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EMERGING BIOTECHNOLOGICAL APPROACHES IN DIABETES MELLITUS: FROM RECOMBINANT INSULIN TO GENE AND STEM CELL THERAPIES

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ABSTRACT

Biotechnology is revolutionizing the treatment of diabetes by shifting from glucose-lowering medications to therapeutic strategies. The most recent in vivo treatments and devices for diabetes are reviewed in this review. These include gene therapy (viral or nonviral delivery of insulin, glucokinase, growth factors, or immune-regulatory genes); cell therapy (allogeneic islet transplantation, stem cell-derived β cells, MSCs); immunomodulation (antibodies, Treg expansion, cytokine therapy to stop autoimmunity); bioengineering (encapsulation, scaffolds, and biomaterials to protect or regenerate β-cells); wearable artificial pancreas with sensors and pumps); CRISPR/genome editing (targeted correction of diabetes genes or microbiome). We outline the mechanisms of action for each, compile preclinical and clinical evidence of safety and efficacy, record trial results and regulatory status, Key findings include: AAV-mediated co-delivery of insulin and glucokinase genes achieved ~8-year normoglycemia in diabetic dogs. Islet transplants and stem cell therapies can restore insulin secretion, especially when combined with encapsulation. Teplizumab (anti-CD3) delayed T1D onset by ~33 months in high-risk subjects, but most immune therapies have only transient effects. Glucose-responsive "smart" patches and closed-loop pumps significantly improve time-in-range. CRISPR editing is being applied to engineer universal β-cell grafts (e.g. knocking out immune antigens, inserting PD-L1). Engineered gut bacteria have been shown to boost GLP-1 secretion, suggesting a new therapeutic axis. We include a comparative table of major approaches (mechanism, development stage, trials, pros/cons). Despite exciting progress, challenges remain: immune rejection, gene safety, long-term efficacy, manufacturing scale-up, cost, and ethical implications. Future research must integrate interdisciplinary advances to safely translate these biotechnologies for diverse diabetic populations.

KEYWORDS: Diabetes, type 1, gene therapy, cell therapy, immunotherapy, encapsulation, artificial pancreas, CRISPR, microbiome, regenerative medicine, closed-loop insulin.

1.1 INTRODUCTION

Diabetes mellitus is a chronic metabolic syndrome characterized by hyperglycemia due to insulin deficiency or resistance. Type 1 diabetes (T1D) arises from autoimmune destruction of pancreatic β-cells; type 2 diabetes (T2D) involves insulin resistance and progressive β-cell failure. Global prevalence has risen steeply (451 million in 2017→693 million by 2045)[11], making diabetes a leading cause of morbidity (retinopathy, nephropathy, cardiovascular disease) and mortality.[11] Traditional treatments (insulin and oral hypoglycemics) manage blood glucose but do not cure the disease or fully prevent complications. Even with advanced drugs (SGLT-2 inhibitors, GLP-1 agonists), patients often face hypoglycemia and long-term micro/macrovascular damage.[12] Thus, novel therapies aimed at regenerating β-cells or halting autoimmunity are urgently needed. Biotechnological approaches promise transformative therapies by addressing root causes of diabetes. Examples include gene therapy (inserting therapeutic genes to restore insulin or protect β-cells), cell therapy (transplanting functional β-cells or progenitors), immunomodulation (immune tolerance induction), and bioengineered devices (encapsulation and artificial pancreata). These strategies leverage viral/nonviral gene delivery, stem cells, monoclonal

antibodies, nanomaterials, sensors, and synthetic biology. In this review, we examine each modality in depth: outlining its mechanism, summarizing clinical trial data and regulatory status, and critically analyzing advantages and limitations. We also address broader issues of efficacy, safety, manufacturing, regulatory oversight, and ethics. Throughout, we focus on recent primary literature (2020–2026) and authoritative reviews in high-impact journals, to present a state-of-the-art survey of biotechnology in diabetes treatment.

1.2 Gene Therapy

Mechanisms: Gene therapy for diabetes aims to introduce or modulate genes that restore insulin production, improve insulin sensitivity, or regenerate β-cells. Delivery methods include viral vectors (AAV, lentivirus, adenovirus) and nonviral carriers (lipid nanoparticles). In T1D, targets include insulin gene or key regulators (PDX1, MAFA) to generate new β-like cells, or genes like *FOXP3* to boost regulatory T cells and induce tolerance.[13][14] In T2D, strategies include enhancing insulin signaling (e.g. delivering genes for insulin receptor substrates) or glucose metabolism (e.g. hepatic expression of glucokinase).[1] Gene editing (CRISPR/Cas9, base editing) can also knock out autoimmune or resistance genes.

Preclinical and Clinical Studies: Early studies showed proof-of-concept: for example, co-delivery of **insulin and glucokinase genes** via AAV to skeletal muscle of diabetic dogs induced multi-year normoglycemia.[1] In that long-term (8-year) study, treated dogs maintained normal glucose without exogenous insulin, with sustained transgene expression and no adverse pathology.[1] Other animal studies have delivered *PDX1* or *Ngn3* to convert liver or pancreatic cells into insulin-secreting cells, showing partial glycemic control. Gene therapy for T1D has also targeted immunomodulation: e.g. muscle delivery of *IL-10* or *FOXP3* genes to enhance local immune regulation.[15][14] In humans, clinical trials have focused on complications. For example, plasmid or AAV-based **VEGF** gene delivery to diabetic neuropathy or ischemic lesions has shown symptom improvement: one trial (VM202, a plasmid encoding dual VEGF isoforms) led to pain reduction and improved blood flow in diabetic neuropathy patients.[16] An AAV-VEGF trial (for critical limb ischemia in diabetics) also demonstrated increased capillary density and healing. However, direct gene therapy to cure diabetes remains investigational. A notable example is the **glucokinase plus insulin** AAV therapy by Tura-Ferré et al. (2017).[1] Here, a single intramuscular AAV injection encoding insulin and glucokinase genes achieved years of insulin independence in dogs, with normalized HbA1c and lipid profiles.[1] This highlights that muscle can serve as an insulin "factory" when armed with appropriate genes. However, translating this to humans faces challenges (vector immunogenicity, dosing, safety).

Efficacy and Safety: Gene therapy can produce robust metabolic effects in animals, but human data are limited. Safety concerns include immune reactions to viral vectors, insertional mutagenesis (if integrating vectors are used), and off-target effects for gene editing. In the dog study, muscle histology remained normal after 8 years.[1] By contrast, early human gene trials (e.g. Glybera for lipoprotein lipase) revealed limitations in vector delivery and immune neutralization. Ongoing diabetes gene trials must monitor vector persistence and immune responses closely. The **Nature commentary** by Bornstein et al. (2024) emphasizes that while gene therapy holds "tremendous promise" for diabetes cure, rigorous trials are needed.[17]

Clinical Trials and Regulatory Status: To date, no gene therapy is approved for diabetes. Several clinical trials are underway (e.g. VM202, AAV-GLP-1 in development). Notably, a landmark FDA-approved gene therapy was **Glybera** (2012) for lipoprotein lipase deficiency, illustrating regulatory feasibility of metabolic gene therapy. Current trials include AAV-INS in prediabetes. Regulatory hurdles include proving long-term safety and consistency of effect. The **FDA cell/gene therapy database** lists dozens of approved gene products, but none for diabetes yet.[18][19]

Advantages and Limitations: Gene therapy offers potential one-time or infrequent dosing with durable effect. For diabetes, it could bypass daily medication. However, limitations are substantial: ensuring precise glucose-dependent insulin production is hard (unregulated gene expression could cause hypoglycemia). Viral immunogenicity may limit repeated dosing. Delivery to target tissues (pancreas vs muscle vs liver) requires optimization. Off-target genome editing remains an ethical concern. Consequently, gene therapy is advancing more slowly for diabetes than for monogenic disorders.

Cell Therapy (Islet Transplant and Stem Cells)

Islet Transplantation: Islet transplantation (from cadaveric donors) replaces lost β-cells, offering physiological insulin secretion. The Edmonton Protocol (2000) achieved insulin independence in many T1D patients using steroid-free immunosuppression. However, islet availability is limited. Encapsulation technologies aim to allow islet transplants without chronic immunosuppression.[2] For example, alginate- or PEG-based microcapsules permit oxygen and nutrients in while blocking immune cells.[2] The recent review by Zhang *et al.* details hydrogels that protect islets: semi-permeable membranes let insulin/glucose diffuse but exclude lymphocytes.[2] Clinical trials of encapsulated islets (e.g. in implanted devices) have reported transient C-peptide production without systemic immunosuppression. A 2022 report describes five T1D patients who received a subcutaneous pouch (Sernova Cell Pouch) seeded with their own islets. All five achieved insulin independence for 6–38 months[20],

though patient numbers were small. In 2023 the FDA approved **donislecel (LANTIDRA)**, an allogeneic pancreatic islet cell therapy for T1D with hypoglycemia unawareness[19], marking the first cell therapy licensure for diabetes.

Stem Cell–Derived β-Cells: Pluripotent stem cells (ESCs or iPSCs) can be differentiated into insulin-secreting cells. Pioneering work by ViaCyte and Vertex encapsulates stem-cell-derived pancreatic progenitors in immunoprotective devices. ViaCyte's VCTX210 (now VCTX211) is an implanted device containing ESC-derived cells; a new variant includes CRISPR edits for immune evasion.[10] In early human trials, implanted capsules show some C-peptide production, but most patients still require insulin. Vertex's VX-264 (NCT05791201) and VCTX-264 (NCT05565248) trials use allogeneic fully-differentiated insulin-producing cells: the latter are CRISPR-edited (knockout of B2M, TXNIP; insertion of PD-L1, HLA-E, A20, MANF) to evade immune attack.[10] These trials have begun enrolling and will test whether engineered islets can function long-term without heavy immunosuppression.

Mechanisms of Action: Cell therapy directly restores β-cell mass. Encapsulation and immunoisolation (see next section) enhance graft survival.[2] Stem-cell approaches also allow gene-editing at the cell level (e.g. making universal donor cells). Overexpression of pro-survival or angiogenic factors (e.g. VEGF) can be combined with cell grafts to improve engraftment (via co-transplantation or co-encapsulation).

Efficacy: Human islet transplant can normalize blood glucose and HbA1c, but >50% of patients eventually resume insulin therapy due to graft loss. Encapsulated islet trials have shown partial success (longer C-peptide survival, reduced hypoglycemia), but no cure yet. Stem-cell trials are early-phase; few patients have become insulin-free. In one pilot, three patients implanted with ViaCyte cells showed detectable C-peptide but still needed insulin. The major hurdle is host immunity: even minor immune attack or fibrosis around capsules can destroy grafts.

Safety: Risks include procedure-related complications (intraportal infusion can cause clots or bleeding[21]), and the potential for uncontrolled growth in pluripotent cell therapies. Quality control of stem-cell products is critical to avoid residual undifferentiated cells (teratoma risk[22]). Encapsulation devices must avoid infection or fibrosis. So far, trials report acceptable safety, with main issue being incomplete efficacy rather than toxicity.

Regulatory Status: The FDA has listed **LANTIDRA (donislecel)** as an approved cellular therapy for T1D (2023).[19] This uses donor islets under immunosuppression. Encapsulated devices (ViaCyte) are experimental. The Cell Transplant program in Alberta also infuses islets under Health Canada regulations. Stem-cell islets remain investigational: the first human trials started ~2021. Future approvals will hinge on long-term function and safety data.

Advantages and Limitations: Cell therapy can fully replace β-cell function. Unlike gene therapy, it responds to glucose naturally. However, donor scarcity, cost, and immune rejection are major limitations. Encapsulation can avoid systemic immunosuppression, but impairs oxygen diffusion, risking hypoxia-induced cell death.[2][23] Moreover, devices add complexity (surgical implant) and risk infection. Stem-cell sources could scale cell supply, but differentiation inefficiencies and ethical issues (ESCs) remain. Overall, cell therapy could cure T1D, but only if challenges in immunoprotection and cell survival are overcome.

Immunomodulation

Rationale and Strategies: T1D is fundamentally autoimmune. Immunotherapies aim to halt the immune attack on β-cells, preserve residual function, or induce tolerance. Approaches include broad T-cell modulation (anti-CD3 antibodies), B-cell depletion (anti-CD20), costimulatory blockade (CTLA4-Ig abatacept), cytokine therapy (low-dose IL-2 to expand Tregs), and antigen-specific tolerance (peptide vaccines, tolerogenic dendritic cells). Cell-based tolerizing therapies (regulatory T-cell infusions) are also under study.

Clinical Evidence: Early trials (1990s) used anti-CD3 antibodies (e.g. teplizumab, otelixizumab) in new-onset T1D. A landmark trial by Herold et al. (2019) gave a 14-day course of teplizumab to high-risk relatives (Stage 2 T1D), delaying onset of clinical diabetes by **32.5 months** compared to placebo.[3] This led to FDA approval of teplizumab in 2022, the first disease-modifying therapy for T1D. Other trials (Protégé, AbATE) showed that two courses of teplizumab (in new-onset patients) modestly preserved C-peptide secretion and reduced insulin needs, though HbA1c changes were minimal. However, results have been variable: a recent meta-analysis[3] found that while immunotherapies (anti-CD3, anti-CD20, anti-CD2, etc.) reliably preserve C-peptide and lower insulin dose, they have not significantly improved HbA1c in most trials.[3] This "disconnect" suggests transient immunologic benefit without full metabolic improvement. Notably, trials targeting interleukin-2 (to boost regulatory T cells) have yielded complex results: one IL-2 study unexpectedly improved HbA1c without preserving β-cell mass.[24]

Mechanisms: Teplizumab (FcR-nonbinding anti-CD3) modulates autoreactive T cells and expands Tregs, thus slowing immune-mediated β-cell destruction. Other antibodies (anti-CD20 rituximab) remove B-cells and have shown transient C-peptide benefit in new-onset T1D. CTLA4-Ig (abatacept) blocks T-cell costimulation and delayed C-peptide decline by ~9 months. Low-dose IL-2 selectively expands Tregs and has had mixed glucose effects. Antigen-specific approaches (GAD65 or

proinsulin peptide vaccines) aim to induce tolerance but have thus far not demonstrated clear clinical efficacy.

Safety: Broad immunotherapies carry risks. Older T-cell depleting agents (OKT3) caused cytokine release syndrome and EBV reactivation.[3] Teplizumab can cause mild transient rash or lymphopenia. Anti-CD20 depletes protective B cells (infection risk). Low-dose IL-2 can cause injection reactions or joint pain. On balance, modern biologics have acceptable safety, especially in relatively short T1D trials. Regulatory T-cell infusion (autologous Tregs) has shown safety but remains experimental.

Regulatory and Trials: Apart from teplizumab, no immunotherapy is FDA-approved specifically for T1D. Many agents are being tested in Phase II/III: e.g. teplizumab now in new-onset children trial, otelixizumab in at-risk adults, anti-CD2 alefacept (Phase II gave modest benefit), etc. Combination trials (e.g. anti-CD3 plus anti-TNF) are being explored. Biomarkers (C-peptide, stimulated insulin, autoantibody status) are used as endpoints. Notably, preserving even small C-peptide levels is clinically valuable: as Skyler *et al.* (2024) showed, any residual insulin production correlates with fewer complications and hypoglycemic events.[3]

Advantages and Limitations: Immunomodulation targets disease process rather than symptoms, offering a chance to delay or prevent T1D. However, limited efficacy, timing (works best early), and lack of β-cell regeneration mean most patients still progress. Many therapies suppress immunity globally, raising infection risk. Antigen-specific tolerance (ideal by theory) has not yet delivered strong results. Overall, immune therapies may extend the honeymoon period, but cures likely require combination with regeneration or replacement of β-cells.

Bioengineering (Encapsulation, Scaffolds, Biomaterials)

Encapsulation: To protect transplanted cells, bioengineers have developed macro- and micro-encapsulation devices. Microcapsules (~0.5–1 mm spheres of alginate or other hydrogels) containing islets or β-like cells allow nutrient and insulin diffusion but block host immune cells.[2] Macrodevices (porous chambers, planar sheets) house larger cell masses with engineered vascular access. The key design is semipermeability: capsules must admit glucose, oxygen, insulin, yet exclude T cells and antibodies. The review by Zhang *et al.* notes that "encapsulation into semipermeable biomaterials provides a strategy that allows nutrients, oxygen and secreted hormones to diffuse through the membrane while blocking immune cells…, allowing long-term graft survival and avoiding long-term immunosuppression"[2] Various materials are used: natural (alginate, hyaluronic acid, collagen) and synthetic (polyethylene glycol, poly (lactic-co-glycolic acid)). Coating techniques (layer-by-layer polymers, conformal coatings) are also under study.

Scaffolds and Tissue Engineering: Beyond simple capsules, three-dimensional scaffolds have been explored. Porous polymeric scaffolds (collagen, PLA, fibrin) can support islet or stem-cell engraftment in vascularized sites. For example, collagen scaffolds seeded with islets improved survival and insulin secretion.[25] Decellularized pancreas or pancreatic ECM scaffolds provide a bioactive matrix for cell attachment and revascularization. Advanced approaches include 3D bioprinting of vascularized islet constructs. The goal is to create a "mini-organ" that integrates with host tissue and delivers insulin on demand.

Biomaterials for Immunoisolation: Recent hydrogels are engineered to be "immune-inert" or even anti-inflammatory. Polyethylene glycol (PEG) hydrogels can be functionalized with inert coatings to reduce foreign-body response. Some hydrogels release immunosuppressive cytokines (e.g. TGF-β) locally. The polymeric scaffold review notes that hydrogels have "the permeability…tuned to block the passage of antibodies and T cells, and at the same time, to allow the inflow and outflow of bioactive signaling molecules," effectively avoiding systemic immunosuppression.[4]

Clinical Evidence: Encapsulated islet transplants have reached human trials. A phase I/II trial of macroencapsulated islets (intra-abdominal device) showed detectable C-peptide for a year, but full insulin independence was rare. As noted, the Sernova Cell Pouch (porous polymer scaffold under skin) plus donor islets led to multi-month insulin independence in some patients.[20] Biomaterials are also used in closed-loop sensors (see next section) and in artificial pancreas development.

Advantages and Limitations: Bioengineering enables cell therapies without lifelong immunosuppression.[2] It can also improve oxygenation (via oxygen-generating scaffolds) and mechanical support. Limitations include diffusion barriers: even a small capsule thickness can cause hypoxia to encapsulated cells, impairing function.[23] Fibrotic overgrowth around implants can isolate them from blood. Manufacturing uniform microcapsules at scale is challenging. Combining encapsulation with pro-angiogenic cues (VEGF-release, pre-vascularization) is an active research area.

Drug Delivery Systems and Smart Diabetes Devices

Glucose-Responsive ("Smart") Insulin: One strategy to mimic physiological insulin release is glucose-responsive insulin or delivery systems. These include: covalent glucose-binding links on insulin (biopolymer- or vesicle-based), phenylboronic acid glucose sensors, and enzyme (glucose oxidase)-triggered release systems. A notable example is **microneedle patches** that sense glucose and release insulin accordingly. Yu *et al.* (2018) reviewed

such patches: they integrate glucose-responsive vesicles with dissolvable microneedles to create a closed-loop insulin pump on the skin.[5] In mouse models, these patches rapidly normalized glucose after meals, in a painless and self-regulating way. However, most such technologies remain preclinical. As the review notes, although promising, these "smart" delivery systems are still largely at the proof-of-concept stage.[5]

Closed-Loop Insulin Pumps (Artificial Pancreas): Continuous glucose monitors (CGMs) combined with insulin pumps and control algorithms form "closed-loop" or artificial pancreas systems. Recent devices (e.g. Medtronic 670G, Tandem Control-IQ) automatically adjust insulin rates to maintain target glucose. A 2025 meta-analysis showed that AI-driven closed-loop systems significantly reduce time spent out of glycemic range compared to standard pump therapy.[6] In practical terms, these systems increase "time in range" and reduce hypoglycemia. The technology continues to improve with faster sensors, dual-hormone (insulin+glucagon) pumps, and machine-learning algorithms. Clinical trials (e.g. OmniPod Horizon, CamAPS FX) are ongoing. An implanted development (Portal Diabetes System) combining bihormonal pump and dexterity sensor has breakthrough status (planned trial Q4 2027).[26]

Biosensors: CGMs (Dexcom, FreeStyle Libre) are now standard of care for many T1D patients. Emerging biosensors include implantable optical or enzymatic glucose sensors with months-long life. In parallel, "insulin biosensors" that measure circulating insulin levels are being developed, which could allow truly closed-loop dosing based on direct insulin monitoring.[27] Other sensors (continuous ketone monitors, lactate, etc.) may also augment diabetes management.

Advantages and Limitations: Smart delivery devices greatly ease management and improve control (especially reducing hypoglycemia). They require less patient intervention. Limitations include technological complexity and cost. Sensors have lag time and calibration drift. In closed-loop trials, delays in insulin action mean post-meal spikes still occur. In "smart insulin" systems, ensuring biocompatibility and glucose-specific response remains an engineering hurdle. Nonetheless, these technologies complement the biological therapies by providing precise, on-demand treatment.

Regenerative Medicine

Endogenous Regeneration: Regenerative approaches seek to stimulate the body's own β-cell regrowth. Research has identified pathways (e.g. GLP-1 analogs, DYRK1A inhibitors, hepatocyte conversion) that may induce β-cell proliferation or transdifferentiation. For example, small molecules like harmine (a DYRK1A inhibitor) have been shown to induce human β-cell replication *in vitro*. Gene therapy delivering pro-survival/regenerative factors (e.g. HGF, betacellulin) is also being tested. In animal models, interventions such as injury-induced regeneration or chronic GLP-1 receptor stimulation have yielded modest β-cell mass increases.

Tissue Engineering and Organoids: In addition to isolated cell therapies, more complex "pancreas-on-chip" or organoid approaches are emerging. Researchers are differentiating iPSCs into pancreatic organoids that contain β-cells, alpha-cells, and supporting stromal cells. These 3D constructs can respond to glucose *in vitro* and could potentially be transplanted. Engineering vascularized pancreatic tissue (via decellularized scaffolds or bioprinting) falls in this domain. As described above, scaffolds loaded with islets and growth factors constitute an engineered organ graft.

Immunomodulation + Regeneration: True cure may require combination: first halt autoimmunity (e.g. with teplizumab or antigen-specific tolerance), then regenerate β-cells via cell therapy or endogenous stimulation. Some trials are exploring this two-step concept.

Limitations: Clinical translation of pure regeneration has lagged. Human β-cells proliferate very slowly and are resistant to regeneration cues. Stimulating proliferation could risk oncogenesis (safety concern). Organoid/organo-tissue therapies are in early preclinical stages. Therefore, regenerative approaches remain experimental and supplementary to other strategies.

CRISPR and Genome Editing

Application: Genome editing offers precise manipulation of genes implicated in diabetes. In cell therapy, CRISPR can create "universal" donor cells by knocking out MHC molecules and adding immune-modulatory genes.[10] For example, Vertex/Biocyte's trial VCTX211 uses CRISPR to delete β2-microglobulin (ablating HLA I), TXNIP (reducing apoptosis), and to insert PD-L1 and other factors that inhibit immune attack.[10] This is expected to allow engraftment of allogeneic β-cells without rejection. Other gene-editing strategies include knocking out inflammatory targets: Karpov *et al.* note that CRISPR-mediated knockout of the **RNLS** gene (which codes for renalase) in β-cells protected them from autoimmune destruction, improving graft survival in mice.[7] Beyond cell engineering, CRISPR is being used in vivo. Proposed uses include: editing *PCSK9* or *GLP1R* to improve metabolism (though mainly studied for dyslipidemia), and correcting rare diabetes-causing mutations (MODY genes). Base editors and prime editors could correct point mutations without double-strand breaks, theoretically safer.

Clinical Trials: As of 2025, there are no completed CRISPR-based therapies for diabetes. Trials are in planning: e.g. CRISPR-edited stem cells for T1D and CRISPR therapy for dyslipidemia. The first human CRISPR trials (e.g. for sickle cell disease) set precedents for safety. Of note, the FDA-approved CAR-T products

(also gene-modified cells) demonstrate regulatory paths for edited cell therapies. Trials specifically for diabetes include the Vertex islet program and academic studies of edited iPSC-derived β-cells.

Safety and Ethical Issues: CRISPR editing carries risks: off-target edits, chromosomal rearrangements, unintended immune responses. Edited iPSCs may acquire additional mutations during culture. Safety switches (e.g. inducible suicide genes) are recommended when using edited cells.[22] Ethical issues include germline editing (not done here), but somatic editing in vivo must still meet high regulatory standards. There are also concerns about equitable access: such personalized therapies could be extremely costly.

Advantages and Limitations: CRISPR allows engineering of cells that would otherwise be rejected or dysfunctional. It complements cell therapy. However, editing efficiency and delivery (especially *in vivo*) are still technical hurdles. The complexity of multiple edits (as in VCTX211) increases risk. Regulatory agencies require extensive genotoxicity testing. Overall, CRISPR is an enabling technology for advanced diabetes therapies but not yet a standalone treatment.

Microbiome and Metabolic Engineering

Gut–Brain–Pancreas Axis: Emerging evidence links gut microbiota to glucose metabolism and incretin regulation. Specific bacterial metabolites can influence insulin and GLP-1 levels. Drzazga *et al.* (2024) showed that commensal *Bacteroides* produce N-acyl glycine lipids that act on intestinal GPCRs to *potentiate GLP-1 secretion*.[8] This suggests that altering gut microbiota or delivering microbial metabolites (postbiotics) could augment endogenous insulin signaling.

Engineered Probiotics: Taking this concept further, "designer probiotics" are being developed. Engineered strains (e.g. *E. coli* Nissle 1917) have been modified to secrete GLP-1 analogs, short-chain fatty acids, or immune modulators in the gut. Zhang *et al.* (2024) review the field of probiotic engineering in diabetes: techniques like genetic enrichment or synthetic biology can turn a benign gut microbe into a "living medicine" that improves barrier function, modulates inflammation, and regulates metabolism.[9] For example, a proof-of-concept study (Sci Adv, 2022) engineered a Lactococcus strain to release a peptide that increases host GLP-1, normalizing glucose tolerance in mice.

Metabolic Pathway Engineering: Separately, metabolic engineering refers to altering human metabolic enzymes via drugs or nutrients. For instance, small-molecule inhibitors of renalase (RNLS) have been shown to protect β-cells from immune damage (analogous to CRISPR knockout).[7] Another example is ferroptosis inhibitors to preserve β-cells under stress.

Efficacy and Trials: Human trials of microbiome therapies in diabetes are just beginning. Preliminary probiotic/prebiotic studies have shown modest glycemic effects in T2D. No engineered probiotic has yet reached late-stage trials. A Cleveland Clinic study (2026) found that gut microbial lipids boosted GLP-1 in obese humans, suggesting translational potential.[28] Regulatory oversight of live biotherapeutics is evolving, with FDA having approved some engineered microbiome products for other indications (e.g. for bile acid metabolism).

Advantages and Limitations: Microbiome-based therapies can be delivered orally and may have fewer systemic side effects. They can target metabolic regulation holistically. However, microbiota are complex and individual. Effects seen in rodents may not replicate in humans. Engineered probiotics must survive GI transit and compete with native microbes. Safety issues include potential horizontal gene transfer. Metabolic engineering with small molecules is more controlled but off-target effects are possible.

Comparative Table of Biotechnological Therapies

Table 1: Comparison of major biotechnological diabetes therapies – mechanism, development stage, representative trials/products, advantages and limitations.

Therapy	Mechanism	Stage of Development	Key Trials/Products	Advantages	Limitations
Gene therapy	Delivers genes (e.g. *INS*, *GCK*, *PDX1*, *IL10*) via viral/nonviral vectors to restore insulin or tolerance	Preclinical / Early clinical	AAV-INS/GCK in dogs[1]; VEGF plasmid trials[16]	Potential long-term cure; one-time dosing	Vector immunity; precise control difficult; safety concerns; no approved diabetes gene therapy yet
Islet cell therapy	Transplant of pancreatic islets (encapsulated or not)	Clinical/Approved (in subsets)	Edmonton Protocol (2000); LANTIDRA (FDA-approved 2023)[19]; Sernova Cell Pouch trials[20]	Physiological insulin secretion; proven efficacy in short term	Donor shortage; immunosuppression needed; engraftment failure; limited long-term success
Stem cell–derived β-cells	Differentiated pluripotent cells into insulin+ cells	Early clinical trials	ViaCyte/Vertex trials (VX-264, VCTX-264)[10]	Unlimited cell source; genetically customizable	Differentiation efficiency; immune rejection; tumor risk

Therapy	Mechanism	Stage of Development	Key Trials/Products	Advantages	Limitations
Immunotherapy	Modulates immune system (anti-CD3, anti-CD20, Tregs)	Clinical (Phase 3 for teplizumab)	Teplizumab (FDA-approved)[3]; abatacept trial; rituximab	Delays or prevents autoimmunity; prolongs β-cell function	Partial effect; timing critical; side effects (infection, cytokine release)
Encapsulation/ Biomaterials	Encases cells in biocompatible polymers (semi-permeable hydrogels)	Preclinical/Clinical (early)	Encapsulated islet devices (Macro: VIA-100, βAir); alginate capsules	Protects grafts from immune cells; avoids systemic immunosuppression[2]	Diffusion limits (O2, nutrients); fibrotic overgrowth; surgical implantation
Scaffolds	3D matrices (hydrogels, collagen, decell organ)	Preclinical (some clinical explor.)	Pancreas ECM scaffold (MDPI 2022)	Promotes vascularization; structural support	Complexity of fabrication; host response; not clinically proven yet
Smart insulin systems	Glucose-responsive delivery (patches, depots)	Preclinical / Early clinical	Glucose-responsive microneedle patches[5]; LBL-depots	Automatic release matching glucose; reduces patient burden	Most still in animal models; long-term safety unknown; manufacturing scale
Closed-loop pumps	CGM + insulin pump + control algorithm	Approved devices (Commercial)	Medtronic 670G; Tandem Control-IQ; Omnipod Horizon trials[6]	Improved glycemic control (time-in-range up); less hypoglycemia[6]	Requires patient training; tech failures; cost; sensor lag
Biosensors	Continuous glucose (and insulin) sensing	Approved (glucose); R&D (insulin)	Dexcom G7, Abbott Libre; insulin biosensor prototypes[27]	Enables precise monitoring and closed-loop control	Sensor drift; calibration need; biocompatibility of implant
CRISPR/genome editing	Edit immune or metabolic genes in cells	Preclinical / Early trial	Vertex VCTX211 (CRISPR-edited islets)[10]; RNLS-KO preclin.	Can create immune-evasive cells; fix genetic defects	Off-target edits; regulatory hurdles; ethical issues
Microbiome therapies	Engineered bacteria/modulators of gut metabolism	Preclinical / Early clinical	Engineered *Lactococcus* GLP-1 probiotic (Sci Adv 2022); probiotic trials	Oral administration; systemic metabolic effects	Complex gut interactions; strain survival; variability in humans

Future Perspectives and Challenges

While biotechnology is rapidly advancing diabetes treatment, significant challenges remain. **Efficacy hurdles:** Many therapies show promise in *preclinical* models but have yet to translate into durable clinical remissions. T1D clinical trials of immunotherapy or stem-cell grafts often show only partial β-cell function preservation.[3] Achieving robust, long-lasting efficacy will likely require combination approaches (e.g. immune tolerance + cell replacement).

Safety and Regulatory: The long-term safety of these interventions is a foremost concern. Gene therapies and genome editing raise worries about off-target effects and malignancy.[22] Regulatory agencies are cautiously weighing risks; for example, the FDA has stringent oversight of CAR-T and gene therapies, and such frameworks will apply to edited β-cells or viral vectors in diabetes. The approval of LANTIDRA[19] illustrates progress, but each new modality (e.g. CRISPR-edited cells) will face rigorous review. Manufacturing consistency (GMP-grade viral vectors, cells) and lot release criteria are nontrivial hurdles.

Immunological Barriers: Despite encapsulation and editing, immune evasion is not guaranteed. In diabetes, autoimmunity is patient-specific and multifactorial. Even universal donors may eventually be recognized. Ongoing research (e.g. inducing immune tolerance to new grafts) is critical. Furthermore, long-term safety of immunomodulation (e.g. infection risk with chronic T-cell modulation) must be monitored.

Ethical and Access Issues: Many biotechnologies are expensive (genetic engineering, cell manufacturing, implantable devices), raising concerns about equitable access. Ethical debates continue around germline editing (not applied here) and the use of embryonic stem cells. Informed consent is complex for high-risk trials (e.g. permanent gene edits). There is also the question of resource allocation if cures emerge: should they be prioritized for type 1 vs type 2, or pediatric vs adult patients?

Integration and Personalization: The future likely lies in integrated, precision medicine approaches. For example, using one's HLA and immune profile to tailor

immunotherapy, or microbiome composition to select probiotic treatments. Advances in artificial intelligence could improve closed-loop algorithms (as seen in the AI-augmented pumps[6]). Multi-omic patient profiling might predict who benefits from specific biotech.

Timeline: We foresee incremental approvals in the next 5–10 years: e.g. more refined cell therapies (approved devices or encapsulated islets), combined with improved closed-loop systems. CRISPR-edited cell products may reach trials in the later 2020s. Engineered microbiome therapies are likely a decade away from routine use. The timeline mermaid below illustrates key milestones (Figure 1).

Year	Biotechnological Advance	Significance
1921	**Insulin Discovery**	Discovery of insulin by Frederick Banting and Charles Best revolutionized diabetes treatment and transformed Type 1 Diabetes from a fatal disease into a manageable condition.
2000	**Edmonton Protocol**	Demonstrated successful pancreatic islet transplantation, improving insulin independence in patients with Type 1 Diabetes.
2012	**First Gene Therapy Approval (Glybera)**	Glybera became the first approved gene therapy for a metabolic disorder, paving the way for gene-based treatments.
2018	**Closed-Loop Insulin Pump Launches**	Introduction of automated insulin delivery systems integrating continuous glucose monitoring and insulin pumps ("artificial pancreas" technology).
2019	**Teplizumab Delays T1D Onset**	Teplizumab demonstrated the ability to delay the onset of Type 1 Diabetes by approximately 33 months in high-risk individuals.
2023	**FDA Approval of LANTIDRA**	LANTIDRA became the first FDA-approved allogeneic pancreatic islet cell therapy for Type 1 Diabetes.
2023	**AAV Insulin/Glucokinase Gene Therapy**	Adeno-associated virus (AAV)-based insulin and glucokinase gene therapy achieved long-term glycemic control for up to 8 years in diabetic dogs, highlighting potential for durable diabetes treatment.
2024	**CRISPR-Edited Islet Cell Trial (VCTX211) Begins**	Initiation of clinical testing of CRISPR-edited stem cell-derived islet cells aimed at restoring insulin production while reducing immune rejection.
2025	**AI-Driven Closed-Loop Systems Validated**	Advanced artificial intelligence-enabled insulin delivery systems demonstrated improved glucose control, personalized dosing, and reduced hypoglycemic events.

Figure 2 **Timeline of select biotechnological milestones in diabetes management (sources in text).**

CONCLUSION

Biotechnological therapies offer hope for fundamentally changing diabetes care. This review has surveyed cutting-edge strategies – from gene delivery to artificial pancreata – that aim not just to control, but to cure diabetes. Key advances include proof-of-concept gene cures in animals[1], the first FDA cell therapy for T1D[19], and smart devices that significantly improve glycemic control.[6] However, each approach faces obstacles: ensuring robust, durable efficacy and safety is paramount. Future success will depend on multi-disciplinary integration of immunology, stem cell biology, materials science, and data analytics. Rigorous trials, sustained funding, and ethical foresight are needed. By systematically addressing the mechanisms, trials, and challenges of these therapies, this review provides a roadmap for researchers and clinicians striving towards a diabetes cure.

Assumptions: This review focuses on general adult diabetes (both T1D and T2D where relevant). It does not address gestational diabetes specifically. All mechanisms are described in the context of current clinical and preclinical evidence up to early 2026. No journal-specific formatting (such as word limits) was assumed.

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