevuur CRH, Feijen J. In vivo fragmentation of microporous polyurethane-based and copolyesterether elastomer-based vascular prostheses. *Biomaterials*

[Internet]. 1992;13(9):585–93. Available from: [http://www.sciencedirect.com/science/article/pii/S014296129290026K%5Cn%3CGo to ISI%3E://WOS:A1992JG77200003](http://www.sciencedirect.com/science/article/pii/S014296129290026K%5Cn%3CGo%20to%20ISI%3E%3F%3EWOS%3A1992JG77200003)

56. Treiser M, Abramson S, Langer R, Kohn J. Degradable and resorbable materials. In: Biomaterials Science: An Introduction to Materials in Medicine. 2013 p. 179–95.
57. Taylor MS, Shalaby SW. Sutures. In: Biomaterials Science: An Introduction to Materials in Medicine. 2013 p. 1010–24.
58. Bowald S, Busch C, Eriksson I. Arterial regeneration following polyglactin 910 suture mesh grafting. *Surgery*. 1979;86(5):722–9. [PubMed: 494064]
59. Bowald S, Busch C, Eriksson I. Absorbable material in vascular prostheses: A new device. *Acta Chir Scand*. 1980;146(6):391–5. [PubMed: 7468070]
60. Greisler HP. Arterial regeneration over absorbable prostheses. *Arch Surg*. 1982;117:1425–31. [PubMed: 6291492]
61. Greisler HP, Kim DU, Price JB, Voorhees AB. Arterial regenerative activity after prosthetic implantation. *Arch Surg*. 1985;120(3):315–23. [PubMed: 2982343]
62. Greisler HP, Joyce KA, Kim DU, Pham SM, Berceli SA, Borovetz HS. Spatial and temporal changes in compliance following implantation of bioresorbable vascular grafts. *J Biomed Mater Res*. 1992;26(11):1449–61. [PubMed: 1447229]
63. Greisler HP, Cabusao EB, Lam TM, Murchan PM, Ellinger J, Kim DU. Kinetics of collagen deposition within bioresorbable and nonresorbable vascular prostheses. *ASAIO Trans*. 1991;July/Sept:M472–5. [PubMed: 1836337]
64. Greisler HP, Endean ED, Klosak JJ, Ellinger J, Dennis JW, Buttle K, et al. Polyglactin 910/polydioxanone bicomponent totally resorbable vascular prostheses. *J Vasc Surg*. 1988;7(5):697–705. [PubMed: 3130496]
65. Galletti PM, Trudell LA, Chiu TH, Sasken H, Richardson PD, Parhizgar A, et al. Coated bioresorbable mesh as vascular graft material. *ASAIO Trans*. 1985;31:257–63.
66. Liu L, Guo S, Chang J, Ning C, Dong C, Yan D. Surface modification of polycaprolactone membrane via layer-by-layer deposition for promoting blood compatibility. *J Biomed Mater Res - Part B Appl Biomater*. 2008;87(1):244–50. [PubMed: 18386834]
67. Eshraghi S, Das S. Mechanical and microstructural properties of polycaprolactone scaffolds with one-dimensional, two-dimensional, and three-dimensional orthogonally oriented porous architectures produced by selective laser sintering. *Acta Biomater* [Internet]. 2010;6(7):2467–76. Available from: 10.1016/j.actbio.2010.02.002
68. Sun H, Mei L, Song C, Cui X, Wang P. The in vivo degradation, absorption and excretion of PCL-based implant. *Biomaterials*. 2006;27(9):1735–40. [PubMed: 16198413]
69. Bai W, Zhang ZP, Li Q, Chen DL, Chen HC, Zhao N, et al. Miscibility, morphology and thermal properties of poly(para-dioxanone)/poly(D,L-lactide) blends. *Polym Int*. 2009;58(2):183–9.
70. Ulery BD, Nair LS, Laurencin CT. Biomedical applications of biodegradable polymers. *J Polym Sci Part B Polym Phys*. 2011;49(12):832–64.
71. Mäkelä P, Pohjonen T, Törmälä P, Waris T, Ashammakhi N. Strength retention properties of self-reinforced poly L-lactide (SR-PLLA) sutures compared with polyglyconate (MaxonR) and polydioxanone (PDS) sutures. An in vitro study. *Biomaterials*. 2002;23(12):2587–92. [PubMed: 12033607]
72. Ethicon. Wound Closure Manual. 2007.
73. Wang Y, Ameer GA, Sheppard BJ, Langer R. A tough biodegradable elastomer. *Nat Biotechnol*. 2002;20(6):602–6. [PubMed: 12042865]
74. Wang Y, Kim YM, Langer R. In vivo degradation characteristics of poly(glycerol sebacate). *J Biomed Mater Res Part A*. 2003;66(1):192–7.
75. Thomas S, Pothan LA. Wettability and AFM studies of natural fibres and their composites. In: *Natural Fibre Reinforced Polymer Composites*. 2009 p. 420–1.
76. Kureha. Kuredex [Internet]. 2017 Available from: http://www.kuredex.com/pdf/Kuredex_Brochure_EN.pdf
77. Miller ND, Williams DF. The in vivo and in vitro degradation of poly(glycolic acid) suture material as a function of applied strain. *Biomaterials*. 1984;5(6):365–8. [PubMed: 6098316]

78. Belibel R, Avramoglou T, Garcia A, Barbaud C, Mora L. Effect of chemical heterogeneity of biodegradable polymers on surface energy: A static contact angle analysis of polyester model films. *Mater Sci Eng C* [Internet]. 2016;59:998–1006. Available from: 10.1016/j.msec.2015.10.010
79. Chu C-C. Biodegradation properties. In: *Wound Closure Biomaterials and Devices*. 1996 p. 146.
80. Heath DE, Cooper SL. Polymers: Basic principles. In: *Biomaterials Science: An Introduction to Materials in Medicine*. 2013 p. 70.
81. Matsusue Y, Yamamuro T, Oka M, Shikunami Y, Hyon S-H, Ikada Y. In vitro and in vivo studies on bioabsorbable ultra-high-strength poly(L-lactide) rods. *J Biomed Mater Res*. 1992;26(12):1553–67. [PubMed: 1484062]
82. Wang X, Lian K, Chen T. Experiment research on bonding effect of poly (lactic-co-glycolic acid) device by surface treatment method. *Int J Polym Sci*. 2015;2015(825287).
83. Park JJ, Yu EJ, Lee WK, Ha CS. Mechanical properties and degradation studies of poly(D,L-lactide-co-glycolide) 50:50/graphene oxide nanocomposite films. *Polym Adv Technol*. 2014;25(1):48–54.
84. Galletti PM, Aebischer P, Sasken HF, Goddard MB, Chiu T-H. Experience with fully bioresorbable aortic grafts in the dog. *Surgery*. 1988;103(2):231–41. [PubMed: 3340992]
85. Drews JD, Miyachi H, Shinoka T. Tissue-engineered vascular grafts for congenital cardiac disease: Clinical experience and current status. *Trends Cardiovasc Med* [Internet]. 2017;27(8):521–31. Available from: 10.1016/j.tcm.2017.06.013
86. Kurobe H, Maxfield MW, Tara S, Rocco KA, Bagi PS, Yi T, et al. Development of small diameter nanofiber tissue engineered arterial grafts. *PLoS One* [Internet]. 2015;10(4):e0120328 Available from: <http://dx.plos.org/10.1371/journal.pone.0120328>
87. Janairo RRR, Zhu Y, Chen T, Li S. Mucin covalently bonded to microfibers improves the patency of vascular grafts. *Tissue Eng Part A* [Internet]. 2014;20(1–2):285–93. Available from: <http://www.scopus.com/inward/record.url?eid=2-s2.0-84891539911&partnerID=tZOTx3y1>
88. Yu J, Wang A, Tang Z, Henry J, Lee B, Zhu Y, et al. The effect of a stromal cell-derived factor-1 α /heparin coating of a biodegradable vascular graft on recruitment of both endothelial and smooth muscle progenitor cells and accelerated healing. *Biomaterials*. 2012;33(32):8062–74. [PubMed: 22884813]
89. Sugiura T, Agarwal R, Tara S, Yi T, Lee YU, Breuer CK, et al. Tropoelastin inhibits intimal hyperplasia of mouse bioresorbable arterial vascular grafts. *Acta Biomater* [Internet]. 2017;52:74–80. Available from: 10.1016/j.actbio.2016.12.044
90. Yokota T, Ichikawa H, Matsumiya G, Kuratani T, Sakaguchi T, Iwai S, et al. In situ tissue regeneration using a novel tissue-engineered, small-caliber vascular graft without cell seeding. *J Thorac Cardiovasc Surg* [Internet]. 2008;136(4):900–7. Available from: 10.1016/j.jtcvs.2008.02.058
91. Torikai K, Ichikawa H, Hirakawa K, Matsumiya G, Kuratani T, Iwai S, et al. A self-renewing, tissue-engineered vascular graft for arterial reconstruction. *J Thorac Cardiovasc Surg*. 2008;136(1):7–11. [PubMed: 18603045]
92. Greisler HP, Ellinger J, Schwarcz TH, Golan J, Raymond RM, Kim DU. Arterial regeneration over polydioxanone prostheses in the rabbit. *Arch Surg*. 1987;122(6):715–21. [PubMed: 3107517]
93. Pan Y, Zhou X, Wei Y, Zhang Q, Wang T, Zhu M, et al. Small-diameter hybrid vascular grafts composed of polycaprolactone and polydioxanone fibers. *Sci Rep* [Internet]. 2017;7(1):3615 Available from: <http://www.nature.com/articles/s41598-017-03851-1>
94. Pektok E, Nottelet B, Tille JC, Gurny R, Kalangos A, Moeller M, et al. Degradation and healing characteristics of small-diameter poly(ϵ -caprolactone) vascular grafts in the rat systemic arterial circulation. *Circulation*. 2008;118(24):2563–70. [PubMed: 19029464]
95. Nottelet B, Pektok E, Mandracchia D, Tille JC, Walpoth B, Gurny R, et al. Factorial design optimization and in vivo feasibility of poly(ϵ -caprolactone)-micro- and nanofiber-based small diameter vascular grafts. *J Biomed Mater Res - Part A*. 2009;89(4):865–75.
96. de Valence S, Tille J-C, Mugnai D, Mrowczynski W, Gurny R, Möller M, et al. Long term performance of polycaprolactone vascular grafts in a rat abdominal aorta replacement model.

- Biomaterials [Internet]. 2012 1 [cited 2014 Nov 9];33(1):38–47. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21940044>
97. Kuwabara F, Narita Y, Yamawaki-Ogata A, Satake M, Kaneko H, Oshima H, et al. Long-term results of tissue-engineered small-caliber vascular grafts in a rat carotid arterial replacement model. *J Artif Organs*. 2012;15(4):399–405. [PubMed: 22806242]
 98. Ye L, Wu X, Duan HY, Geng X, Chen B, Gu Y-Q, et al. The in vitro and in vivo biocompatibility evaluation of heparin-poly(e-caprolactone) conjugate for vascular tissue engineering scaffolds. *J Biomed Mater Res - Part A*. 2012;100 A(12):3251–8.
 99. Wang Z, Cui Y, Wang J, Yang X, Wu Y, Wang K, et al. The effect of thick fibers and large pores of electrospun poly(e-caprolactone) vascular grafts on macrophage polarization and arterial regeneration. *Biomaterials* [Internet]. 2014 7 [cited 2014 Nov 9];35(22):5700–10. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24746961>
 100. Valence S De, Tille JC, Chaabane C, Gurny R, Bochaton-Piallat ML, Walpoth BH, et al. Plasma treatment for improving cell biocompatibility of a biodegradable polymer scaffold for vascular graft applications. *Eur J Pharm Biopharm* [Internet]. 2013;85(1):78–86. Available from: 10.1016/j.ejpb.2013.06.012
 101. Kuwabara F, Narita Y, Yamawaki-Ogata A, Kanie K, Kato R, Satake M, et al. Novel small-caliber vascular grafts with trimeric peptide for acceleration of endothelialization. *Ann Thorac Surg* [Internet]. 2012;93(1):156–63. Available from: 10.1016/j.athoracsur.2011.07.055
 102. Wang Y, Chen S, Pan Y, Gao J, Tang D, Kong D, et al. Rapid in situ endothelialization of a small diameter vascular graft with catalytic nitric oxide generation and promoted endothelial cell adhesion. *J Mater Chem B* [Internet]. 2015;3(47):9212–22. Available from: 10.1039/C5TB02080H
 103. Tang D, Chen S, Hou D, Gao J, Jiang L, Shi J, et al. Regulation of macrophage polarization and promotion of endothelialization by NO generating and PEG-YIGSR modified vascular graft. *Mater Sci Eng C* [Internet]. 2017;84(November):1–11. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S092849311732790X>
 104. Zheng W, Wang Z, Song L, Zhao Q, Zhang J, Li D, et al. Endothelialization and patency of RGD-functionalized vascular grafts in a rabbit carotid artery model. *Biomaterials* [Internet]. 2012;33(10):2880–91. Available from: 10.1016/j.biomaterials.2011.12.047
 105. Wang Z, Zheng W, Wu Y, Wang J, Zhang X, Wang K, et al. Differences in the performance of PCL-based vascular grafts as abdominal aorta substitutes in healthy and diabetic rats. *Biomater Sci* [Internet]. 2016;4(10):1485–92. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27537499%5Chttp://pubs.rsc.org/en/content/articlepdf/2016/bm/c6bm00178e>
 106. Wang Z, Wu Y, Wang J, Zhang C, Zhu M, Wang K, et al. The effect of resveratrol on modulation of endothelial cells and macrophages for rapid vascular regeneration from electrospun poly (e-caprolactone) scaffolds. *ACS Appl Mater Interfaces*. 2017;9(23):19541–51. [PubMed: 28539044]
 107. Wang Z, Lu Y, Qin K, Wu Y, Tian Y, Wang J, et al. Enzyme-functionalized vascular grafts catalyze in-situ release of nitric oxide from exogenous NO prodrug. *J Control Release* [Internet]. 2015;210:179–88. Available from: 10.1016/j.jconrel.2015.05.283
 108. Mrowczynski W, Mugnai D, De Valence S, Tille J-C, Khabiri E, Cikiricioglu M, et al. Porcine carotid artery replacement with biodegradable electrospun poly-e-caprolactone vascular prosthesis. *J Vasc Surg*. 2014;59(1):210–9. [PubMed: 23707057]
 109. Fukunishi T, Best CA, Sugiura T, Shoji T, Yi T, Udelsman B, et al. Tissue-engineered small diameter arterial vascular grafts from cell-free nanofiber PCL/chitosan scaffolds in a sheep model. *PLoS One*. 2016;11(7):1–15.
 110. Young RJ, Lovell PA. Elastomers. In: *Introduction to Polymers*. 2011 p. 511–30.
 111. Hong Y, Ye SH, Nieponice A, Soletti L, Vorp DA, Wagner WR. A small diameter, fibrous vascular conduit generated from a poly(ester urethane)urea and phospholipid polymer blend. *Biomaterials* [Internet]. 2009;30(13):2457–67. Available from: 10.1016/j.biomaterials.2009.01.013
 112. Guan J, Sacks MS, Beckman EJ, Wagner WR. Synthesis, characterization, and cytocompatibility of elastomeric, biodegradable poly (ester-urethane)ureas based on poly (caprolactone) and

- putrescine. J Biomed Mater Res [Internet]. 2002;61(3):493–503. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/jbm.10204/full>
113. Soletti L, Nieponice A, Hong Y, Ye SH, Stankus JJ, Wagner WR, et al. In vivo performance of a phospholipid-coated bioerodable elastomeric graft for small-diameter vascular applications. J Biomed Mater Res - Part A. 2011;96 A(2):436–48.
 114. Gade PS, Lee K, Pfaff BN, Wang Y, Robertson AM. Degradation and erosion mechanisms of bioresorbable porous acellular vascular grafts: an *in vitro* investigation. J R Soc Interface [Internet]. 2017;14(132):20170102 Available from: <http://rsif.royalsocietypublishing.org/lookup/doi/10.1098/rsif.2017.0102>
 115. Wu W, Allen RA, Wang Y. Fast-degrading elastomer enables rapid remodeling of a cell-free synthetic graft into a neoartery. Nat Med [Internet]. 2012 7 [cited 2014 Nov 10];18(7):1148–53. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3438366&tool=pmcentrez&rendertype=abstract>
 116. Allen RA, Wu W, Yao M, Dutta D, Duan X, Bachman TN, et al. Nerve regeneration and elastin formation within poly(glycerol sebacate)-based synthetic arterial grafts one-year post-implantation in a rat model. Biomaterials [Internet]. 2014 1 [cited 2014 Nov 2];35(1):165–73. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24119457>
 117. Lehn Jean-Marie. Supramolecular chemistry - Scope and perspectives: Molecules, supermolecules, and molecular devices. Angew Chemie - Int Ed. 1988;27(1):89–112.
 118. Muylaert DEP, van Almen GC, Talacua H, Fledderus JO, Kluin J, Hendrikse SIS, et al. Early in-situ cellularization of a supramolecular vascular graft is modified by synthetic stromal cell-derived factor-1 α derived peptides. Biomaterials [Internet]. 2016;76:187–95. Available from: 10.1016/j.biomaterials.2015.10.052
 119. Söntjens SHM, Renken RAE, Van Gemert GML, Engels TAP, Bosman AW, Janssen HM, et al. Thermoplastic elastomers based on strong and well-defined hydrogen-bonding interactions. Macromolecules. 2008;41(15):5703–8.
 120. Khosravi R, Best CA, Allen RA, Stowell CET, Onwuka E, Zhuang JJ, et al. Long-term functional efficacy of a novel electrospun poly(glycerol sebacate)-based arterial graft in mice. Ann Biomed Eng [Internet]. 2016; Available from: <http://link.springer.com/10.1007/s10439-015-1545-7>
 121. Greisler HP, Schwarcz TH, Ellinger J, Kim DU. Dacron inhibition of arterial regenerative activities. J Vasc Surg. 1986;3(5):747–56. [PubMed: 3009903]
 122. Greisler HP, Kim DU, Dennis JW, Klosak JJ, Widerborg KA, Endean ED, et al. Compound polyglactin 910/ polypropylene small vessel prostheses. J Vasc Surg. 1987;5(4):572–83. [PubMed: 3550160]
 123. Sugiura T, Tara S, Nakayama H, Yi T, Lee YU, Shoji T, et al. Fast-degrading bioresorbable arterial vascular graft with high cellular infiltration inhibits calcification of the graft. J Vasc Surg [Internet]. 2017;66(1):243–50. Available from: 10.1016/j.jvs.2016.05.096
 124. Greisler Howard P., Tattersall CW, Klosak JJ, Cabusao EA, Garfield JD, Kim DU. Partially bioresorbable vascular grafts in dogs. Surgery. 1991;110(4):645–55. [PubMed: 1833846]
 125. Valentin A, Holzapfel GA. Constrained mixture models as tools for testing competing hypothesis in arterial biomechanics: Survey. Mech Res Commun. 2012;42(6):126–33. [PubMed: 22711947]
 126. Miller KS, Lee YU, Naito Y, Breuer CK, Humphrey JD. Computational model of the in vivo development of a tissue engineered vein from an implanted polymeric construct. J Biomech [Internet]. 2014;47(9):2080–7. Available from: 10.1016/j.jbiomech.2013.10.009
 127. Doi K, Matsuda T. Significance of porosity and compliance of microporous, polyurethane-based microarterial vessel on neoarterial wall regeneration. J Biomed Mater Res. 1997;37(4):573–84. [PubMed: 9407307]
 128. Miller KS, Khosravi R, Breuer CK, Humphrey JD. A hypothesis-driven parametric study of effects of polymeric scaffold properties on tissue engineered neovessel formation. Acta Biomater [Internet]. 2014 10 5 [cited 2014 Nov 17];11:283–94. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25288519>
 129. Lepidi S, Abatangelo G, Vindigni V, Deriu GP, Zavan B, Tonello C, et al. In vivo regeneration of small-diameter (2 mm) arteries using a polymer scaffold. FASEB J [Internet]. 2006;20(1):103–5. Available from: <http://www.fasebj.org/cgi/doi/10.1096/fj.05-4802fje>

130. Pennel T, Bezuidenhout D, Koehne J, Davies NH, Zilla P. Transmural capillary ingrowth is essential for confluent vascular graft healing. *Acta Biomater* [Internet]. 2017;65:237–47. Available from: [10.1016/j.actbio.2017.10.038](https://doi.org/10.1016/j.actbio.2017.10.038) [PubMed: 29111372]
131. Madden LR, Mortisen DJ, Sussman EM, Dupras SK, Fugate JA, Cuy JL, et al. Proangiogenic scaffolds as functional templates for cardiac tissue engineering. *Proc Natl Acad Sci U S A* [Internet]. 2010 8 24 [cited 2014 Oct 14];107(34):15211–6. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2930533&tool=pmcentrez&rendertype=abstract>
132. Zhu M, Wang Z, Zhang J, Wang L, Yang X, Chen J, et al. Circumferentially aligned fibers guided functional neoartery regeneration in vivo. *Biomaterials*. 2015;61:85–94. [PubMed: 26001073]
133. Wang K, Zheng W, Pan Y, Ma S, Guan Y, Liu R, et al. Three-layered PCL grafts promoted vascular regeneration in a rabbit carotid artery model. *Macromol Biosci*. 2016;16(4):608–918. [PubMed: 26756321]
134. Zhong S, Zhang Y, Lim CT. Fabrication of large pores in electrospun nanofibrous scaffolds for cellular infiltration: A review. *Tissue Eng Part B Rev*. 2012;18(2):77–87. [PubMed: 21902623]
135. Roach MR, Burton AC. The reason for the shape of the distensibility curves of arteries. *Can J Biochem Physiol* [Internet]. 1957;35(8):681–90. Available from: <http://www.nrcresearchpress.com/doi/10.1139/o57-080>
136. Salacinski HJ, Goldner S, Giudiceandrea A, Hamilton G, Seifalian AM, Edwards A, et al. The mechanical behavior of vascular grafts: A review. *J Biomater Appl* [Internet]. 2001;15(3):241–78. Available from: <http://journals.sagepub.com/doi/10.1106/NA5T-J57A-JTDD-FD04>
137. Abbott WM, Megerman J, Hasson JE, L'Italien G, Warnock DF. Effect of compliance mismatch on vascular graft patency. *J Vasc Surg*. 1987;5(2):376–82. [PubMed: 3102762]
138. Zenni GC, Gray JL, Appelgren EO, Kim DU, Berceli S, Ligush J, et al. Modulation of myofibroblast proliferation by vascular prosthesis biomechanics. *ASAIO J*. 1993;39(3):M496–500. [PubMed: 8268586]
139. Beamish JA, He P, Kottke-Marchant K, Marchant RE. Molecular regulation of contractile smooth muscle cell phenotype: Implications for vascular tissue engineering. *Tissue Eng Part B Rev* [Internet]. 2010;16(5):467–91. Available from: <http://www.liebertonline.com/doi/abs/10.1089/ten.teb.2009.0630>
140. Patel A, Fine B, Sandig M, Mequanint K. Elastin biosynthesis: The missing link in tissue-engineered blood vessels. *Cardiovasc Res*. 2006;71(1):40–9. [PubMed: 16566911]
141. Gogolewski S, Pennings AJ, Lommen E, Wildevuur CRH, Nieuwenhuis P. Growth of a neo-artery induced by a biodegradable polymeric vascular prosthesis. *Macromol Rapid Commun* [Internet]. 1983;4:213–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6673235>
142. van der Lei B, Wildevuur CRH, Nieuwenhuis P. Mechanical stimulation of smooth muscle cells by arterial pulsations: An important stimulus for the formation of elastic laminae in arterial tissue. *Cell Biol Int Rep*. 1985;9(1):1985.
143. van der Lei B, Wildevuur CRH, Nieuwenhuis P. Compliance and biodegradation of vascular grafts stimulate the regeneration of elastic laminae in neoarterial tissue: An experimental study in rats. *Surgery*. 1986;99(1):45–52. [PubMed: 3942000]
144. Bashur CA, Venkataraman L, Ramamurthi A. Tissue engineering and regenerative strategies to replicate biocomplexity of vascular elastic matrix assembly. *Tissue Eng Part B Rev*. 2012;18(3):203–17. [PubMed: 22224468]
145. Jeffries EM, Allen RA, Gao J, Pesce M, Wang Y. Highly elastic and suturable electrospun poly(glycerol sebacate) fibrous scaffolds. *Acta Biomater* [Internet]. 2015;18(July):30–9. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1742706115000689>
146. Sonoda H, Takamizawa K, Nakayama Y, Yasui H, Matsuda T. Coaxial double-tubular compliant arterial graft prosthesis: time-dependent morphogenesis and compliance changes after implantation. *J Biomed Mater Res Part A* [Internet]. 2003;65(2):170–81. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12734809>
147. Doi K, Nakayama Y, Matsuda T. Novel compliant and tissue-permeable microporous polyurethane vascular prosthesis fabricated using an excimer laser ablation technique. *J Biomed Mater Res*. 1996;31(1):27–33. [PubMed: 8731146]

148. Wise SG, Byrom MJ, Waterhouse A, Bannon PG, Ng MKC, Weiss AS. A multilayered synthetic human elastin/polycaprolactone hybrid vascular graft with tailored mechanical properties. *Acta Biomater* [Internet]. 2011;7(1):295–303. Available from: [10.1016/j.actbio.2010.07.022](https://doi.org/10.1016/j.actbio.2010.07.022)
149. Song Y, Kamphuis MMJ, Zhang Z, Sterk LMT, Vermes I, Poot AA, et al. Flexible and elastic porous poly(trimethylene carbonate) structures for use in vascular tissue engineering. *Acta Biomater* [Internet]. 2010;6(4):1269–77. Available from: [10.1016/j.actbio.2009.10.002](https://doi.org/10.1016/j.actbio.2009.10.002)
150. Engler AJ, Sen S, Sweeney HL, Discher DE. Matrix elasticity directs stem cell lineage specification. *Cell* [Internet]. 2006 8 25 [cited 2014 Jul 9];126(4):677–89. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16923388>
151. Wang JHC, Thampatty BP. An introductory review of cell mechanobiology. *Biomech Model Mechanobiol*. 2006;5(1):1–16. [PubMed: 16489478]
152. De Valence S, Tille JC, Giliberto JP, Mrowczynski W, Gurny R, Walpoth BH, et al. Advantages of bilayered vascular grafts for surgical applicability and tissue regeneration. *Acta Biomater* [Internet]. 2012;8(11):3914–20. Available from: [10.1016/j.actbio.2012.06.035](https://doi.org/10.1016/j.actbio.2012.06.035)
153. Brown BN, Sicari BM, Badylak SF. Rethinking regenerative medicine: A macrophage-centered approach. *Front Immunol*. 2014;5:1–11. [PubMed: 24474949]
154. Greisler HP, Dennis JW, Endean ED, Ellinger J, Friesel R, Burgess W. Macrophage/biomaterial interactions: The stimulation of endothelialization. *J Vasc Surg*. 1989;9(4):588–93. [PubMed: 2523491]
155. Talacua H, Smits AIPM, Muylaert DEP, van Rijswijk JW, Vink A, Verhaar MC, et al. In situ tissue engineering of functional small-diameter blood vessels by host circulating cells only. *Tissue Eng Part A* [Internet]. 2015;21(19–20):2583–94. Available from: <http://online.liebertpub.com/doi/10.1089/ten.tea.2015.0066>
156. Roh JD, Nelson GN, Brennan MP, Mirensky TL, Yi T, Hazlett TF, et al. Small-diameter biodegradable scaffolds for functional vascular tissue engineering in the mouse model. *Biomaterials* [Internet]. 2008 4 [cited 2014 Nov 5];29(10):1454–63. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2375856&tool=pmcentrez&rendertype=abstract>
157. Hibino N, Mejias D, Pietris N, Dean E, Yi T, Best C, et al. The innate immune system contributes to tissue-engineered vascular graft performance. *FASEB J*. 2015;29(6):2431–8. [PubMed: 25713026]
158. Fukunishi T, Best CA, Ong CS, Groehl T, Reinhardt J, Yi T, et al. Role of bone marrow mononuclear cell seeding for nanofiber vascular grafts. *Tissue Eng Part A* [Internet]. 2017;0(0):ten.tea.2017.0044. Available from: <http://online.liebertpub.com/doi/10.1089/ten.tea.2017.0044>
159. Tara S, Kurobe H, De Dios Ruiz Rosado J, Best CA, Shoji T, Mahler N, et al. Cilostazol, not aspirin, prevents stenosis of bioresorbable vascular grafts in a venous model. *Arterioscler Thromb Vasc Biol*. 2015;35(9):2003–10. [PubMed: 26183618]
160. Lee Y-U, de Dios Ruiz-Rosado J, Mahler N, Best CA, Tara S, Yi T, et al. TGF- β receptor 1 inhibition prevents stenosis of tissue-engineered vascular grafts by reducing host mononuclear phagocyte activation. *FASEB J* [Internet]. 2016;1(4):1–10. Available from: <http://www.fasebj.org/cgi/doi/10.1096/fj.201500179R>
161. Duncan DR, Chen PY, Patterson JT, Lee YU, Hibino N, Cleary M, et al. TGF β R1 inhibition blocks the formation of stenosis in tissue-engineered vascular grafts. *J Am Coll Cardiol*. 2015;65(5):512–4. [PubMed: 25660932]
162. Fetz AE, Neeli I, Rodriguez IA, Radic MZ, Bowlin GL. Electrospun template architecture and composition regulate neutrophil NETosis in vitro and in vivo. *Tissue Eng Part A* [Internet]. 2017;23(5):1054–63. Available from: <http://online.liebertpub.com/doi/10.1089/ten.tea.2016.0452>
163. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: Time for reassessment. *F1000Prime Rep* [Internet]. 2014;6:13 Available from: <http://www.f1000.com/prime/reports/b/6/13>
164. Enomoto S, Sumi M, Kajimoto K, Nakazawa Y, Takahashi R, Takabayashi C, et al. Long-term patency of small-diameter vascular graft made from fibroin, a silk-based biodegradable material. *J Vasc Surg* [Internet]. 2010;51(1):155–64. Available from: [10.1016/j.jvs.2009.09.005](https://doi.org/10.1016/j.jvs.2009.09.005)

165. Díez M, Musri MM, Ferrer E, Barberá JA, Peinado VI. Endothelial progenitor cells undergo an endothelial-to-mesenchymal transition-like process mediated by TGF β RI. *Cardiovasc Res*. 2010;88(3):502–11. [PubMed: 20631156]
166. Bobryshev YV, Orekhov AN, Chistiakov DA. Vascular stem/progenitor cells: current status of the problem. *Cell Tissue Res*. 2015;362(1).
167. Rotmans JI, Heyligers JMM, Verhagen HJM, Velema E, Nagtegaal MM, de Kleijn DPV., et al. In vivo cell seeding with anti-CD34 antibodies successfully accelerates endothelialization but stimulates intimal hyperplasia in porcine arteriovenous expanded polytetrafluoroethylene grafts. *Circulation* [Internet]. 2005;112(1):12–8. Available from: <http://circ.ahajournals.org/cgi/doi/10.1161/CIRCULATIONAHA.104.504407>
168. Lu S, Zhang P, Sun X, Gong F, Yang S, Shen L, et al. Synthetic ePTFE grafts coated with an anti-CD133 antibody-functionalized heparin/collagen multilayer with rapid in vivo endothelialization properties. *ACS Appl Mater Interfaces*. 2013;5(15):7360–9. [PubMed: 23859593]
169. Vasa M, Fichtlscherer S, Aicher A, Adler K, Urbich C, Martin H, et al. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. *Circ Res* [Internet]. 2001;89(1):e1–7. Available from: <http://circres.ahajournals.org/cgi/doi/10.1161/hh1301.093953>
170. Row S, Peng H, Schlaich EM, Koenigsknecht C, Andreadis ST, Swartz DD. Arterial grafts exhibiting unprecedented cellular infiltration and remodeling in vivo: The role of cells in the vascular wall. *Biomaterials* [Internet]. 2015;50:115–26. Available from: 10.1016/j.biomaterials.2015.01.045
171. Greisler HP, Klosak JJ, Endean ED, McGurrin JF, Garfield JD, Kim DU. Effects of hypercholesterolemia on healing of vascular grafts. *J Investig Surg*. 1991;4(3):299–312. [PubMed: 1911576]
172. Ahmed M, Hamilton G, Seifalian AM. The performance of a small-calibre graft for vascular reconstructions in a senescent sheep model. *Biomaterials* [Internet]. 2014;35(33):9033–40. Available from: 10.1016/j.biomaterials.2014.07.008
173. Syedain ZH, Graham ML, Dunn TB, O'Brien T, Johnson SL, Schumacher RJ, et al.. A completely biological “off-the-shelf” arteriovenous graft that recellularizes in baboons. *Sci Transl Med* [Internet]. 2017;9(414):eaan4209. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29093182%0Ahttp://stm.sciencemag.org/content/9/414/eaan4209.full>
174. Koobatian MT, Row S, Smith RJ, Koenigsknecht C, Andreadis ST, Swartz DD. Successful endothelialization and remodeling of a cell-free small-diameter arterial graft in a large animal model. *Biomaterials* [Internet]. 2016;76:344–58. Available from: 10.1016/j.biomaterials.2015.10.020
175. Dantas AP, Jiménez-Altayó F, Vila E. Vascular aging: Facts and factors. *Front Physiol*. 2012;3:1–2. [PubMed: 22275902]
176. Williamson K, Stringer SE, Alexander MY. Endothelial progenitor cells enter the aging arena. *Front Physiol*. 2012;3:1–7. [PubMed: 22275902]
177. Neves J, Sousa-Victor P, Jasper H. Rejuvenating strategies for stem cell-based therapies in aging. *Cell Stem Cell* [Internet]. 2017;20(2):161–75. Available from: 10.1016/j.stem.2017.01.008

Figure 1. Resorbable graft concept. An acellular, polymeric graft is implanted orthotopically. Host cells invade the graft, degrade the polymer, proliferate, and synthesize new ECM. The artificial graft is replaced by a living vascular conduit.

Figure 2. Cellular and structural complexity of the artery. Replicating such an extraordinary design by tissue engineering is a challenge. **(A)** H&E staining of the sheep common carotid. **(B)** Second harmonic generation image of a rat aorta. Elastin autofluoresces in green, collagen autofluoresces in red, and the nucleic stain spills over into the green channel. Bars: 100 μm . Image in (B) courtesy of Piyusha S. Gade and Anne M. Robertson.

Figure 3.

Transformation is enabled by a balance between the rates of polymer degradation and neotissue synthesis. The polymer initially bears all the load of pressurization, but it contributes less as it degrades (gold). The load is taken up by newly deposited matrix (red). To prevent dilation, the sum of the mechanical contributions of the polymer and neotissue (grey) must always be greater than some critical level (dotted, black). Mechanics should ideally approach those of the native vessel (dashed, black). (Figure memorably presented by Frederick J. Schoen, M.D., Ph.D.)

Figure 4. Idealized J-shaped pressure-diameter relationship exhibited by an artery under biaxial inflation.

Figure 5.

Proposed mechanisms of graft remodeling. Transanastomotic healing involves migration of SMCs (green) and ECs (yellow) from the adjacent arterial stubs. Fall-out healing involves adhesion, differentiation, and proliferation of various circulating stem/progenitor cells (purple, brown). Transmural healing involves migration of vascular cells (green, yellow) from adventitial capillaries or adventitial progenitors (blue) from the perivascular space. Remodeling is largely directed by macrophages (orange), which interpret material and chemical cues and coordinate the infiltrating cell responses through cytokine signaling (teal).

Table 1.

Comparative advantages of prosthetic grafts, traditionally tissue-engineered grafts, and acellular synthetic grafts.

Graft Type	Easy to implant?	Good patency?	Grows with patient?	Simple storage and production?
Prosthetic		X	XX	
Tissue-engineered		(?)		XX
Acellular synthetic		(?)		

Table 2.

Sample properties of polymers commonly used in resorbable vascular grafts.

Material	Chemical Structure	Θ (°)	E/UTS (MPa)	Strength/Mass Loss	Notes
Poly(ϵ -caprolactone) (PCL)		71 (66)	340 (67)/19.3 (67)	2 yrs. (68)/3 yrs. (68)	Θ is estimated as the average of the advancing and receding Θ .
Poly(<i>p</i> -dioxanone) (PDO)		32 (69)	1,500 (70)/ 575 (71)	2 mo. (72)/6 mo. (72)	
Poly(glycerol sebacate) (PGS)		32 (73)	0.3 (73)/>0.5 (73)	2 mo. (74)/ 2 mo. (73)	R signifies either a hydrogen or an ester crosslink to a neighboring chain.
Poly(glycolic acid) (PGA)		70 (75)	12,500 (70)/130 (76)	1 mo. (77)/2-5 mo. (78)	
Poly(lactic acid) (PLA)		77 (78)	3400 (70)/53 (80)	5 mo. (81)/> 1-2 yrs. (81)	
Poly(lactic-co-glycolic acid) (PLGA)		72 (82)	203 (83)/4.3 (83)	1 mo. (72)/2-3 mo. (72)	Properties shown combine polymers with varying monomer ratios.