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Engineering the Vasculature for Islet Transplantation

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Abstract

The microvasculature in the pancreatic islet is highly specialized for glucose sensing and insulin secretion. Although pancreatic islet transplantation is a potentially life-changing treatment for patients with insulin-dependent diabetes, a lack of blood perfusion reduces viability and function of newly transplanted tissues. Functional vasculature around an implant is not only necessary for the supply of oxygen and nutrients but also required for rapid insulin release kinetics and removal of metabolic waste. Inadequate vascularization is particularly a challenge in islet encapsulation. Selectively permeable membranes increase the barrier to diffusion and often elicit a foreign body reaction including a fibrotic capsule that is not well vascularized. Therefore, approaches that aid in the rapid formation of a mature and robust vasculature in close proximity to the transplanted cells are crucial for successful islet transplantation or other cellular therapies. In this paper, we review various strategies to engineer vasculature for islet transplantation. We consider properties of materials (both synthetic and naturally derived), prevascularization, local release of proangiogenic factors, and co-transplantation of vascular cells that have all been harnessed to increase vasculature. We then discuss the various other challenges in engineering mature, long-term functional and clinically viable vasculature as well as some emerging technologies developed to address them. The benefits of physiological glucose control for patients and the healthcare system demand vigorous pursuit of solutions to cell transplant challenges.

Graphical Abstract

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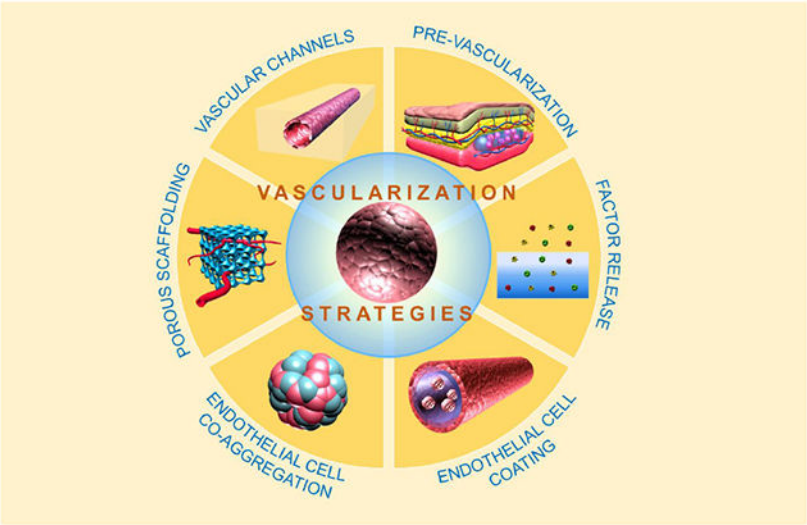

Keywords

vascularization; Type 1 Diabetes; islet transplantation; endothelial cell; microvasculature

1. Introduction

The vascular system perfuses nearly every tissue to deliver nutrients and remove waste products. Endothelial cells (ECs) are the blood-contacting cells of the vascular system, which mediate many vascular adaptations [1]. Following initial development, establishment of new vascular sections during adulthood occurs through angiogenesis, vasculogenesis, or arteriogenesis [2]. New endothelial lumen structures are formed in angiogenesis by proliferation of existing ECs, while vasculogenesis is mediated by progenitors that differentiate into ECs [3]. By contrast, arteriogenesis can form a vessel network by maturation of an endothelial tube primarily through increases in diameter, addition of support cells, and participation of monocytes [4]. These processes ensure that most cells are no more than ~100 μm away from a blood vessel [5]; however, this essential network is not available in tissues that are harvested from a donor or derived from stem cells for transplant, such as pancreatic islets.

Vascularization is not a problem unique to islet tissue engineering [6] but is under investigation for a wide range of tissue types including muscle [7, 8], cardiac tissue [9–11], hepatic tissue [12], bone [13, 14], neural tissue [15], skin [16–18], thyroid tissue [19], and kidney tissue [20], as well as multi-tissue materials [21]. This review evaluates strategies to induce vascularization with a focus on those that have been used in islet transplantation. Physical properties of synthetic scaffolding or encapsulation materials and the benefits of using natural extracellular matrix materials to induce vascularization are reviewed first. We then consider prevascularization, factor delivery, and angiogenic cell co-transplantation. The discussion concludes with perspectives on challenges and consideration of future approaches. First, we present a brief consideration of islet vascular biology.

1.1. Islet Vascular Biology

Islets have been described as micro-organs [22] with unique microvasculature characteristics compared to many other tissue microvasculatures. Qualities include high density, high fenestration [23], and sensitive glucose responsiveness [24]. Combined with the spatial arrangement and flow patterns of vessels and endocrine cells [25], the islet vasculature promotes a rapid physiological response to maintain glycemia. One spatial arrangement is that mouse insulin-producing β-cells are usually adjacent to ECs and attach to the vascular basement membrane [26]. Observations about the direction of blood flow through the islet also contribute to our understanding of islet function. The intra-islet blood flow has been characterized to be one of the three patterns: (1) flowing first to the islet core and then to the islet shell, (2) the islet shell and then the islet core, or (3) simply from one side of the islet to the other, perfusing core and peripheral islet endocrine cells equally depending on which hemisphere the cells reside [27]. The blood flow pattern, with the specific cell arrangement, is important given that paracrine effects between the islet cell types are affected by blood and interstitial flow that is dictated by capillary network architecture [28, 29]. However, the effects of capillary and endocrine cell layout in human islets are not yet fully known due in part to the differential arrangement of cell types [30, 31].

In further studies of the microvascular architecture, an intra-pancreatic and intra-islet portal system has been observed. Vascular portal systems describe locations where a capillary bed supplies two types of tissues before returning to the heart (sometimes converging into a vein between two capillary beds) such as in the liver and kidney [32]. In the case of the intra-pancreatic portal system, capillaries flow from within the islet to the surrounding exocrine pancreatic tissue before converging into a vein [33]. The intra-islet portal system describes a flow pattern where β-cells are perfused before other cell types within the islets [29]. Thus, the intra-islet portal system provides a method for β-cell secretions to affect non-β-cell islet cells, and the intra-pancreatic portal capillary pattern extends the effect of the endocrine islet secretions to the exocrine pancreas. Overall, it is clear that the intra-islet vascular structure is tightly linked to islet function.

The function of the vasculature also adapts to the diabetic state. Nyman *et al.* quantified islet perfusion using confocal imaging of *in situ* islets to show that islet perfusion increases in hyperglycemia while the exocrine pancreatic tissue surrounding the islets is not affected [24]. Canzano *et al.* examined the islet microvasculature in human islets histologically to reveal that the blood vessels inside the islet of diabetic pancreas were smaller and greater in number than those in the non-diabetic pancreas. By contrast, the exocrine tissue vessels remained the same in the diabetic state [34]. This may be a contrasting effect observed in mouse islets. It would not be the first case where mouse islets are different from human islets, or an individual islet is different from another, depending on the location in the pancreas [30, 35, 36]. Canzano *et al.* further showed that islets in a diabetic pancreas containing residual β-cell mass (insulin positive β-cells) had a normal intra-islet microvasculature compared to insulin negative β-cells in the islets [34]. Indeed, measuring perfusion of native islets may be predictive of type 1 diabetes (T1D) autoimmune disease onset [37]. While it is not yet clear whether the vascular changes contribute to the β-cell

damage or the β-cell damage causes vasculature changes, it nonetheless underscores the close connection between the vasculature and islet function.

Ideally, the vascular structure of transplanted islets could become re-perfused, ensuring that a healthy network is formed. Sometimes intra-islet capillaries remain as channels without an endothelial lining for many months post-transplantation [38]. These acellular channels may still be useful, as freely transplanted islets are capable of re-growing an intra-islet portal system [29]. The population of ECs remaining in the islets likely participates in islet revascularization [39]. This population is capable of anastomosing to vasculature in the recipient [39, 40], possibly even when there is a species mismatch [41, 42]. Harnessing the ability of donor ECs or intra-islet vascular channels to participate in re-vascularization may be important for islet transplant success.

1.2. Importance of Vascularization in Islet Transplantation

Following transplantation, several factors reduce the ability of an islet to re-vascularize after separation from the native pancreatic environment and vasculature [43]. Aside from collagenase digestion, the cell source can sometimes mandate safety requirements that also decrease the ability of an islet to become vascularized.

Non-human- or stem cell-derived islet transplantation is a solution to the shortage of cadaveric transplantable quality tissue. However, xenogeneic islets can stimulate a more aggressive immune response [44], and stem-cell derived islets present a risk of undesired differentiation [45]. Cell encapsulation can reduce immunologic toxicity to the transplanted tissue by preventing contact of immune cells [46] and undifferentiated cell escape. However, cell encapsulation also prevents intra-islet vessel development. Upon un-encapsulated transplantation, avascular islets experience insufficient mass transfer of nutrients and waste as well as function of specific molecules (e.g., glucose and hormones) (Figure 1 a,b) [47], which is worsened by encapsulation (Figure 1 c).

An ideal encapsulation barrier would be able to prevent all immunological access to the graft while simultaneously allowing all necessary nutrients to enter and products to leave the graft [48], requiring precise control over diffusional properties. Membrane diffusional characterization is not a primary subject in this review; however, there is exciting work on this topic, which we will not be able to give full attention [49, 50]. Briefly, materials can be characterized by their permeability to molecules. Hydrogels, for instance, can be characterized by their permeability across a range of molecular weights. Materials can also be characterized by their permselectivity to certain molecules or groups of molecules with similar properties (i.e., charge). Tightly controlled pore sizes in solid materials can be utilized to impart permselectivity by imposing a molecular weight cutoff or by excluding depending on other molecular properties. Much of the pore size discussion in this review occurs on the scale of tens to hundreds of micrometers for vascularization. Molecular diffusional characterization is less relevant at those scales but is nonetheless an important topic.

Generating a vasculature similar to the native islet vasculature could improve results in islet transplantation; however, different qualities may be required to overcome the encapsulation

diffusion barrier. Furthermore, efforts are being made to develop functionalized encapsulation materials [51] that can target immune cells, interfere with coagulation, mitigate fibrotic reactions, reduce reactive oxygen species, and induce vascularization [52], some of which may increase graft survival without being immunoisolating.

Vascular growth around an implant needs time to develop. The time course of vasculature growth in nonencapsulated transplanted islets has been studied. Regeneration of vasculature in or around transplanted syngeneic islets was observed to take one to two weeks [53]. In some intraportally transplanted islets, vascular density appeared to reach native islet levels within a few days and was at supernormal levels between days 5 and 30 (the last time point recorded) [54]. Similarly, the first vessels were observed in intramuscularly transplanted islets at three days [55]. Any delay in microvasculature formation can cause immediate cell death and reduction of long-term islet engraftment [56, 57]. Thus, the rest of this review is devoted to understanding various methods to bring sustained vasculature to the transplanted cells as quickly as possible.

2. Vascularization Strategies

2.1. Porosity, Surface Roughness, and Stiffness Modulate Vascularization

Physical characteristics of a material can drive increases in angiogenic activity. In this section, we review studies that are conducted for the purpose of islet transplantation alongside studies that are conducted for the reconstruction of other tissues to suggest possible new strategies for transplanted islet vascularization. In one of the most influential papers surrounding this topic, Brauker *et al.* quantified membrane pore size and positively correlated pore sizes of 0.8-8 μm to both cell infiltration and an altered foreign body reaction that allowed vascular structures to be close to the membrane [58]. By examining a large number of membranes made from various materials and with varied pore sizes, a conclusion was drawn that cell infiltration permissive membranes reduce the thickness of a fibrotic capsule when implanted subcutaneously (Figure 2 a). In a more recent study, vessels were found in the large pore outer mesh and immediately adjacent to the immunoisolation membrane [59], which should improve mass transfer.

The time course of microarchitecture-driven vascularization was studied by Padera and Colton, which demonstrated a temporal pattern similar to a normal wound healing cascade. A combination of neutrophils and macrophages was present within the pores of the membrane, followed by macrophages that peaked between 7 and 21 days but then decreased by day 329 [60]. The number of close vascular structures, on the other hand, reached a plateau at day 21 and remained the same until day 329, differing from a normal wound healing cascade where the number of vessels is expected to decrease due to regression of a fraction of vessels in a newly formed network [61, 62].

Pore size has also been examined in beta-tricalcium phosphate scaffolds where all pore sizes (~337, 415, 557, and 632 μm) supported vascular ingrowth from surrounding tissues; however, the diameter and extent of vessel ingrowth were modestly decreased by the 337 μm scaffolds [63]. Choi *et al.* examined the pore size of poly(lactic-co-glycolic acid) (PLGA) scaffolds formed around sacrificial microsphere templates of diameter 79, 147, 224, and 312

μm to evaluate the effect of pore diameter on subcutaneous vascularization [64]. While all scaffolds in that study supported vascularization to some degree, scaffolds constructed with microspheres of 200 μm or greater supported vessels that penetrated deeper into the scaffold. The 200 μm sphere size threshold correlated to a 35-40 μm window size (the size of openings between spherical pores, i.e., the limiting hole size for intrapore vessel formation).

Pore size can also be controlled in hydrogels to modulate vascularization. Three polyethylene glycol (PEG) hydrogels with pore sizes 134 ± 28, 82 ± 6, and 41 ± 0.1 μm were tested for their ability to support cells and vascularization. The authors found that the 41 μm pore group did not support vascular ingrowth into the pores until after the second week of implantation, while the larger pore sizes (82 and 134 μm) contained vessels at the one week time point (Figure 2 b) [65]. The dorsal skinfold window chamber was used to study the dynamics of vascularization surrounding three scaffolds presenting pores of diameters 20-75, 75-212, and 250-300 μm over the course of 20 days following implantation. Results showed that the large-pore size scaffolds supported consistent vessel growth at 8, 12, 16, and 20 days compared to the medium- and small-pore size scaffolds in the area of the scaffold, while the trend was not significant at the border or outside the scaffold [66].

The minimum pore size required to obtain noteworthy vascular in-growth depends on the particular scaffold material properties. However, according to the reviewed studies, a pore size greater than 200 μm may be required to facilitate vascularization into scaffolds, while a smaller pore size (greater than 100 μm) may be sufficient for hydrogel scaffolds. There is no substitute for testing the scaffold under question [67, 68]. Awareness of pore quantification methods such as porogen size and the resulting window size mentioned above are also important to consider. Furthermore, some materials may be able to circumvent pore size requirements while still initiating vascularization [69, 70].

Changes in pore size can also affect surface roughness, although surface roughness is an independent material property. Interestingly, Rosengren *et al.* studied subcutaneous implantation of smooth and textured low-density polyethylene disks and observed that the smoother disk was surrounded by a larger fibrotic capsule. More necrotic tissue was noted at the interface, especially near the edges where shear forces with surrounding tissue would be greater [71]. Following this hypothesis, smaller pore sizes not only would prevent vascular in-growth but may also present a smoother surface that induces a greater amount of cell necrosis at the tissue interface. This would help to explain the observation by Brauker *et al.* [58] that larger pore sizes stimulated closer vessels, as the fibrotic capsule was thinner. Khosravi *et al.* showed that during *in vivo* implantation, a nanotopographical surface significantly increased peri-implant blood vessel density on days 7, 11, and 28 compared to the smooth surface of the same titanium (Figure 2 c) [72]. The pore size of 3D collagen scaffolds was used to select cell types that were able to invade, giving the possibility that a scaffold may be able to select out for a population of desired cells [73], perhaps someday providing a new kind of immunoisolation material. It is clear that the scale of pores and surface roughness affect the biological response to implanted materials, and hence, they should be considered carefully when designing implants for cell encapsulation.

Material stiffness varies with material characteristics and formulations [74, 75] and can affect the vascularizing potential of a material. Similarly, tissue stiffness correlates with islet biology in addition to EC functionality. Islet stiffness is known to affect insulin expression [76], vary with islet inflammation [77], and provide a method to distinguish acinar versus islet tissue [78]. Stiffness plays a complex role in vascularization processes, primarily through ECs. Substrate stiffness downregulates EC network formation in 2D, while in 3D, the converse may be true [79]. Other material properties such as matrix density often vary with stiffness; however, Mason *et al.* demonstrated an effect of stiffness independent of density [80]. Stiffness responses are cell type dependent [81], including the EC source location in the vascular tree [82]. Matrix stiffness can also affect the ability of cells to interact with their neighbors, potentially affecting tissue formation [83] and lymphatic sprouting [84]. *In vivo*, angiogenic activity can degrade or secrete new matrix, dynamically affecting stiffness at different stages of vessel growth [85, 86].

2.2. Natural Extracellular Matrix-Based Scaffolding

Physiologically, the native matrix to which vascular cells attach is tightly regulated, including material properties such as stiffness and porosity. The native extracellular matrix (ECM) is composed of the basement membrane and the interstitial matrix. This matrix provides structural support for tissue-specific cells and vasculature, as well as transport regulation [87]. ECM-based materials and synthetic materials designed to mimic the ECM offer great potential in regenerating and engineering the pancreas as well as islets [88–92]. To be clear, direct regeneration of islets would be complicated by the original autoimmune attack and is not yet clinically viable but would be a considerable advance. Engineering an environment suitable for transplanted insulin-producing cells can be improved by considering those that increase vascularization.

Fibrin is commonly used for islet vascularization and transplantation. Fibrin is a fibrous protein polymerized by the protease thrombin on fibrinogen, and it is known to participate in vascularization during wound healing [93]. Individual fibrinogen molecules have two pairs of arginine-glycine-aspartic acid (RGD) ligands [94] for integrins expressed on pancreatic cells (i.e., $\alpha v\beta 3$, $\alpha 5\beta 1$, and $\alpha v\beta 1$) [95], Therefore, attachment to integrin recognition sites in fibrin gels can prevent cell anoikis (apoptosis resulting from lack of integrin engagement) and facilitate islet cell survival [96, 97]. Interactions between fibrin-binding sites and integrins (i.e., $\alpha v\beta 3$ and $\alpha 5\beta 1$) are involved in controlling EC behavior and vessel formation during angiogenesis [93]. As fibrin enhances islet cell survival and is cell cleavable, thereby supporting angiogenesis, it is an attractive natural scaffold for islet vascularization.

Fibrin, being a component of US Food and Drug Administration (FDA)-approved clinical products (e.g., FIBRIN SEALANT, TachoSil, EVARREST, and EVICEL), is a suitable material for translational studies. Ricordi and Pileggi groups developed an approach where plasma was polymerized by recombinant thrombin (Figure 3 a). Islets were embedded in the fibrinogen pregel and transplanted onto the diabetic rat recipient's omentum, followed by the application of recombinant thrombin to polymerize the fibrinogen *in situ* with omental closure to contain and protect the graft. Promising pre-clinical results demonstrated a potential to vascularize, to function similarly to intrahepatically transplanted islets, and to

reduce circulating levels of leptin and α-2 macroglobin [98]. Safety of the approach was demonstrated in a non-human primate [98]. In a recent phase I/II clinical trial, human islets were embedded in a patient's autologous plasma gel. Glucose levels were in the upper nondiabetic range at a six-month follow-up, while at 12 months, insulin independence had deteriorated, perhaps complicated by a change in the immunosuppressive agent used [99].

Fibrin can be tailored by modulating formulations to obtain desirable properties. For example, compared to a higher concentration of fibrinogen and thrombin (10 mg/mL and 10 U/mL, respectively), islets in a fibrin scaffold made with lower concentrations (5 mg/mL and 1 U/mL, respectively) reached normoglycemia quicker and supported vascularization inside and around the islets [100]. In addition to the effects on the density of the gel [101], adjusting the thrombin concentration may affect islets in other ways. For instance, thrombin can cleave protease-activated receptor-3 (PAR3), which can, in turn, stimulate insulin secretion, perhaps leading to hyperstimulation of insulin secretion [102]. In addition, given the integral role of thrombin in the Instant Blood-Mediated Inflammatory Reaction (IBMIR) [103] and positive results that have been found with counteracting thrombin activation [104–106], caution is warranted in the selection of a site where a fibrin gel is used to facilitate islet transplantation [107]. To further reduce these concerns, fibrinogen formulations that are free of complement may avoid a loss of viability from thrombin-activated compliment [98, 103, 108]. Nevertheless, the proclivity of a fibrin gel to promote angiogenesis is a beneficial property for the improvement of islet transplantation.

Vascularization can be enhanced by conjugating pro-angiogenic factors (i.e., vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)) into fibrin gels. Improved islet function in a VEGF/PDGF-conjugated fibrin gel was associated with enhanced and earlier vascularization (<7 days) [109]. Factor release will be further discussed in Section 2.4. Other than fibrin, commercial Matrigel and collagen have also been used as biological scaffolds for islet vascularization.

Matrigel is a gelatinous mixture primarily composed of structural proteins, proteases, growth factors, and related proteins secreted by Engelbreth-Holm-Swarm (EHS) mouse sarcoma cells (formulations available from manufacturers (e.g., Coming) or from literature [110]) (Figure 3 a). It is used to study differentiation and tumor growth [111], as well as evaluation of angiogenesis both *in vitro* and *in vivo* [112, 113], partially because of the inclusion of growth factors in the standard formulation. For the application of transplantation, mouse islets were embedded in growth factor-reduced Matrigel specifically supplemented with VEGF and hepatocyte growth factor (HGF). Restored normoglycemia in diabetic severe combined immunodeficient (SCID) mice in the subcutaneous space [114] demonstrated the suitability of Matrigel for islet transplantation. Although very useful in preclinical studies, clinically viable alternatives need to be identified that are not animal derived and can be chemically defined.

Collagen, a major component of Matrigel and the main protein in the islet niche [115], may be critical for maintaining islet function (Figure 3 a) [26, 116]. During angiogenesis, sprouting vascular ECs are exposed to an interstitial ECM rich in type I collagen [117]. Similarly, the integrins expressed on ECs (i.e., α1β1 and α2β1) are known to bind to

collagen [118]. To apply this knowledge, a recent study used porous collagen scaffolds to support vessel growth [119]. Re-vascularization of implanted islets was clearly observed, and the engraftment and blood glucose correction was achieved at a low islet number (250 islets) [119]. In another report, freshly isolated rat islets in type I collagen (3 mg/mL) were sandwiched by two layers of precultured and prevascularized type I collagen containing rat microvascular fragments. After subcutaneous implantation into SCID mice, the vascularized construct enhanced islet survival by supporting islet viability and maintaining structures of intra-islet ECs [120].

To stimulate the growth of islet supporting vasculature, it may be useful to provide ECM components that mimic the ECM composition of the natural islet perivascular space in addition to collagen. Naba *et al.* studied the ECM composition of healthy islets as well as insulinomas. Murine islets undergoing metastatic transformation become highly vascularized at a predictable age and rate, allowing for study of ECM changes. While these highly angiogenic islets may be of some interest, it may not be desirable to create an insulinoma-like environment therapeutically. Normal islet characterizations are, for that reason, perhaps the most interesting source of ECM information. Naba *et al.* found a group of 120 ECM or ECM-associated components in the healthy islet. Several abundant components included collagen I, III, and V; fibronectin and fibrillin I; and laminins and nidogens [121]. The increased functionality of such an ECM mimic, compared to alternatives with fewer components, could provide enough advantages to be worth considering despite increased cost and barriers to regulatory approval.

Another method to mimic the ECM of the natural pancreas and support vascularization is to remove all cellular materials from the pancreatic tissue in a decellularization process. Cells are then reintroduced into the remaining material (Figure 3 b) [122]. Preservation of the vascular structure of the pancreas was a benefit noted by Napierala *et al.* during recent development of a rat pancreas-specific decellularization and islet repopulation procedure [123], as well as Yu *et al.* working on a pancreas tail-specific protocol [124]. Mirmalek-Sani *et al.* also showed that porcine pancreas vasculature was patent after decellularization, increasing metabolic rate at seven days of culture and glucose responsiveness at three days [125]. Islets have also been supported on decellularized rat pericardium with a layer of collagen derived from tendon implanted syngeneically in the epididymal fat pad in mice. Histology showed well-vascularized islets at approximately 11 months post-transplantation [119]. Working toward the goal of being able to use decellularized pancreatic proteins in tissue engineering or transplant procedures, Sackett *et al.* developed a procedure to create a hydrogel from donated human pancreas with a high fat content that was not used for transplantation [126]. Continued development of procedures to isolate and process decellularized matrices is key to realizing the benefits of a tissue-specific matrix for vascularized islet transplantation.

2.3. Prevascularization of sites for islet transplantation

Prevascularizing a site can reduce the time required to achieve an appropriate vessel supply at the prospective site. One method to prevascularize a transplantation site is to implant a vascularization-promoting device before islet loading (Figure 4 a). One of the most well-

studied device concepts in this area is the TheraCyte device, currently under continued development and adaptation by ViaCyte. In a small rodent study, three months of subcutaneous implantation was used to induce vascularization, followed by islet transplantation into the TheraCyte device to cure diabetes faster than with simultaneous device and islet implantation (6 of 6 vs. 1 of 6 cured) (Figure 4 b) [127]. Other prevascularizing devices are also under intensive development. For example, a cylindrical stainless steel mesh tubing (pore size: 450 μm, diameter: 6 mm) was implanted in the subcutaneous space [128] and omentum [129] before islet transplantation. After connective tissue rich in vascular structures formed in the pores of the mesh, a solid polytetrafluoroethylene (PTFE) plunger was removed, and islets were implanted into the lumen. Implanted islets in the prevascularized tubular tissue space restored normoglycemia, sustained long-term function (>100 days), and showed intense vascular regeneration. On the other hand, the return to normoglycemia was slightly better, with blood glucoses and body weight being slightly worse, in intra-portally transplanted control recipients from the study by Pileggi *et al.* [128, 130]. In another approach, Smink *et al.* restored normoglycemia to animals with islets transplanted into a subcutaneous device that was prevascularized *in vivo* for four weeks, at a rate comparable to that of kidney capsule controls at 45 days post transplant [130].

A different set of approaches do not leave foreign materials behind following the prevascularization period. The Shapiro group inserted a nylon vascular access catheter under the mouse subcutaneous tissue for one month to induce vascularization around the catheter. After removing the catheter, a prevascularized pouch was formed for mouse and human islets. Normoglycemia was achieved and maintained over 100 days in diabetic mice, while the nonpreconditioned subcutaneous site did not restore normoglycemia at any timepoint (Figure 4 c) [131, 132]. A prevascularized pouch can also be created by angiogenic-promoting cells. For example, adipose tissue-derived stromal cells (ADSCs) and minced adipose tissue were co-implanted in mouse subcutaneous tissue. Vascularized pockets were formed after four weeks to prepare for islet transplantation. The blood glucose level reached a normal range within a week after islet transplantation, was sustained for eight weeks, and was significantly lower than that in the three control groups of ADSCs only, minced fat tissue only, or nothing pre-implanted [133].

In addition, pro-angiogenic factors can be incorporated into devices to reduce the time required to achieve a more robust vascular network. For example, silicone tubing (length 5 mm, inner diameter 3.35 mm) was filled with Matrigel supplemented with fibroblast growth factor (FGF)-2 (1 μg/mL), The prepared tubing was split and placed around the epigastric vascular pedicle. After three weeks of prevascularization, ~500 islet equivalents were loaded into the pre-vascularized tubing, thereby resulting in lower nonfasting blood glucose than that in the implants without a delay for prevascularization [134].

Another approach to increase subcutaneous vasculature used agarose rods with basic FGF (bFGF) and heparin preimplanted in the rat dorsal subcutaneous space. After rod removal at one week, 1,500 islets were transplanted into the prevascularized pockets that rapidly reversed hyperglycemia in diabetic rats compared to unprepared subcutaneous spaces [135]. In another system, a bFGF-releasing device was transplanted into rat subcutaneous tissue for

one week to induce vessel growth around the device. Rat islets were loaded into the vascularized pocket after device removal or into the device without removal. Normoglycemia was maintained for at least one [136, 137] if not three [138] months and was better than the control no-device animals [136], control devices without collagen sponges [137], and control devices without bFGF or no device preconditioning [138] (Figure 4). Pre-vascularization is an effective method to prepare the transplant site for the therapeutic cells, so that an islet incompatible environment is avoided [139]. Despite needing multiple surgical procedures, the advantages may outweigh the disadvantages of prevascularization.

2.4. Release of Proangiogenic Factors

Factor delivery is a powerful approach to induce vascularization [140] and can include single factor, multiple factors, and multiple sequential factor delivery (Figure 5). Several methods exist for sequential delivery from materials including layered materials in planar, spherical, and cylindrical configurations [141] and light-triggered release [142–145]. In this section, examples of proangiogenic factor delivery will be considered within several delivery systems focusing on the functional outcome. Some of these methods can be categorized by their ability to cause angiogenesis, arteriogenesis, or a combination of both blood vessel network growth modes (Figure 5 a).

2.4.1. Single Factor Release—VEGF is one of the most well-studied angiogenic factors and has indeed already shown up in earlier discussions. Focusing on just VEGF as a model to consider methods of factor release, two categories can be found: (1) those where the VEGF is free to diffuse out of the material and (2) those where VEGF has been conjugated to the material to provide a sustained release. An example of the conjugated release method is 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide/N-hydroxysuccinimide (EDC/NHS) conjugation to alginate. Yin *et al.* were able to show prolonged release of VEGF and an increase of approximately 36 days of encapsulated islet effectiveness using subcutaneous implantation [146]. Marchioli *et al.* evaluated the ability of a 3D-printed heparin-conjugated scaffold to bind VEGF and therefore induce vascularization of an alginate hydrogel. Using a chicken chorioallantoic membrane assay, the authors showed that heparin modulated the activity of VEGF [147]. Presenting only heparin can also increase vascularization [148], likely due to natural growth factor depot and local concentration functions. Complimentary results support the use of VEGF when it is released from the cells themselves (produced by gene transfection [149] or by stimulation of VEGF production pharmacologically [150]) or supplemented with rotational culture [151].

PEG hydrogels are a versatile synthetic system that allows tuning of mechanical properties [152], addition of cleavable sites [153, 154], antifouling functionality [152], and delivery of drugs through bulk release or a number of other methods [155]. Marchioli *et al.* established two fully hydrogel-based models for transplantation where a vascularizing layer had conformally coated islets or cell clusters embedded into it, or the vascularizing layer was attached to an islet containing hydrogel layer with natural ECM proteins [156]. A PEG-maleimide-based hydrogel, loaded with VEGF, was then cross-linked with a degradable linker to be used as a tissue-adhesive pro-angiogenic vehicle for islet transplant on the

mesentery by Phelps *et al.* [157]. This approach offered surgical feasibility in addition to the adhesive properties. Carefully combining these functionalities, Weaver *et al.* assembled a 4-arm PEG degradable hydrogel that presented cell adhesive RGD and VEGF with islets. At the epididymal fat pad site, cure rates were best with the VEGF included in the PEG hydrogel [158]. Thus, adding degradability into synthetic hydrogels can improve the *in vivo* functionality.

Overcoming the diffusion barrier presented by a fibrotic layer is one of the goals of angiogenic factor release. For instance, Hunter *et al.* studied the release of EC growth factor (ECGF) from an alginate hydrogel encased inside a semipermeable membrane tube made of either polyvinylidene difluoride (PVDF) or polyethersulfone. Marked neovascularization occurred in the fibrotic layer for subcutaneous implants when ECGF was included [159]. Both ECGF [160, 161] and VEGF [162] are chemotactic for ECs as one of their functions in angiogenesis. Attention should be paid to the vascularization response within the fibrotic layer, as this could address fibrotic diffusion hindrances in the long term.

2.4.2. Multiple and Sequential Factor Release—Single factor delivery is more straightforward to understand scientifically and may have a comparatively simple path to the clinic. Yet, delivering multiple factors may introduce some significant benefits to the growth of sustainable vascular systems. An EC growth supplement (ECGS) was delivered by an alginate hydrogel inside a semi-permeable tubing to study the effects of sequential release of a variety of factors (MW range: 10-250 kDa) based on diffusion release. Tilakaratne *et al.* demonstrated increased blood vessel structures near the membranes when the growth factor supplement was delivered [163]. Alginate hydrogels have also been used as a vehicle for combination pre-treatment of an intra-muscular space for islet transplant by delivery of VEGF and platelet-derived growth factor (PDGF). The drug containing groups were the only ones that fully restored blood glucose control [164]. In a study of modified dextran PEG hydrogels, Sun *et al.* found that delivery of 4 angiogenic growth factors induced a greater number and diameter of blood vessels within the hydrogel than any combination of fewer factors tested [165]. Thus, multiple factor delivery is advantageous with sequential delivery possibly playing an important role.

Sequential delivery has been investigated in studies that use the advantage of biological understanding to improve outcomes (Figure 5 b). Delivery of sphingosine-1-phosphate (SIP) following VEGF delivery largely improved the area of CD31-positive structures, and their maturity, over both factors delivered together or in a different sequence [166]. Similarly, while delivery of VEGF alone can induce angiogenesis, sequential delivery of VEGF followed by PDGF from a poly(lactide-co-glycolide) scaffold resulted in a more mature network than at the two week timepoint (Figure 5) [167]. Interestingly, if PDGF or angiopoietin-1 (Angl) was delivered at the same time as VEGF or angiopoietin-2 (Ang2), the proangiogenic effects of VEGF and Ang2 were blocked. On the other hand, the effect was synergistic if PDGF or Angl was delivered subsequently [168]. Ishihara *et al.* showed that by delivering the proangiogenic peptides VEGF-A165 and PDGF-BB from an α-chain laminin-type G domain with a heparin-binding domain, diabetic wound healing was improved [169], providing insight into ways to improve vascularization in a diabetic

environment. Balancing the types of factors delivered is important considering that overstimulation with VEGF can be counterproductive to mature vessel formation [170].

Other materials have been used as the vehicle for combination delivery of vascularization-promoting factors. Fibrin hydrogels have been investigated as a carrier and delivery vehicle for transplanted islets as discussed earlier. Najjar *et al.* studied a VEGF-A165 and PDGF-BB-loaded hydrogel both in the subcutaneous space and on the epididymal fat pad in mice. Results showed that mechanical support from the hydrogel was important for overall function of the graft in the subcutaneous site, making the benefits of having the islets in direct contact with the fat pad in the intraperitoneal space (covered by the drug-loaded fibrin gel) not applicable to the subcutaneous space. Vascularization was associated with graft success in this study evidenced by increased CD31-positive area assayed immunohistologically [109].

Platelet-rich plasma, known to have multiple healing functions, has been investigated to improve vascularization of subcutaneously implanted chambers for cell transplantation [51]. Although perhaps more complex, natural collections of factors are useful, as they contain already developed ratios of factors that can be quite effective. Similarly, focusing on the natural process of wound healing may be informative [171, 172]. Typically, fibrin clot matrix is rapidly vascularized to form granulation tissue, which is highly dependent on FGF-2 released from cells in the wound bed. Interestingly, FGF-2 peaks almost immediately after a cutaneous wound, while VEGF peaks at approximately day 5 [173], perhaps in part driven by the fact that FGF-2 can stimulate VEGF secretion [174]. A factor release sequence mimicking this pattern could be effective in generating vascularized tissues [175]. Toward this idea, a combination of VEGF and FGF-2 has been released from heparin-binding peptide nanofibers. The growth factor-loaded hydrogel resulted in a 78% cure rate, while the unloaded peptide nanofiber hydrogel produced only a 30% cure rate in isogeneic mouse transplants [176]. Interestingly, when similar heparin mimetic peptide amphiphile materials were loaded with the same angiogenic factors (VEGF and FGF-2), islets were functional for longer in culture (up to seven days), displaying a stimulation index that was not different from freshly isolated islets [177]. This raises a possibility that angiogenic molecules have effects on the function of islets aside from inducing a vasculature, perhaps including the earlier referenced EC–islet cell interactions.

In parallel to the blood vascular network, a system of vessels that drain interstitial fluid forms the lymphatic vessel system. Delivery of a fibrin-binding VEGF-C variant to an ear cartilage defect model demonstrated an increase in lymphatic vessels, and delivery to a diabetic wound increased the rate of healing [178]. A primary function of the lymphatic system is immunological surveillance. Interestingly, islets and the central nervous system are among the few tissues thought to lack a lymphatic system [179, 180]. Some investigators have found a relationship between lymphangiogenesis and modulation of the immune response [181, 182]. Lymphangiogenesis has not yet been studied to the extent of angiogenesis, although the lymphatics may play an important role in successful tissue regeneration. While single or sets of factors may be able to stimulate a pro-angiogenic response, and sequential delivery may potentiate these responses, cells can also powerfully orchestrate the factors in the tissue milieu.

2.5. Co-culture and co-transplantation of islets with pro-angiogenic supporting cells

Co-culturing and co-transplanting vascularization supporting cells can promote network growth around implanted islets or within islets (sometimes with the participation of residual donor ECs). Therefore, co-culturing and co-transplanting can facilitate anastomoses between intra-islet vasculatures and the recipient vascular system. Mesenchymal stem cells (MSCs) and fibroblasts are the most commonly used cell types for co-culture and co-transplantation to support ECs. These cells actively participate in vascularization at the cellular level and have a unique role in vascular regeneration. ECs comprise the blood-contacting surface in vessels. Moreover, ECs attract other supportive cells to promote the formation of new blood vessels through paracrine secretion and signaling [183]. The main functions of MSCs in vascularization include the secretion of proteases to degrade ECM for EC migration and sprouting [184], enhancement of angiogenesis by up-regulating angiopoietin and VEGF expression in ECs [185], stabilization of vasculature by differentiating into pericytes [186] and suppression of immune or inflammatory responses [187, 188]. During angiogenesis and neovascularization, fibroblasts can generate diverse angiogenic factors such as VEGFs and FGFs to facilitate EC tube formation controlling blood vessel development [189]. Co-culture and co-transplantation of vessel-forming cells can be realized in different approaches.

First, we consider formation of a simple mixture of islets and supporting cells (Figure 6 a). Co-transplantation of porcine islets and MSCs has been performed under the kidney capsule and subcutaneous space in diabetic mice and primates [190, 191]. Oh *et al.* studied a bone marrow-derived mononuclear spheroid culture method to generate highly angiogenic cells. When co-transplanted with islets, the cure rate and the mean blood glucose were improved compared with mononuclear cells that did not spontaneously incorporate into the spheroids or islets without support cells [192]. Before co-transplantation, islets and supporting cells can also be embedded in ECM scaffolds. MSCs and fibroblasts along with mouse and rat islets were loaded together in collagen and fibrin scaffolds for transplantation in the omental pouch and subcutaneous space of diabetic mice [193, 194]. Compared to islets alone, overall co-transplantation results include increased glucose-stimulated insulin secretion [190], higher graft oxygenation [191], enhanced angiogenesis and vascularization [191, 194], better glycated hemoglobin correction [191], earlier normoglycemia [190], improved glucose tolerance [190, 193], and increased insulin content [190]. The simplicity of mixing cells before transplantation is a notable advantage for the translatability of these approaches.

Next, we consider co-aggregation of islets and supporting cells (Figure 6 b). Takebe working in the Taniguchi group demonstrated that vascularization of different types of tissue fragments can be achieved by co-aggregating with human umbilical vein ECs (HUVECs) and human MSCs [195–197]. When seeding on Matrigel or in a U-bottomed conical 96-well plate, pancreatic islets, HUVECs, and MSCs self-assembled into a miniaturized organoid in which HUVECs and MSCs played key roles in vascularization [198]. The vascularized islets showed more intra-islet blood vessels and better blood glucose control. In addition, a composite pellet of mouse islets and human bone marrow-derived multipotent adult progenitor cells (MAPCs) showed a higher blood vessel area, density, and vessel/islet ratio when transplanted under the kidney capsule [199].

Vascularization supporting cells can also be coated on islets (Figure 6 c). Rat islets were coated with rat ECs before transplantation under the kidney capsule in diabetic rats [200]. Similarly, human islets were also coated with human dermal microvascular ECs (HDMECs) and human bone marrow-derived MSCs [201]. Rat MSC sheets, created with temperature-responsive cultureware, had rat islets attached before lifting to co-transplant subcutaneously into SCID mice. MSC–islet composite sheets displayed greater stimulated insulin secretion *in vitro*. Only when 2,000 islets were combined with MSC sheets glucose was corrected *in vivo* for more than three weeks compared to 1,000 islets with MSC sheets, 2,000 islets with MSCs (not in sheet form), or 2,000 islets alone [202]. Anchoring VEGF to a heparinized islet surface has been used to increase the attachment of ECs *in vitro* [203], as a preparation for accelerating vascularization. Clearly coating islets with supporting cells can improve engraftment.

Recently, the Sefton group created a unique and elegant way to deliver islets with coated vascularization supporting cells. In this protocol, type I collagen (3 mg/mL) tubing sections, encasing rat islets (~1 islet per module), were seeded with HUVECs on the collagen surface (Figure 6 d). Seven hundred fifty islet modules were subcutaneously implanted into SCID-Beige mice, and a vascularized microenvironment was developed [41, 204]. Coating approaches offer the advantage of even distribution of cells across the islets being prepared for transplantation. All these results suggest that the addition of vascularizing support cells to islets can improve transplantation success, and this should be further investigated.

3. Challenges, Perspectives, and Emerging Approaches

3.1. Selection of Vascularizing Cells

Although promising co-transplantation and co-culture systems have been demonstrated in the literature, several challenges remain from a scientific and translational point of view. The source and history of supporting cells (such as donor age) can influence cell function [205, 206]. Compared with younger donors, cell morphology and viability of MSCs from older donors can be varied. In addition, proliferation, trophic factor secretion, and angiogenic potential of aged MSCs are significantly reduced [207–209]. These variables can affect the results of preclinical experiments while also hampering clinical translation. The methods to acquire sufficient autologous human vascular or supporting cells are still under development. Induced pluripotent stem cells (iPSCs) have tremendous potential for transplantable tissues, thereby prompting increasing numbers of investigators to utilize them in vascular bioengineering studies [210]. Starting somatic cells (e.g., dermal fibroblasts or fat stromal fractions) can be acquired in minimally invasive procedures. After expressing genes Oct-4, Sox2, Klf4, and c-Myc to induce pluripotency [211], it is possible to expand the cells *in vitro* [212] for differentiation toward vascular cells [213–217], as well as the endocrine cells of the islet [218–224]. There remain concerns about possible uncontrolled differentiation and proliferation arising from cells that escaped the intended differentiation program. Despite these concerns, as well as further protocol development being required, iPSCs avoid the ethical concerns of embryonic stem cells and do not have the same functional decline with donor age. It is likely that iPS cells will continue to develop as part of the specific tissue engineering solution to vascularization and to general tissue shortages.

3.2. Determination of Transplantation Site

Selection of the site to test an engineered tissue can affect the outcome and the translatability of the results. Transplantation sites vary in the degree to which they are naturally vascularized, as well as the potential to vascularize a transplanted tissue or device. As such, the site affects what prevascularization treatments may be required to induce a sufficient vessel network including interfacing with location-associated inflammatory responses [225]. Many transplantation sites used to evaluate vascularization, such as the kidney capsule [226, 227] or within the central nervous system [228], although conducive to islet engraftment, are not applicable to human clinical treatment. Therefore, the methods tested in these sites should be evaluated in other practical transplantation sites such as the subcutaneous space or peritoneal cavity.

Despite agreement that an extrahepatic site for islet transplantation is needed, there are still relatively few studies that compare candidate sites. In a recent well-designed study by Weaver *et al.*, an epididymal fat pad site was superior in terms of islet survival, islet vascularization and inflammatory reaction when compared to a small bowel mesentery and especially when compared to the subcutaneous site [158]. All sites were transplanted with unloaded PEG or PEG hydrogels containing proteolytically releasable VEGF to improve the vascularity of the encapsulated single donor islets. Thus, the site should be considered in light of the preclinical evaluation potential and translatability.

3.3. Expedient vascular regeneration

Understanding how quickly an islet needs to be vascularized to prevent an ischemic loss of islets may inform vascularizing strategies. Islets in the native pancreas are integrated with a vascular system consisting of different types of cells (i.e., ECs and fibroblasts) [229]. It is therefore of great importance to quickly achieve the anastomoses between donor islets and recipient blood vessels or regenerate sufficient vasculatures around encapsulation devices. Unaided re-vascularization of islets occurs over a period of 7-14 days post-transplantation to reach a stable vascular density [53, 230]. A benchmark for studies should be accelerating the establishment of a vascular network, ideally within seven days. During the avascular period, transplanted islets are solely dependent on diffusion to receive oxygen/nutrients and clear metabolic waste [42]. Furthermore, encapsulated islets can, at best, have diffusive processes from the surface of the device to regenerated blood vessels.

In addition to *in vivo* prevascularization strategies discussed earlier in this review, *in vitro* preformed vasculatures might aid islets in the days following transplantation. Previous reports have shown that in contrast to the random mixture of ECs in ECM, predefined parallel-patterned EC tubes promoted the vascularization and overall function of co-implanted human hepatocytes [231–234]. Similarly, Hiscox *et al.* developed a device where a layer of hydrogel containing islets was surrounded above and below by layers containing vascular segments isolated from the fat pad one week before transplant [120]. These studies imply that an “ideal” organization of vascular architectures might exist and could be preformed to facilitate the vascularization and anastomoses of islets.

Even if a preformed vasculature and a preconditioned recipient site are combined, driving quick anastomosis, there will still be a period of time that the transplanted tissue is not yet perfused and is ischemic. To support islet survival during this period, it may be useful to supply oxygen [235]. Following transplantation, oxygen can be supplied in gaseous form directly [236–238] or generated by chemical reaction [239], electrochemically [240], or photosynthetically [241]. Before transplantation, the oxygen tension can also be controlled to reduce anoxia during culture [242]. Even before digestion, the donor pancreas can be oxygenated with techniques such as persufflation [243]. Oxygen supplementation techniques post-transplant may be useful to support fully encapsulated islets that will never vascularize and are therefore an important line of investigation for which the reader may find several excellent reviews with more information [235, 244, 245].

3.4. Manipulating the spatial positions of islets and vascular structures

Controlling the spatial positions of islets and adjacent vascular structures *in vitro*, which mimics their interactions and density in the pancreas [246, 247], might be an effective way to secure optimal diffusion kinetics in and out of the graft. The spatial density of islets can affect survival as a result of increased oxygen consumption with higher densities of cells [248–250]. Although production of proangiogenic factors by islets has been shown to increase in hypoxic environments [251–253], islet vascularization may still be reduced [254]. Three-dimensional (3D) printing is a powerful tool to achieve spatial control of cells [255]. Therefore, 3D printing may be a useful tool to accurately control the homogeneous spacing of islets, rather than a bulk average that varies spatially.

Over the last decade, various methods have been developed to spatially deposit cells and materials in 3D [256–258]. Among different 3D printing techniques, sacrificial molding is particularly suitable for generating hollow channels in which ECs are perfused and adhered on the channel walls to form an endothelial lining structurally similar to blood vessels (Figure 7 a) [259–262]. Other types of cells (such as cardiomyocytes, hepatocytes, MSCs, and fibroblasts) can be co-printed or added later into the interspaces between the endothelial channels [258–260, 263, 264] (Figure 7 b). ECs deposited between the channels can also anastomose to the 3D-printed channels to create perfused capillary structures *in vitro* [265]. A wide range of heterogeneous cellular constructs have been printed, and several reports indicated the beneficial effects of endothelial channels as blood vessel-like structures [258, 264]. Application to islet transplantation and encapsulation has been assessed for a variety of structures that can exhibit features unique to 3D printing [266–271]. In a recent study, Chen’s group demonstrated that for a rodent model of hindlimb ischemia, parallel endothelial channels integrated with the recipient and recreated blood perfusion, whereas random endothelial patches did not show any therapeutic effect [100] (Figure 7 c). These results indicate that 3D printing of islets and endothelial luminal networks might provide a biomimetic vascular-like network that quickens anastomoses and re-vascularization of islets.

3.5. Avoiding poorly formed vasculature

Growing a vasculature into or around a transplanted tissue does not ensure that it will be able to provide all the functions required by the cells for a long period of time. Rather, the vasculature needs to transition from a nascent structure to a stable one that is able to adapt to

the tissue needs [272]. This concept has been assessed in vasculature targeted cancer treatments where both blocking angiogenesis and guiding the existing vasculature to a more stable state have been investigated to reduce patient mortality [273]. In the case of transplanted islets, some studies have compared the developed vasculature to that of the native islets [274].

Studies that examine the quality of vessel network formation to correlate with graft success are needed. It is possible to measure vessel networks with the dorsal skinfold window chamber [275, 276], mesentery windows or exteriorization [277, 278], contrast-enhanced MRI [279, 280], contrast-enhanced ultrasound [281], live cell markers [282–284], and immunostaining of tissues [285–287]. Quantification of parameters such as perfusion [288–290], flow dynamics [291–293], tortuosity [294, 295], fractal parameters [296], branching [297–299], endothelial permeability [300–303], and length and diameter [304, 305] can all be measured to determine the status of a vessel network. In some cases, automated analysis is possible [290, 295–297, 299, 304–307]. Buitinga *et al.* developed a smart analysis method where the vessels (and cell arrangement) were quantified in islets. Capillary structures were binned based on their radial location in the islet [247], adding value to the comparison of treatment groups. While the target for bare islets is a native vasculature, it is mostly unknown what is required for encapsulated islets, except an increase over basal vessel network density in tissues such as skin. Quantitative vascular metrics are, therefore, important to set requirements for vasculature in all types of islet grafts.

Some efforts aim to avoid needing to induce a vascularization at all. Interesting techniques are being investigated to address the diffusion challenge using convective rather than diffusive flux. Using an intravascular device would reduce the need for microvascular networks around the device because transport could be driven by ultrafiltrate convection through the islet-containing chamber [308]. Another promising approach to circumvent the diffusion barrier is to use a nanocoating that permits vascularization while camouflaging surface antigens [309, 310]. Successful β-cell replacement is a challenging goal that may not be feasibly addressed with a single technique. These emerging techniques, coupled to growing a robust vasculature, have various surmountable challenges to be addressed before clinical viability.

3.6. Biological Challenges – Immune–Vascular Cooperation and Hyperglycemia

Throughout this review, it has been implied that more vasculature will benefit the transplanted tissue or device. It is important to keep in mind, however, that the benefit of increased vasculature has limits. It is key to consider not only short term but also long-term effects. If a treatment shortens the time to normoglycemia, while hindering the long-term cure, it might be necessary to add another treatment that will improve long-term graft stability [311]. The vascular system is constantly adapting to needs in tissues as diverse as islets, muscles, and the brain. During inflammation, the vasculature grows to support tissue regeneration and facilitates access from the systemic immune system. Unfortunately, this may also increase exposure of implanted materials to the immune system.

Immune and vascular contributions to the post-implantation period must be balanced. Vascularization of transplanted tissues is known to affect the type of immune response that

occurs [312], where an abundance of vasculature can cause inflammation and β-cell death [313, 314]. A certain degree of immune system involvement is important to induce healing [315–320] and stable vasculature. Anti-inflammatory or pro-regenerative monocytes [321–324], smooth muscle cells [325], and other pericytes [326, 327] can support blood vessel maturation. Furthermore, Christoffersson *et al.* showed that neutrophils, a less commonly identified pro-regenerative cell type, are required for a native-like vascular structure to form in islets transplanted on striated muscle [274]. One way to modulate the immune system is to prevent protein adsorption with zwitterionic materials [328–335]. Zhang *et al.* showed that compared to a low fouling poly(2-hydroxyethyl methacrylate) hydrogel, the ultra-low-fouling zwitterionic poly(carboxybetaine methacrylate) hydrogel not only had a reduced fibrotic layer but also had greater vasculature density near the hydrogel [336]. This effect appeared to be due to macrophage polarization [336].

The innate and adaptive immune systems are known to participate in vascularization. When using HUVECs as the source of ECs in preclinical models, it is necessary to use an immunocompromised model to prevent rejection. While formation of a functional vasculature in these animals suggests that the cells of the adaptive immune system are not essential participants in the response, it is quite likely that the response is altered. Subsets of T-cells are capable of directly producing VEGFs [337, 338]. Both T- and B-cells exert their immune functions and participate in modulating the angiogenic environment partly by interacting with effector subsets of the innate immune system (i.e., macrophages and neutrophils) [339, 340]. A revascularizing tissue in an immunocompromised mouse may be capable of achieving healing and measurable vascularization, but it is in an environment that more closely represents an immunosuppressed individual. Thus, we must be careful about how far we extrapolate these results without first verifying them in fully immune competent models.

EC is a key mediator of both immunity and blood vessel growth. ECs form sprouts that become new blood vessels as well as participating in vascularization signaling pathways. ECs also participate in immunity during extravasation of cells from the blood to the tissue. During this process, not only inflammatory cells can be hindered or allowed through by ECs but the expression of stimulatory molecules may also modulate the activation state of cells as a result of contact with the endothelium. Furthermore, functional differences are known to exist between primary ECs and immortalized EC lines [341].

The inter-communication of the vascular and immune system has another level of complexity when sites and species differences are considered. Some immunosuppression drugs such as rapamycin [342, 343] are known to interfere with vascularization. However, even with immunosuppression (i.e., daclizumab, tacrolimus, and sirolimus), allogenic islets intraportally transplanted into rhesus macaques were able to vascularize by 30 days post-transplantation [344]. Furthermore, other immunosuppressive drugs (including cyclosporine, RS-61443, and prednisolone) have been shown to delay or reduce but not prevent intra-islet capillary formation [345–348]. Toxicity of immune suppression drugs to islets has also been shown [349–353] and should be taken into consideration in transplant schemes [354, 355]. Interestingly, sirolimus has been associated with decreased VEGF release from β-cells, perhaps forming the link between sirolimus and reduced transplanted islet viability [356].

In some cases, xenotransplantation can last for a period of time without needing immunosuppression while still gaining access to nutrients, such as arteriovenous shunt devices [357]. Similarly, in some reports of planar or tubular encapsulation systems made of PTFE [238, 358, 359], acrylic copolymer [360], alginate [361], and polyethersulfone [362], as well as spherical capsules made of alginate [359, 363–367], survival has been observed without immunosuppression or using an immune compromised recipient. Preclinical investigations have shown that prevascularization of subcutaneous sites can create spaces where allogeneic islets can survive without immunosuppression [135]. Subcutaneously transplanted islets without preconditioning did not survive in this study, perhaps due to a combination of allo-immunity (which may have been ameliorated by FGF-2-dependent MSC recruitment [368]) and a lack of vascularization [135]. In a different material-based prevascularizing scheme without delivered factors during the preconditioning, immunosuppression was required to prevent islet rejection in an allogenic model [132]. Relevant to the goal of allowing vascularization for xenogenic transplants, some glucose correction has been noted without pharmacologic immunosuppression or polymer encapsulation in a human trial, with Sertoli cell co-transplantation [369]. Endothelialized collagen modules have been able to increase the vascularity surrounding transplanted islets into syngeneic or immuno-suppressed allogenic rat recipients compared to collagen modules without ECs or free islets, respectively [370], supporting an idea that some vascularizing strategies can function with or without immunosuppressive drugs present.

It is also important not to overlook the existing conditions of the recipient of a treatment. In the case of islet transplant, microvascular complications are common in those with longstanding hyperglycemia [371, 372]. Hyperglycemia can cause dysregulated microvascular remodeling (increased or decreased, depending on the tissue) [373, 374]. A high glucose environment, or the effect of previous hyperglycemia, is likely to be encountered by islets following transplantation that may cause anti-angiogenic factors to be secreted [375]. Vascular pericytes have been shown to initiate apoptosis through PKC-delta SHP-1- or NF-kappaB-dependent pathways when exposed to hyperglycemia [376]. The diabetic environment adds an additional challenge to finding the appropriate level of immune-regulated therapeutic vascularization.

Some challenges with islet transplant, or cell transplant in general, may interfere with a clear understanding of experiments intended to elucidate vascular contributions to graft success. Differences in success in rodents versus larger animals may be related to many factors including difficulty of completely digesting the pancreas to harvest pure islets [377]. On a related note, although an argument can be made for larger islets recruiting intra-islet vasculature due to a greater hypoxic response from the center of a larger islet [378], when islets are to be encapsulated and will never be vascularized, smaller islets may be more viable [379, 380]. While delivering islets in a growth factor-supplemented matrix usually supports islet transplant, the site and the recipient species may be a factor to consider. For instance, islets transplanted into the porcine gastric submucosa were not improved by the inclusion of Matrigel [381].

Finally, it may also be important to acknowledge here that interpretation of results in literature is not always the same in retrospect. For instance, some early experiments that

utilized alginate as the encapsulating material may have been conducted before the knowledge that highly purified alginates are necessary [382]. Moving forward, some experiments may need to be repeated for input into the immunoisolation membrane design process.

4. Conclusions

Rapid advancements have been made in the closed-loop artificial pancreas [383–385], oral insulin formulations [386], and smart insulin [387–390]; yet, none so far have achieved the physiological control over an extended period of time that a pancreatic islet can provide [391]. The promise of higher patient quality of life and reduced healthcare costs motivate progress toward the ideal curative treatment. Our understanding of islet biology includes an intricate connection between the endocrine cells of the islets and the unique intra-islet capillary network. The quicker this can be developed in a transplanted islet, the greater is the probability of graft success through exchange of oxygen, nutrients, and wastes for islets, ensuring an adequate dispersal of secreted insulin.

Accelerated vascularization can be accomplished by tuning material physical properties, delivering factors, and delivering support cells. When a vessel network is developed before implantation of the therapeutic cells, anastomosis with the host vasculature can further reduce the time to function. The choice of implant site is important for the evaluation of therapeutic vascularization strategies. Cell sources for vascularized tissue-engineered constructs are an area of continued development.

Inadequate transplantable tissue supply from organ donation encourages consideration of alternate sources of cells including xenogeneic or stem cell-derived cells. These cell sources benefit from a robust encapsulation membrane to control immune responses and control the location of the foreign cells. Stem cell-derived islet-like clusters do not contain ECs unless the protocol specifically adds them. Therefore, in a stem cell-derived immunoprotected transplantation scheme, it is imperative that the host vasculature be as developed as possible to provide nutrient supply and waste removal from the encapsulated cells. If the immunoprotection provided is robust, any increase in inflammatory activity enabled by a richer vasculature should be tolerable. A possible solution to this immunoprotection–vascularization paradox is conformal coatings, which can camouflage surface antigens to reduce immunological recognition, while not necessarily preventing vessel penetration. An example of this is a study by Rengifo *et al.*, where a three-layered conformal coating prevented complete graft rejection in a fully MHC mismatched murine model, while allowing vessel infiltration [392]. Although it was not clear from the results whether the islets that were integrated with blood vessels had complete and robust coatings [392], it nonetheless provides for the possibility that camouflaging surface antigens could prevent rejection even if cell infiltration is still permitted.

In conclusion, we have summarized strategies to accelerate, shape, or develop vasculature for supporting the survival of transplanted islets. These strategies are also applicable to other microtissues, therefore being useful for a collection of tissue engineering problems including modular bio-printed tissues and organs [393]. A successful strategy for islet vascularization

is likely to inform the field of regenerative medicine as we move toward being able to create functional transplantable tissues.

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Statement of Significance

Insulin-dependent diabetes affects more than 1.25 million people in the United States alone. Pancreatic islets secrete insulin and other endocrine hormones that control glucose to normal levels. During preparation for transplantation, the specialized islet blood vessel supply is lost. Furthermore, in the case of cell encapsulation, cells are protected within a device, further limiting delivery of nutrients and absorption of hormones. To overcome these issues, this review considers methods to rapidly vascularize sites and implants through material properties, prevascularization, delivery of growth factors, or co-transplantation of vessel supporting cells. Other challenges and emerging technologies are also discussed. Proper vascular growth is a significant component of successful islet transplantation, a treatment that can provide life-changing benefits to patients.

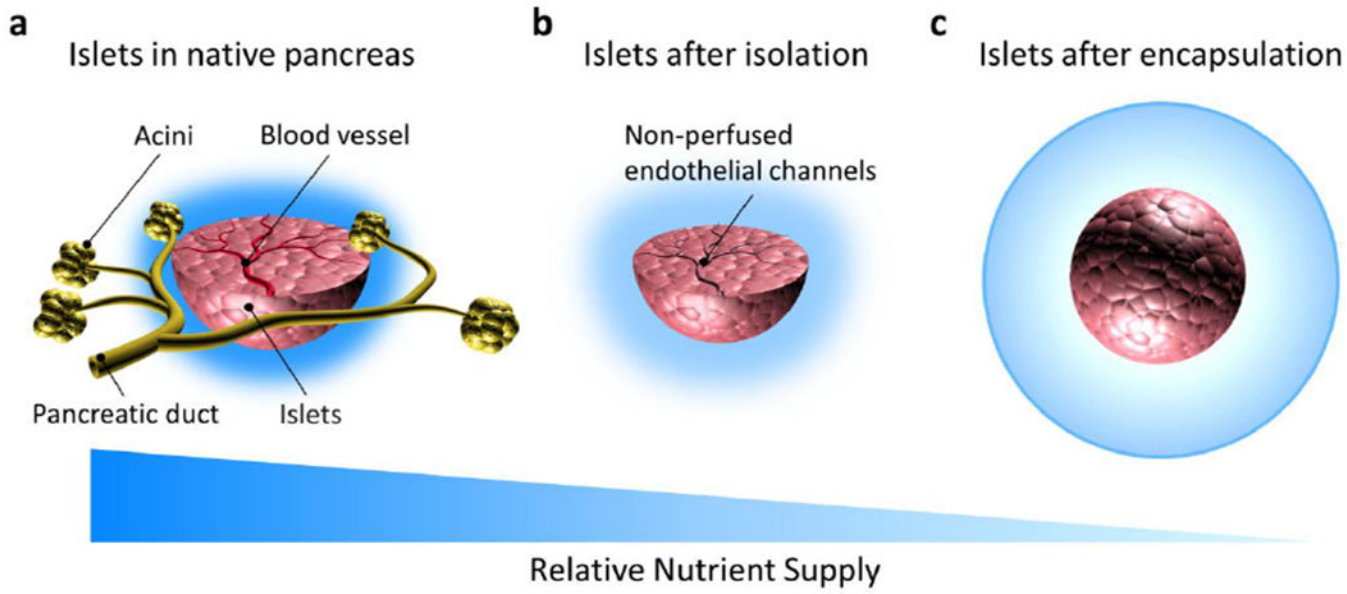

Figure 1. Mass transfer to islets is limited by isolation and encapsulation.

Compared to the native pancreas **(a)**, islets experience reduced diffusion to the majority of cells (especially in the core of the cell mass) as a result of loss of blood perfusion following isolation from the acinar tissue **(b)**. Furthermore, encapsulation of any kind (microencapsulation shown here) increases the distance of islet cells to the surrounding fluid or blood vessels **(c)**. Dark blue represents greater mass transport. Drawings not to scale.

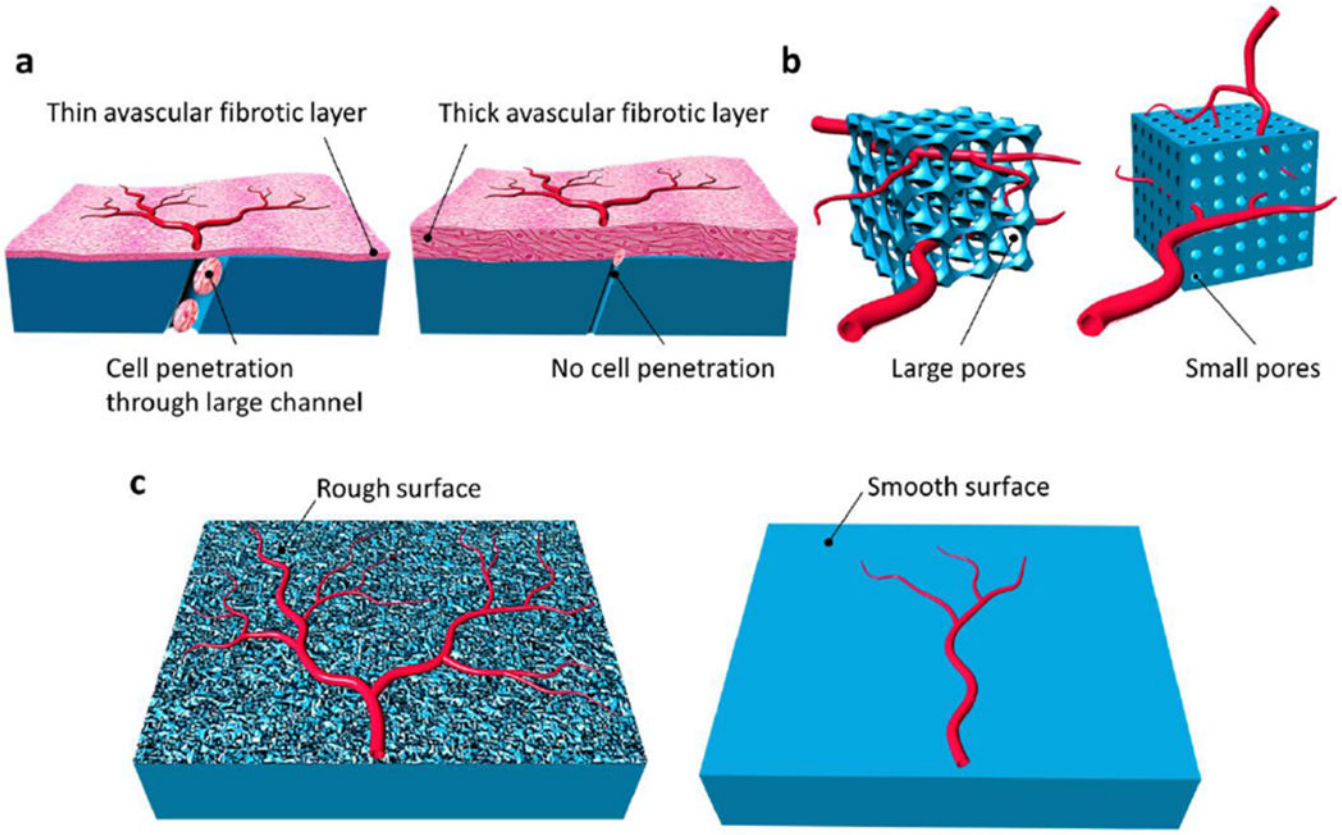

Figure 2. Material properties that influence vascularization.

The thickness of the avascular fibrotic layer (shown in light red) can be reduced by constructing an implant that allows cell migration into the membrane **(a)**. Larger pores can facilitate more blood vessel investment than pores that are only sufficiently large enough to allow blood vessels to form **(b)**. Increases in nanotopographical roughness can increase vascularization compared to smooth substrates **(c)**.

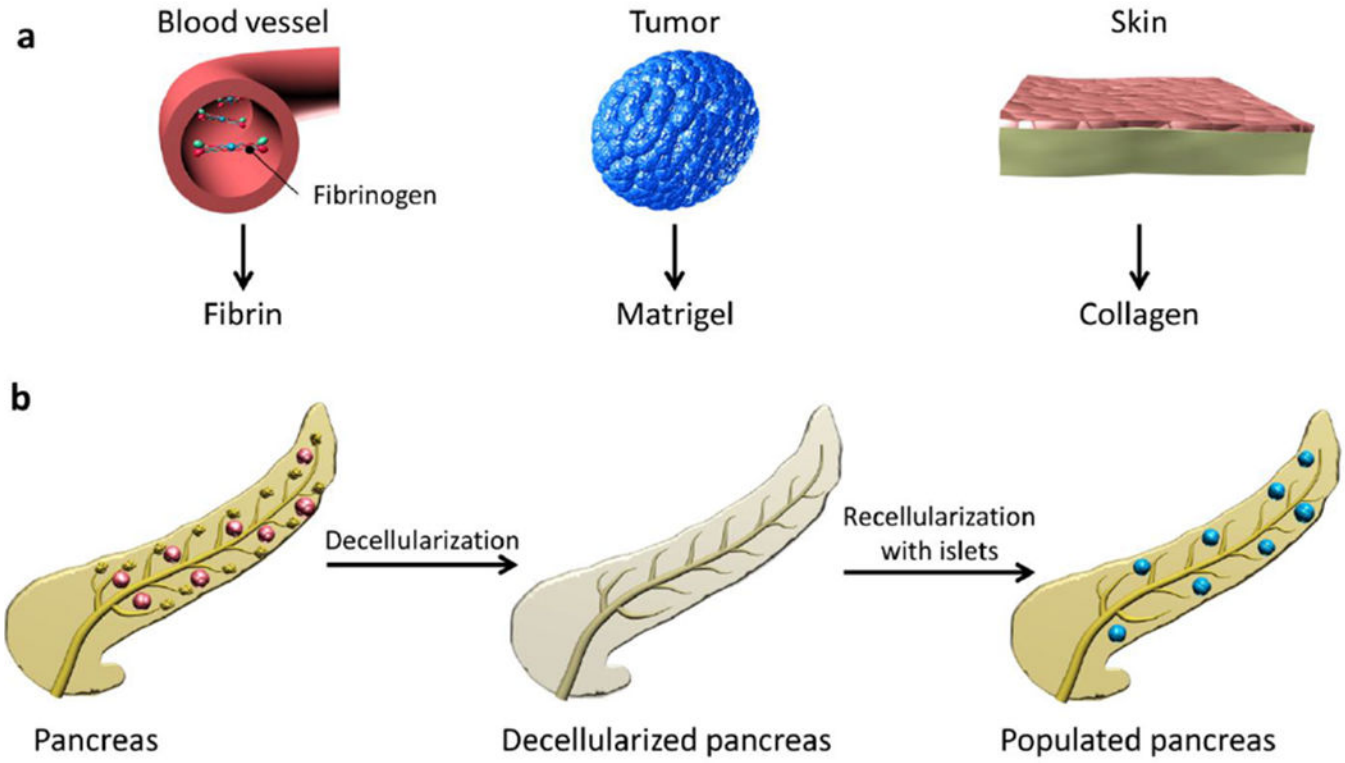

Figure 3. ECM materials that can be used to scaffold and vascularize transplanted islets.

Fibrin scaffolds are polymerized from fibrinogen present in the blood plasma **(a)**. Matrigel is isolated from a murine sarcoma **(a)**. Collagen can be isolated from many sources, with skin shown here as an example **(a)**. Decellularized pancreatic tissue may be a natural scaffold for islet transplant **(b)**. Matrix materials can be selected and combined to promote islet vascularization and health.

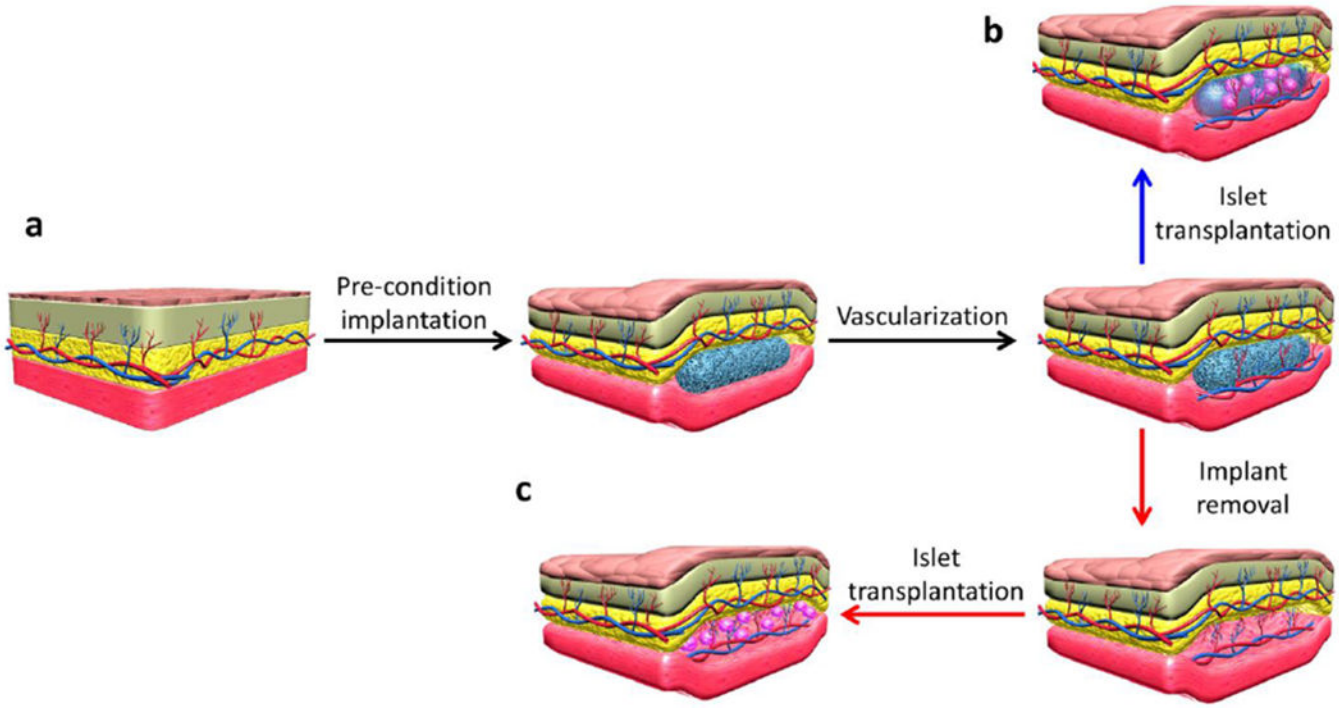

Figure 4. Preparing a site by prevascularization to improve engraftment.

Preimplantation of a material stimulates vascular enrichment **(a)**. The islets can then be introduced into the preimplanted device **(b)** or the device can be removed to create a space left by the device that the islets can be introduced into **(c)**. All of these approaches result in a space for the islets that has a greater vascular supply at the time of transplantation than an unprepared site.

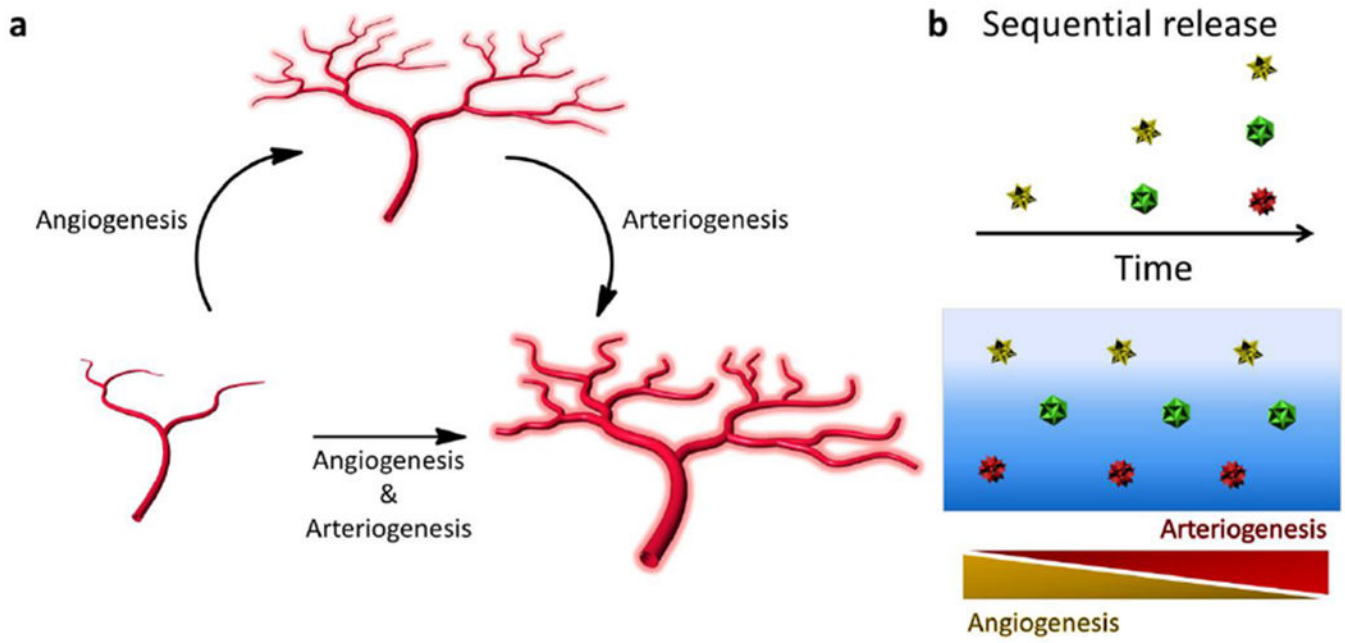

Figure 5. Release of angiogenic factors to drive implant angio- or arteriogenesis.

Angiogenesis is the formation of new capillary sprouts from existing vessels and can be driven by factors such as VEGF **(a)**. Arteriogenesis is the maturation of blood vessels, often characterized by the addition of support cells to an endothelial tube and the increase in lumen diameter. Arteriogenesis can be driven by factors such as PDGF-BB **(a)**. Multiple factors can also be sequentially released (e.g., VEGF then S1P, VEGF then PDGF) to push both of these vessel network expansion paradigms **(a,b)**.

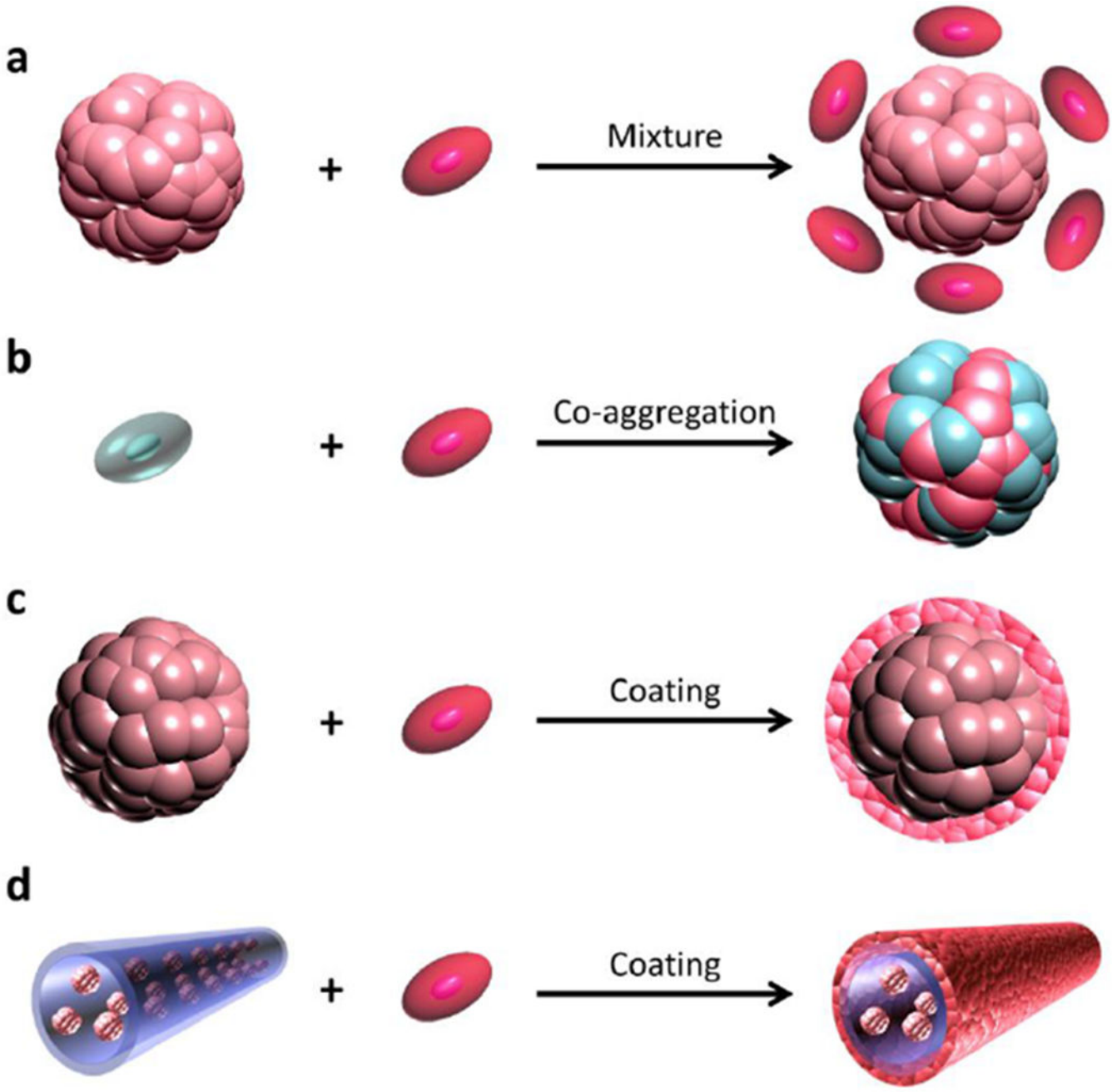

Figure 6. Co-transplantation of vascularization supporting cells to improve engraftment.
Vascularization supporting cells can be mixed with islets or cell aggregates before transplantation **(a)**. Vascularization supporting cells can be included with hormone-producing cells during aggregation **(b)**. Vascularization supporting cells can be coated on islets or cell aggregates before transplantation **(c)**. It is also possible to coat vascularization supporting cells on or in islet-matrix modules **(d)**.

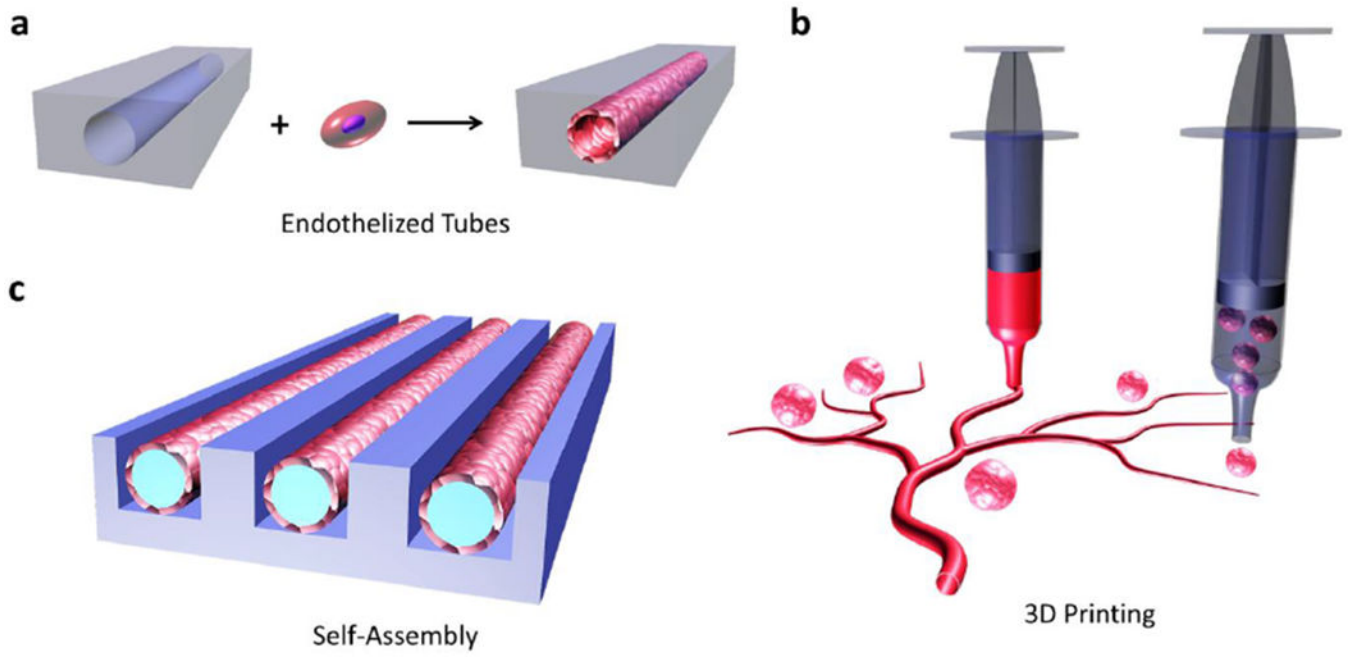

Figure 7. Organization of vascular structures in engineered environments.

Engineering of vascular regeneration can be accomplished utilizing some emerging approaches. Tubular voids in constructs can be formed and then endothelialized **(a)**. Three-dimensional printing can be used to arrange vascular tissues and the islets or cell clusters in logical patterns **(b)**. Endothelialized modules can be formed *in vitro* using microfabricated molds.