

Review

Bioengineering of vascular macrodevices for transplantation of insulin-producing cells

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Type 1 diabetes (T1D) is caused by the autoimmune destruction of insulin-producing cells (IPCs), resulting in disruptions to blood glucose regulation. Cell therapy is an established, FDA-approved treatment for T1D. Incorporating IPCs into vascularized devices provides a promising strategy to enhance therapeutic efficacy. Here, we discuss the challenges of device vascularization and its role in successful IPC transplantation. We explore state-of-the-art engineering strategies used for the efficient vascularization of IPC encapsulation devices, including material selection, design criteria, and fabrication methods for the production and assembly of vascularization device components. In addition, the current state of research and future clinical applications in this field are discussed.

Cell therapy for treatment of type 1 diabetes

Type 1 diabetes (T1D) is an autoimmune disorder characterized by the destruction of insulin-producing β cells, leading to insufficient insulin secretion and impaired glucose homeostasis. Cell transplantation has become a therapeutic approach for the treatment of T1D. Recent advances in pancreatic **islet** (see [Glossary](#)) isolation, along with the development of human **pluripotent stem cell** (hPSC)-derived β cells, have enabled significant progress in the generation of functional insulin-producing cells (IPCs) that can then be transplanted. Although these IPCs have shown favorable results in preclinical studies and clinical trials [1,2], immune rejection, **hypoxia**, and choice of transplantation site, all contribute to poor cell engraftment ([Box 1](#)). In particular, the therapeutic efficacy of IPC transplantation is hindered by the high metabolic demands of these cells and their sensitivity to hypoxia after transplantation as native pancreatic islets are vascularized by a dense capillary network that provides an adequate supply of oxygen and nutrients [18].

The formation of a functional vascular network during the early post-transplantation period is critical for the success of diabetes cell therapy. Delayed and insufficient device **vascularization** can result in the death or irreversible dysfunction of the IPCs, reducing therapeutic efficacy [19]. Re-establishment of functional vascularization into or around the transplanted cells and the presence of an adequate oxygen supply are necessary to ensure successful engraftment [20]. Recently, encapsulation has become an attractive strategy for overcoming the challenges related to IPC transplantation [21]. IPC encapsulation is categorized based on device size and includes nanoencapsulation, microencapsulation, and macroencapsulation approaches. Macroencapsulation devices allow thousands to millions of IPCs to be encapsulated within a protective structure (>1 mm) for transplantation, depending on the target species and the therapeutic dose required [22,23]. Herein, ‘device’ refers to a frame-based structure used for transplantation that supports cell homing and engraftment. The application of transplantation devices may provide immunoprotection and also offer the potential for retrieval, **refilling**, long-term stability, and precise cell localization [24]. In addition to the frame and IPCs, the device may also include

Highlights

Challenges in current approaches in diabetes cell therapy highlight the critical need to develop solutions for promoting cell engraftment.

Macroencapsulation device with vascularization capacity remains a key limitation in IPC transplantation as it is essential for overcoming hypoxia and nutrient diffusion barriers to ensure cell survival and function.

The selection of polymeric biomaterials for different device components, including the frame and hydrogel, directly influences vascularization efficiency.

Vascularization devices are constructed using a variety of fabrication approaches tailored to material properties, design complexity, cost, and scalability. These methods enable the production of structural frameworks, porous membranes, and hydrogel-based components, supporting the encapsulation of IPCs for improved transplantation outcomes.

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hydrogels, supporting cells, and angiogenic factors (Figure 1). Due to recent advances in the isolation and generation of functional IPCs, together with the clinical success of cell-encapsulation technology, there has been growing attention to the development of vascularized encapsulation devices with complex engineered designs that hold significant promise for improving IPC therapeutic efficacy in T1D treatment. In this review, we examine the engineering strategies underlying frame-based vascularized macrodevices, with a focus on key design parameters that influence device performance, selecting the appropriate biomaterial for device components, and the fabrication process for the production of the final product.

Designing a vascular device

Encapsulation devices must be precisely designed to promote vascularization and enable efficient exchange of oxygen, nutrients, insulin, glucose, and other essential factors. The device design also depends on the transplantation strategy used for IPCs. In the conventional approach, IPCs are encapsulated within the device before transplantation [25]. However, in the prevascularization strategy, the device is first implanted to induce vascularization and subsequently loaded with IPCs [26]. Moreover, the device's potential for sequential IPC incorporation may also be advantageous for replacement with fresh and functional cells, thereby supporting long-term insulin independence. There are three main techniques for introducing cells into a vascularized device. The first and minimally invasive strategy integrates a port directly into the device, allowing cell delivery via a needle or tube without the need for an additional incision [20,27,28]. In the second technique, a small incision is made near the transplantation site to access the device inlet, enabling the infusion of cells into the device [26,29]. The third and most invasive method involves reopening the implantation site to retrieve the entire device and replace it with a new one [30] (Figure 2B).

The physical parameters of a device, including its shape, size, porosity, and surface **topography**, are critical factors influencing its vascularization potential. Vascularization may be induced around

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Box 1. Encapsulation challenges related to vascularization

A primary concern in **allogeneic** cell transplantation is the activation of a host immune response, which results in the rejection of the transplanted cells [3]. The Edmonton protocol for human islet transplantation commonly relies on **immunosuppressive** drugs to reduce this response and prevent allogeneic rejection. These drugs carry numerous side effects and could decrease vascularization by inhibiting endothelial cell proliferation [4]. Recent studies indicate that some **immunomodulatory** factors can reduce immune responses without the adverse effects associated with immunosuppressants. Particularly, some immunomodulators may also actively promote vascularization of the transplant site (Figure 1a) [5,6].

In addition to the immune responses against transplanted cells, host tissues also respond to the implanted biomaterials by initiating a **foreign body reaction (FBR)**. This response involves fibroblast–macrophage interactions that facilitate vascularization through the secretion of growth factors [7]. However, the fibrotic capsule formed during FBR can inhibit the infiltration of new blood vessels into the device (Figure 1b) [8].

Hypoxia can stimulate vascularization by upregulating hypoxia-inducible factor (HIF) in β cells or supportive cells within the device. This time-consuming process can have irreversible effects on IPCs [9]. Conversely, the oxygenation approaches may reduce vascularization by the inhibition of HIF signaling and reduction in the secretion of angiogenic factors (Figure 1c) [10,11].

Among the different transplantation sites, the hepatic portal vein eliminates the need for vascularization due to the direct access to the bloodstream; however, macroencapsulation devices cannot be implanted at this site due to the limited available volume [12]. The kidney capsule provides access to a capillary-rich network. However, its clinical application is limited due to invasive surgical procedures and insufficient space for device implantation [13]. Muscle tissue possesses numerous vessels with **neovascularization** potential, offering a favorable environment for devices [14]. The peritoneal cavity combines a high vascular network with a large space, facilitating the implantation of micro- and macrodevices, although large devices are prone to central necrosis and often require **prevascularization** to enhance local blood supply [15]. The subcutaneous site allows minimally invasive implantation and facile **retrieval**. However, vascularization is inadequate, and devices are highly prone to hypoxia in the absence of prevascularization strategies. Because of the limited subcutaneous space and the large therapeutic cell dose required, devices typically require a broad surface area and are often designed as flat or thin round structures to maximize oxygen and nutrient diffusion efficiency (Figure 1d) [16,17].

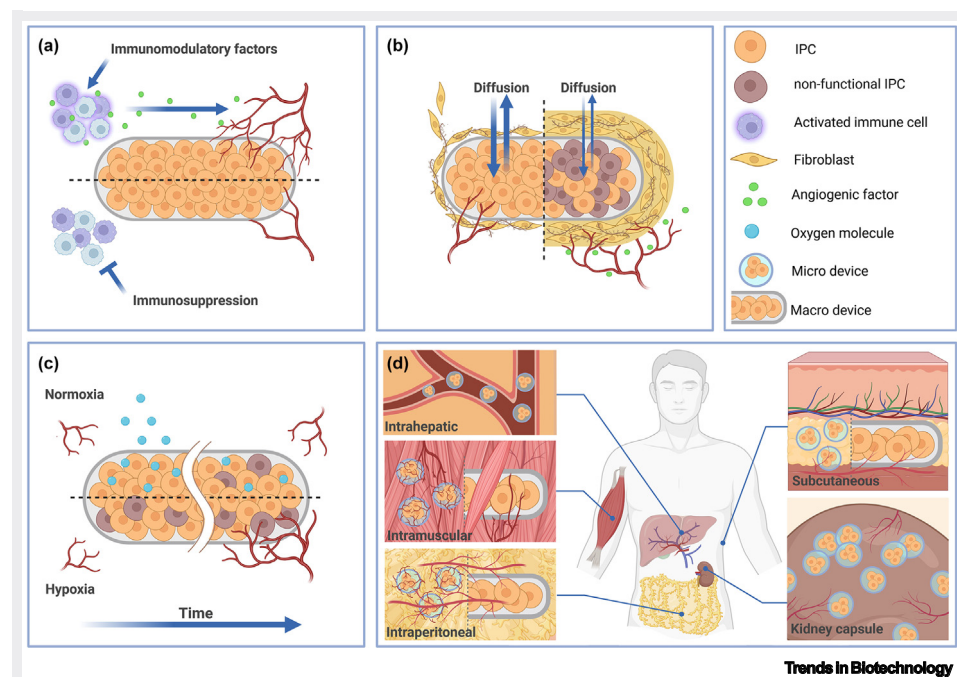


Figure 1. Encapsulation challenges related to vascularization. (a) Immunosuppressants prevent transplant rejection but can inhibit vascularization, whereas immunomodulatory drugs generally have fewer side effects and may promote vascularization. (b) The double-edged sword of fibrosis formation and vascularization. The FBR can stimulate the secretion of growth factors that promote vascularization, but excessive fibrosis and fibrous capsule formation can eventually prevent vessel infiltration into the device. (c) Hypoxia can stimulate vascularization; however, this slow process may induce irreversible damage to transplanted IPCs. (d) The limitations and benefits of different transplantation sites (see Box 1 for full details). Abbreviation: FBR: foreign body reaction.

(external) or inside (internal) these encapsulation devices [10,31]. The external vascularization approach relies on preventing the infiltration of the host vascular system, which is used as a platform for **immunoisolation** of the IPCs [10].

Geometry and shape

In device vascularization, the geometric design criteria are crucial for the successful formation of a vascular network within the device. Cubic [25,32], disk [20,33], cylindrical [34], and tube-like structures are among the various device shapes used for cell encapsulation (Figure 1) [30,35]. There is no evidence that the device shape plays a significant role in vascularization. However, some studies have shown that the size and shape of the implant affect the **immune response**, and this might indirectly affect the vascularization process. For instance, circular rods elicited a moderate immune response compared with triangular shapes, while implants with angular geometry elicited a stronger foreign body reaction [36]. A proper surface-to-volume ratio is one of the most important geometric design considerations to enhance the passive diffusion of oxygen and nutrients into the device with an adequate number of encapsulated IPCs (Figure 2A) [27]. Devices fabricated with a reduced thickness, as discs or thin films, can be used to achieve this purpose [29,37].

Size

Another important design factor is the device size. Several critical points must be considered when determining the optimal size of vascularization devices. One major challenge is delivering a therapeutic dose of IPCs while avoiding issues related to high cell density, which prevents

Glossary

Allogeneic: genetically nonidentical donor of the same species.

Angiogenesis: the growth of new blood vessels from pre-existing ones.

Edmonton protocol: clinical islet transplantation method for type 1 diabetes mellitus (T1DM) that infuses islets into the liver portal vein with immunosuppression.

Foreign body reaction (FBR): host response to implanted biomaterials, marked by inflammation, macrophage activation, and fibrous encapsulation.

Hydrogels: water-swollen polymer networks with tunable properties, used for cell encapsulation and drug delivery.

Hypoxia: insufficient tissue or cellular oxygen levels below physiological needs.

Immune response: body's defense mechanism involving immune cell activation and antibody production in response to foreign antigens.

Immunomodulatory: strategies that alter immune responses to enhance tolerance or minimize graft rejection.

Immunoisolation: shielding of transplanted cells from immune rejection using physical barriers.

Immunosuppressive: agents that suppress immune activity to prevent graft rejection.

Islets: clusters of pancreatic cells composed of different cell types, including β cells, which are responsible for producing insulin.

Neovascularization: natural assembly of new vascular structures.

Organoid: miniaturized *in vitro* model that mimics the structure and function of a native organ.

Photopolymerization: process using light to initiate polymerization reactions.

Plunger: movable, piston-like component for filling encapsulation devices.

Pluripotent stem cells: cells with the capacity for self-renewal and the ability to differentiate into nearly any cell type in the body, which include embryonic stem cells and induced pluripotent stem cells.

Prevascularization: inducing vascular networks at the implant site before transplantation to enhance blood supply post transplantation.

Refilling: the capacity of an implantable device to be reloaded with therapeutic agents or cells without full replacement.

Retrieval: the ability to safely remove an implanted device or graft from the body

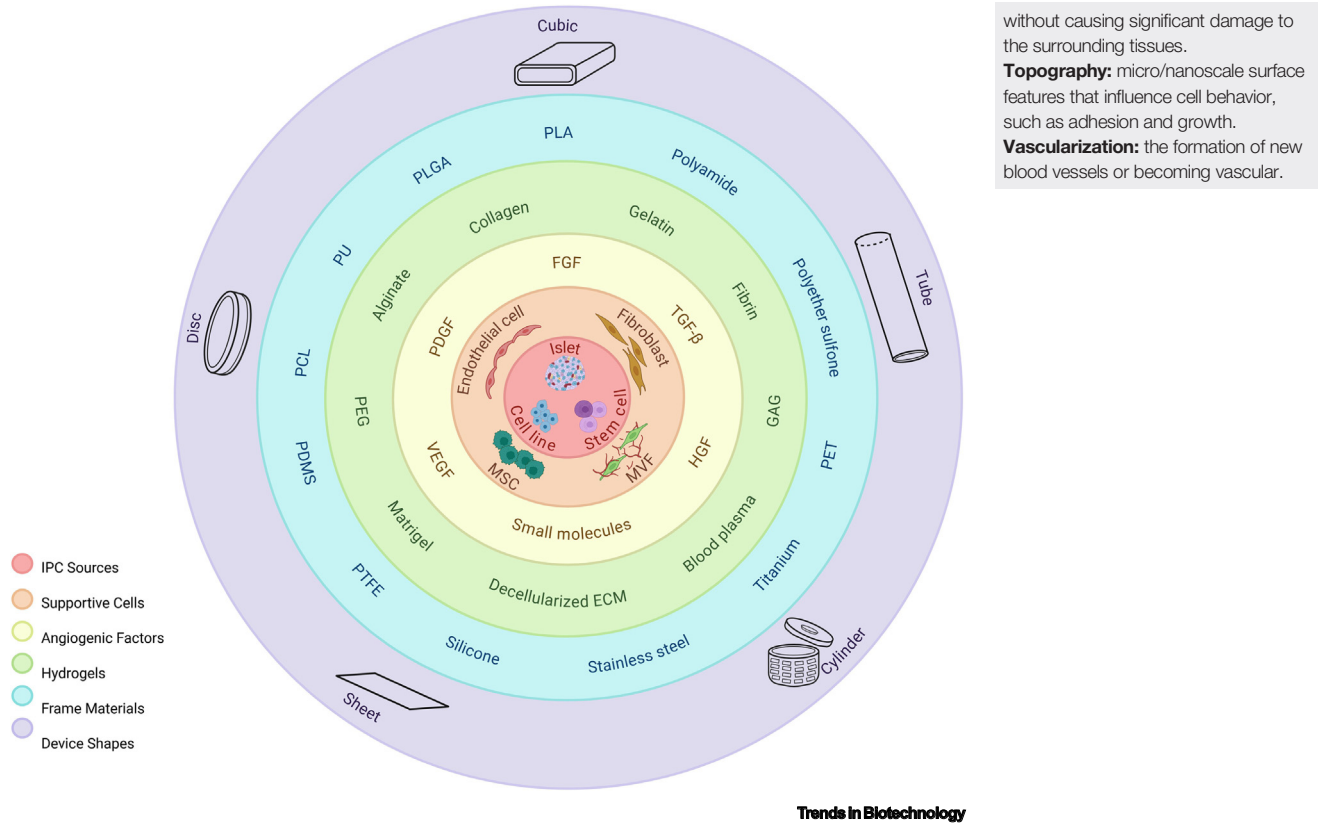
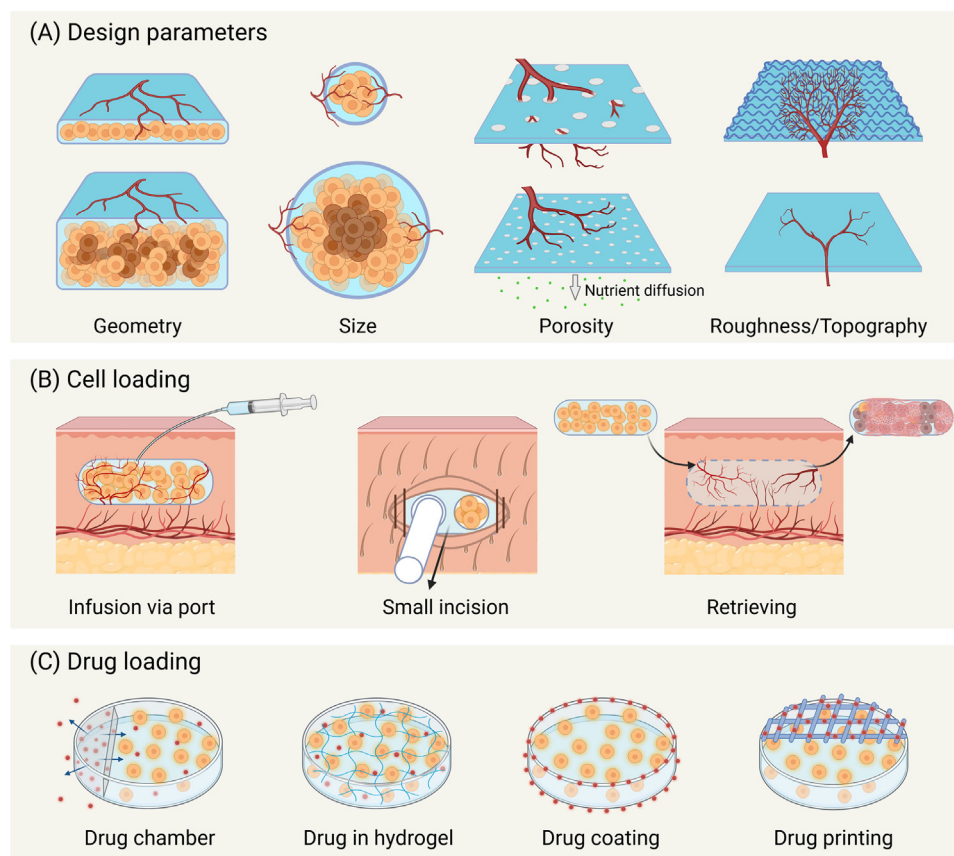


Figure 1. Selection of biomaterials and components for the fabrication of a vascularization device. The circles, arranged from the innermost to the outermost layer, represent sources of IPCs, vascular-promoting cells, vascular-inducing molecules, the incorporation of vasculogenic hydrogels, biomaterials used to construct the framework, and types of device shapes. Abbreviations: ECM: extracellular matrix; FGF: fibroblast growth factor; GAG: glycosaminoglycan; HGF: hepatocyte growth factor; IPC: insulin-producing cell; MSC: mesenchymal stem cell; MVF: microvascular fragment; PCL: polycaprolactone; PDGF: platelet-derived growth factor; PDMS: polydimethylsiloxane; PEG: polyethylene glycol; PET: polyethylene terephthalate; PLA: polylactic acid; PLGA: poly(lactic-co-glycolic acid); PTFE: polytetrafluoroethylene; PU: polyurethane; TGF- β : transforming growth factor β ; VEGF: vascular endothelial growth factor.

efficient and homogeneous oxygen and nutrient delivery (Figure 2A) [38]. The weight and size of the animal model strongly influence the required cell number. To meet this requirement, the device must be large enough to transport a sufficient number of islets. In devices without internal vascular infiltration, the encapsulated cells should be located within 200–300 μm of the permeable membrane because of the limitations of oxygen diffusion [36]. In addition to a cell reservoir, some devices have drug [16,32], nutrient [33], or oxygen reservoirs [39], which increase the total size of the device (Figure 2C). One approach for macroencapsulation devices to address the challenge of the large device size is the implantation of multiple devices per patient. For example, ViaCyte, Inc. has implanted 2–6 Encaptra® devices in four sites per patient (NCT02239354), and β -O2 Technologies, Ltd. has used 1–2 β Air devices (NCT02064309) per patient [39]. Sernova usually implants 2–4 prevascularization devices (Cell Pouch) for a patient with T1D (NCT03513939, NCT01652911) [26].

Porosity

Device porosity is a key design parameter determined by the selected vascularization approach. Porosity is defined by two main criteria—pore size and density. The pore size of a vascularization



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Figure 2. Design considerations for vascular devices. (A) Design parameters, including geometry, size, porosity, and surface topography, can influence the vascularization of the device. (B) Cell loading strategies, including delivery through a port using a needle or tube without requiring a new incision; reopening the implant site for cell infusion; and complete retrieval followed by cell refilling. (C) Drug loading approaches, including drug loading into a reservoir; loading angiogenic factors into hydrogels within the device; surface coating; and incorporation into the device frame by printing.

device should be tailored to its intended application (Figure 2A). In the first case, devices are designed to completely inhibit vascular infiltration, and the viability of encapsulated cells depends on passive diffusion [34]. These devices prioritize immunoprotection, and nanopores that range from 20 to 1000 nm are optimal for preventing antibody and immune cell penetration [33]. Commercial membranes with pore sizes between 200 and 450 nm are routinely used for this purpose [40]. Custom-made nanoporous membranes that range from 200 to 1000 nm have also been used [20,33]. In the second and third cases, the design allows for the infiltration of small capillaries and larger vessels, respectively [41,42]. In these cases, 5–500 μm macropores are used [35]. Although the smallest capillaries measure 5–10 μm in diameter, pores smaller than 50 μm generally inhibit vascularization to the surface [43], and pores between 50–150 μm support the development of dense, mature vascular networks with shallow infiltration [30]. Pore sizes of 200–250 μm promote the formation of larger vessels with lower density and deeper infiltration, which facilitates endothelial cell migration [44]. However, pore sizes larger than 400 μm permit the entry of larger vessels without significantly improving total vascularization [45]. Some devices use two porous layers. The microporous outer layer provides mechanical support for the encapsulated cells and allows blood vessels to infiltrate in proximity, while the nanoporous inner layer

offers immunoprotection [46–48]. In 2022, ViaCyte created an immunoisolation semipermeable pouch with nanoscale pores that lacked vascular infiltration and resulted in subsequent cell necrosis (NCT02239354). In later clinical trials, the device was modified to include macropores (approximately 100 μm) with vascularization throughout the membrane but without the capability for immunoisolation (NCT03162926, NCT03163511) [23,31].

Surface properties

The surface properties of the device can also influence vascularization. Compared with smooth surfaces, engineered surface topographies that mimic the micro- and nanostructures of the extracellular matrix (ECM) have demonstrated an enhanced angiogenic potential of implanted biomaterials by activating integrins that lead to endothelial cell adhesion, spreading, proliferation, and the secretion of angiogenic growth factors (Figure 2A) [49,50].

Components of vascularization devices

Frame

Several biomaterials are used in frame fabrication according to their biocompatibility, mechanical properties, processability, and commercial availability. These biomaterials are typically nondegradable and include polytetrafluoroethylene (PTFE) [28,38], polyamide [16,32], silicon [51,52], and polypropylene (PP) [35,40], or they have a slow degradation rate, such as polycaprolactone (PCL) [20,30] and polylactic acid [29,53], whose degradation rate is tailored to match the lifespan of the encapsulated cells (Figure 1). Although the effectiveness of the frame material has not been definitively determined for promoting vascularization, some materials have better vascularization. PCL induces new vessel formation and infiltration compared with poly(D,L-lactide-co-caprolactone), PP, poly(lactic-co-glycolic acid), and polyvinylidene fluoride, without using proangiogenic factors [34,45,48]. The frames can be used individually as prevascularized devices without the need for vascular-inducing factors. Sernova fabricated a device from microporous PP membranes that contains chambers filled with PTFE plugs. Once prevascularized, the plugs are removed, and the islets are subsequently infused into the empty chambers (NCT03513939, NCT01652911) [26]. The ViaCyte Encaptra® device (NCT04678557, NCT03163511) [23] and the β Air device both use PTFE in their membranes (NCT02064309) [39]. These frames can be combined with hydrogels, angiogenic factors, and cells or their combinations to improve device efficiency and promote vascularization.

Hydrogels

Hydrogels serve as a supportive matrix that facilitates cell adhesion, migration, and the absorption of growth factors involved in vascularization (Figure 1). Hydrogels provide a stable microenvironment that maintains and improves the engraftment of IPCs [54]. Fibrin is commonly used in preclinical and clinical studies for IPC encapsulation due to its potential for vascularization and support for islet survival [45,55]. However, the rapid biodegradation of fibrin limits its application, which can be mitigated by conjugation or physically combining fibrin with other polymers to enhance mechanical properties and reduce degradation [56]. Collagen (types I and IV) is the primary protein in the pancreatic islet niche and is considered an excellent hydrogel for promoting blood vessel growth around IPCs [53,57]. Matrigel, another hydrogel, effectively vascularizes the transplant site by facilitating the generation of complex structures consisting of IPCs and vessels, which lead to vascularized pancreatic **organoid** formation [52,53]. Another approach uses decellularized tissues. These tissues are valuable for their angiogenic potential, which is attributed to retained proangiogenic proteins and factors, and for their ability to reconstitute the native pancreatic ECM [58,59]. Synthetic alternatives to ECM are based on polymers such as polyethylene glycol functionalized with biomimicking motifs that provide cell adhesion and migration for **angiogenesis** [60]. In addition to inducing angiogenesis, hydrogels such as alginate can be used for immunoisolation by

preventing vessel and immune cell infiltration into the device, while vascularization develops around the device to ensure oxygen and nutrient entry via passive diffusion [30,42,51].

Angiogenic factor

A well-known angiogenesis strategy involves introducing angiogenic factors, including growth factors and small molecules, into the devices to enhance vascularization at the transplant site. Vascular endothelial growth factor, fibroblast growth factor, hepatocyte growth factor, transforming growth factor β , and platelet-derived growth factor are the most important growth factors used for this purpose (Figure 1) [29,40,52]. An alternative approach relies on hypoxia-mimicking materials that promote angiogenesis by stimulating the upregulation of hypoxia-inducible factor 1- α , enhancing the secretion of proangiogenic factors. This method could be used to promote angiogenesis in the prevascularized device before the incorporation of IPCs [61]. A key consideration is the localized and sustained release of these angiogenic factors to enhance their biological effects. The delivery approach involves loading growth factors into hydrogels within the devices [62], pretreatment of the transplant site before implantation [40,63], incorporation into the device frame [64,65], coating of the device surface [66,67], and loading into the reservoir (Figure 2C) [32,33].

Cells

Transplantation of human islets is the only FDA-approved diabetes cell therapy based on immunosuppression that uses the **Edmonton protocol** [68]. Recent efforts for diabetes cell therapy predominantly include the transplantation of stem cell-derived progenitors or β cells. Vascularization is crucial for engraftment and *in vivo* maturation of progenitors into functional β -cells [53]. In some clinical trials, genetic modification was performed in hPSCs to obtain hypoimmunogenic β cells that evade immune rejection. Hypoimmunogenic IPCs pave the way for the promotion of internal device vascularization with angiogenic hydrogels without the concern for immune rejection [69]. Beyond immune compatibility, significant challenges encompass the potential for tumorigenesis, off-target genomic modification, and the ethical concerns of genome editing [70].

Vascular supporting cells are a strategy used to facilitate vascularization in IPCs transplantation. Endothelial cells (ECs) are the most common cells used for this purpose [32,37]. The function of ECs in vascularization could be enhanced through genetic engineering with ETV2 as a key transcription factor in the vascularization process [71]. ECs could be transplanted in the presence of other cells, such as mesenchymal stem cells (MSCs) [38,72] and fibroblasts (Figure 1) [73,74]. The application of MSCs or fibroblast cells, along with ECs, may induce the formation of vascularized organoids in transplanted devices [53]. Matrigel, fibrin, and collagen hydrogels exhibit cell-responsive degradation and have been used to support the formation of organoid structures and to vascularize transplanted multicellular constructs. In addition, complex tissue structures such as microvascular fragments isolated from fat showed rapid vascularization and could be used in a cell transplantation device for T1D treatment [75,76].

Fabrication methods for transplantation devices

Vascularization devices consist of various components. Depending on the specific requirements of each component, one or a combination of fabrication methods may be used (Figure 3). The choice of the manufacturing technique depends on the geometrical features of the structure, physical properties of the material, processability, production cost, and scalability.

3D printing

3D printing is one of the most widely used methods to fabricate the frame, porous layers, membranes, and **puncher** of encapsulation devices. Among the various 3D printing techniques,

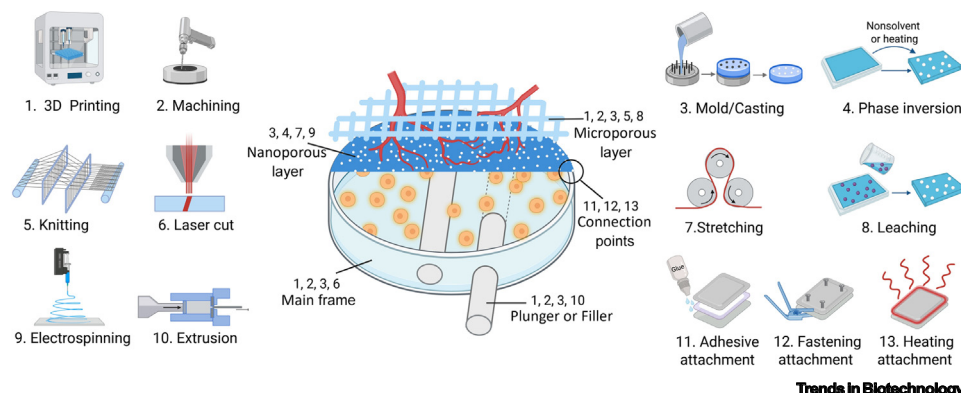


Figure 3. Fabrication methods for vascular devices. The figure illustrates the main components of vascular devices and presents several key methods for fabricating these components. These components may include the main frame, a nano- or microporous membrane, and a plunger. Overall, the figure highlights which fabrication techniques are applicable to each device component. These methods include 3D printing (1), machining (2), molding/casting (3), phase inversion (4), knitting (5), laser cut (6), stretching (7), leaching (8), electrospinning (9), extrusion (10), and attachment methods (11,12, and 13). The main frame can be fabricated using methods 1, 2, 3, and 6, while the microporous layer can be produced via methods 1, 2, 3, and 5. The nanoporous layer can be fabricated using methods 3, 4, 7, and 9. Component assembly is achieved through methods 11, 12, and 13, and the plunger can be produced using methods 1, 2, 3, and 10.

stereolithography (SLA), fused deposition modeling (FDM), selective laser sintering (SLS), and melt electro writing (MEW) are the most commonly applied ones in device manufacturing. SLA is a UV light-based technique that is based on layer-by-layer **photopolymerization**, which offers enhanced resolution (25–100 μm), and it is an ideal method for fabricating parts with intricate details [28]. In FDM, a polymer filament is melted and extruded through a nozzle layer-by-layer to create the structure. Precision is decreased (100–300 μm), and this can limit the fabrication of delicate structures [53,77]. SLS uses a laser to selectively sinter polymer or metal powders, fusing them point-by-point to create shapes that have a moderate resolution range (50–200 μm) [32,42]. MEW combines electrospinning and FDM techniques, which permit melted polymers to be deposited as ultrafine fibers under the influence of an electric field with exceptional precision (5–10 μm) [30]. In addition to the fabrication of the frame, 3D printing methods have been widely used for the preparation of the cell-encapsulated hydrogel part in the device. Several studies have demonstrated the formation of 3D-patterned IPC constructs using FDM within hydrogels composed of alginate [59], type I collagen [78], and pancreatic ECM [79]. The photocrosslinkable polymers, including gelatin methacrylate and hyaluronic acid methacrylate, have been applied for IPC encapsulation using light-based techniques [75,80].

Fiber fabrication methods

Electrospinning is a widely used technique to produce 2D fibrous membranes on the nano- to micrometer scale (0.1–5 μm). It is primarily used to fabricate randomly distributed nanoporous layers in multilayer devices that have immunoprotective functions. Knitting is a mechanical technique used to fabricate mesh-like structures with micropores (100–500 μm) that exhibit suitable mechanical properties [81].

Phase inversion/particulate leaching

In phase inversion, a polymer solution is typically cast and immersed in a nonsolvent bath to fabricate porous membranes that have submicron to micron pore sizes (0.1–10 μm). These

membranes have an irregular pore distribution and offer high selectivity for molecular transport [16]. In leaching, a porous polymeric structure is formed by mixing with fine particles, known as porogens, which are removed by dissolving them. The resultant pores typically range from 100 to 500 μm , depending on the size of the porogen [34,48].

Casting/molding

It is a technique for fabricating device frame components without complex internal architectures at the nano- and microscale sizes. In this method, a mold with a defined geometry is used to shape the polymer—typically in the form of a solution, melt, or prepolymer [34,82].

Subtractive manufacturing

Machining and laser cutting are used to fabricate various devices. In machining, solid blocks of material are shaped using mechanical tools such as drilling, milling, or turning [28,39]. By contrast, laser cutting uses a highly focused laser beam to melt, vaporize, or burn the material at specific locations to achieve the desired pattern. Machining has limitations in producing highly complex or hollow geometries. Laser cutting has limitations in cutting depth and requires expensive equipment [83].

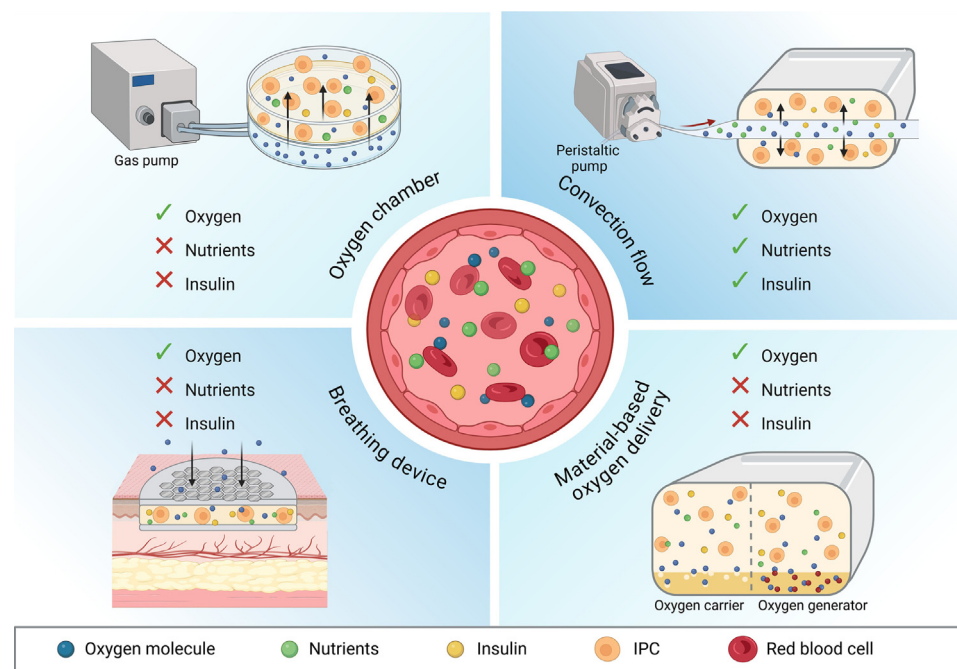
Miscellaneous methods

Stretching is another technique used to fabricate nano- and microscale membranes and is notably applied in the production of commercial expanded PTFE (ePTFE) membranes. The PTFE powder is mixed with a lubricant, extruded, and compressed into a sheet through rolling. The sheet is then sintered to fuse the PTFE particles and mechanically stretched to induce porosity [25,39].

In addition to the fabrication methods, devices that consist of separate parts must be assembled. This is typically achieved through the use of adhesives and fasteners or by the application of heat to the connection points to bond the parts.

Alternative approaches for device vascularization

Given the limitations and challenges associated with the vascularization of encapsulation devices, alternative or auxiliary approaches may be required to meet the high metabolic demands of transplanted IPCs. These challenges include slow neovascularization, implantation sites with limited vascularity (such as the subcutaneous site), and the absence of vascularization within immunoprotective devices. These alternative approaches include convection flow systems, oxygen chambers, gas-permeable ‘breathing’ devices, and oxygen-generating materials (Figure 4). In the convection-based approach, a system designed to mimic vascular blood flow delivers oxygen and nutrients via convective flow that is sustained by continuous pumping [83]. The second approach involves oxygen and nutrient chambers containing an oxygen reservoir that directs fresh air to the cell chamber, thereby providing a continuous oxygen supply. The B-O2 Technologies β Air device is an example of this strategy, requiring regular reloading of the gas module [39]. Some designs also incorporate reservoirs to supply nutrients during the initial post-transplantation phase [33]. The breathing approach maintains high oxygen levels by enabling gas exchange between the atmosphere and the topical membrane through direct air contact. The external placement of this device further allows cell refilling without additional surgery [28]. Oxygen delivery approaches, including oxygen carriers and generators, rely on materials capable of *in situ* oxygen release. Although such oxygen-releasing systems have been approved for human wound healing, currently, no clinical trials have evaluated their application in T1D cell therapy [84,85].



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Figure 4. Alternative approaches to vascularization. This figure illustrates various approaches used in recent studies to replace vascularization and support the function and survival of transplanted IPCs, including convection flow systems, oxygen chambers, gas-permeable ‘breathing’ devices, and oxygen-generating materials. While oxygen chambers, gas-permeable breathing device, and oxygen-generating materials enhance oxygenation alone, convection flow systems facilitate the exchange of oxygen, nutrients, and insulin. Abbreviation: IPC: insulin-producing cells.

Concluding remarks and future perspectives

The current approach to T1D management based on insulin administration fails to achieve tight glycemic control. Diabetes treatment with IPCs presents a new tool for continuous and smart insulin delivery to achieve physiological glucose homeostasis. Recent advances in stem cell technology have enabled the generation of IPCs from hPSCs that have functionality similar to native human islets. A cell encapsulation device that induces vascularization may represent an effective strategy to enhance the efficacy of cell therapy for T1D.

The selection of appropriate biomaterials, along with precise control of device geometry with novel micro/macro fabrication techniques, has significantly improved the therapeutic potential of implantable devices by determining biomolecule transportation and cellular infiltration. Next-generation vascular devices for IPC transplantation are expected to leverage personalized medicine by incorporating patient-specific factors, such as autologous cells and customized device designs, to optimize performance and improve long-term graft survival and function.

The clinical translation of vascularized devices faces several hurdles, including the absence of robust preclinical models for transplantation, fibrotic capsule formation, the lack of FDA-approved angiogenic cells or drugs, and challenges in achieving reproducible and scalable fabrication under good manufacturing practice conditions.

Ultimately, successful clinical translation requires overcoming all major challenges associated with device implantation, particularly those related to vascularization and immune responses. These hurdles could potentially be addressed through combined strategies, such as integrating

Outstanding questions

What are the effective parameters in the designing of an engineered macrodevice for IPC transplantation at a specific site?

How can vascularization be induced at the transplant site to ensure that IPCs receive sufficient oxygen and nutrients immediately post-transplantation? What is the best approach to guarantee early and adequate exposure of IPCs to the host vasculature?

What vascularization approaches are most suitable for clinical application and offer the greatest translational potential?

What are the primary barriers to achieving consistent clinical success with vascular devices for IPCs transplantation, and how can they be overcome?

Are there viable alternative strategies for vascularization suitable for clinical use in terms of efficacy and practicality?

How can a balance be achieved between immune protection and vascularization in encapsulation devices, without compromising either function?

What advancements in fabrication methods are needed to ensure reproducibility and precision of the desired design while supporting design complexity and biological performance?

intravascular devices with localized drug delivery or developing hypoinmunogenic cells for future cell-based therapies for T1D. Despite advances in the application of vascularized devices, their widespread clinical translation remains a significant challenge (see [Outstanding questions](#)).

Declaration of AI-assisted technologies in the manuscript preparation

The authors used the QuillBot AI writing assistant (QuillBot, Inc., Chicago, IL, USA) to improve grammar, clarity, fluency, and overall language quality when preparing this manuscript. After using this tool, the authors thoroughly reviewed and edited the content of this manuscript. All authors have read and accepted full responsibility for the published article.

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Declaration of interests

The authors declare that they have no competing interests.

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