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Lipid-Based Nanocarriers for Targeted Delivery to Pancreatic β-Cells in Obese Diabetic Models

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ABSTRACT

Obesity-linked type 2 diabetes is driven by chronic insulin resistance coupled to progressive dysfunction and loss of pancreatic β-cells. Standard glucose-lowering therapies improve glycemia but either protect β-cells only indirectly or require high systemic exposure, which invites adverse effects. Lipid-based nanocarriers offer a modular approach to concentrate therapeutics within β-cells while shielding labile molecules, extending residence time, and minimizing off-target exposure. By tuning lipid composition, size, surface charge, and corona, these systems can traverse gastrointestinal and vascular barriers, engage islet microvasculature, and exploit receptor-mediated endocytosis on β-cells. Contemporary designs include liposomes, solid lipid nanoparticles, nanostructured lipid carriers, ionizable lipid nanoparticles, and lipid–polymer hybrids, each adaptable to diverse payloads such as small molecules, peptides and proteins, nucleic acids, and genome editors. Targeting tactics range from GLP-1 receptor and sulfonylurea receptor–binding peptides to zinc and manganese-coordination motifs that sense the β-cell secretory niche, as well as islet endothelium–addressing ligands that facilitate transendothelial passage. In obese diabetic models, β-cell–directed lipid nanocarriers improve glucose tolerance, preserve glucose-stimulated insulin secretion, reduce endoplasmic reticulum and oxidative stress, and limit dedifferentiation, often at doses below the thresholds needed for free drugs. Translation now depends on robust potency assays that reflect β-cell–specific mechanisms, biodistribution profiling in metabolically diseased animals, cGMP manufacturing with tight control of critical quality attributes, and safety evaluations that consider complement activation and repeated-dosing kinetics in obesity. This review synthesizes the biological rationale, engineering principles, targeting strategies, therapeutic payloads, preclinical outcomes, and translational considerations for lipid-based β-cell–targeted delivery in obesity-associated diabetes.

INTRODUCTION

Type 2 diabetes associated with obesity evolves from a sustained mismatch between energy intake and expenditure that reprograms endocrine and immune networks across the body[1–3]. Adipose tissue hypertrophy drives hypoxia, extracellular matrix remodeling, and macrophage infiltration that together establish a proinflammatory milieu[2, 4–6]. The resulting cytokines, lipids, and extracellular vesicles propagate insulin resistance to liver and skeletal muscle, where diacylglycerols and ceramides activate kinases that blunt insulin receptor signaling and impair GLUT4 translocation[7]. Hepatocytes increase gluconeogenesis and very-low-density lipoprotein secretion, while myofibers reduce mitochondrial oxidative capacity and switch fuel preference in ways that exacerbate hyperglycemia and dyslipidemia. Against this background of systemic insulin resistance, pancreatic β-cells initially compensate by expanding insulin output and, to a limited extent, mass[8–10]. Over time, glucolipotoxic stress, oscillatory calcium overload, endoplasmic reticulum unfolded protein response activation, and reactive oxygen species accumulation converge to diminish stimulus–secretion coupling and trigger dedifferentiation, senescence, or apoptosis.

Preserving β-cell identity and function is central to altering the natural history of obesity-linked diabetes[11]. Direct β-cell–targeted therapies promise to restore glucose-sensing, protect organelles, and reduce maladaptive transcriptional programs while minimizing systemic exposure. Yet pharmacologic access to the islet is nontrivial. The endocrine pancreas occupies a small fraction of pancreatic mass, islets are dispersed and highly vascularized but shielded by specialized endothelium and extracellular matrix, and β-cells share receptors with

other tissues, increasing the risk of off-target effects[11]. Furthermore, many molecules with favorable β-cell pharmacology are hydrophobic, chemically labile, or macromolecular, and thus poorly traverse biological barriers or survive gastrointestinal and hepatic metabolism.

Lipid-based nanocarriers emerged to reconcile this biological promise with the biopharmaceutical realities of drug delivery[12, 13]. Liposomes, solid lipid nanoparticles, nanostructured lipid carriers, ionizable lipid nanoparticles, and lipid–polymer hybrids can solubilize hydrophobic compounds, protect peptides and nucleic acids from degradation, and bias biodistribution using nanoscale size and surface chemistry[14–17]. Ionizable lipids promote endosomal escape of nucleic acids, while rigid or mixed lipid matrices modulate the release kinetics of small molecules. For β-cell applications, the same modularity supports the attachment of ligands that recognize receptors enriched on β-cells or on islet endothelium. By combining passive targeting via size and hemodynamics with active receptor-mediated uptake, lipid carriers can raise intracellular concentrations relative to circulation and to exocrine pancreas or other off-target organs[15, 18, 19].

Obesity imposes additional constraints and opportunities. Complement activation, reticuloendothelial activity, and altered protein corona composition can accelerate clearance of conventional nanoparticles and obscure targeting ligands; conversely, heightened islet blood flow in hyperglycemia, fenestrated islet capillaries, and perivascular niches rich in zinc and manganese can be leveraged to guide carriers. Islet inflammation involving resident macrophages and endothelial activation modifies the local receptor landscape and endocytic pathways in ways that can be harnessed by carefully chosen ligands, while chronically elevated free fatty acids and cytokines reshape endocytic trafficking inside β-cells, influencing the fate of internalized carriers and their payloads[20].

The therapeutic armamentarium that benefits from β-cell–directed lipid carriers spans modalities. Small molecules that stabilize mitochondrial function, reduce oxidative and endoplasmic reticulum stress, or modulate K_ATP channel activity can be deployed at lower doses when concentrated in islets[21]. Peptides and proteins, including incretin mimetics, antiapoptotic factors, and unfolded protein response modulators, require protection from proteolysis and assistance crossing cellular membranes, tasks suited to lipidic encapsulation and fusogenic lipids[22]. Nucleic acids, from siRNA and antisense oligonucleotides to mRNA and CRISPR base editors, open avenues to reprogram β-cell identity, calcium handling, and antigen presentation, but demand carriers that condense, shield, and release cargo into the cytosol with minimal innate immune activation[22].

A rigorous framework for β-cell–targeted nanotherapy must therefore integrate disease biology, material science, and pharmacokinetics–pharmacodynamics. It must define how lipid composition, particle size, and ligand density translate into islet biodistribution and intracellular routing; how payload choice maps to measurable restoration of glucose-stimulated insulin secretion; and how manufacturing and quality attributes govern clinical performance[23–26]. It must also address safety in the specific context of obesity and diabetes, where repeated dosing may provoke accelerated clearance, and where subclinical steatohepatitis or kidney dysfunction can shift exposure and risk. In the sections that follow, we examine the rationale for β-cell targeting, the principal lipid nanocarrier classes and their engineering levers, targeting ligands and strategies suited to islet biology, payload options and their mechanistic readouts, evidence from obese diabetic models, and the translational path from bench to first-in-human evaluation[24].

Finally, we consider how β-cell–directed lipid systems can be situated within combination regimens. Because insulin resistance in the liver and muscle remains a dominant driver of hyperglycemia, nanocarriers that protect β-cells may best be paired with agents that relieve peripheral resistance. By aligning β-cell–specific restoration with systemic insulin sensitization, it may be possible to reduce β-cell secretory stress, lower glycemic variability, and achieve durable control with less reliance on high-dose incretin therapy or exogenous insulin[27]. The promise of lipid nanocarriers lies not only in their capacity to reach β-cells, but in their ability to make β-cell–centered strategies practical, precise, and safe.

2. Biological Rationale for β-Cell Targeting in Obesity-Associated Diabetes

The β-cell is uniquely positioned as both the sensor and responder in glucose homeostasis. Its hallmark is the tight coupling of nutrient metabolism to electrical activity and insulin granule exocytosis, mediated by mitochondrial ATP generation, closure of ATP-sensitive potassium channels, calcium influx through voltage-gated channels, and a downstream exocytic machinery tuned by second messengers[28]. In obesity, chronic exposure to elevated glucose and free fatty acids disrupts each step. Mitochondria accumulate damage that blunts ATP production and increases reactive oxygen species; endoplasmic reticulum protein load and calcium dysregulation trigger maladaptive unfolded protein response signaling; and inflammatory cytokines from resident macrophages and systemic sources activate NF-κB and JNK pathways that depress insulin gene transcription and promote dedifferentiation toward α-like states[29]. These stressors erode the fidelity of glucose-stimulated insulin secretion, leading to hyperglycemia that intensifies β-cell stress in a vicious cycle [30].

Directly addressing β-cell pathology promises leverage that downstream glycemic control cannot provide. Protective agents that stabilize mitochondrial membrane potential, scavenge reactive oxygen species, or tune unfolded protein response arms can restore stimulus–secretion coupling. Transcriptional programs governed

by factors such as PDX1, MAFA, and NKX6.1 can be reinforced to maintain identity, while epigenetic regulators can be modulated to prevent lineage drift[31]. Modest enhancements in β-cell survival and function yield outsized clinical benefits because insulin secretion has a nonlinear relationship with glycemic control; small gains in first-phase secretion dampen postprandial excursions and lower glucotoxicity throughout the day[31].
The challenge lies in delivering such modulators selectively to β-cells within a pancreas dominated by exocrine tissue and in a body where many β-cell receptors are shared with the cardiovascular and central nervous systems. Lipid-based nanocarriers provide tools to resolve this selectivity problem. Islet capillaries are fenestrated and highly perfused, allowing nanoparticles in the 70–120 nm range to access perivascular spaces more readily than in other tissues[32, 33]. β-cells display a set of surface proteins suitable for targeting, including GLP-1 receptors, sulfonylurea receptor subunits of K_ATP channels, and gangliosides that differ from neighboring α and δ cells[34]. The islet microenvironment is enriched in zinc ions co-stored and co-released with insulin, and this local chemistry can be harnessed by carriers that present chelating motifs to increase residency within β-cell–dense niches[34]. Endothelial cells in islets express unique markers and adhesion molecules, particularly under metabolic stress, offering an indirect route where carriers first bind endothelium and then transit to β-cells via transcytosis.
Obesity modulates these features in ways that must be anticipated by design. Inflammatory activation of islet endothelium can increase permeability and receptor availability but also expose complement and coagulation factors that promote nanoparticle opsonization[35, 36]. Resident macrophages may sequester carriers unless surfaces are engineered to present self-like signals or zwitterionic headgroups that resist protein adsorption. Systemic changes in lipoprotein composition alter the protein corona around lipid nanoparticles, which can either facilitate or hinder β-cell targeting depending on the recruited apolipoproteins. Consequently, a successful β-cell–targeted lipid carrier balances passive hemodynamic access, active ligand-mediated recognition, corona management, and stealth against the heightened reticuloendothelial scavenging characteristic of obesity[37].
The rationale extends to therapeutic timing. Early in diabetes progression, preserving first-phase insulin secretion prevents postprandial spikes that drive cumulative glucotoxicity, making β-cell–targeted antioxidants, calcium-handling modulators, or incretin-pathway sensitizers valuable. Later, when dedifferentiation and senescence predominate, nucleic acid–based reprogramming tools may be needed to restore identity and proliferative capacity within safe bounds[37]. Lipid carriers can stage these interventions over time, altering ligands and payloads as the disease state evolves, and thus sustain β-cell competence as peripheral insulin resistance is addressed by complementary therapies.

3. Lipid Nanocarrier Classes and Engineering Levers for β-Cell Delivery

Liposomes are the most established lipid nanocarriers and consist of phospholipid bilayers enclosing an aqueous core. For β-cell applications, their membranes can embed hydrophobic small molecules that stabilize mitochondria or reduce endoplasmic reticulum stress, while the aqueous core carries peptides or nucleic acids[14, 16, 18]. Cholesterol modulates membrane rigidity and leakage, and incorporation of phosphatidylserine or sphingomyelin tunes membrane order and fusion behavior. PEGylation extends circulation and reduces opsonization, but excessive PEG density can hinder receptor engagement at the islet; thus, short PEG chains or cleavable PEG linkers are often favored[38]. Thermo- and pH-responsive lipids permit triggered release in endosomal compartments after β-cell uptake, enhancing cytosolic delivery without relying on high membrane-disruptive content that could injure cells.
Solid lipid nanoparticles and nanostructured lipid carriers replace fluid bilayers with solid matrices composed of triglycerides or waxes (SLN) or with mixed solid–liquid lipids (NLC)[39–41]. These platforms suit hydrophobic β-cell protectants like curcuminoids or thiazolidinedione-inspired antioxidants that benefit from sustained intracellular release. NLC outperforms SLN in loading capacity and burst-release control because liquid lipids introduce structural imperfections that accommodate higher drug payloads. Surface functionalization with peptides is straightforward via maleimide–thiol chemistry on lipid anchors, and the solid matrix provides physical stability during storage and gastrointestinal transit for oral or intraduodenal dosing aimed at hepato-pancreatic portal delivery[42, 43].
Ionizable lipid nanoparticles are optimized for nucleic acid delivery. At neutral pH they are relatively uncharged and stealthy, but in endosomes, they become protonated, destabilizing membranes and promoting cargo escape[40, 43]. For β-cells, such carriers enable siRNA or antisense suppression of stress mediators, mRNA expression of protective factors, or base editing of loci that regulate calcium handling or identity. Fine control of the ionizable lipid pK_a ensures activity in endosomal pH while minimizing extracellular membrane disruption. Helper lipids, including DSPC and cholesterol, and PEG–lipids with tuned desorption kinetics, shape particle stability and in vivo behavior[41, 44]. The same scaffolds can co-load small molecules to provide immediate functional support while nucleic acids enact longer-term reprogramming.
Lipid–polymer hybrid nanoparticles combine the fusogenic properties of lipid shells with the structural integrity of polymeric cores such as PLGA. This architecture compartmentalizes cargo, allowing hydrophilic peptides or nucleic acids near the surface for rapid access and hydrophobic small molecules in the core for sustained release[45]. The lipid shell improves interaction with β-cell membranes and simplifies ligand presentation, while the polymer core controls kinetics and enhances storage stability. Across all classes, critical engineering

levers include mean size in the 70–120 nm range to exploit islet capillary features, low polydispersity to ensure predictable biodistribution, near-neutral zeta potential to balance mucus compatibility and cellular association, and controlled ligand density to maximize avidity without provoking off-target binding[23, 24].

Protein corona management is increasingly recognized as a determinant of targeting success. Lipid composition influences which plasma proteins adsorb; intentional recruitment of specific apolipoproteins can direct particles to receptors present on β-cells or islet endothelium[46]. Conversely, presenting zwitterionic headgroups or CD47-mimetic peptides reduces nonspecific opsonization and macrophage capture. Process analytics, dynamic light scattering, nanoparticle tracking analysis, cryo-electron microscopy, and lipidomics tie these design choices to stable manufacturing[47]. For chronic metabolic indications, excipient selection favors pharmacopeial lipids and biodegradable polymers with documented safety, and assembly methods such as microfluidic mixing provide scalable, reproducible control of size and composition suited to good manufacturing practice constraints.

4. Targeting β-Cells: Ligands, Tropism Cues, and Transislet Transport

Active targeting complements passive hemodynamic access by engaging receptors enriched at β-cells or within their microenvironment. Peptides derived from or mimicking GLP-1 bind the GLP-1 receptor present on β-cells and facilitate receptor-mediated endocytosis[48]. Short GLP-1 fragments or stabilized analogs attached via flexible linkers preserve signaling while improving uptake, and biased agonists can be selected to avoid excessive cAMP signaling that might desensitize pathways. Sulfonylurea receptor–recognizing motifs offer another route, although care is needed to avoid unintended K_ATP channel modulation; non-activating binding peptides that leverage SUR1 for uptake but lack channel gating have been engineered for this purpose[48].

Ganglioside- and glycan-binding ligands exploit differences in membrane composition between β-cells and neighboring endocrine cells. Lectin-inspired peptides that recognize β-cell–enriched glycosylation patterns can provide selectivity, and synthetic aptamers identified by cell-SELEX discriminate β-cells based on complex surface signatures without relying on a single receptor[49]. Coordination chemistry provides an orthogonal strategy: zinc ions co-released with insulin create a transiently zinc-rich perivascular niche. Ligands presenting histidine-rich or other chelating motifs increase dwell time in these zones, raising the chance of β-cell encounter. Similarly, exploiting manganese-enhanced environments associated with glucose-stimulated activity has been proposed, with manganese-binding lipids or peptides modulating local affinity[49].

Islet endothelium offers a gateway. Under metabolic stress, endothelial cells upregulate adhesion molecules and unique receptors that can be addressed by targeting ligands to achieve transcytosis[50]. Once across the endothelial layer, local concentration near β-cells increases, making even moderate β-cell selectivity sufficient to yield meaningful uptake. Matrix-binding peptides that interact with perivascular extracellular matrix components can further prolong residency, acting as depots that release carriers in proximity to β-cells over time. Combining endothelial and β-cell ligands on the same carrier, or staging them on separate carriers administered sequentially, can compound selectivity without saturating a single receptor pathway[50].

Ligand density and spatial presentation matter. Multivalency increases avidity but risks engaging off-target tissues that share low-level receptor expression; too sparse a presentation yields insufficient binding under physiological shear[51]. Cleavable linkers that shed ligands after endocytosis minimize intracellular burden and potential signaling perturbation. Corona-aware design acknowledges that serum proteins may mask ligands; positioning ligands on PEG spacers of optimized length, using zwitterionic backbones, or preconditioning the corona with selected proteins preserves accessibility. Ultimately, successful β-cell targeting emerges from layered design: islet-directed endothelial engagement, perivascular niche anchoring, β-cell receptor binding, and intracellular routing cues working in concert to raise productive uptake relative to other tissues[51].

5. Therapeutic Payloads: Small Molecules, Biologics, and Genetic Modulators

Restoring β-cell function requires payloads that operate across organelles and pathways stressed by glucolipotoxicity. Small molecules that stabilize mitochondria, such as mild uncouplers or electron transport chain modulators at sub-toxic exposures, reduce reactive oxygen species and restore ATP dynamics necessary for K_ATP channel closure[52]. Lipid-encapsulated antioxidants and redox cycling agents can be dosed at lower concentrations when concentrated in islets, decreasing systemic risk. Endoplasmic reticulum stress modulators that tune PERK and IRE1 signaling preserve protein folding capacity without inducing apoptosis; encapsulation prevents off-target effects in the liver or the brain[52]. Calcium-handling agents that correct oscillatory defects can be delivered in pulses aligned with feeding windows using carriers engineered for rapid on–off release.

Peptides and proteins expand options. Incretin mimetics and co-agonists that support β-cell survival and insulin biosynthesis can be packaged to avoid gastrointestinal degradation and pulse-delivered to minimize nausea[53]. Antiapoptotic proteins, chaperones, and factors that reinforce identity, such as analogs that upregulate PDX1 or MAFA, require cytosolic access, achievable with fusogenic lipids or ionizable formulations that promote endosomal escape. Enzyme replacement or decoy receptors that neutralize local cytokines within islets provide microenvironmental relief without systemic immunosuppression[53].

Nucleic acids allow precise reprogramming. siRNA and antisense oligonucleotides can silence stress mediators or negative regulators of insulin gene transcription, while microRNA mimics restore networks that maintain β-

cell phenotype[54]. mRNA therapies express protective proteins transiently, avoiding genomic integration while offering rapid reversibility. CRISPR base editors and epigenome editors provide durable tweaks to transcriptional control regions of identity genes or to channels that coordinate stimulus–secretion coupling. For these cargos, ionizable lipid nanoparticles are preferred, with helper lipids and optimized pK_a ensuring efficient endosomal escape in β-cells[54]. Co-loading strategies deliver immediate functional support via small molecules while nucleic acids enact longer-lived remodeling, producing additive or synergistic gains in glucose-stimulated insulin secretion.

Dosing paradigms should reflect the mechanism. Agents that influence transcription and organelle biogenesis may benefit from steady, low-level exposure, achievable with sustained-release NLC or depot injections of liposomal formulations[55]. Acutely acting modulators of ion channels or calcium flux require rapid, transient delivery aligned to meals. Chronotherapeutic scheduling acknowledges circadian regulation of β-cell responsiveness, potentially improving efficacy without increasing dose. Across modalities, potency assays must connect delivery to β-cell–specific readouts: first- and second-phase insulin secretion profiles, mitochondrial membrane potential dynamics, calcium oscillation fidelity, unfolded protein response markers, and identity transcription factor levels[55]. These metrics, measured in isolated islets and in vivo via minimally invasive biomarkers, anchor dose selection and enable mechanism-based go/no-go decisions.

6. Evidence from Obese and Diabetic Models: Biodistribution, Efficacy, and Mechanism

Preclinical studies in diet-induced obesity and genetic insulin resistance have established the feasibility and value of β-cell–targeted lipid carriers. Biodistribution analyses using radiolabels, near-infrared dyes, or lipid mass spectrometry show increased pancreatic and intrainsular signal for ligand-decorated liposomes and ionizable lipid nanoparticles compared with non-targeted counterparts, with improved islet-to-exocrine ratios when corona-aware designs are used[23, 24]. Transendothelial accumulation is enhanced by endothelial ligands, while zinc- or matrix-anchoring features prolong perivascular residence, increasing the probability of β-cell engagement. Importantly, in obese animals with heightened reticuloendothelial clearance, zwitterionic or low-density PEG coatings maintain circulation long enough to realize targeting benefits without provoking complement activation[24].

Functionally, β-cell–directed carriers improve glucose tolerance and insulin secretion at lower total drug load. Liposomal antioxidants or ER stress modulators localize to islets, reducing CHOP and XBP1s markers and restoring first-phase insulin secretion in hyperglycemic clamps[56]. Ionizable lipid nanoparticles delivering siRNA to stress kinases or microRNA mimics that reinforce identity genes increase insulin content and granule docking, correlating with enhanced stimulus–secretion coupling. Co-loaded systems that pair small molecules with nucleic acids produce broader effects, combining rapid restoration of calcium oscillations with longer-term transcriptional stabilization. These gains typically translate into reduced fasting glucose, improved oral glucose tolerance, and lower glycemic variability without weight gain or hypoglycemia, especially when paired with interventions that reduce peripheral insulin resistance[56].

Mechanistic dissection reveals multi-level benefits. Mitochondrial function improves, reflected by increased ATP/ADP ratios and normalized NAD(P)H responses to glucose. Calcium imaging demonstrates restored oscillatory patterns that align with granule exocytosis. At the transcriptional level, PDX1 and MAFA protein levels recover, while dedifferentiation markers decline[57]. Islet macrophage profiles shift toward reparative phenotypes when local cytokine loads are reduced by targeted decoy receptors or anti-inflammatory payloads, illustrating that β-cell–centric delivery can secondarily remodel the islet niche[58]. Pharmacokinetic–pharmacodynamic modeling links intrapancreatic exposure to these functional readouts, enabling dose scaling and prediction of durability after dosing cessation.

Comparisons with non-targeted formulations or free drugs underscore the value of β-cell targeting. Equivalent systemic exposures produce inferior islet outcomes without targeting, and higher doses needed to match efficacy elevate off-target risks in liver and heart. In head-to-head regimens with standard incretin therapies, β-cell–targeted nanocarriers allow lower incretin doses while preserving glycemic benefits and reducing gastrointestinal adverse effects. Some studies document sustained improvements after washout, consistent with partial network reprogramming rather than transient pharmacology[58]. Together, these results make a compelling case for advancing β-cell–targeted lipid carriers toward human evaluation, provided that safety and manufacturability hurdles are addressed.

7. Safety, Manufacturability, and the Path to Translation

Chronic metabolic indications demand a conservative safety profile. Lipid nanocarriers must avoid complement activation–related pseudoallergy, minimize immunogenicity from PEG or cationic components, and prevent accumulation in reticuloendothelial organs over repeated dosing[59]. Selecting pharmacopeial phospholipids, cholesterol, and biodegradable polymers, employing zwitterionic headgroups, and controlling PEG chain length and density mitigate innate immune activation. Ionizable lipids require careful pK_a tuning to balance endosomal escape with extracellular safety, and degradable ionizable chemistries reduce long-term tissue burden[59]. Endotoxin control, residual solvent limits, and sterility assurance are non-negotiable in assembly workflows.

Manufacturability hinges on scalable, reproducible processes with tight process analytical control. Microfluidic mixing provides narrow polydispersity and consistent encapsulation for liposomes and ionizable lipid nanoparticles, while high-pressure homogenization suits solid lipid systems. Spray- or freeze-drying yields stable intermediates for oral or parenteral reconstitution[60]. Critical quality attributes such as mean size and distribution, zeta potential, lipid composition, ligand density, encapsulation efficiency, release kinetics, residual solvent and endotoxin levels, and sterility must be tied to potency assays relevant to β-cells, such as restoration of glucose-stimulated insulin secretion in human islets and suppression of unfolded protein response markers[60]. Corona profiling under physiologic protein conditions becomes part of release characterization when targeting depends on ligand accessibility in vivo.

Regulatory strategy benefits from precedents in lipid nanoparticle vaccines and gene therapies, but β-cell targeting adds organ-specific considerations[61, 62]. Biodistribution studies should quantify intrapancreatic and intrainsular accumulation in obese, dyslipidemic animals, with repeated dosing to probe accelerated clearance phenomena. Safety pharmacology must include cardiac conduction and vascular tone assessments when ligands or cargos could interact with shared receptors[23, 26]. First-in-human trials will likely start with hepatosafe small molecules or RNA cargos with clear pharmacodynamic biomarkers such as meal-stimulated C-peptide profiles, mixed-meal tolerance tests, and continuous glucose monitoring variability before advancing to gene editors. Patient selection should focus on individuals with preserved β-cell reserve but high glycemic variability, where β-cell restoration can be detected sensitively and translated into clinical benefit.

CONCLUSION

Integration with standard-of-care therapies is pragmatic. Combining β-cell–targeted nanocarriers with insulin sensitizers or low-dose incretin agonists aligns mechanisms and may permit de-escalation of systemic drugs that drive adverse events. Real-world deployment will depend on convenient dosing formats, preferably infrequent subcutaneous injections or oral systems that achieve pancreatic exposure through portal routes. Digital monitoring of glycemic patterns can guide adaptive dosing and chronotherapy, reflecting circadian variation in β-cell responsiveness. If safety, manufacturing, and regulatory alignment converge, lipid-based β-cell–targeted delivery could shift diabetes management from reactive glucose control to proactive preservation of the insulin-secreting apparatus, making durable remission a realistic objective rather than an exception.

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