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Review Article

Engineering the Islet: A Renaissance in 3D Bioprinting for Beta Cell Regeneration

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ABSTRACT

Diabetes is driven by the impairment or destruction of the pancreas' insulin-producing beta cells a significant global health burden. That burden is primarily due to the limitations of our current treatments: mainly insulin therapy and transplanting pancreatic islets. Those options are restricted by factors like donor shortages, the risk of the immune system rejecting the transplant and the fact they don't fully restore the body's natural glucose-regulating mechanisms. As a result, researchers are turning to three-dimensional bioprinting technology to generate those beta cells from scratch. This review looks at the building blocks of 3D bioprinting, the materials and techniques being used to create pancreatic beta cells—and where we stand on that research. We also examine the potential for those engineered beta cells to be used in future treatments for diabetes. We discuss the ongoing challenges and the research needed to overcome them. The key to that will be collaboration across disciplines. By combining advanced bioprinting methods with regenerative medicine, we may be able to fundamentally change how we treat diabetes mellitus.

Introduction

The Global Diabetes Challenge and the Imperative for Beta Cell Restoration

Diabetes mellitus is a serious & growing public health issue worldwide. Trends point towards a spectacular increase in prevalence, with estimates showing an increase from 537 million adults with diabetes worldwide in 2021 to an estimated 783 million in 2045 almost 45.8% increase. This trend disproportionately affects nations like India, which in 2019 had 77 million adults with diabetes. Estimates put this number at 134 million in 2045, with a jump of 74.0%, making India the world's second most diabetic nation after China. The broader Southeast Asian region mirrors this dismal trend, with estimated numbers rising from 88 million in 2019 to 153 million in 2045, representing the climb of 73.9%. India and Southeast Asia are growing ~1.6× the global rate, indicating a regional crisis as shown in figure 1. *(Yesudian et al., 2014)*

Diabetes poses a significant socioeconomic and health burden in India, with annual costs averaging Rs. 10,000 in urban and Rs. 6,260 in rural areas (Anjana et al., 2011). Urban regions show higher prevalence rates, such as Chandigarh (13.6%), Maharashtra (11.2%), and Tamil

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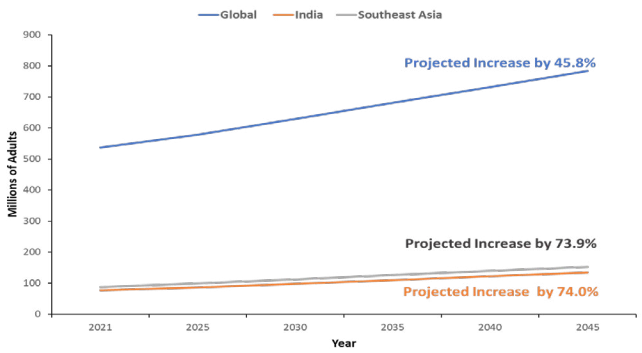

Figure 1. Diabetes Trends and Burden (Global, India & Southeast Asia) Projected Increase in Diabetes Burden (2021→2045)

Nadu (8.4%) *(Narayan & Kanaya, 2020).* Rising obesity, poor diet, and inactivity have also led to an increase in type 2 diabetes among youth *(Narayan & Kanaya, 2020).* Diabetes mellitus, defined by chronic hyperglycemia due to insulin secretion or action defects, leads to cardiovascular, renal, and ocular complications. Current treatments—insulin therapy, oral drugs, and lifestyle modification—control blood sugar but do not restore lost beta cell function *(Ashcroft & Rorsman, 2012).*

Restoration of pancreatic beta cells is essential for achieving normal glucose regulation and potentially curing diabetes *(American Diabetes Association, 2014).* Regeneration-based therapies, including beta cell proliferation, trans-differentiation, and stem cell-derived transplantation, show promise *(DeFronzo, 2004).* However, challenges such as immune rejection and poor graft integration remain *(Nathan, 2015).* Emerging 3D bioprinting technologies can engineer functional pancreatic tissues with vascular and immune protection, offering a novel approach to diabetes treatment *(Davies et al., 2018; Zhou & Melton, 2018; Pagliuca et al., 2014).*

Biological Characteristics & Functional Dynamics of Pancreatic Beta Cells

Beta cells, located in the islets of Langerhans in the pancreas, are endocrine cells that synthesize, store, and secrete insulin to regulate blood glucose levels *(Bonner-Weir & Weir, 2005).* These cells are polarized, releasing insulin granules toward nearby blood vessels to ensure rapid hormone delivery. Insulin secretion is tightly linked to glucose metabolism. When glucose enters beta cells through GLUT2 transporters, it undergoes glycolysis and mitochondrial respiration, increasing the intracellular ATP-to-ADP ratio. This rise in ATP leads to the closure of ATP-sensitive potassium (K^+ATP) channels, causing membrane depolarization. As a result, voltage-dependent calcium channels open, allowing calcium influx, which triggers exocytosis of insulin-containing granules. This process enables insulin to be released proportionally to blood glucose levels. In addition to glucose, incretin hormones such as glucagon-like peptide-1 (GLP-1) further enhance insulin secretion through cyclic AMP (cAMP)-mediated pathways. This finely tuned regulatory mechanism highlights the essential role of beta cells in maintaining metabolic balance and explains their vulnerability to dysfunction in diseases like diabetes *(Bonner-Weir & Weir, 2005).*

Mechanisms Responsible for Beta Cell Dysfunction in Diabetes

The pathophysiological processes involved in diabetes mellitus include death or functional loss of pancreatic beta cells; but the underlying processes are very different between Type 1 diabetes (T1D) & Type 2 diabetes (T2D), as they have different etiological determinants. T1D is due to autoimmune destruction of pancreatic beta cells. This is mediated by the development of autoantibodies along with the action of autoreactive T lymphocytes against some beta cell antigens, resulting in reduced beta cell mass & absolute insulin deficiency along with a lifetime reliance on exogenous insulin therapy. T2D is due to a multifactorial interaction between peripheral tissue insulin resistance with progressive beta cell functional defect as shown in figure 2. Initially, beta cells can compensate by hyper-secretion of insulin as a response to counteract reduced insulin sensitivity. However chronic exposure to metabolic stressors like hyperglycemia (glucotoxicity) sum with hyper-free fatty acids (lipotoxicity) progressively drains the beta cells' functional capacity, decreases cell mass through apoptotic processes, eventually drains the cells' reserve capacity for compensation *(Aguayo-Mazzucato et al., 2010).* This gradual loss usually necessitates insulin supplementation, similar to the terminal phase of T1D; but the precipitating furthermore worsening determinants are very different. Understanding these different pathways of beta cell failure is critical in the design of targeted therapeutic approaches to preserve or restore beta cell function.

Challenges Confronting Beta Cell Physiology Replication Ex Vivo

It is extremely difficult to reconstitute the complex biology of beta cells into stable in vitro models. Isolated beta cells or intact islets are extremely sensitive to their microenvironment in addition to rapidly losing function when removed from their natural pancreatic environment. Two-dimensional (2D) culture systems conventionally employed are not effective in preserving the beta cells' differentiated insulin-secreting functions in the long term *(Murphy & Atala, 2014).* This loss is mainly due to the breakdown of vital cell-cell contacts & interaction with the extracellular matrix (ECM), both being crucial in the preservation of the differentiated state as well as function. The inherent three-dimensional (3D) structure of islets in vivo, involving a multi-dimensional ECM framework abundant in collagen with laminin

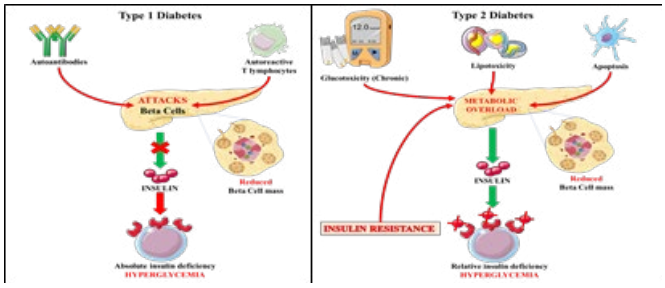

Figure 2. Pathophysiology of Diabetes

components, plays a crucial role in preserving beta cell viability, and specialized function—attributes poorly replicated in conventional flat culture models. Besides, the lack of an integrated vascular system in conventional in vitro models inhibits the efficient delivery of oxygen along with nutrients while impeding the elimination of waste, thereby inducing cellular stress plus promoting de-differentiation or apoptosis *(Wang et al., 2013).* These limitations severely restrict basic research into beta cell physiology besides preclude the development of viable cell-based therapeutic approaches, hence emphasizing the importance of sophisticated culture systems more closely mimicking the in vivo environment.

The Significance of Microenvironment to the Viability & Functionality of Beta Cells

Maintenance of a proper in-vitro microenvironment is also of utmost importance for beta cell viability, proliferative capacity besides insulin secretory activity because these features are intrinsically reliant on a complex interplay between spatial organization, mechanical stress with biochemical signals within their islet microenvironment. In vivo, beta cells are present in an extremely vascularized and innervated microenvironment that is supportive of a normal ECM composition plus controlled by paracrine signaling with neighboring endocrine along with non-endocrine cell types *(Kahn, Hull, et al., 2006).* Replicating this complex environment in vitro is a challenging task. Solutions to this problem involve the use of 3D culture systems, co-culture establishment with permissive cell types such as endothelial or mesenchymal stromal cells, use of biomimetic scaffolds that are capable of replicating essential cell-matrix, cell-cell interactions. For example, solutions such as encapsulating islets in hydrogels with properties similar to ECM have proven to be effective in maintaining cell survival moreover preserving insulin secretory activity *(Halban et al., 2014).* Likewise, supplementation with angiogenic factors or pre-vascularization of constructs is directed towards supporting enhanced oxygen supply & nutrient exchange. Further optimization in optimizing the beta cell microenvironment in vitro is likely to further speed up beta cell replacement therapy & offer more physiologically relevant models to study the pathogenesis of diabetes, thereby converting laboratory information into clinical application *(Khin, Lee, & Jun, 2023).*

Principles and Methodologies of 3D Bioprinting for Beta Cell Engineering

Three-dimensional (3D) bioprinting is a sophisticated fabrication technique based on additive manufacturing principles. It entails the computer-driven, accurate deposition & construction of biological matter, such as living cells with supportive non-living materials (biomaterials) into a pre-specified three-dimensional geometry. The aim is to build bio-engineered tissues or constructs to be used in regenerative medicine, drug screening. At the heart of this technology is the controlled deposition of specialized formulations called 'bioinks'—which are cells suspended in a biomaterial matrix, with added biochemical cues—via a specialized bioprinting device *(Weir B. et al., 2013)*. Under the direction of a digital blueprint of the desired construct, the bioprinter deposits the bioink in successive layers, incrementally constructing the desired 3D structure. The theoretical basis of 3D bioprinting typically relies on three majors' approaches: first biomimetics while second autonomous cellular self-assembly and last micro-tissue module assembly.

Pancreatic tissue engineering primarily uses two strategies: biomimetic and self-assembly. The biomimetic method replicates the natural structure of the islets of Langerhans by imitating cell organization, extracellular matrix (ECM) composition, and signaling interactions. Success relies on understanding cellular populations, ECM molecules, and biophysical forces while integrating engineering, materials science, and biology *(Sbrana et al., 2021).* In contrast, the self-assembly approach mimics embryonic development by using cells' inherent ability to produce ECM, move, and differentiate, allowing tissues to form naturally through endocrine and stromal cell aggregates. However, achieving structural consistency and reproducibility remains a challenge. A modular tissue engineering approach uses "mini-tissues," such as organoids or micro-tissues, as functional building blocks *(Sankar et al., 2011).* In beta-cell regeneration, this involves forming beta-cell clusters or islet-like organoids combined into larger, functional tissues, guided by biomimetic or self-assembly principles *(Lansberry et al., 2024).* Ensuring viability and integration of these modules requires attention to both micro- and macro-scale engineering factors. 3D bioprinting follows three stages: pre-bioprinting (digital modeling and bioink preparation), bioprinting (layer-by-layer deposition via extrusion, inkjet, or light-assisted methods), and post-bioprinting (maturation in bioreactors to enhance stability and function) *(Wang et al., 2012; Papaioannou et al., 2019).*

Bioprinting Techniques for Beta Cell Regeneration: Tools for Constructing Pancreatic Tissue

A wide range of technologies comes under the umbrella

of 3D bioprinting, all being different in operational mechanisms, intrinsic strengths with its limitations. Three primary bioprinting methods have drawn a lot of attention with studies about the particular aim of generating functional pancreatic beta cells for developing pancreatic tissue structures: extrusion-based, inkjet-based & laser-assisted bioprinting. While other additive manufacturing methods like stereolithography (SLA), digital light processing (DLP) are used in the overall discipline of tissue engineering, direct encapsulation for the sensitive beta cells is not as common, is typically limited by factors related to material compatibility or processing conditions that may be harmful to cell survival *(Mbaye et al., 2025)*.

Extrusion-Based Bioprinting

Extrusion-based bioprinting is widely used due to its operational flex
ibility and ability to process bioinks with varied viscosities and cell densities (*Bishop et al., 2017*). It works by mechanically dispensing bioink through a nozzle using pneumatic, piston, or screw-driven mechanisms. Innovations such as semi-solid extrusion (SSE) allow printing of highly viscous materials, while coaxial extrusion—with concentric nozzles—enables simultaneous deposition of multiple materials to create complex structures like core–shell fibers or pre-vascularized channels. The Freeform Reversible Embedding of Suspended Hydrogels (FRESH) technique further enhances structural resolution by printing within a support gel bath, preventing collapse of low-viscosity bioinks.

In pancreatic beta-cell regeneration, extrusion printing offers practical advantages: it is accessible, cost-effective, and avoids high-energy methods that could harm cells (*Ibrahim et al., 2016*). Its capability to print multiple materials and cell types simultaneously helps recreate the heterogeneous architecture of pancreatic islets and supports vascular network formation. It also facilitates scaffold fabrication to provide the mechanical support needed for engineered tissue.

However, limitations exist. Extrusion printing typically yields lower resolution than other methods, limiting the accurate replication of islet microstructures (*Ghosh et al., 2023*). Cells experience shear stress during extrusion, especially with viscous bioinks, which can reduce viability. Achieving adequate porosity for nutrient and oxygen delivery remains difficult, leading to variable cell survival rates (40–80%). Optimizing bioink rheology and printing parameters is therefore crucial to maintain both structural fidelity and beta-cell function.

Inkjet-Based Bioprinting

Working as a contact-free deposition technology, inkjet bioprinting accurately extrudes Pico liter-volume of bioink onto a support substrate. Actuation is by thermal components (producing vapor bubbles to propel droplets) or piezoelectric transducers (inducing acoustic waves to eject droplets), reminiscent of traditional printing. Systems either work continuously (CIJ) or on drop-on-demand (DOD) basis. Piezoelectric DOD systems are especially well-suited to pattern thin or complex soft tissue architectures potentially associated with beta cell constructs *(Ramadan et al., 2020)*.

Major advantages for beta cell printing involve the non-violent droplet ejection process, which is conducive to high cell viability. Inkjet techniques are capable of relatively high print resolutions (usually in the order of 50 μm) which can allow for exact spatial control of cells, allowing patterned arrays that reflect islet structure. The method facilitates high rates of deposition speeds in multi-nozzle arrays is for high-throughput fabrication together with the production of heterogeneous constructs with specified cellular configurations. Inkjet platforms are relatively less expensive, more available than alternative high-resolution bioprinting systems *(Rossi et al., 2024)*.

There are however notable limitations. A main limitation is a severe demand for low-viscosity bioinks with well-defined surface tension properties to achieve stable droplet generation, to avoid clogging of the nozzle. This limitation diminishes the choices of biomaterials available to impart strong mechanical support or define certain microenvironmental signals to beta cells. Even though nature is in general cell-friendly, potential thermal or mechanical stresses induced upon droplet generation still linger. The consistent distribution of cells within the droplets, along with addressing the issue of clogged nozzles- especially for cell-infused or slightly more viscous bioinks- remains a practical problem. Additionally, constructing extensive, spacious 3D tissues may be less feasible when using inkjet compared to extrusion.

Laser-Assisted Bioprinting (LAB)

Laser-assisted bioprinting (LAB) uses a unique, nozzle-free method. It uses focused laser pulses to eject bio ink from a donor substrate onto a receiving surface. A common setup includes a laser source, a 'ribbon' (a transparent substrate coated sequentially with a laser-energy absorbing layer of the bioink) with the receiving substrate positioned nearby. The intense laser pulse illuminates the absorbing layer producing localized vaporization & a resulting pressure wave that expels a microdroplet of bioink onto the receiver. Methods such as Laser-Induced Forward Transfer (LIFT) illustrate this concept *(Ghasemi, et al., 2021)*.

The major utility of LAB for beta cell regeneration is in applying it to very high printing resolution that can achieve single-cell placement accuracy, thus allowing the development of highly organized, biomimetic cellular patterns. As a non-invasive, nozzle-induced shear stress-avoiding method, LAB shows extremely high cell viability rates (>95%) with negligible disturbance to sensitive beta cells. It also shows the capability to deal with a wide range of bioink viscosities from highly viscous substances or

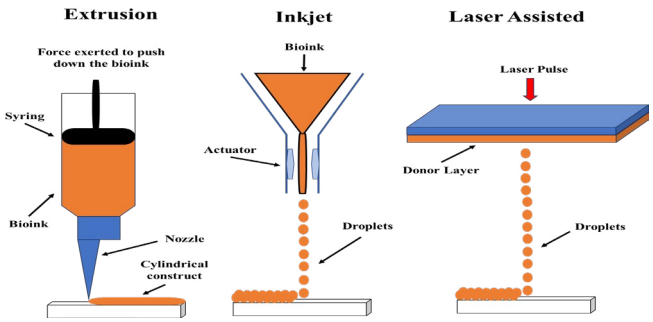

Figure : 3. Representation of 3-D Bioprinting Techniques

concentrated cell suspensions that are troublesome for other methods thereby broadening the range of usable biomaterials available for the construction of supportive beta cell niches. LAB also presents an opportunity for the fabrication of intricate 3D architecture even in situ bioprinting onto biological surfaces *(Skeldon, et al., 2018)*. Even with such benefits, there are limitations LAB must overcome. The technology requires greater initial expenses than extrusion or inkjet systems. Print speed and general throughput are reduced, limiting the scalability for the fabrication of large tissue or high-level therapeutic production. Construct size attainable is commonly more restricted. Technical challenges involve avoiding dehydration of bio-ink on the donor ribbon during printing *(Wu & Xu, 2018)*. Additionally, success relies on the accurate optimization with meticulous control of laser parameters (e.g., energy fluence, pulse length) based on the particular bioink properties to provide efficient droplet transfer while maintaining optimal cell survival as shown in figure 3.

Tables 1 show the fundamental characteristics of the three major bioprinting techniques in the context of beta cell regeneration, emphasizing their strengths plus drawbacks for this particular application.

Biomaterials for Beta Cell Regeneration in 3D Bioprinting: The Ink for Life

The successful construction of functional tissues by three-dimensional (3D) bioprinting is critically dependent on the choice & use of suitable biomaterials. Such materials serve not only as passive structural scaffolds but as active elements providing vital biochemicals with physical cues that strongly regulate cellular functions, including attachment, growth, differentiation with functional competence. In the particular application of regenerating pancreatic beta cells through 3D bioprinting, the requirements put on prospective biomaterials are especially rigorous. Key requirements are outstanding biocompatibility, guaranteeing non-toxicity plus lack of harmful immunological response; carefully controlled biodegradability, allowing for progressive replacement by host tissue with smooth integration; appropriate mechanical properties that ensure structural stability against physiological loads while maintaining the desired architecture; most importantly the ability to support the survival specialized function of the implanted beta cells *(Chang & Sun, 2023)*. Thus, the informed selection of a single biomaterial or well-designed composite constitutes perhaps the most critical determinant of the therapeutic efficacy of bioprinted constructs for beta cell replacement since it directly controls the long-term viability with functional yield of the engineered pancreatic tissue. Generally, materials utilized for such intent are grouped into types based on their source: natural polymers, man-made engineered materials, or composite systems that bring in aspects of both *(Bhatt, S. et al., 2022)*.

Discovery of Natural Polymers for Beta Cell Bioprinting

Collagen, the most abundant structural protein in the mammalian extracellular matrix (ECM), is a key natural biomaterial in 3D bioprinting because of its strong biocompatibility and low immunogenicity (*Guillemot et al., 2011*). Its integrin-binding sites promote cell adhesion and proliferation, which are essential for functional pancreatic tissue development. However, its weak mechanical strength and poor thermal stability lead to

Table 1: Comparison of 3D Bioprinting Techniques for Beta Cell Regeneration

Feature	*Extrusion-Based*	*Inkjet-Based*	*Laser-Assisted*
Principle	Continuous filament extrusion	Droplet deposition	Laser-induced bioink transfer
Resolution	~100 µm40	Up to 50 µm41	Micron level42
Speed	Medium	Fast	Slow
Cell Viability	Moderate (40-90%)43	High (>85%)43	Very High (>95%) 43
Viscosity Range	High	Low	Medium to High
Cell Density	High	Low	High
Cost	Medium44	Low45	High46
Complexity	Moderate	Limited	High
Beta Cell Application	Scaffold fabrication, high cell density delivery	Precise cell patterning, thin tissue constructs	Complex islet structures, high precision models

rapid degradation in vivo. To address this, collagen is often combined with synthetic polymers or chemically crosslinked to form durable hybrid bio-inks suitable for long-term implantation (*Hinton et al., 2015*).

Alginate, derived from brown seaweed, is another widely used polymer due to its low toxicity, biocompatibility, affordability, and simple gelation with divalent cations such as calcium. It enables cell encapsulation within hydrogels that protect transplanted beta cells while maintaining high cell viability. Yet, alginate lacks native cell-binding motifs and degrades quickly, which limits cell adhesion unless modified with bioactive sequences like RGD peptides (*Gudapati et al., 2016*). Decellularized extracellular matrix (dECM) offers a tissue-specific biomaterial that retains native 3D architecture and biochemical cues. Pancreas-derived ECM (pdECM) provides adhesion ligands and signaling molecules that support beta cell survival, function, and differentiation. Incorporation of pdECM into bio-inks shows promise for creating bioengineered pancreatic models (*Li et al., 2016*). Other natural polymers such as chitosan and hyaluronic acid (HA) are also noteworthy. Chitosan supports islet survival and angiogenesis, while HA, a key ECM glycosaminoglycan, aids cell signaling and tissue hydration, improving stability and printability in multi-component systems (*Langhans et al., 2018*).

Synthetic & Hybrid Material Approaches

Synthetic biomaterials, particularly hydrogels, are valuable in tissue engineering because their physicochemical properties can be precisely tailored. These hydrophilic polymer networks swell in water, mimicking the hydration of the extracellular matrix and allowing fine control over chemical composition, mechanical behavior, degradation, and bioactivity (*Barui et al., 2018*). Such tunability supports 3D bioprinting applications, especially in beta cell regeneration. Functionalization with peptides like RGD and growth factors such as VEGF enhances cell survival and proliferation. Common examples include polyethylene glycol (PEG) and gelatin methacrylate (GelMA), which offer shear-thinning, self-healing, and stable crosslinking features favorable for printing (*Wu et al., 2024*). Other synthetic polymers, such as polycaprolactone (PCL) and polylactic acid (PLA), contribute mechanical strength to bioprinted scaffolds. Though naturally hydrophobic, their surfaces can be modified to improve cell adhesion. These polymers often combine with cell-laden hydrogels to create composites that balance biological functionality and structural stability (*Kim et al., 2023*).

Hybrid biomaterials, which combine natural and synthetic components, seek to combine the biocompatibility and cell recognition of natural materials with the mechanical strength, controlled degradation, and programmable functionality of synthetic polymers. The proper selection and mix of these materials can result in scaffolds that not only provide mechanical support but also improve beta cell survivability and function via improved adhesion or growth factor distribution, hence boosting angiogenesis and tissue integration. Examples include alginate-methylcellulose for islet encapsulation, PCL scaffolds with VEGF-releasing alginate hydrogels for vascularization, and pdECM-HAMA bio-inks that promote adhesion, shape, function, and blood vessel formation as shown in (table 2).

The Importance of Biomaterial Selection for Beta Cell Outcomes

The success of regenerating pancreatic beta cells through three-dimensional (3D) bioprinting hinges on the careful selection of the right biomaterials. The properties of the chosen matrix play a crucial role in determining key cellular outcomes, which significantly affect survival rates, functional performance & the essential development of vascular networks within the engineered tissue.

Ensuring Beta Cell Endurance

For encapsulated beta cells to survive over the long term, biomaterials are essential. They must be biocompatible in order to prevent toxicity and immunological responses that endanger cell health and guarantee survival. Porosity and connection allow for efficient mass movement, giving nutrients and oxygen while eliminating waste, making scaffold design equally crucial. In large bioprinted constructions in particular, poor transport can result in oxygen and food shortages that kill cells *(Moss et al., 2024).* Mechanical characteristics are also important; scaffolds that resemble pancreatic tissue in rigidity promote survival. Degradation products also need to be non-toxic. In general, biomaterials need to strike a compromise between metabolic exchange and structural support *(de Vries et al., 2023).*

Facilitating Physiological Performance: Impact on Beta Cell Function

Selection of biomaterials has a dramatic effect on the insulin-secretion function of bioprinted beta cells in response to blood glucose levels. Biomaterial engineered scaffolds can deliver specific bioactive signals. Incorporation of the extracellular matrix components, such as laminins, along with the growth factors, enables beta cell maturation with insulin production. The mechanical properties of the matrix, including stiffness, elasticity, influence the cell behaviour as well. Additionally, the three-dimensional scaffold architecture enables islet-like organization, facilitating cell communication & coordinated insulin secretion. Thus, the biomaterial must do more than shield cells; it must facilitate efficient insulin production plus secretion on glucose, in a manner similar to pancreatic islets.

Promoting Integration: Biomaterial Influence on Vascularization

Finally, choosing the right biomaterials is important for

Table 2: Properties along with Applications of Key Biomaterials for Beta Cell Regeneration

Specific Material	*Biomaterial Type*	*Key Properties*	*Applications in Beta Cell Regeneration*
Collagen	Natural	Biocompatible, promotes cell adhesion, abundant in ECM.	Creating bioinspired scaffolds, often used in combination with other materials to improve mechanical strength.
Alginate	Natural	Biocompatible, low toxicity, easy gelation, allows immunoisolation.	Encapsulation of islets and beta cells, often modified to improve cell interaction and printability.
Decellularized Tissues (pdECM)	Natural	It retains native ECM structure and bioactive components and has low immunogenicity.	Creating tissue-specific bioinks that mimic the pancreatic microenvironment, promoting beta cell survival and function.
Chitosan	Natural	Biocompatible, biodegradable, protective effects on islets.	Potential for immunoprotective matrices, often combined with collagen for enhanced mechanical strength.
Hyaluronic Acid (HA)	Natural	Biocompatible, involved in tissue hydration, can be chemically modified.	Used in combination with other materials to improve cell viability and reduce inflammation, & be modified for better printability.
Hydrogels (PEG, GelMA)	Synthetic	Tunable properties (mechanical, degradation), can mimic ECM.	Creating tailored microenvironments for beta cells, can be functionalized to enhance cell adhesion and viability.
Polymers (PCL, PLA)	Synthetic	Strong mechanical properties, biodegradable.	Providing structural support for beta cell constructs, often require surface modifications to improve cell interaction.
Alginate/ Methylcellulose, PCL/Alginate, pdECM/HAMA	Hybrid	A combination of beneficial properties from natural and synthetic components.	Aim to enhance biocompatibility, mechanical strength, printability and provide specific cues for beta cell survival, function, and angiogenesis. Examples include islet encapsulation with improved vascularization.

the stimulation of angiogenesis with the creation of a well-functioning vascular network within printed pancreatic tissue. Proper vascularization is a vital consideration for beta cell viability with its in long-term large engineered constructs because it provides a uniform supply of nutrients rich oxygen as well as assists in waste expulsion *(Debnath et al., 2025)*. Biomaterials have important effects on angiogenesis in numerous ways. Some materials, like certain collagens or decellularized extracellular matrix (ECM) preparations, naturally have components that promote blood vessel formation. Scaffolds can also be specifically designed to include pro-angiogenic agents, like vascular endothelial growth factor (VEGF), which actively promotes the formation of new blood vessels *(Osidak et al., 2020)*. The physical properties of the scaffold, such as porosity with channel design, also guide the formation & maturation of this critical vascular network. Therefore, the strategic use of biomaterials with intrinsic pro-angiogenic capability or their tunability for increased vascular support is pivotal in achieving the maximum therapeutic potential of 3D printed beta cell constructs for their durable in vivo functionality *(Kim et al., 2002)*.

D Bioprinting Strategies for Beta Cell Regeneration

In Vitro Models of Diabetes Research

Technological advancements in 3D bioprinting have significantly driven the creation of in vitro models for the study of healthy as well as diseased pancreatic tissues. With their sophistication along with advanced nature, the models have been at the center of attention in the life sciences, with unprecedented ability to deconstruct the complexity of pancreatic function plus disease. For instance, 3D bio-printed models create more representative tumor microenvironments, enabling scientists to model the intricate tumor growth & metastasis processes with higher fidelity than the traditional two-dimensional (2D) cell cultures. More representative platforms for preclinical cancer treatment studies & drug discovery are offered by the innovation. Moreover, sophisticated 3D models of pancreatic islets have been demonstrated to have improved physiological properties compared to traditional monolayer cultures. This means that such bio-printed models have tremendous potential to deconstruct the sophisticated behaviors of beta cells *(Gadre et al., 2023)*. The field of diabetic disease modeling has also been greatly enhanced by the development of 3D cell culture systems with bio-printing. The three-dimensional models have great advantages over the traditional 2D cultures & animal models through the delivery of a more physiologically relevant microenvironment that closely mimics the complex cell-cell with its cell-matrix interactions of native pancreatic tissue. Consequently, 3D bio-printed models are increasingly being employed as platforms for the discovery of diabetic drugs, allowing for a more accurate prediction of drug efficacy and toxicity before the transition to in vivo studies. They are also excellent tools for advancing knowledge of the mechanisms of diabetes development& the validation of new therapeutic targets *(Ho, Teo, & Ng, 2024)*. The greater physiological relevance of these in vitro

Table 3: Summary of Preclinical Studies on 3D Bio-printed Beta Cells

Study	*Bioprinting Technique*	*Cell Source*	*Biomaterials*	*Animal Model*	*Key Outcomes*
Alipio et al.	Not specified	Mouse skin fibroblast-derived iPSCs differentiated into beta-like cells	Not specified	Diabetic mice	Controlled hyperglycemia
Ahn et al.	Multi-head deposition-based 3D printing	Mouse insulinoma-6 (MIN-6) cells	Alginate bioink, poly(caprolactone)	Type 1 diabetes mice	3x higher insulin secretion, controlled glucose at 8 weeks, higher survival rate

Table 4: Analysis of Research Studies on 3D Bioprinting for Beta Cell Regeneration

Study	*Cell Source*	*Bioprinting Approach*	*Scaffold Design*
Xu et al., 2010	ADSCs, pancreatic islets	Extrusion-based	Alginate/gelatin/fibrin hydrogels, mimicking pancreas structure
Duin et al., 2019	Rat islets	Extrusion-based	Alginate/methylcellulose hydrogel blend, macroporous
Hu et al., 2021	Beta cells	Extrusion-based	Alginate/Pluronic F127 with hypomethylated pectin, enhanced printability plus flexibility, resistance against inflammation
Marchioli et al., 2015	INS1E β-cell line, human& mouse islets	Extrusion-based	Alginate/gelatin bioink, macroporous self-standing constructs
Liu et al., 2019	Islets, endothelial progenitor cells, Tregs	Coaxial extrusion	Alginate with GelMA, core-shell macroporous constructs for re-vascularization& immunoisolation
Kim et al., 2019	Primary islets	Extrusion-based	Pancreatic tissue-derived extracellular matrix (pdECM) bioink, mimicking native microenvironment
Hwang et al., 2021	Islet-like aggregates	Multi-head bioprinting	Macroporous PCL capsule& nanoporous pdECM hydrogel, hybrid encapsulation for protection& nutrient/oxygen diffusion
Idaszek et al., 2021	Islets, HUVECs	Microfluidic 3D bioprinting	Alginate/pECM for islets, alginate/fibrinogen for HUVECs, porous vascularized grafts
Wang et al., 2022	Islet cells	Extrusion-based	Hybrid bioink of HAMA& pdECM, mimicking pancreatic microenvironment
Song et al., 2016	Stem cell-derived β-cell clusters	Extrusion-based	Macroporous PLA scaffold housing cells within a fibrin gel
Farina et al., 2017	Pancreatic islets	Extrusion-based	Functionalized PLA cell encapsulation system dispensing VEGF
Marchioli et al., 2016	Islets	Extrusion-based	3D ring-shaped PCL scaffold surrounding alginate hydrogel core, functionalized with VEGF

models, through the controlled organization of cells & the application of relevant biomaterials, makes it an important step towards the creation of more effective therapies for diabetes.

Preclinical trials for improved hyperglycemic state

Preclinical studies indicate that 3D bio-printed beta cell constructs can restore insulin secretion and improve glycemic control in diabetic models. Transplantation of beta-like cells derived from mouse fibroblast iPSCs controlled hyperglycemia in diabetic mice. Similarly, 3D bioprinted pancreatic models with islets enhanced insulin secretion and glucose homeostasis (Nagaraja et al., 2024). In Type 1 diabetic mice, implants increased insulin secretion threefold and maintained glucose control for eight weeks, improving survival rates. Porcine islet-laden pancreatic petals lowered plasma glucose in NOD-SCID mice, while PLA/Fibrinogen scaffolds with hESC-derived beta cells in non-diabetic mice showed sustained insulin production and C-peptide positivity over twelve weeks. These observations together support the therapeutic potential of 3D bioprinting to create functional beta cell replacements that are capable of correcting hyperglycemia in preclinical models of diabetes *(Fang et al., 2023)*. The enhancement in survival rates in treated animals speaks volumes about the potential of this strategy to have a significant impact on disease outcomes as show in table 3.

Development of Implantable Bioartificial Pancreas

Significant work is being conducted on the development

of implantable bioartificial pancreas devices through 3D bioprinting technology as a long-term solution for diabetes. Scientists at Washington University in St. Louis have developed 3D-printed devices specifically designed for the subcutaneous transplantation of stem cell-derived beta cells in diabetic patients. The devices incorporate features designed to address the limitations of traditional transplantation *(Wang et al., 2021)*. They are designed to reduce hypoxia through vascularization, delivering adequate oxygen in addition to nutrients to the encapsulated cells. The devices are also designed to provide structural integrity after transplantation too, more importantly, to be removable if needed. The ultimate goal of such research is to engineer a cell-based implant that can restore the body's ability to produce its own insulin on a controlled basis, hopefully resulting in a functional cure for type 1 diabetes *(Ghasemi, A. et al., 2021)*. Encapsulating lab-grown beta cells in protective hydrogel is a potential method to treating Type 1 diabetes because it protects cells from immune attack while allowing nutrition and waste exchange to sustain cell viability *(Du et al., 2022). A* fully vascularized bionic pancreas constructed via 3D bioprinting provides a physiologically appropriate environment with functional vascular beds for oxygen and nutrient delivery *(Sathisaran et al., 2024).* This bio-printed pancreas, ready for on-demand transplantation, secretes insulin, glucagon, and C-peptide to correct fundamental physiological deficiencies. Such advancements in implantable bioartificial pancreas devices constitute significant milestones toward insulin independence *(Wu et al., 2024).*

Cell Sources for Beta Cell Regeneration

The success of 3D bioprinting for beta cell regeneration largely depends on selecting an appropriate cell source. Researchers are evaluating various options, including donor islets, embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and pancreatic progenitor cells. Due to the limited availability of donor islets, stem cell–based alternatives offer a scalable solution. Multipotent stem cells can be differentiated into functional beta cells suitable for both autologous and allogeneic transplantation (*Parvaneh et al., 2023*). Among these, iPSCs are particularly promising because they can be reprogrammed from adult somatic cells, enabling personalized therapy and reducing immune rejection risks. MSCs also show potential as they can form insulin-producing cells and possess immunomodulatory properties that protect against immune attacks. ESCs, when guided by precise differentiation protocols, can produce pancreatic beta-like cells that mimic natural development. The choice of cell source directly impacts feasibility, scalability, and immunogenicity. Overall, stem cells—especially iPSCs—are emerging as a leading candidate for creating functional, patient-specific beta cell constructs (*Cui et al., 2022*).

Recent Research in 3D Bioprinting for Beta Cell Regeneration

The application of recent advancement in the application of 3D Bioprinting for beta cell regeneration are shown in table 4.

Cases study of 3D Bio-Printed Constructs that Enhance Beta Cell Function and Longevity

A number of research studies have proved considerable advances in the application of 3D bioprinting for producing functional beta-cell constructs with enhanced survival plus insulin-secreting functions. Most of these advances tend to encompass novel approaches towards overcoming fundamental hurdles, including effective vascularization including immune rejection prevention *(Lam, Yu. Et al., 2023)*.

Approaches for Enhanced Neovascularization in Bioprinted Constructs

Successful engraftment and long-term survival of bioprinted beta cell constructs depend on establishing a functional vascular network to ensure adequate oxygen, nutrient supply, and waste removal (*Piper et al., 2004*). Various strategies have been explored to enhance vascularization, including embedding endothelial cells or precursors in bioinks and releasing pro-angiogenic molecules. Xu and colleagues developed a composite hydrogel of alginate, gelatin, and fibrin containing pancreatic islets and adipose-derived stem cells (ADSCs). The ADSCs differentiated into endothelial-like cells, forming vascular structures that improved glucose-responsive insulin secretion and uptake, indicating better islet function due to vascular support (*Liu et al., 2019*). Another approach by *Thakur et al. (2023)* used coaxial 3D bioprinting to co-deposit islets, endothelial progenitor cells (EPCs), and regulatory T cells (Tregs) in alginate bioink. This promoted revascularization via EPCs and provided immunoprotection through Tregs, resulting in insulin secretion similar to native islets. Similarly, *Kim et al. (2019)* demonstrated that incorporating vascular endothelial growth factor (VEGF) into a PLA-based 3D-printed encapsulation device induced rapid vascular infiltration post-implantation. Collectively, these studies highlight that stimulating angiogenesis is vital for the functionality and long-term viability of bioprinted beta cell grafts.

Methods to Mitigate Immune-Mediated Rejection

One of the major hurdles for the clinical use of allogeneic or xenogeneic beta cell transplantation is the host immune rejection. 3D bioprinting provides new opportunities for creating immune-protective barriers to protect the transplanted cells *(Skrzypek, B. et al., 2023)*. For example, Hu with his colleagues developed a new bioink by adding Pluronic F127 to augment alginate adding hypomethylated pectin in order to increase resistance to

inflammatory insults. Cellular structures printed using this altered bioink showed decreased tissue rejection after implantation in murine models, indicating its possible immunomodulatory advantage. The work described above by Liu et al. also strategically incorporated Tregs, cells known for their immunosuppressive activity, directly into the bioprinted structure to further increase the immune-isolation of the encapsulated islets.

In addition, methods like coaxial extrusion allow for the creation of core-shell architectures. These designs have the therapeutic beta cells living inside a central hydrogel matrix, surrounded by an outer shell layer. This outer shell is engineered with immunomodulatory cells or materials to form a physical & biological barrier against infiltration of host immune cells. The general purpose of these techniques is to create an immuno-privileged environment that allows critical nutrient & oxygen diffusion while keeping the graft apart from cytotoxic immune effectors, thus eliminating rejection risk *(Hwang et al., 2021)*.

Evidence Supporting Long-Term Functional Performance

Recent advances in 3D bioprinting show strong potential for developing long-lasting beta cell therapies for Type 1 Diabetes. Sustained insulin secretion and glucose responsiveness remain key indicators for successful clinical translation. *Idaszek et al. (2021)* demonstrated this by creating a 3D-printed construct using MIN-6 cells embedded in an alginate bioink and supported by a poly(caprolactone) matrix. When implanted subcutaneously in diabetic mice, the construct-maintained glucose regulation for eight weeks and improved survival compared to controls. Similarly, *Wang et al. (2023)* developed islet organoids using a hybrid bioink of hyaluronic acid methacrylate (HAMA) and pancreatic decellularized extracellular matrix (pdECM), closely replicating native pancreatic conditions. Their implants effectively normalized blood glucose and increased insulin secretion for 90 days, confirming strong long-term activity. Together, these findings suggest that 3D bioprinting can produce functional, durable beta cell constructs capable of restoring glucose homeostasis, marking a promising step toward practical regenerative therapies for diabetes. *(Idaszek et al., 2021; Wang et al., 2023).*

Future Research Paths in 3D Bioprinting for Pancreatic Beta Cells

Recent advances in 3D bioprinting have focused on developing biomaterials that support pancreatic beta-cell survival and function. Hydrogels that mimic the extracellular matrix, such as alginate, are commonly used for islet encapsulation due to their affordability and mild gelation, though they degrade quickly and have limited cell adhesion (*Song & Millman, 2016*). Alternatives like chitosan and collagen improve mechanical strength and angiogenesis, while hyaluronic acid (HA) reduces immune reactions (*Marchioli et al., 2016*). However, combining biocompatibility, durability, and printability remains a major challenge (*Farina et al., 2017*). Composite and hybrid bioinks—such as alginate–methylcellulose, gelatin–alginate–fibrin, and PEGDA–HA blends—enhance printability, vascularization, and beta-cell survival (*Huang et al., 2024; Duin et al., 2022; Xie et al., 2020*). Chemical modifications like gelatin methacrylation allow finer control of scaffold properties (*Shi et al., 2022*). Microfluidic systems and dynamic bioreactors improve oxygen and nutrient exchange, supporting tissue maturation and organ-on-a-chip applications (*Hwang, Choi, & Jang, 2021; Wan et al., 2024*). Real-time imaging tools aid in monitoring cell viability and insulin secretion (*Ahlfeld et al., 2020; Wu et al., 2017*). Clinical translation requires reliable vascularization, immune protection, scalable manufacturing, and clear regulatory guidelines (*De Spirito et al., 2024; Shiwarski et al., 2024*). Combining induced pluripotent stem cells with gene editing and advanced bioinks could enable vascularized, immune-tolerant bio-artificial pancreases for long-term diabetes therapy (*Ghosh et al., 2023; Margarita et al., 2025*).

Conclusion

Follow-on research in the field of 3D bioprinting of pancreatic beta cells is strategically focused on overcoming the challenges inherent in current diabetes management modalities & on pioneering new therapeutic avenues. Perhaps the most important areas to be explored in the future include the continued development of next-generation biomaterials that possess greater biological integration, tailored mechanical properties along with better printability. The highly integrated microfluidic perfusion platforms with bioreactor technologies will be at the forefront of optimizing the mass transport of nutrients, oxygen, waste to ensure sustained cell viability in large constructs. Additionally, advanced non-invasive imaging modalities will remain crucial to real-time evaluation besides its characterization of the structure & function of in situ bioprinted tissue. Finally, overcoming the daunting complexities inherent in clinical translation—namely, for large-scale manufacturing, secure immunoisolation plus stable, effective vascularization—will prove to be crucial in translating the therapeutic potential of this technology to patients. The anticipated impact of such a breakthrough is significant, with a viable pathway toward achieving long-term insulin independence and radically enhancing the quality of life.

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