Opinion

Bioprinting and Cellular Therapies for Type 1 Diabetes

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Type 1 diabetes mellitus is a chronic autoimmune disease that results from the destruction of beta (β) cells in the pancreatic islets, leading to loss of insulin production and resultant hyperglycemia. Recent developments in stem cell biology have generated much excitement for β-cell replacement strategies; β cells are one of many cell types in the complex islet environment and pancreas. In this Opinion, we discuss recent successful attempts to generate β cells and how this can be coupled with bioprinting technologies in order to fabricate pancreas tissues, which holds great potential for type 1 diabetes. Possibilities of integrating vascularization and encapsulation in bioprinted tissues are expounded, and future prospects, such as pancreas-on-a-chip, are also presented.

Epidemiology and Pathophysiology of Diabetes
Type 1 diabetes mellitus (T1D) (see Glossary) is a chronic autoimmune disease, which results from the destruction of beta cells (β cells) in the pancreatic islets of Langerhans (see Box 1 for background information on T1D) [1]. Genetically susceptible individuals are exposed to an environmental trigger, which induces autoantibodies to form and autoreactive T cells to destroy β cells. Prior to the development of clinical diabetes, >80–90% of β cells are lost. Their reduction leads to persistently elevated blood glucose levels. Longstanding hyperglycemia leads to microvascular and macrovascular complications including neuropathy, cardiovascular disease, nephropathy, and retinopathy. Managing T1D requires significant patient compliance with multiple daily blood glucose measurements and subcutaneous insulin injections; however, stringent control is often associated with an increased risk of acute hypoglycemia, which may be fatal [2]. Hypoglycemia is mitigated through the counter regulatory action of glucagon, which elevates blood glucose levels. Glucagon is produced in the pancreatic islets through the action of alpha cells (α cells). However, with diabetes progression, the α-cell mass is lost as well, leading to the inability to regulate both hyper- and hypo-glycemia [3]. Therefore, both patients and clinicians alike would welcome cellular replacement strategies for both α and β cells.

Recent Advances in Cell-Based Therapies for T1D
Current β-cell replacement strategies include whole pancreas or islet allotransplantation. Portal vein injection is a common method for islet allotransplantation, but this procedure necessitates passing a catheter through the liver and confers risk of bleeding and blood clots [1]. However, in a recent seminal work, researchers have achieved long-term insulin independence after islet cells were placed in a fibrin scaffold (derived from the patient’s plasma) and transplanted into the omentum of a patient with T1D [4]. The omentum is well vascularized and therefore able to accept a large volume of islets. Similarly, in experimental studies, islets have also been implanted in the renal capsule, which also has a rich blood supply. However, both technologies require invasive surgeries. Although the exact numbers of cells required for transplant is unknown, >90% β-cell loss is required prior to development of diabetes;

Trends
Improving the transformation of stem cells to functional β cells and other pancreatic cells will speed up the development of cell-based bioprinting-enabled therapies for type 1 diabetes.

Bioprinting for tissue and organ fabrication has the advantages of precise component deposition, controllable construct size and anatomical geometry, biomimetic cellular organization and interactions, integration of vascular or vascular network, and high-throughput capability.

Combining bioprinting with encapsulation of pancreatic tissues may be necessary for protection of constructs from the immune system. Integration of encapsulated vascularized pancreatic islets into a scale-up perfusable pancreatic organ will be promising for type 1 diabetes.

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8.8% of the adult population worldwide has diabetes [53]. Of all individuals with diabetes 10–15% have T1D. T1D is the most common form of diabetes in children. Greater than 500,000 children are living with this condition globally. In 2012, 1.5 million deaths were directly attributed to diabetes.

Pathogenesis

T1D results from lack of insulin production secondary to autoimmune destruction of insulin producing β cells in the pancreas. Antigen presenting cells present self-peptides to T-lymphocytes resulting in immunologic attack of β cells and subsequent molecular events leading to apoptosis. CD4 and CD8 T cells, natural killer cells, and innate immune cells infiltrate the pancreas leading to insulitis and then diabetes. Programmed death ligand 1 released during insulitis leads to β-cell self-destruction. CD8 T cells initiate cytotoxic targeting and cytokines such as IFN-γ result in free radical production leading to cell death. B lymphocytes present insulin-specific antigen to CD4 T cells, which further adds to β-cell destruction [54]. T1D is believed to be caused by a combination of both genetic and environmental triggers.

Pancreas Anatomy

The pancreas is 15 cm long and consists of a head, neck, body, and tail. The head is approximately 5 cm in width with the other components being up to 2.5 cm wide. The pancreas is a composite gland with both endocrine and exocrine functions.

Islet Anatomy and Physiology

Pancreatic islets are composed of α, β, δ, γ, and ε cells associated with robust vasculature for hormonal actions. Islets are scattered throughout the gland but only constitute about 2% of the pancreatic parenchyma.

β cells are the predominant cell (75% of each islet) and are responsible for insulin production. α cells produce glucagon in the pancreatic islets. β and α cells are involved in stringent glucose homeostasis through the actions of insulin and glucagon. δ cells are responsible for the production of somatostatin, which inhibits both insulin and glucagon secretion. The peptide hormone Ucn3 is a major local signal that is released from β cells (and α cells in primates) to induce the local secretion of somatostatin [19]. Pancreatic polypeptide (PP) self-regulates pancreatic secretion and its release is enhanced by hypoglycemia and decreased by somatostatin. ε cells release ghrelin, which regulates appetite and energy usage [55].

It is therefore likely that loss of normal β-cell physiology in T1D adversely affects all cellular function in the pancreatic islet. This is observed clinically as long-standing T1D leads to the hormone glucagon becoming dysregulated and unable to counteract potentially life-threatening hypoglycemic episodes [56].

therefore, we assume 10% of the normal amount of β cells would be sufficient for replacement. A typical pancreatic islet contains 1140 β cells and there are approximately one million islets in a normal human pancreas [5]. The current cost is unknown, but as technology improves the cost will decline [6]. Current challenges in transplantation for T1D include graft loss of isolated islets secondary to ischemia, donor scarcity, and requisite immune suppression [7]. Therefore, development of novel therapies that can tackle these issues is highly desirable.

Significant progress has been made in the transformation of stem cells to pancreatic progenitors and β cells over the past decade. Both human embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have been transformed in a multistage differentiation process, that progresses through endoderm, pancreatic endoderm, and endocrine phases prior to becoming functioning β cells (Figure 1A) [8]. Recently, Pagliuca and colleagues [9] demonstrated the generation of functional human β cells in vitro from human iPSCs. The authors demonstrated a scalable protocol, which yielded cells expressing appropriate surface markers (NKX6-1/C-peptide), packaging insulin into secretory granules, and the ability to ameliorate hyperglycemia following transplantation into diabetic mice (Figure 1B). It has been suggested by in vitro data that a dysfunctional islet endothelial phenotype may contribute to

Glossary

Adipose-derived stem cells (ADSCs): mesenchymal stem cells abundant in fat tissue and adherent to plastic.

Alpha cells (α cells): the second most abundant cell in pancreatic islets; they produce glucagon.

Beta cells (β cells): the main cell in pancreatic islets, which are responsible for insulin production.

Bioink: materials that mimic the extracellular matrix to support bioprinted cells.

Bioprinting: the layer-by-layer deposition of living cells and biomaterials to fabricate tissue engineered tissues and organs.

Droplet-based bioprinting: generates bioink droplets.

Encapsulation: enclosing cells and constructs to protect them from the surrounding environment.

Endocrine pancreas: comprises cells that produce hormones such as insulin and glucagon, which are important in glucose homeostasis.

Exocrine pancreas: generates secretory enzymes critical for digestion and bicarbonate.

Extracellular matrix: collection of molecules secreted by cells to provide structural and biochemical support to surrounding cells.

Extrusion-based bioprinting: generates a continuous strand of bioink.

Laser-based bioprinting: utilizes a laser pulse to generate bioink droplets.

Omentum: a layer of intra-abdominal fatty tissue that covers the intestines and other organs.

Organ-on-a-chip: a 3D microfluidic chip that stimulates the activities, mechanics, and physiological response of an organ model.

Perfusable: able to force a fluid through.

Portal vein: a large blood vessel which carries blood to the liver.

Spheroid: aggregated cells organized in three dimensions created in a scaffold-free manner.

Stem cells: undifferentiated cell which is capable of giving rise to an infinite number of the same type of cell and can differentiate into a number of other cell types.

Teratoma: tumor containing multiple tissue or organ components that resemble germ layer derivatives.

Type 1 diabetes mellitus (T1D): a form of diabetes in which not enough
impaired insulin release from the β cell [10]. Autologous endothelial cell coculture during the differentiation process may therefore represent a productive area of future research. Millman and colleagues demonstrated that it was possible to generate β cells from the skin fibroblasts of patients with T1D [11] and the authors did not observe major differences in stem-cell-derived β cells when comparing T1D versus nondiabetic donors. It is exciting that patients with T1D may still hold the promise of an intrinsic treatment or cure.

Although iPSCs and ESCs have been utilized extensively in laboratory settings, their clinical translation appears to be hampered by ethical concerns [12] and teratoma formation risk [13]. These ongoing concerns have led to the investigation of other stem cell sources. Mesenchymal stem cells (MSCs) are multipotent nonblood adult stem cells and they have been demonstrated to have a broader differentiation capacity, including β cells. Recently, Bai and colleagues used new technology of targeted small RNA transfection to transform umbilical cord MSCs into insulin producing cells [14]. This technology may offer an avenue to simplify the multistep, month-long differentiation pathway utilized by most research groups. Adipose-derived stem cells (ADSCs) have also recently been investigated [15]. Dave and colleagues described two patients who were infused with in vitro generated insulin-making cells transdifferentiated from donor ADSCs and bone marrow-derived hematopoietic stem cells [16]. Over a follow-up of 13 and 22 months, they reported stable blood sugar levels with hemoglobin A1c levels in the range of 6.5% and a profound decrease in insulin requirements. There are major clinical trials evaluating MSCs as a treatment for T1D [17], which may offer additional insight into therapeutic potential.

Figure 1. Recent Studies on Cell- and Biofabrication-Based Therapies for T1D.
(A) An overview of fate choices during normal β-cell development. Adapted from [8]. (B) Blood glucose levels in streptozosin (STZ)-treated C57BL/6 mice implanted with SC-β cells encapsulated with TMTD alginate at a dose of 250 clusters/mouse, healthy C57BL/6J mice not treated with STZ, and STZ-treated nonimplanted mice. Cohorts of n = 5 mice are shown, and the experiment was repeated 3 times for a total of 15 mice per condition. Reproduced, with permission, from [49]. (C) Bioprinted fluorescent islets in alginate 4% (w/v)/gelatin 5% (w/v), bulk material, bulk alginate, and bulk ultrafilters alginate. Images taken at 0, 4, and 7 days (scale bar 50 μm). Reproduced, with permission, from [24]. (D) Nearly 3 cm-long pancreatic core-shell tissue strand. (E) A photograph demonstrating recovered 3D-printed device-loaded with clusters of IPSC-derived β cells. Reproduced, with permission, from [26].
Clustered regularly interspaced short palindromic repeat (CRISPR) gene editing strategies are another new technology which may offer improvements for generation of β cells. It may also allow for the conversion of adjacent pancreatic cells, such as α cells, δ cells (delta), PP cells (γ), and ε cells (epsilon) (see Box 1 for more information on these cells), into β cells via activation of developmental genes [18]. In fact, van der Meulen and colleagues [19] demonstrated that the pancreatic islet periphery contains a privileged environment that supports the conversion between α and β cells, with urocortin3-negative (Ucn3-negative) β cells a keystone in conversion potential. These studies indicate that a cellular remedy for T1D may be achieved without using stem cells. Despite the cellular source, the complex nature of the composite pancreas will require the precise placement of cells in order to recreate native functionality. Bioprinting is an innovative approach that when integrated with biologic materials can prove useful in recapitulating both the endocrine and exocrine components of the pancreas.

**Bioprinted Endocrine Pancreas and Its Anticipated Use in Medicine**

Three-dimensional (3D) bioprinting takes advantage of additive manufacturing technology to print cells, biomaterials, and cell-laden biomaterials individually or in tandem, layer by layer, directly creating 3D tissue-like structures [20]. It offers great precision for the spatial placement of cells, proteins, genes, drugs, and biologically active particles to better guide tissue generation and formation [21] (see Box 2 for background information on bioprinting and its clinical implications). Therefore, this technology is poised to offer a unique role in the restoration of the complete pancreatic islet and other structures through its potential in recreating the complex morphology and multicellular environment. While engineered β cells are an exciting development towards a cure for T1D, the overall function of the endocrine pancreas is interdependent on the coordinated action of varying cell types. Specifically, the pancreatic islet is a tightly woven cluster of diverse cell types intertwined with a robust vascular network allowing for secreted hormonal actions throughout the body (see Box 1 for background information on islet anatomy and physiology). The islet is composed of α, β, δ, γ, and ε cells in the corresponding percentages: 20%, 70%, <10%, <5%, and <1%. Therefore, it would be ideal to engineer pancreatic endocrine progenitors to produce all the other endocrine hormone cell types (α, γ, δ, and ε) and reconstruct the morphology and proportions found in human islets. The deposition of α, β, δ, γ, and ε cells in appropriate ratios and orientations will seek to recapitulate the complex hormonal interactions seen present in the native pancreatic islet. To maintain cellular organization, construct ‘stiffness’ can be adjusted by changing the characteristics of the bioink. This includes optimizing the materials that are used to recapitulate the extracellular matrix. Bioink parameters can be fashioned for the desired architectural pattern that can be customized in the construct blueprint. We believe bioprinting cells in controlled amounts and locations in 3D culture will enable the formation of islets with biomimetic composition and improved functionality with further advances allowing for complete pancreas restoration.

In addition to bioprinting different types of pancreatic cells into a tissue construct for self-assembly, engineered islets can be fabricated first and then encapsulated during the bioprinting process (in the form of a spheroid), and deposited into a larger-scale vascular bed or vascularized tissue construct as shown in Figure 2. Such islets can be engineered in 3D using different biofabrication approaches. For example, cell-repellent microwells can be used to facilitate aggregation of β cells into a spheroid form [22]. In addition, engineered islets can be prevascularized to allow for capillary formation after bioprinting into the gel. This necessitates the encapsulation of such gel (containing capillarized islets) after the bioprinting process. Furthermore, to mimic true pancreatic endocrine function, an adjacent microcirculation should be incorporated, which will also provide for nutrient delivery and waste removal. To limit graft loss, the engineered islet would need to be immediately perfusable upon implantation.
**Box 2. Bioprinting and Its Clinical Implications**

Bioprinting is an innovative additive manufacturing technology for building tissues and organs with precise anatomic control and cellular composition. Bioink materials are added in layers to create a three-dimensional living construct [57]. The bioprinting process can be divided into three stages as follows:

**Pre-Organ Printing**

The pre-organ printing process comprises isolation and/or differentiation of cells, cell expansion in culture, and bioink preparation. Stem cells can be obtained by excision, liposuction or umbilical cord retrieval. Following isolation, they can be expanded in vitro and differentiated.

Stem cells or differentiated cells can be expanded to appropriate quantities in either two-dimensional (2D) or 3D culture. For bioink preparation, cells can be mixed with an extracellular matrix mimic that supports cell growth, such as collagen, to be deposited during the bioprinting process.

**Organ Printing**

Blueprint Modeling

In order to design individualized prints, patient-specific models need to be obtained. Magnetic resonance imaging (MRI) and computed tomography (CT) are widely available and have sufficient detail to formulate a printing plan [58].

Process Modeling

What, where, and when to print is relayed to the bioprinter.

Bioprinting

Parenchymal and stromal structures are deposited along with a supporting framework. Constructs can be printed using any combination of existing modalities, including droplet-, extrusion-, and laser-based bioprinting. Alternative strategies are incorporated for printing ductal or vascular structures, such as utilizing a sacrificial ink that can eventually leave behind a patent lumen.

Extrusion-based bioprinting combines a fluid dispensing and automated robotic system for extrusion and bioprinting, respectively. Bioink is dispensed via computer control, which results in precise deposition of cells encapsulated in cylindrical filaments to generate desired structures.

Droplet-based bioprinting generates droplets using various energy sources such as sound, heat, and electric. It offers great advantages due to its simplicity and precision.

Laser-based bioprinting uses laser energy (i) to deposit cells through transferring them from a donor slide to a receiver slide or (ii) to photocrosslink tissue constructs. It offers great advantages due to its high precision and control of deposition.

**Post-Organ Printing**

Organ Culture

Following printing, constructs need to be transferred to a bioreactor for long-term culture. During this process, cells form connections, deposit their own extracellular matrix and undergo tissue maturation.

Transplantation

Mature organs would be suitable for transplantation and would require a vascular anastomosis. The immediate perfusability of bioprinted tissues is an ongoing research endeavor.

Monitoring for Efficacy and Safety

Following transplantation patients will need to be monitored extensively for organ function, infection, and immune rejection.
Limited work has been performed on bioprinting of pancreas tissues. Marchioli and colleagues encapsulated human and mouse islets and insulinoma β cells in alginate or alginate/gelatin, and bioprinted them into a mesh pattern (Figure 1C); however, they lost function in seven days, which was attributed to the high calcium concentration in crosslinked alginate [23]. Ozbolat and coworkers biofabricated core-shell tissue strands consisting of rat fibroblasts and mouse insulinoma β cells, which showed strong insulin expression and structural rigidity (Figure 1D) [24]. These strands can be used for scaled-up tissue bioprinting as demonstrated for bioprinting of articular cartilage [25]. Recently, Song and Millman created a novel platform using a polylactic acid encapsulation device housing human iPSC-derived β-cell clusters within fibrin gel (Figure 1E) [26]. Upon transplantation, the cells remained functional for 12 weeks.

There have been multiple examples of bioprinted tissues described [27] and functional pancreatic organs for transplantation represent the next frontier. In the interim, organ-on-a-chip models may be well suited to a bioprinting approach. These models offer a useful tool for observing dynamical changes in endocrine hormones in a glucose-dependent environment and screening therapies for diabetes treatment or pancreatic cancer screening [28,29].

**Clinical Implications**

The accuracy of bioprinting may allow for the complete reconstruction of the pancreatic islet, which includes the correct ratios of α, β, δ, γ, and ε cells. Further, incorporation of an intricate vasculature could allow for the printed islets to function as in the endocrine pancreas. It can be envisioned that in the future both the endocrine and exocrine components of the pancreas can be manufactured to allow for complete organ fabrication.
Can Bioprinting Enable Vascularized Encapsulated Islets?

To mitigate the autoimmune response and subsequent graft loss, encapsulation strategies [30,31] that simultaneously allow for vascularization may need to be developed. Vascular network formation is the limiting factor in creating larger-scale tissue constructs as constructs greater than 100–200 μm in diameter require vascularization for oxygenation and nutrient diffusion [32]. This has been proven by mathematical models in encapsulated cells [33]. Bioprinting can create large, adult-sized organs, but the limitation is vascularization. Two major approaches have been discovered to bioprint vascularized tissue constructs, including indirect and direct bioprinting.

In indirect bioprinting, a sacrificial material is used to create perfusable macro-channels in a bulk hydrogel construct. These channels are able to be endothelialized via perfusion culture and sprout microcapillaries when perfusion conditions are optimized. Various techniques and sacrificial materials have been used in generating these macrochannels such as droplet-based bioprinting of thermally-crosslinking hydrogels (gelatin [34]) or extrusion-based bioprinting of thermally- (Pluronic [35] and agarose [36]) or ionically-crosslinking (alginate [28]) hydrogels. The major advantage of this method is the ability to create highly intricate branched vascular network for perfusion of thick tissue constructs. Since there is no vascular pedicle, it is difficult to create an organ for transplantation purposes, but this method can be used for creating a pancreas-on-a-chip model for diabetic drug testing or high-throughput screening. A third bioprinting method, laser-based bioprinting, can also be used to create constructs with higher precision in cell placement. This method includes two major techniques: (i) laser-assisted bioprinting and (ii) stereolithography and its modifications. The reader is referred to Box 2 for further information on modalities of bioprinting.

Direct bioprinting can be used to create a vascular pedicle suitable for transplantation. Coaxial extrusion has been utilized to bioprint vascular scaffolds. Dolati and colleagues showed that encapsulated smooth muscle cells printed in alginate reinforced with carbon nanotubes created mechanically appealing constructs [37]. However, as CNTs induce toxicity, another group developed a bioink comprised of gelatin methacryloyl, sodium alginate, and 4-arm polyethylene-glycol-tetra-acrylate [38]. Scaffold-free bioprinting has also been integrated with coaxially extruded alginatevasculature [39], where tissue strands self-assembled and matured, and enclosed the vasculature under perfusion. Such an approach has the potential to facilitate the loading of pancreatic islets or β-cell clusters as sodium alginate can prevent the penetration of immune cells and protects β cells from attack. Direct bioprinting of capillaries is currently not feasible due to the limited resolution of current bioprinting techniques [40]; therefore, microvascular (~100 μm) channels are printed alongside adjacent endothelial cells. This technique relies on angiogenesis to create the fine interconnections and may be required in generating islet vasculature.

Further complicating islet fabrication is encapsulation to protect cells from the immune response. Capsules with pores <6 microns are likely protective from the immune response while still potentially allowing for exchange of oxygen and waste products and vascular ingrowth, as immune cells are much larger than this pore size. To limit hypoxia, capsules can be designed with high surface to volume ratios and a variety of materials can be used [41]. In addition, oxygen generators are another potential option to increase the oxygen delivery to cells after transplantation [42]. To augment angiogenesis, proangiogenic membranes [43] or growth factor releasing devices, that slowly release proangiogenic factors such as VEGF [44] and bFGF [45], can be placed in close proximity to the capsules. The Theracyte device has been used to mature pancreatic cells in vivo and prevent rejection in diabetic mice [46]. Pepper and colleagues showed that a subcutaneous cell pouch (CP) device protected islets when implanted in a mouse model [47]. CP islets restored glycemic control and responded to glucose
challenge, whereas ‘naked’ islets placed subcutaneously failed to engraft. Another device, Viacyte, has an oxygen port, which is used for recharging oxygen for diffusion [48]. A recent study showed long-term glycemic control in immune competent diabetic mice implanted with ESC-derived β cells encapsulated in alginate derivatives for 174 days without immunosuppression [49]. Larger animal studies are required to assess the clinical applicability to human subjects [47].

Bioprinting may permit for the coordinated fabrication of a vascularized encapsulated islet. Multiple print heads could be used to bioprint endocrine and endothelial cells within a capsule while still allowing for larger vascular channel fabrication. β-cell clusters or spheroids can first be created, and then be encapsulated and precisely bioprinted into a larger hydrogel construct that also contains endothelial cells to allow for further vascularization. Macroparticles (up to a few mm in diameter) have rough surfaces to promote neovascularization [50]. Hiscox and colleagues developed a tissue-engineered prevascularized pancreatic encapsulating device which enhanced islet survival after in vivo implantation [51]. The evolution of higher-resolution bioprinting techniques [52] can enable native-like morphology in the final construct. Specific signaling cues can be incorporated into the design to optimize both angiogenesis and the development of pancreas tissues. Optimal spatial orientation of the vasculature and adjacent endocrine cells may lead to better viability and enhanced hormonal function, which will be required for the treatment of patients with T1D.

Future Outlook
Despite bioprinting being a revolutionary technology for the study and treatment of T1D and pancreatic dysfunction, there remain many unsolved questions (see Outstanding Questions). While complete pancreatic fabrication may still be on the horizon, a bioprinted pancreas-on-a-chip model can be anticipated in the near future. Such a device could be utilized to better understand the immune systems role in the pathogenesis of T1D and its role in the dysfunction of adjacent islet cells. Bioprinting technologies may be crucial in the organization of diverse cell types and complete organ manifestation. While this would be paramount to treatment for T1D, the clinical implications could be extended to those afflicted with a loss of pancreatic mass, as seen in acute pancreatitis, trauma, or oncologic resection. These entities will require replacement of both the endocrine and exocrine pancreas. The exocrine pancreas requires specialized cells and a ductal system for the delivery of secretory enzymes critical to digestion. With further advances in stem cell biology, vascularization, and bioprinting technologies, the two glands of the pancreas will be intimately mixed together into one engineered organ.

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