REVIEW Pharmacology

Current diabetes drugs: Lessons learned and implications for next-generation therapeutics

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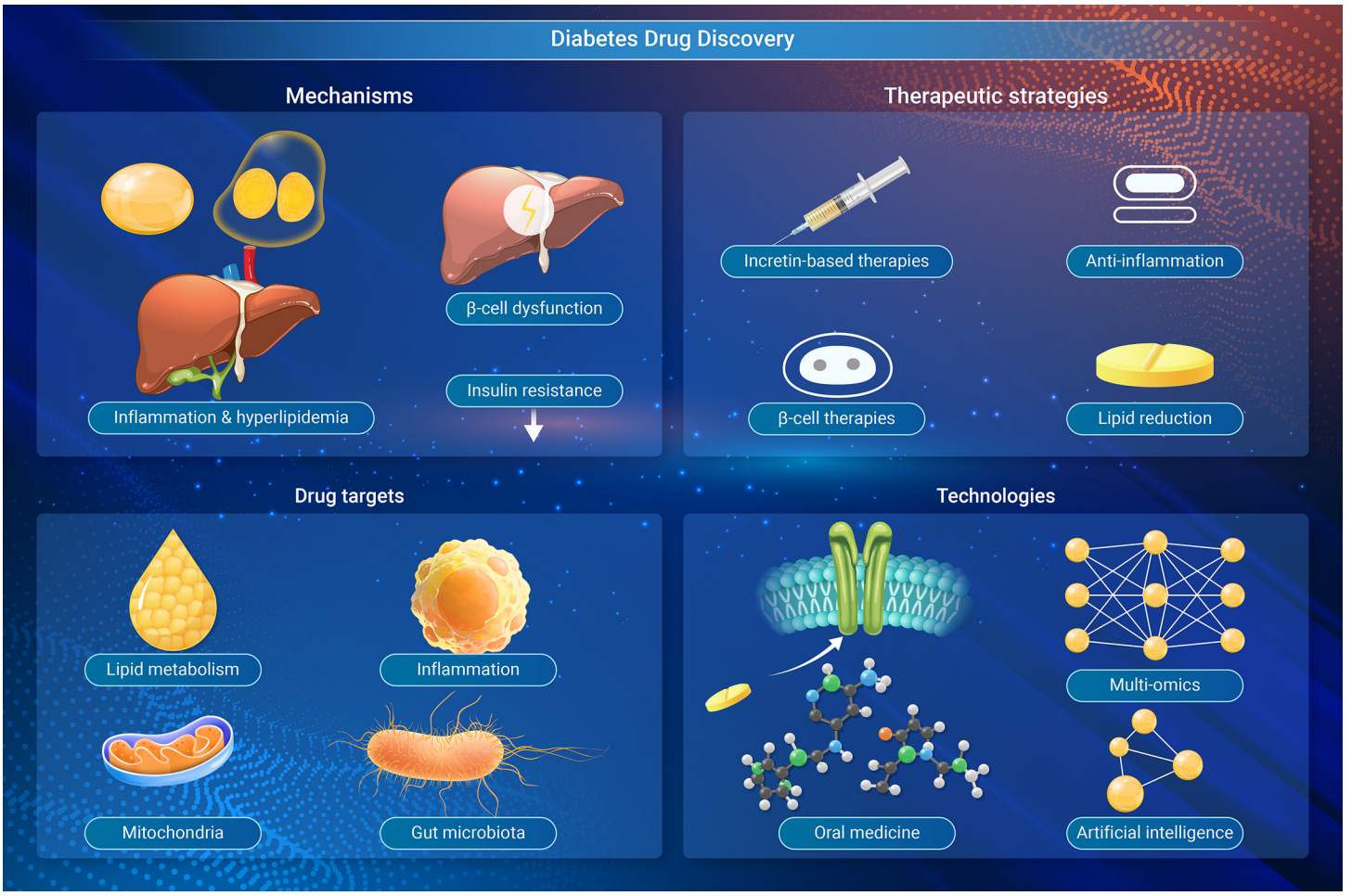
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Insulin resistance and β-cell failure remain central therapeutic targets.
- Incretin multi-agonists deliver unprecedented metabolic and weight-loss efficacy.
- Lipid-metabolism and inflammation pathways offer emerging druggable nodes.
- β-cell regeneration strategies show promise for disease-modifying therapy.
- AI and multi-omics accelerate target discovery and molecular design.

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Pharmacology REVIEW

The Innovation Drug Discovery

Current diabetes drugs: Lessons learned and implications for next-generation therapeutics

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Diabetes mellitus represents one of the most significant and costly health burdens worldwide. Despite major therapeutic advances over the past three decades, substantial unmet needs remain in glycemic durability, β-cell preservation, weight management, metabolic inflammation, lipotoxicity, and long-term cardiovascular and renal protection. This review synthesizes the molecular basis of diabetes pathogenesis, summarizes therapeutic evolution across drug classes, and highlights emerging technologies accelerating target discovery and translational development. Particular emphasis is placed on incretin-based multi-agonists, metabolic-inflammation modulators, β-cell therapeutics, and machine-learning–enabled discovery platforms. More importantly, a new "metabolism-immune-neuroendocrine" integrated therapy framework is proposed for future diabetes intervention. Together, these innovations are reshaping the landscape for the next generation of diabetes therapeutics.

INTRODUCTION

Global epidemiology of T1D and T2D

Diabetes mellitus represents one of the most rapidly expanding global health challenges, with profound implications for drug discovery, healthcare systems, and long-term population health. According to estimates from the International Diabetes Federation (IDF), more than 530 million adults worldwide are currently living with diabetes, a number projected to exceed 853 million by 2050 (Figure 1A).[1,2] This growth is driven overwhelmingly by type 2 diabetes (T2D), which accounts for approximately 90–95% of all cases, whereas type 1 diabetes (T1D) represents ~5–10% of the global burden.[3,4]

Type 1 diabetes is characterized by marked geographic heterogeneity, with the highest incidence observed in Northern Europe, North America, and Australia, and substantially lower rates in East Asia and sub-Saharan Africa.[5,6] Although traditionally considered a childhood-onset disease, adult-onset T1D is increasingly recognized, complicating epidemiological classification and therapeutic stratification.[7] In contrast, type 2 diabetes constitutes the dominant global diabetes burden and is tightly linked to obesity, physical inactivity, population aging, and urbanization.[3,4,8] Notably, more than 75% of individuals with diabetes now reside in low- and middle-income countries, shifting the epicenter of disease burden toward regions with limited healthcare infrastructure.[3,9,10]

A particularly concerning epidemiological trend is the progressive decline in age at diagnosis of T2D, with rising incidence among adolescents and young adults worldwide.[3,11] Early-onset T2D is associated with more aggressive disease progression and earlier development of complications. These epidemiological patterns have profound implications for diabetes drug discovery, emphasizing the need for scalable, durable, and metabolically protective therapies.

Key limitations of current diabetes therapies and implications for future drug discovery

Over the past two decades, the therapeutic landscape for diabetes mellitus has expanded substantially, evolving from a glucose-centric paradigm to a multidimensional strategy that prioritizes organ protection, weight management, and long-term risk reduction(Table S1).[3,4] Although several drug classes—metformin, sulfonylureas, TZDs, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists—have transformed disease management, most patients still progress to complications along the trime, including cardiovascular disease, kidney failure, neuropathy, and advanced liver disease. Therefore, diabetes remains a progressive disease for many patients, highlighting persistent unmet needs that continue to drive drug discovery and innovation.

Type 1 diabetes (T1D) is an autoimmune disease defined by near-complete insulin deficiency. Exogenous insulin replacement remains the cornerstone of therapy and is essential for survival. Advances in insulin analogues, continuous glucose monitoring, and automated insulin delivery systems have markedly improved glycemic control and reduced hypoglycemia risk.[12,13]

Beyond insulin and technology, immunomodulatory strategies have recently entered clinical practice. Teplizumab, an anti-CD3 monoclonal antibody, is approved to delay progression from presymptomatic to clinical T1D, thereby establishing proof of concept for disease interception.[14] However, these approaches currently delay rather than prevent disease onset and are limited to a screened population. Cell replacement strategies, including islet or pancreas transplantation, are reserved for highly selected patients with severe hypoglycemia unawareness due to limitations in donor availability, the need for lifelong immunosuppression, and scalability concerns.[15]

Type 2 diabetes (T2D) accounts for approximately 90–95% of all diabetes cases worldwide and is characterized by insulin resistance and progressive β-cell dysfunction[3]. Current pharmacotherapy targeting several organs responsible for glucose homeostasis increasingly considers comorbidities such as atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, and obesity (Figure 1B). Metformin remains widely used for its long-standing safety record, low cost, and modest glycemic efficacy. Contemporary treatment guidelines increasingly recommend early use of sodium–glucose cotransporter 2 (SGLT2) inhibitors and/or glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with cardiorenal risk, regardless of baseline glycated hemoglobin levels.[16,17] SGLT2 inhibitors have demonstrated robust reductions in hospitalization for heart failure and slowed progression of chronic kidney disease, positioning them as foundational therapies in high-risk T2D populations.[16,18] GLP-1RAs, and more recently dual incretin agonists targeting both GIP and GLP-1 receptors, provide potent glucose-lowering, clinically meaningful weight loss, and cardiovascular benefit in selected populations.[19,20] Additional agents, including thiazolidinediones, sulfonylureas, and insulin therapy, continue to play important roles in specific clinical contexts, particularly in advanced disease stages or when cost and access limit the use of newer therapies.[3]

Despite substantial therapeutic progress, several limitations persist across both T1D and T2D treatments. First, most available therapies address downstream metabolic consequences rather than the underlying disease process, resulting in limited long-term disease modification and continued β-cell decline.[3,21] Second, treatment adherence and persistence are challenged by gastrointestinal adverse effects, hypoglycemia risk, injection burden, and increasing regimen complexity. These factors substantially reduce real-world effectiveness compared with clinical trial efficacy.[19] Third, safety considerations become increasingly important at the population scale. Rare but serious adverse events, including severe hypoglycemia, diabetic ketoacidosis in

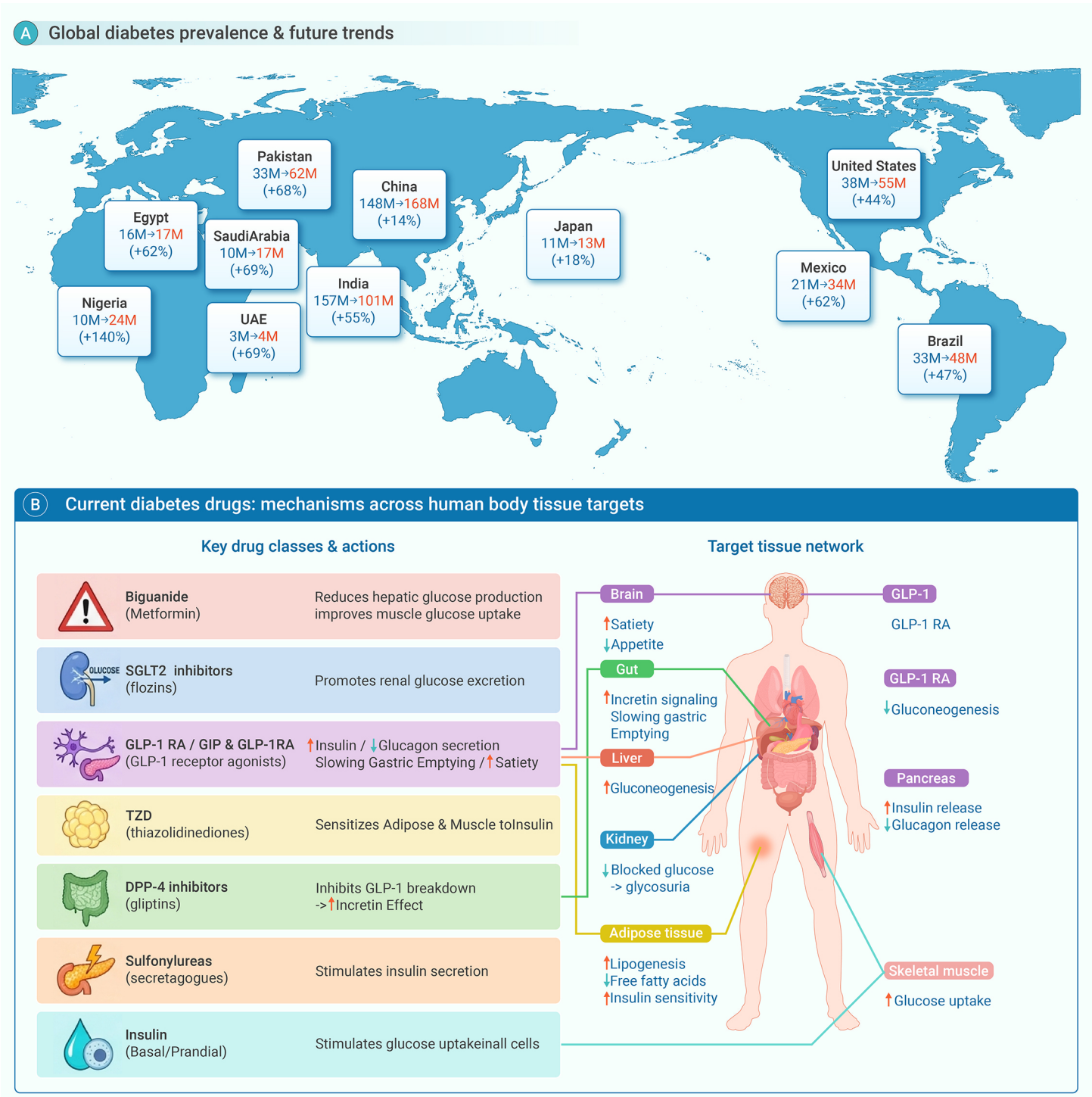

Figure 1. Global diabetes epidemiology of T1D and T2D with a significant trend of incidence in younger age (A) Global distribution and projected growth of diabetes prevalence based on the International Diabetes Federation (IDF) Diabetes Atlas 2025. The world map illustrates country-level diabetes burden in adults aged 20–79 years, with color gradients indicating increasing prevalence. Key country callouts highlight major contributors to the global epidemic, including China, India, the United States, and rapidly growing populations in South and Southeast Asia, Latin America and sub-Saharan Africa. Globally, diabetes affects 589 million adults in 2024, projected to rise to ~853 million by 2050 (+45%, +264 million cases). Several countries—including Pakistan, Nigeria, Bangladesh, and Indonesia—shows disproportionately high relative increases, reflecting the accelerating burden in low- and middle-income settings. The inset panels summarize global trends, growth drivers, and burden-versus-growth relationships. These data underscore a geographic shift of diabetes burden toward emerging economies. (B) Current major diabetes drugs: mechanisms across human tissue targets. Major classes of glucose-lowering therapies act through coordinated effects across multiple organs that regulate systemic glucose homeostasis. Biguanides (metformin) primarily suppress hepatic gluconeogenesis and enhance peripheral glucose uptake. Sodium–glucose cotransporter 2 (SGLT2) inhibitors promote renal glucose excretion, thereby reducing plasma glucose levels independently of insulin. Incretin-based therapies, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual GIP/GLP-1 agonists, enhance insulin secretion, suppress glucagon release, delay gastric emptying, and increase satiety via central and gut-mediated mechanisms. Dipeptidyl peptidase-4 (DPP-4) inhibitors prolong endogenous incretin activity. Thiazolidinediones (TZDs) improve insulin sensitivity in adipose tissue and skeletal muscle. Sulfonylureas stimulate pancreatic insulin secretion, whereas exogenous insulin promotes systemic glucose uptake. Together, these therapies target an integrated brain–gut–pancreas–liver–kidney–muscle–adipose network to restore glycemic control.

susceptible contexts, and volume depletion, influence prescribing decisions and patient outcomes.[16-18] Fourth, access and equity remain major barriers. High costs, supply constraints, and limited availability of injectable therapies and diabetes technologies disproportionately affect patients in low- and

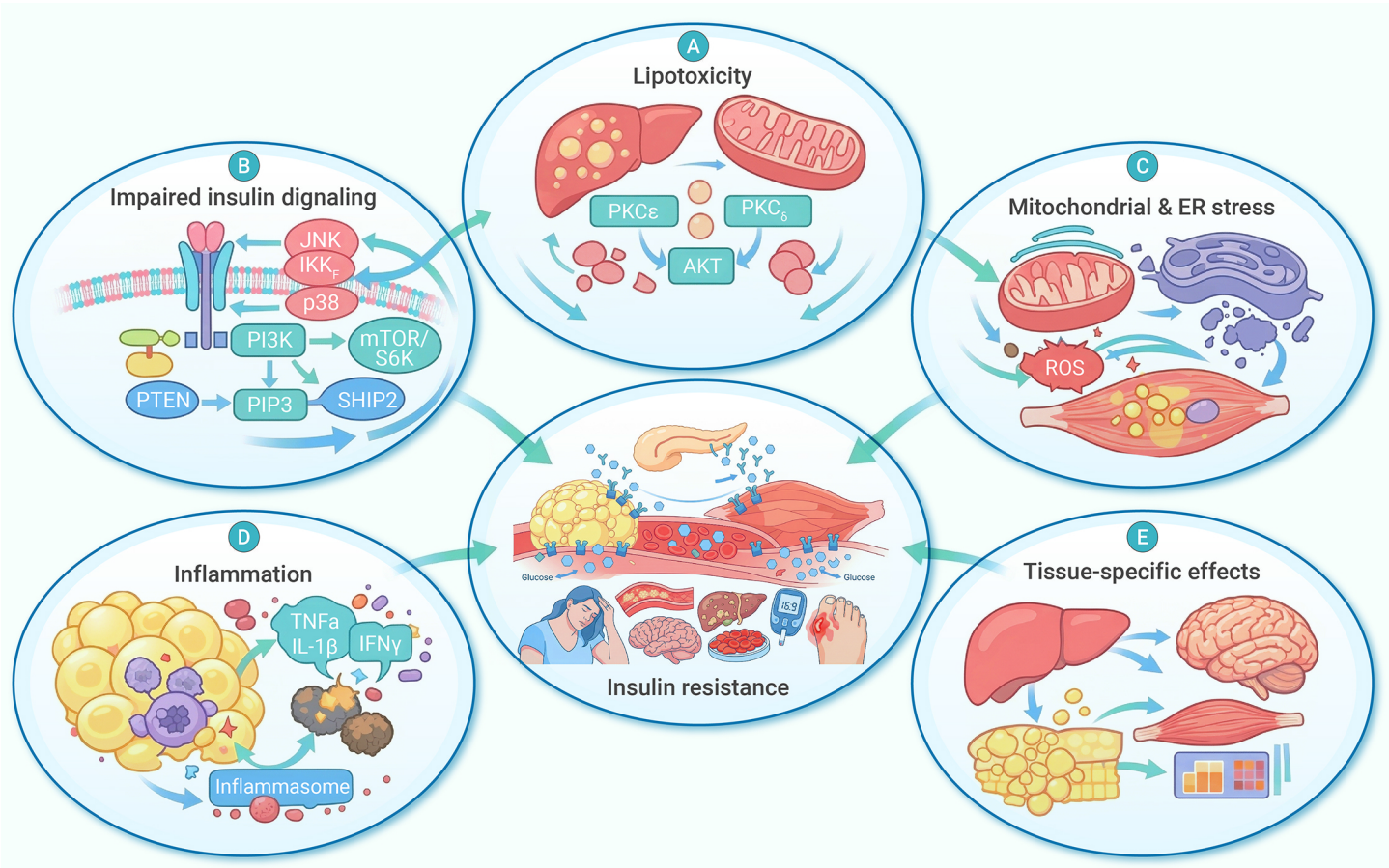

Figure 2. Integrated mechanisms underlying insulin resistance Insulin resistance arises from the convergence of lipid overload, inflammatory signaling, and organelle stress, which impair insulin receptor–IRS–PI3K–AKT signaling in metabolic tissues. Excessive nutrient supply promotes the accumulation of bioactive lipid intermediates, including diacylglycerols and ceramides, which inhibit insulin signaling by activating protein kinase C isoforms and suppressing AKT activity. Mitochondrial and endoplasmic reticulum stress amplify stress kinase signaling and inflammatory responses. Dysfunctional adipose tissue expansion limits lipid storage capacity, driving ectopic lipid deposition in the liver and skeletal muscle. Chronic inflammatory signals, such as TNF-α, IFN-γ, and IL-1β, cause insulin resistance. These processes culminate in tissue-specific insulin resistance, characterized by impaired suppression of hepatic gluconeogenesis, reduced skeletal muscle glucose uptake, and dysregulated central control of energy balance.

middle-income countries and underserved populations.[3,21] Finally, diabetes is a heterogeneous disease. Early-onset T2D, aging populations, and the frequent coexistence of obesity, chronic inflammation, fatty liver disease, cardiovascular disease, and chronic kidney disease underscore the need for stratified, combination-based, and disease-modifying therapeutic approaches.[20]

Together, these limitations highlight the need for next-generation diabetes therapeutics that go beyond glucose-lowering to deliver durable disease modification, preserve or restore β-cell function, modify disease-causing factors, and provide scalable solutions compatible with global healthcare systems. Drug discovery increasingly focuses on multi-pathway modulation, precision medicine, and disease-modifying mechanisms that slow or halt β-cell decline. Integrating metabolic, cardiovascular, renal, and immunological targets will be central to the next phase of diabetes drug discovery.[3,20,21]

Rationale for new drug discovery for diabetes treatment in the next decades

Despite major advances in glucose-lowering therapies, diabetes remains a progressive, heterogeneous, and multisystem disease that continues to impose a substantial global health burden.[1,2] Current treatments primarily mitigate downstream hyperglycemia rather than addressing upstream drivers of disease initiation and progression. Five interrelated biological processes—β-cell failure, insulin resistance, chronic inflammation, obesity, and dyslipidemia, as well as energy expenditure, form the core rationale for continued innovation in diabetes drug discovery.[22]

Progressive pancreatic β-cell dysfunction and loss represent the final common pathway in both type 1 diabetes (T1D) and type 2 diabetes (T2D).[23,24] In T2D, insulin resistance initially induces compensatory hyperinsulinemia, but chronic glucolipotoxicity stress leads to β-cell exhaustion, dedifferentiation, and apoptosis.[25,26] In T1D, autoimmune destruction causes near-complete β-cell loss.[27] Most current therapies do not preserve or restore β-cell mass or identity, underscoring the need for β-cell–protective and β-cell–restorative strategies.[25,28]

Insulin resistance, a systemic and tissue-specific disorder affecting the liver, skeletal muscle, adipose tissue, and brain, is the primary phenotype of T2D (Table S2).[29-31] Existing insulin sensitizers are limited by safety and tolerability, and many newer agents improve glycaemia without correcting intracellular insulin signaling defects.[31,32] Tissue-selective insulin sensitization and mitochondrial optimization, therefore, remain key goals for next-generation therapies.[31,33]

Low-grade chronic inflammation links obesity, insulin resistance, β-cell failure, and vascular complications (Figure 2).[34,35] Activation of innate and adaptive immune pathways, including macrophage polarization and inflammasome signaling, impairs insulin action and β-cell survival.[36] Direct targeting of immunometabolic pathways offers a major opportunity for disease modification.[37]

Obesity is the dominant upstream driver of modern T2D and cardiometabolic disease.[38] Excess adiposity promotes insulin resistance, ectopic lipid deposition, inflammation, and β-cell stress through endocrine and immune mechanisms.[39] Although incretin-based therapies induce substantial weight loss, durability, preservation of lean mass, and normalization of adipose tissue biology remain unmet needs.[40,41]

Dyslipidemia in diabetes reflects abnormal lipid flux and the accumulation of toxic lipid intermediates, such as ceramides and diacylglycerols, in the liver, muscle, and pancreas.[42-44] These lipotoxic species directly impair insulin signaling and β-cell survival.[45] Traditional lipid-lowering therapies reduce

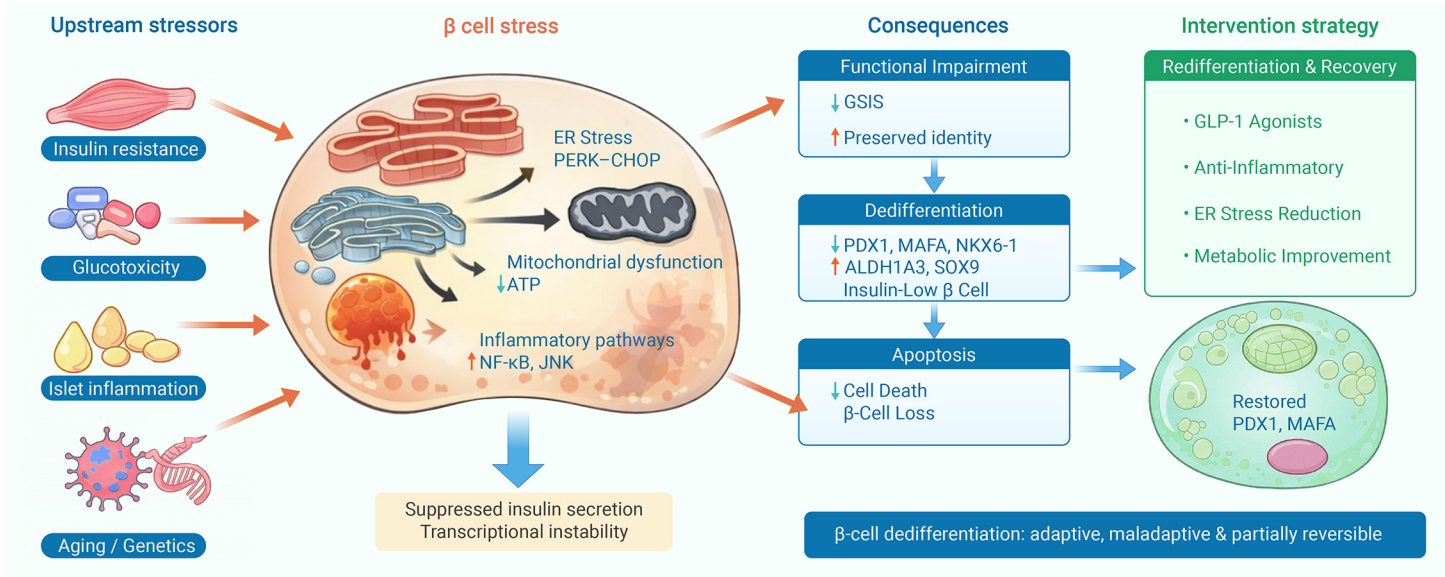

Figure 3. β-cell failure and dedifferentiationas a central mechanism in diabetes Chronic insulin resistance and metabolic stress impose sustained secretory demand on pancreatic β cells, leading to glucotoxicity, lipotoxicity, ER stress, and low-grade islet inflammation. These insults activate intracellular stress pathways including PERK–eIF2α signaling, inflammatory NF-κB/JNK pathways, and dysregulated nutrient sensing via mTORC1 and FoxO1. Rather than undergoing immediate apoptosis, a substantial fraction of β cells lose their mature identity and dedifferentiate into an insulin-low, progenitor-like state characterized by reduced expression of key β-cell transcription factors such as PDX1 and MAFA. Importantly, alleviation of metabolic and inflammatory stress can promote β-cell redifferentiation and functional recovery, highlighting β-cell identity preservation as a therapeutic target in diabetes.

cardiovascular risk but do not fully address intracellular lipotoxicity, supporting the rationale for lipid-flux–targeted therapies.[46]

These five pathogenic processes are mechanistically interconnected, and targeting a single axis rarely yields durable disease control (Figure2).[22,46,47] Future diabetes drug discovery will therefore require combination and multi-target strategies that preserve β-cell function, improve insulin sensitivity, reduce inflammation, normalize adipose biology, and correct dyslipidemia in a stage- and phenotype-specific manner.[22,48]

MOLECULAR PATHOPHYSIOLOGY DRIVING DRUG DISCOVERY

Insulin resistance mechanisms

Insulin resistance is a fundamental pathological feature of type 2 diabetes and of closely related cardiometabolic disorders, including obesity, metabolic syndrome, nonalcoholic fatty liver disease, and atherosclerosis. It is defined by a reduced ability of insulin to promote glucose uptake and utilization in target tissues despite normal or elevated circulating insulin levels. Accumulating evidence indicates that insulin resistance is not a single molecular lesion but rather a systems-level failure arising from chronic nutrient excess, lipid mispartitioning, cellular stress responses, and immune activation, all of which converge on the insulin signaling network (Figure 2 and Table S2).[31,49,50]

Canonical insulin signaling is initiated by insulin binding to the insulin receptor, which results in receptor autophosphorylation and the recruitment of IRS adaptor proteins. Tyrosine-phosphorylated IRS1 and IRS2 serve as docking platforms for PI3K, leading to the generation of PIP3 and activation of AKT, which mediates most of insulin's metabolic actions.[51] These include stimulation of glucose transport via GLUT4 translocation, activation of glycogen synthesis through inhibition of GSK3, suppression of hepatic gluconeogenesis through FOXO1 inhibition, and modulation of lipid metabolism. In insulin-resistant states, signaling is disrupted primarily at the level of IRS proteins. Inhibitory serine and threonine phosphorylation of IRS1/2 reduces their ability to undergo insulin-stimulated tyrosine phosphorylation and promotes ubiquitin-mediated degradation.[52] Stress-responsive kinases, including JNK, IKKβ, p38 MAPK, and ERK, are activated by inflammatory cytokines, oxidative stress, and nutrient excess.[35,53]

Lipotoxicity is a unifying mechanism linking nutrient excess to insulin resistance across tissues[44]. When lipid delivery exceeds storage and oxidative capacity, fatty acids accumulate ectopically. Diacylglycerols activate PKC isoforms, disrupting insulin receptor signaling in the liver and muscle.[43,54] Ceramides inhibit AKT through PP2A activation or sequestration.[45,55] Acylcarnitine accumulation reflects mitochondrial substrate overload and correlates with insulin resistance.[56] Chronic low-grade inflammation is a defining feature of insulin resistance.[44] Obesity is associated with macrophage infiltration into adipose tissue.[57] Pro-inflammatory cytokines impair insulin signaling through stress kinase activation and SOCS induction.[36,58-60]

Mitochondrial abnormalities reflect impaired metabolic flexibility rather than absolute failure.[61] Excess nutrient flux increases ROS production and disrupts redox balance, activating stress kinases and impairing insulin signaling.[62] Defects in mitochondrial quality control further exacerbate lipid-induced insulin resistance. Chronic overnutrition induces ER stress and activation of the unfolded protein response.[63] IRE1α- and PERK-mediated signaling promotes inflammatory and stress kinase activation, linking nutrient overload to insulin resistance.[64]

Adipose tissue regulates systemic insulin sensitivity by storing excess lipids.[65] Dysfunctional adipose expansion characterized by hypertrophy, hypoxia, and fibrosis limits storage capacity.[66,67] Reduced adiponectin secretion diminishes AMPK activation and promotes ectopic lipid accumulation.[68] In the liver, insulin resistance impairs suppression of gluconeogenesis while lipogenic pathways remain active, promoting hyperglycemia and hypertriglyceridemia.[69,70] In skeletal muscle, insulin resistance limits glucose uptake and glycogen synthesis.[71,72] Central insulin resistance alters hypothalamic regulation of metabolism and energy balance.[73,74]

Insulin resistance emerges from a chronic mismatch between nutrient availability and tissue capacity to safely store and oxidize fuels.[75] Lipid-derived signaling, organelle stress, and immune activation converge on insulin signaling pathways, leading to maladaptive fuel partitioning and metabolic disease.[76,77]

β-cell failure and dedifferentiation

Pancreatic β-cell failure is a defining pathological feature of diabetes mellitus and represents the final common pathway leading to chronic hyperglycemia in both type 1 diabetes (T1D) and type 2 diabetes (T2D). Traditionally, β-cell failure was viewed primarily as a consequence of irreversible β-cell death. However, advances in genetic lineage tracing, single-cell transcriptomics, and human islet studies have fundamentally reshaped this paradigm, revealing that loss of β-cell identity—termed dedifferentiation—is a major, and potentially reversible, contributor to insulin deficiency (Figue 3).[23]

β-cell failure encompasses both functional impairment and reduction of β-cell mass. Early in diabetes, β cells exhibit defective glucose-stimulated insulin secretion (GSIS) despite preserved cell numbers. With disease progression, β-cell mass declines due to apoptosis, reduced proliferative

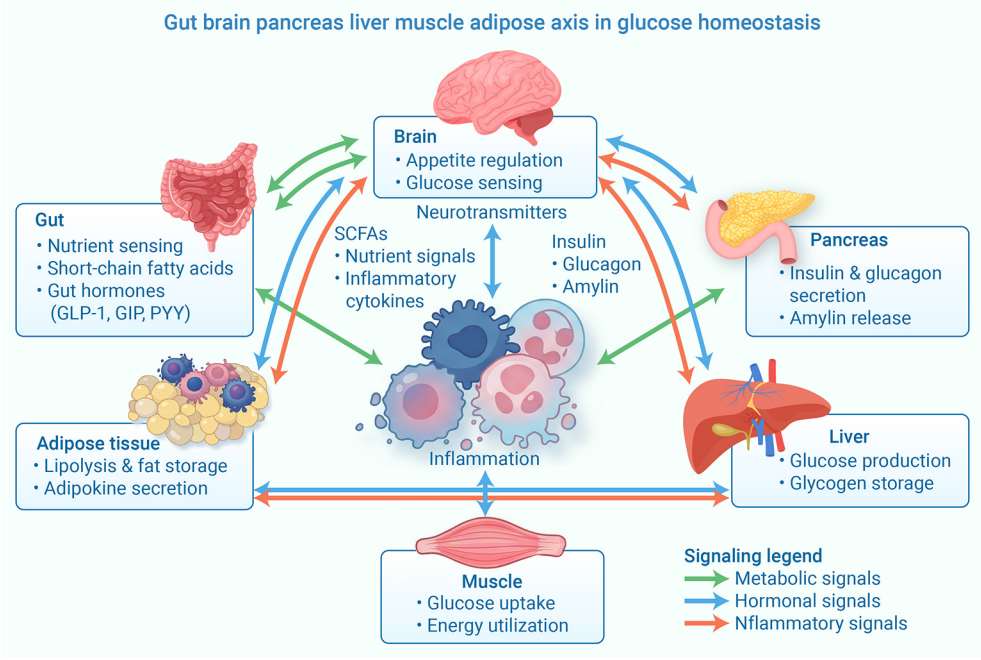

Figure 4. The Integrated gut-pancreases-liver-muscle-adipocytes-brain axis in glucose homeostasis. The integrated multi-organ network governs systemic glucose homeostasis, linking the gut, brain, pancreas, liver, skeletal muscle, and adipose tissue Nutrient sensing in the gut triggers secretion of incretin hormones (GLP-1, GIP, PYY) and microbiome-derived short-chain fatty acids (SCFAs), which modulate pancreatic hormone release and central appetite regulation. The pancreas coordinates glucose control through insulin, glucagon, and amylin, acting on the liver, muscle, and adipose tissue to regulate glucose uptake, storage, and production. The liver balances gluconeogenesis and glycogen storage, while skeletal muscle is the primary site of insulin-stimulated glucose disposal. Adipose tissue contributes via lipid buffering and adipokine secretion. Superimposed low-grade inflammation, mediated by immune cells and cytokines (TNF-α, IL-6, IL-1β), impairs insulin signaling across tissues. Neural circuits further integrate peripheral signals to maintain energy and glucose balance.

capacity, and impaired regeneration. Importantly, numerous studies indicate that a significant fraction of insulin-negative cells in diabetic islets are not lost β cells but rather dedifferentiated descendants of mature β cells.[78]

In T1D, autoimmune-mediated destruction driven by cytotoxic $CD8^+$ T cells, macrophages, and pro-inflammatory cytokines such as IL-1β, IFN-γ, and TNF-α leads to rapid β-cell apoptosis. Nonetheless, even in T1D, stressed β cells often display reduced insulin expression prior to immune-mediated elimination.[79] In T2D, chronic metabolic stress imposed by insulin resistance promotes glucotoxicity, lipotoxicity, ER stress, and islet inflammation, all of which impair β-cell function and identity.[23,80]

Dedifferentiation has emerged as a central mechanism of β-cell failure, characterized by loss of PDX1, MAFA, and NKX6-1 with re-expression of progenitor markers such as SOX9 and ALDH1A3.[26] Key regulators of β-cell identity include FoxO1, mTORC1, Notch, and Wnt/β-catenin signaling, which integrate nutrient and inflammatory cues to determine β-cell fate.[81] Importantly, β-cell dedifferentiation is partially reversible, as improved glycemic control and incretin-based therapies can restore β-cell identity and insulin secretion.[28,81]

Gut–pancreas–liver- muscle-adipocyte-brain axis and its deficiency

The gut–pancreas-liver-muscle-adipocyte-brain axis is a multidirectional hormonal and neural pathway linking gut microbiota, enteroendocrine cells (EECs), endocrine target cells, the enteric nervous system, vagal and spinal afferents, and central circuits that coordinate food intake, autonomic output, and hepatic glucose production (Figure 4).[82] EEC-derived hormones (GLP-1, GIP, PYY, CCK, etc.), pancreatic hormones (insulin, glucagon, amylin), and stomach-derived ghrelin act both endocrine and via ENS pathways to influence pancreatic islet insulin secretion, hepatic glucose production, adipose tissue, muscle cells, and central appetite circuits.[83,84] The gut microbiota adds another regulatory layer through metabolites, including bile acids, short-chain fatty acids, tryptophan derivatives, GABA, and others, which modulate nutrient sensing, incretin secretion, inflammatory responses, and liver metabolism, thereby affecting insulin sensitivity and diabetes risk.[85-88]

GLP-1 and GIP are prototypical incretin hormones released from enteroendocrine L and K cells, respectively, in response to nutrient ingestion. Both peptides potentiate glucose-dependent insulin secretion, thereby amplifying the β-cell response to oral glucose relative to intravenous glucose, an effect that underlies the classical incretin effect and links intestinal nutrient sensing to islet function and systemic glucose homeostasis.[89] GLP-1 and GIP receptors are expressed on pancreatic β cells and on multiple central nervous regions, including hypothalamic and brainstem nuclei involved in energy balance, food intake, and autonomic output, supporting a dual endocrine and neurocrine mode of action in the regulation of energy and glucose metabolism.[90,91] In type 2 diabetes, the incretin effect is markedly reduced, with blunting of GIP insulinotropic action and partial preservation of GLP-1 responsiveness. This pattern has driven preferential pharmacological targeting of GLP-1R, while recent data suggest that GIPR signaling can be at least partially restored after glycemic normalization and exploited in dual or triple agonist strategies.[92,93] Within the broader gut-brain axis, GLP-1 and GIP secreted from enteroendocrine cells act not only via classical endocrine routes but also via vagal and spinal afferents, thereby conveying real-time information about luminal nutrients to hypothalamic circuits.[94] This multi-pathway signaling explains how pharmacological GLP-1R and GIPR agonism influences appetite, nausea, reward processing, and autonomic regulation, in addition to islet function. Current research focuses on the structural and signaling determinants of GLP-1R and GIPR bias, mapping receptor expression at single-cell resolution in the pancreas and brain, and defining how dual GLP-1R/GIPR activation or selective G protein *vs* β-arrestin engagement can maximize metabolic benefits while minimizing gastrointestinal and neuropsychiatric adverse effects.[95]

Amylin, or islet amyloid polypeptide, is co-secreted with insulin from pancreatic β-cells at a relatively constant molar ratio in response to nutrient ingestion and can be considered a neuroendocrine gut-brain axis hormone due to its central actions on satiety and energy expenditure.[96,97] Physiologically, amylin complements insulin by slowing gastric emptying, suppressing postprandial glucagon secretion, and promoting satiation via receptors composed of the calcitonin receptor and receptor-activity-modifying proteins (RAMPs). Key integrative sites in the area postrema, nucleus tractus solitarius, and other hindbrain structures project to hypothalamic and mesolimbic nuclei, thereby linking peripheral nutrient status to central appetite and adiposity signaling.[98,99] Therapeutically, the non-aggregating analogue pramlintide is approved as an adjunctive treatment in insulin-treated diabetes and improves postprandial glycemia, body weight, and insulin requirements. Next-generation long-acting amylin agonists such as cagrilintide, as well as unimolecular GLP-1/amylin co-agonists exemplified by amycretin, demonstrate marked additional weight loss, improved insulin sensitivity, and beneficial effects on hepatic steatosis in preclinical and early clinical studies, positioning amylin analogues as key components of multi-hormonal "diabesity" pharmacology.[100-103]

Peptide YY (PYY), predominantly released from distal L-cells along with GLP-1 and other peptides, functions as a key anorexigenic hormone within the microbiota-gut-brain axis, coupling the degree and site of nutrient absorption and microbial fermentation to central satiety circuits. PYY, the major circulating form, acts on Y2 receptors in the arcuate nucleus and brainstem as well as on vagal afferents, where it inhibits orexigenic neuropeptide Y/agouti-related peptide neurons and facilitates anorexigenic pro-opiomelanocortin signaling, while simultaneously slowing gastric emptying and intestinal transit, thereby prolonging nutrient exposure in the distal

gut.[104-106] Obesity and type 2 diabetes are often characterized by attenuated PYY responses to meals and to colonic short-chain fatty acids, which are microbiota-derived metabolites that potently stimulate both PYY and GLP-1 secretion from L-cells. Ongoing work aims to develop PYY receptor agonists that selectively engage functionally optimal enteroendocrine subpopulations for glucoregulatory and appetite-suppressing benefit.[107-109]

Ghrelin, secreted mainly by enteroendocrine cells of the stomach, is the principal orexigenic gut hormone and provides a fasting-state counterpart to postprandial satiety hormones within the gut-brain axis. Acylated ghrelin rises before meals and falls after eating, acting via the growth hormone secretagogue receptor on hypothalamic arcuate nucleus neurons and other regions to stimulate appetite, increase food intake, and modulate reward-related aspects of feeding, while also influencing autonomic output, gastric motility, and glucose homeostasis through both central and vagal pathways.[110,111] Pharmacological modulation of ghrelin signaling has so far remained largely experimental. Instead, clinically impactful modulation is currently achieved indirectly through interventions that lower ghrelin and concurrently raise GLP-1 and PYY, including bariatric surgery and long-acting incretin or amylin agonists, which together re-set gut–brain communication in favor of reduced energy intake and improved glycemic control.[112-114]

Lipids emerging as new players in glucose homeostasis

Type 2 diabetes and related conditions such as obesity and NAFLD are now seen as diseases of a disturbed gut–microbiota–brain–liver axis. High-fat, high-sugar diets and other environmental factors alter gut microbial composition, leading to dysbiosis, increased intestinal permeability, and leakage of microbial products such as lipopolysaccharide into the portal circulation.[115] This triggers low-grade inflammation and promotes insulin resistance and contributes to β-cell stress. At the same time, dysbiosis reshapes the pool of microbiota-derived metabolites, including short-chain fatty acids (SCFAs), bile acids, and amino acid-derived compounds, which act as signaling molecules through GPCRs and nuclear receptors, central to glucose and energy homeostasis. These insights have directly informed modern diabetes drug discovery, which increasingly targets metabolite–receptor axes rather than glucose alone (Table S2).[116-118]

SCFAs, such as acetate, propionate, and butyrate, are produced by bacterial fermentation of dietary fiber. They signal through free fatty acid receptors FFAR2 (GPR43) and FFAR3 (GPR41) expressed on enteroendocrine cells, islet β-cells, adipocytes, immune cells, and peripheral neurons. In the gut epithelium, SCFA–FFAR2/3 signaling stimulates GLP-1 and PYY secretion, slows gastric emptying, and enhances satiety via gut–brain pathways. In islets, FFAR2/3 can modulate insulin secretion, survival, and proliferation, although chronic high SCFA exposure in the setting of high-fat feeding may negatively regulate β-cell function.[119] These mechanistic links have spurred drug-discovery efforts around FFARs and biased ligands, as well as indirect strategies, such as prebiotics, probiotics, and microbiota-targeted polysaccharides, that increase SCFA production, enhance GLP-1 release, and improve β-cell resilience.[120,121]

Primary bile acids synthesized in the liver are transformed by intestinal bacteria into secondary bile acids, with the overall composition of the bile acid pool tightly controlled by the microbiota. These bile acids signal through the nuclear receptor FXR and the membrane receptor TGR5 (GPBAR1), both expressed in the intestine, liver, adipose tissue, kidney, and other organs. Intestinal FXR overactivation in high-fat diet models promotes ceramide-driven liver fat accumulation and insulin resistance, whereas selective blockade of intestinal FXR improves MAFLD and systemic metabolism.[122,123] TGR5 activation in enteroendocrine L-cells elevates cAMP and robustly increases GLP-1 secretion, improving glucose tolerance, while in brown and white adipose tissue it stimulates energy expenditure and thermogenesis.[124,125]

Beyond SCFAs and classical bile acids, a growing set of microbiota-dependent metabolites is being implicated in the pathophysiology of diabetes and in drug discovery. Microbial metabolism of tryptophan yields indoles, secondary bile acids, and other ligands that influence intestinal barrier integrity, inflammation, serotonin signaling, and GLP-1 secretion.[126,127] Recent work on microbial amino-acid–conjugated bile acids (MABAs), such as Tryptophan-conjugated cholic acid (Trp-CA), a MABA reduced inT2Dpatients, which is inversely correlated with glycemic markers, improves glucose tolerance in diabetic mice via activation of the orphan GPCR MRGPRE, further extending the network connecting microbiota, systemic metabolism, and diabetes comorbidities.[128]

ESTABLISHED DRUG CLASSES: LESSONS LEARNED AND IMPLICATIONS FOR FUTURE DRUG DISCOVERY

Diabetes drug discovery has evolved significantly over the past decades (Table S1). Advances in mechanistic understanding, high-resolution omics, target validation strategies, and translational models have enabled increasingly sophisticated therapeutic development (Figure 1B). However, challenges remain, including patient heterogeneity, response durability, off-target metabolic effects, and safety profiles over long-term use. Emerging evidence suggests that multi-pathway interventions may offer superior disease-modifying potential compared with single-target agents.

Anti-CD3 antibody (Teplizumab) and other immune therapies for type I diabetes

Teplizumab represents a first-in-class disease-modifying therapy for type 1 diabetes (T1D), shifting treatment from glucose reduction to immune intervention.[129] Its key innovation lies in selectively targeting CD3 on T cells to induce partial activation, leading to exhaustion or anergy of autoreactive effector T cells while expanding regulatory T cell (Treg) populations.[129] This mechanism promotes immune tolerance rather than broad immunosuppression, addressing the root autoimmune pathology of T1D.

Clinically, Teplizumab demonstrated efficacy in delaying progression from stage 2 (presymptomatic) to stage 3 (clinical) T1D. In a pivotal randomized trial, a single 14-day course delayed disease onset by a median of approximately 2–3 years compared with placebo[4]. Additional studies in newly diagnosed patients showed preservation of endogenous insulin secretion, as measured by C-peptide, indicating partial β-cell protection.[130] However, the effect is not curative, and durability varies among individuals.

Beyond Teplizumab, multiple immune therapies for T1D aim to preserve β-cell function by modulating autoreactive immunity.[129] B cell–depleting therapy with Rituximab transiently preserves C-peptide by reducing antigen presentation and autoantibody production, but effects are not durable.[129] Costimulation blockade using Abatacept inhibits CD28–CD80/86 signaling, slowing β-cell decline, particularly when administered early after diagnosis. Cytokine-targeted approaches include low-dose interleukin-2 (IL-2), which selectively expands regulatory T cells (Tregs) to restore immune tolerance, and IL-21 blockade, which suppresses pathogenic effector T cell responses; combination IL-2/anti–IL-21 strategies are emerging.[131] Anti-inflammatory agents such as Anakinra have shown limited efficacy, highlighting that precise immune reprogramming is required. Overall, these therapies demonstrate partial and time-limited β-cell preservation, reinforcing a shift toward combination strategies integrating immune modulation with β-cell replacement or regeneration.[132]

In clinical application, Teplizumab is approved for delaying T1D onset in at-risk individuals with positive autoantibodies and dysglycemia.[129] Its use introduces a new paradigm of early intervention before overt hyperglycemia. Limitations include transient efficacy, need for patient stratification, and administration-related adverse events such as cytokine release symptoms.[133] Overall, Teplizumab establishes proof-of-concept for immune modulation in T1D and paves the way for combination strategies with β-cell–restorative therapies.[134]

Insulin and insulin analogues

Since its discovery, insulin has remained indispensable for diabetes management. Insulin therapy has evolved from animal-derived preparations to recombinant human insulin and, more recently, to engineered analogues designed to more closely replicate physiological insulin secretion patterns.[135]

Basal insulin primarily suppresses hepatic glucose production and limits fasting and intermeal hyperglycemia.[136] Landmark trials, including the Diabetes Control and Complications Trial (DCCT), established that intensive insulin therapy using multiple daily injections or continuous subcutaneous insulin infusion significantly lowers glycated hemoglobin and improves long-term microvascular and macrovascular outcomes.[137–138]

To better mimic endogenous basal insulin secretion, first- and second-generation basal insulin analogues such as insulin glargine U-300 (Sanofi)

and insulin degludec (Novo Nordisk) were developed. These agents exhibit flatter, more prolonged pharmacokinetic profiles, resulting in reduced glycemic variability and a lower risk of nocturnal hypoglycemia compared with intermediate-acting human insulins.[139] Third-generation basal insulins currently under development, including insulin icode and insulin efsitora alf, are engineered to form circulating insulin depots through albumin binding or fusion with the human IgG2 Fc domain, enabling a sustained half-life and once-weekly administration.[140–141] These advances aim to further extend the duration of action, reduce clearance, and better approximate physiological basal insulin exposure.

A major limitation of exogenous insulin is its inability to reproduce the rapid postprandial insulin surge, resulting in suboptimal control of postprandial hyperglycemia.[142] Rapid-acting insulin analogues were developed to accelerate absorption compared with soluble human insulin, thereby improving postprandial glucose control and reducing the risk of hypoglycemia. Ultra-rapid-acting formulations, such as faster-acting insulin aspart and ultra-rapid insulin lispro, incorporate excipients, including nicotinamide and citrate, to enhance subcutaneous absorption.[143] These agents demonstrate earlier onset and higher early exposure than conventional rapid-acting analogues and have shown particular benefit in insulin pump therapy and hybrid closed-loop systems by reducing postprandial glucose excursions.[144]

Metformin and AMPK-centric drugs

Metformin remains the first-line pharmacotherapy for type 2 diabetes (T2D) because of its efficacy, safety, and low cost. However, its modest glycemic potency and tolerability limitations have fueled intense interest in next-generation AMP-activated protein kinase (AMPK) agonists. Metformin lowers plasma glucose primarily by suppressing hepatic gluconeogenesis. This effect is linked to inhibition of mitochondrial respiratory chain complex I, which increases the AMP/ATP ratio and reduces energy availability for gluconeogenesis.[145–146] Elevated AMP also suppresses glucagon-stimulated cAMP-PKA signaling, further inhibiting hepatic glucose output.[147]

At clinically relevant concentrations, metformin can activate AMPK through a lysosome-associated pathway involving PEN2, v-ATPase, AXIN, and LKB1, independent of overt cellular energy depletion.[148] This pathway provides a mechanistic bridge between low-dose metformin exposure and AMPK activation *in vivo*. Metformin also exerts major gut-centric effects, including increased intestinal glucose utilization, altered bile acid signaling, and microbiome remodeling, which together contribute to systemic glycemic improvement.[149]

Despite its benefits, metformin has clear limitations in T2D. Glycemic efficacy plateaus at moderate HbA1c reductions, and it provides minimal weight loss compared with incretin-based therapies.[150] Gastrointestinal intolerance is common and dose-limiting, while chronic use is associated with vitamin B12 deficiency.[151] Rare but serious lactic acidosis risk restricts its use in advanced renal or hypoxic states. Importantly, metformin is not a selective AMPK agonist; its effects depend on transporters, tissue exposure, and multiple AMPK-dependent and independent pathways, resulting in inter-individual variability in response.

Direct AMPK activators targeting the allosteric drug and metabolite site offer clean target engagement and robust metabolic effects. However, systemic pan-AMPK activation has been associated with cardiac hypertrophy and glycogen accumulation, as exemplified by MK-8722, limiting chronic use in T2D.[152] Current strategies emphasize isoform-selective or tissue-biased AMPK activation, particularly favoring liver-enriched β1-containing AMPK complexes while avoiding cardiac β2 activation. Compounds such as PXL770 have demonstrated human target engagement, including suppression of hepatic de novo lipogenesis, with metabolic benefits relevant to T2D.[153]

In the modern T2D therapeutic landscape dominated by GLP-1/GIP agonists and SGLT2 inhibitors, next-generation AMPK agonists are best positioned as insulin-sensitizing, lipid-flux-correcting agents that complement rather than replace existing therapies.

Sulfonylureas & insulin secretagogues

Insulin secretagogues enhance insulin release from pancreatic β cells. Classical agents, including sulfonylureas and meglitinides (glinides), stimulate insulin secretion by directly targeting the β-cell ATP-sensitive potassium (KATP) channel.[154–155] Although effective glucose-lowering drugs exist, their glucose-independent mechanism underlies safety and durability concerns that have limited further development.

The β-cell KATP channel couples intracellular energy status to membrane excitability. It comprises four Kir6.2 subunits (KCNJ11) and four regulatory SUR1 subunits (ABCC8).[156–157] Under low-glucose conditions, the channel remains open, maintaining membrane hyperpolarization. Glucose metabolism raises the ATP/ADP ratio, leading to channel closure, membrane depolarization, calcium influx, and insulin granule exocytosis.[158] Sulfonylureas bind to SUR1 and stabilize the closed conformation of the KATP channel independently of intracellular ATP levels, thereby bypassing physiological glucose sensing.[158] Meglitinides bind to overlapping sites on SUR1 but dissociate rapidly, enabling short-acting, mealtime insulin secretion with reduced fasting hypoglycemia, although glucose independence remains intrinsic to the mechanism.[159–160]

Chronic stimulation of insulin secretion increases β-cell workload and cellular stress. Sustained depolarization and calcium influx promote endoplasmic reticulum stress due to increased proinsulin synthesis, oxidative stress from elevated mitochondrial activity, and impaired proinsulin processing.[80,161] These stresses can contribute to the loss of β-cell identity and dedifferentiation, thereby reducing long-term secretory capacity.[26] Hypoglycemia is the principal limitation of classical secretagogues because insulin release is uncoupled from ambient glucose levels, particularly in elderly patients or those with renal impairment.[162] Chronic hyperinsulinemia also promotes weight gain and may worsen insulin resistance.[163]

TZDs and PPAR modulators

Peroxisome proliferator–activated receptor-γ (PPARγ) is a ligand-activated nuclear receptor that plays a central role in glucose and lipid homeostasis. In metabolic tissues, particularly adipose tissue, PPARγ orchestrates transcriptional programs governing adipocyte differentiation, lipid storage, adipokine secretion, and inflammatory tone.

Thiazolidinediones (TZDs), including rosiglitazone and pioglitazone, are high-affinity PPARγ ligands that function as near-full agonists. These compounds stabilize helix 12 of the ligand-binding domain, promoting strong recruitment of canonical coactivators and broad transcriptional activation to increase adipose lipid storage capacity, reducing ectopic lipid accumulation and improving adipokine profiles, thereby enhancing insulin sensitivity. The insulin-sensitizing effects of PPARγ activation arise largely from systemic rewiring of lipid partitioning and endocrine crosstalk rather than direct potentiation of insulin signaling in muscle or liver[164–165]. However, enhanced adipogenesis also leads to increased adipose mass and fluid retention, contributing to weight gain and an increased risk of heart failure in susceptible individuals.[166–167]

Adverse effects associated with TZDs, including edema, heart failure risk and bone fractures, largely reflect on-target PPARγ activity. These effects arise from altered renal sodium handling, plasma volume expansion, and shifts in mesenchymal stem cell lineage allocation. Complete dissociation of efficacy from these liabilities has proven challenging.[168–169] A major advance in PPARγ biology was the identification of CDK5-mediated phosphorylation of PPARγ at Ser273, which dysregulates genes linked to insulin resistance. Several ligands block this phosphorylation independently of classical agonism, and inhibition of Ser273 phosphorylation correlates with insulin-sensitizing efficacy in preclinical models.[170–171]

Selective PPARγ modulators (SPPARMs) aim to retain metabolic benefits while minimizing adverse effects through partial agonism, conformational bias and selective cofactor recruitment. Although no SPPARM has yet fully replaced TZDs clinically, this strategy has reshaped nuclear receptor drug discovery and continues to inform next-generation metabolic therapies.[172–173]

Box 1 Functional specialization of PPARα, PPARδ and PPARγ in metabolic disease

PPARα, PPARδ (β/δ) and PPARγ are closely related nuclear receptors that regulate complementary but distinct aspects of metabolic homeostasis. Despite sharing DNA-binding motifs and heterodimerization with RXR, their tissue distribution, transcriptional programs and therapeutic liabilities diverge

markedly, shaping isoform-specific drug discovery strategies.

(1) PPARα is enriched in liver, heart and oxidative tissues, where it promotes fatty acid uptake, β-oxidation, ketogenesis and lipoprotein remodeling. Pharmacological activation primarily lowers triglycerides and addresses dyslipidemia, with modest indirect effects on insulin sensitivity.

(2) PPARδ is broadly expressed and enhances fatty acid oxidation, mitochondrial biogenesis and metabolic flexibility, particularly in skeletal muscle and adipose tissue. Although PPARδ activation improves insulin sensitivity and energy expenditure, safety concerns from preclinical models have limited clinical translation.

(3) PPARγ is highly expressed in adipose tissue and serves as the master regulator of adipocyte differentiation and lipid storage. Its activation improves insulin sensitivity through adipose remodeling and adipokine secretion but also drives weight gain, fluid retention and skeletal effects, motivating the development of selective PPARγ modulators.

Together, these distinctions highlight why selective and biased modulation—rather than uniform agonism—has emerged as the dominant paradigm for targeting PPARγ in metabolic disease.

DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors, or "gliptins," enhance endogenous incretin activity and have become widely used for the treatment of type 2 diabetes due to their oral administration, weight neutrality, and low risk of hypoglycemia.

DPP-4 is a ubiquitous serine protease that rapidly degrades glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide *in vivo*.[174–175] DPP-4 inhibitors (DPP-4i) promote glucose-dependent insulin secretion and inhibit glucagon release by prolonging the half-life of endogenous incretins. In addition to systemic endocrine pathways, they may also exert their effects through local neural and endocrine pathways. However, local feedback inhibition of incretin secretion limits the efficacy of inhibitors.

DPP-4i therapy can improve glycemic control by increasing insulin secretion from pancreatic islet cells, reducing HbA1c levels, decreasing adipocyte size, and suppressing inflammation.[178–179] It demonstrates neutral effects on body weight and a favorable safety profile, making them attractive for elderly patients and those at risk of hypoglycemia.[180] The cardiovascular effects of DPP-4 inhibitors have been reported due to GLP-1 receptor expression in blood vessels and heart tissues.[181] However, the results of large-scale clinical trials remain controversial.[178,182–183]

SGLT2 inhibitors

SGLT2 inhibitors exert their hypoglycemic effect by targeting renal glucose reuptake transporter through a unique mechanism of action independent of insulin secretion or insulin resistance. They also exhibit significant cardioprotective and renal protective effects.

In the healthy kidney, approximately 180 g of glucose is filtered daily by the glomeruli, with nearly all reabsorbed in the proximal tubule via SGLT2 (accounting for ~90%) and SGLT1 (accounting for ~10%), resulting in low glucose being excreted in the urine.[184] SGLT2 inhibitors block this high-capacity transporter, inducing glucosuria and lowering plasma glucose in an insulin-independent manner.[185–186] Due to related beneficial effects, including improved fasting and postprandial blood glucose control and HDL cholesterol, lowering glycated hemoglobin (HbA1c), weight, and blood pressure.[187]

In addition to blood sugar control, SGLT2 inhibitors have also been found to have renal and cardioprotective effects, and a small number of inhibitors have also shown anticancer activity.[188] Large-scale clinical outcome trials have consistently demonstrated that SGLT2 inhibitors can reduce heart failure hospitalization rates, delay the progression of chronic kidney disease, and reduce cardiovascular and all-cause mortality in high-risk populations.[189–190] These benefits extend to patients with and without diabetes, leading to their adoption as foundational therapies in heart failure with reduced and preserved ejection fraction, as well as in CKD across a broad range of estimated glomerular filtration rates.[191–192] Proposed mechanisms include restoration of tubuloglomerular feedback, reduction of intraglomerular pressure, improved myocardial energetics, modulation of inflammation and oxidative stress, and favorable hemodynamic effects.[192]

Alpha-glucosidase inhibitors (AGIs)

Alpha-glucosidase inhibitors (AGIs), such as Acarbose, Miglitol and Voglibose**,** are oral antidiabetic medications used to manage type 2 diabetes by slowing carbohydrate digestion and reducing post-meal blood glucose spikes. AGIs are an orally administered α-glucosidase inhibitors that lower blood glucose by acting locally within the gastrointestinal tract rather than through systemic metabolic pathways. It competitively inhibits brush-border α-glucosidases, including maltase, sucrase, and isomaltase, in the proximal small intestine, thereby delaying the enzymatic hydrolysis of oligo- and disaccharides into absorbable monosaccharides.[193–194] As a result, glucose absorption is slowed, and postprandial glucose excursions are attenuated, with minimal effects on fasting plasma glucose.

By blunting postprandial hyperglycemia, acarbose reduces postprandial insulin secretion and insulin demand, which may transiently decrease β-cell workload in early type 2 diabetes. Because systemic absorption of acarbose is negligible, the drug carries a very low intrinsic risk of hypoglycemia when used as monotherapy.[194] However, its glycemic efficacy is modest, with typical HbA1c reductions of approximately 0.5–0.8%, substantially less than those achieved with metformin, GLP-1 receptor agonists, or sodium–glucose co-transporter-2 (SGLT2) inhibitors.[48]

The principal limitation of acarbose is gastrointestinal intolerance, which is unavoidable on mechanistic grounds. Undigested carbohydrates reach the colon, where bacterial fermentation produces gas and short-chain fatty acids, causing flatulence, abdominal bloating, and diarrhea.[193,195] These adverse effects often limit dose escalation and long-term adherence. Critically, acarbose has not demonstrated consistent cardiovascular or renal outcome benefits in large contemporary outcome trials, unlike newer antidiabetic drug classes.[189] Consequently, its role in modern treatment algorithms is largely restricted to selected patients with early disease and predominant postprandial dysglycemia.

MODERN BREAKTHROUGHS

GLP-1 Therapeutics

Incretin biology, clarifying why oral glucose stimulates much more insulin than intravenous glucose, provided the initial conceptual framework for GLP-1-based therapies and for a broader "incretin-related" multi-agonist pharmacology aimed simultaneously at glucose control, weight loss, and cardio-renal protection.[29] The incretin defect, blunted insulinotropic response to GIP with partly preserved GLP-1 responsiveness, directly motivated GLP-1R agonist development and later dual/triple-agonist strategies.[196-198] In addition to the incretin receptors, multiple G protein-coupled receptors (GPCRs) expressed in islets, gut, liver, adipose tissue and brain link these defects to therapeutic opportunities, including GCGR, AMYRs,[199] FFARs,[200–201] TGR5,[202] GPR123,[203] MRGPRE,[128] GPR119,[204] muscarinic M3,[205] adrenergic,[206] and other GPCRs.

Generations of GLP1 receptor peptide agonisits (liraglutide, dulaglutide, weekly semaglutide) extended half-life via acylation and albumin/Fc fusion and established GLP-1RAs as core therapies for T2D and obesity with cardiovascular and renal benefit.[207–208] For example, the strongest glucose-lowering among approved GLP-1R peptides, semaglutide, is the standout. In the Ozempic monotherapy trial, once-weekly semaglutide lowered HbA1c by 1.4% (0.5 mg) and 1.6% (1 mg) at 30 weeks, versus 0.1% with placebo; 73% and 70% of patients reached HbA1c below 7%, respectively.[209] For weight loss in obesity, the best human data among pure GLP-1 peptides are from semaglutide 2.4 mg weekly and liraglutide 3 mg daily. In the STEP 1 trial, semaglutide produced a mean body-weight change of −14.9% at 68 weeks, versus −2.4% with placebo. In the FDA Wegovy label, the same study shows 83.5% of semaglutide-treated patients achieved at least 5% weight loss.[210]

Although Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as highly effective therapies for obesity and type 2 diabetes, producing clinically meaningful reductions in body weight and cardiometabolic risk, an underappreciated limitation is the non-selective nature of weight loss, whereby a substantial fraction of total weight reduction—typically 25–40%—is derived from lean mass loss, including skeletal muscle.[210–211] Clinical trials using dual-energy X-ray absorptiometry (DEXA) and MRI consistently demonstrate that lean mass loss constitutes a significant proportion of total weight reduction. In the STEP 1 trial of semaglutide, approximately one-third of weight loss was attributable to lean tissue reduc-

tion.[210] Similar findings have been reported across incretin-based therapies, although variability exists depending on baseline adiposity, age, and intervention duration. This phenomenon has important implications for metabolic health, functional capacity, and long-term durability of therapeutic benefit.

Another safety concern, tachycardia (increased heart rate), is a known potential side effect of GLP-1 receptor agonist drugs, such as Ozempic (semaglutide), Wegovy, and liraglutide.[212–213] While usually mild, these medications can increase resting heart rate by an average of 1–4 beats per minute, with some cases showing higher increases. Additional safety considerations include an increased risk of gallbladder disease, a debated association with pancreatitis, and rodent findings of thyroid C-cell hyperplasia, though the latter has unclear relevance in humans.[214] Moreover, inter-individual variability in therapeutic response highlights underlying heterogeneity driven by genetic, microbiome, and neuroendocrine factors.

Finally, GLP-1RAs exhibit limited efficacy across broader metabolic domains such as hypertriglyceridemia, hepatic steatosis, and chronic inflammation, underscoring the need for multi-target or poly-agonist therapeutic strategies.

Inflammation and immunometabolism targets

Type 2 diabetes (T2D) is increasingly recognized as a disorder of immunometabolic dysregulation, in which chronic, low-grade inflammation emerges as both a consequence and a driver of metabolic stress.[215–216] This state, termed metaflammation, arises when nutrient excess, lipotoxicity, glucotoxicity, and tissue hypoxia activate innate immune pathways in metabolic organs, including adipose tissue, liver, skeletal muscle, and pancreatic islets.[215] Unlike classical inflammation, metaflammation is persistent, spatially compartmentalized and tightly coupled to cellular metabolism, posing distinct challenges for therapeutic intervention.[216]

In obesity and insulin resistance, stressed parenchymal cells release damage-associated molecular patterns (DAMPs) such as saturated fatty acids, ceramides, cholesterol crystals, mitochondrial DNA, and advanced glycation end-products.[215,217] These signals activate pattern-recognition receptors, inflammasomes, and stress kinases in resident and recruited immune cells, particularly macrophages.[215] Immune cells undergo metabolic rewiring — increased glycolysis, altered mitochondrial function, and lipid accumulation — which stabilizes inflammatory transcriptional programs and perpetuates insulin resistance.[215–216]

Tumor necrosis factor-α (TNFα) was among the first cytokines mechanistically linked to insulin resistance via JNK and IKKβ activation, inhibitory serine phosphorylation of insulin receptor substrates, and promotion of adipose tissue lipolysis.[217] Despite a strong biological rationale, systemic TNFα blockade has yielded inconsistent and modest improvements in insulin sensitivity in metabolic syndrome and T2D.[218] These findings suggest that TNFα functions primarily as an amplifier rather than an ignition node of metabolic inflammation.[216]

The NLRP3 inflammasome–IL-1β pathway lies close to the metabolic ignition point of metaflammation. Diverse metabolic stressors converge on NLRP3 activation, leading to caspase-1–dependent maturation of IL-1β and IL-18.[219] IL-1β impairs insulin action in peripheral tissues and directly compromises β-cell function.[219–220] While IL-1 receptor antagonism improves glycaemic control in subsets of patients, large outcome studies highlight the need for early intervention and patient stratification, motivating upstream NLRP3 inhibition strategies.[221–222]

Recruitment of circulating monocytes into adipose tissue and the liver is a defining feature of metaflammation.[215] Chemokine pathways, including CCL2–CCR2 and CCL5–CCR5, regulate this process and sustain inflammatory macrophage niches.[223–224] CCR2 antagonism reduces macrophage infiltration and improves metabolic and renal endpoints in preclinical models and selected clinical populations, although effects on glycaemic indices alone are often modest.[223]

These insights indicate that effective immunometabolic therapies for diabetes will require precision patient stratification, targeting of upstream ignition nodes, immune state editing, and combination with metabolic unloading strategies.[216,219] Integration of multi-omics, single-cell atlases, and AI-enabled analytics will be essential for identifying causal immune pathways and optimizing future clinical trial design.[216]

Box 2 Target landscape for immunometabolic intervention in diabetes

(1) TNFα: Stress-kinase activation and lipolysis; strong biology but limited standalone efficacy.

(2) IL-1β / NLRP3: Metabolic stress ignition and β-cell dysfunction; upstream inhibition favored.

(3) CCR2 / CCR5: Monocyte recruitment and inflammatory niche maintenance; best for liver and kidney disease.

(4) TREM2 / LAM: Macrophage lipid handling and adaptation; state-editing paradigm.

(5) JAK / BTK: Cytokine and innate signal amplification; potency limited by safety.

(6) Resolution mediators: Inflammation termination and efferocytosis; emerging chronic-use strategy.

(7) STING / TLRs: Nucleic-acid and pattern sensing; context-dependent opportunities.

Lipid flux–centric metabolic targets for improving insulin sensitivity

Insulin resistance is increasingly recognized as a disorder of dysregulated lipid flux rather than a primary defect in glucose metabolism. Hypolipidemia is commonly defined clinically as abnormally low circulating concentrations of triglycerides, LDL-cholesterol, or free fatty acids. Among the diverse lipid species present in mammalian tissues, ceramides, diacylglycerols, and free fatty acids have emerged as dominant mediators of insulin resistance, and therefore targets of next generation of drugs(Table S3).

Excess delivery of triglyceride-rich lipoproteins and free fatty acids (FFAs) to non-adipose tissues promotes ectopic lipid deposition in the liver and skeletal muscle, leading to accumulation of bioactive lipid intermediates, including diacylglycerol (DAG) and ceramides.[50,225–226] These intermediates activate protein kinase C (PKC) isoforms (PKCε in liver and PKCθ in muscle), which impair insulin receptor–AKT signaling and reduce insulin-stimulated glucose uptake and suppression of gluconeogenesis.[43,45,54]

Acetyl-CoA carboxylase (ACC) occupies a central node in this lipid-driven network. ACC1 supports hepatic de novo lipogenesis, whereas ACC2 generates malonyl-CoA that suppresses mitochondrial β-oxidation.[227] Pharmacological ACC inhibition therefore simultaneously reduces lipid synthesis and enhances fatty acid oxidation, lowering hepatic DAG content and improving hepatic insulin sensitivity.[228–229] Clinical ACC inhibitors have consistently reduced hepatic steatosis, although compensatory increases in circulating triglycerides have been reported.[230]

Diacylglycerol acyltransferases (DGAT1 and DGAT2) regulate the final step of triglyceride synthesis and directly control intracellular DAG availability. DGAT2 plays a dominant role in hepatic insulin resistance; its inhibition reduces hepatic DAG and restores AKT signaling even when total triglyceride content is only modestly altered.[231–232] DGAT1 inhibition primarily affects intestinal and postprandial lipid handling, reducing acute lipotoxic exposure but with gastrointestinal limitations.[233]

At the systemic level, triglyceride flux is governed by lipoprotein lipase (LPL), regulated by angiopoietin-like proteins (ANGPTL3 and ANGPTL4) and apolipoprotein C-III (ApoC-III).[234-236] Inhibition of ANGPTL3 accelerates triglyceride clearance and improves insulin sensitivity.[174,237] ApoC-III antisense and siRNA therapies produce profound triglyceride lowering and improve lipid-driven insulin resistance.[238-240]

Elevated FFAs represent a mechanistic bridge between adipose insulin resistance and impaired insulin action in liver and muscle.[44,241] Collectively, triglyceride lowing drugs support a unifying model in which triglyceride lowering reflects normalization of lipid flux rather than depletion of inert lipid stores(Table S3).

Thus, effective metabolic therapies should prioritize improving lipid flux efficiency and compartmentalization rather than simply lowering total lipid levels. This paradigm integrates organ cross-talk and highlights coordinated regulation across adipose tissue, liver, and muscle as essential for restoring insulin sensitivity.

Liver-targeted therapies

Excess hepatic glucose production and dysregulated lipid handling are central to the pathophysiology of type 2 diabetes. Liver-targeted therapies offer a compelling opportunity to lower fasting and postprandial glycemia

while avoiding direct β-cell stress. Current approaches for hepatic glucose control mainly focus on gluconeogenesis blockers, hepatic GPCR modulators—most notably glucagon receptor antagonism—and novel small-molecule and RNA-based approaches that reprogram very-low-density lipoprotein secretion and lipogenesis.[163,226,242]

In type 2 diabetes, fasting hyperglycemia is driven predominantly by excessive hepatic glucose production (HGP), resulting from increased gluconeogenesis, impaired insulin-mediated suppression, and exaggerated glucagon signaling.[243–244] Concurrently, hepatic steatosis and altered lipid partitioning exacerbate insulin resistance and promote atherogenic dyslipidemia.[245] Fructose-1,6-bisphosphatase (FBP1) catalyzes a rate-limiting step in gluconeogenesis and has long been pursued as a therapeutic target. Early clinical candidates demonstrated proof-of-mechanism glucose lowering but raised concerns about hypoglycemia risk and metabolic compensation.[246–247] Hepatoselective glucokinase activators increase hepatic glucose uptake and glycogen synthesis but may promote de novo lipogenesis and hypertriglyceridemia if flux is not tightly controlled.[248–249] The glucagon receptor (GCGR) is a dominant regulator of hepatic glucose output via cAMP–PKA signaling. GCGR antagonists robustly reduce fasting glucose and HbA1c in type 2 diabetes.[250] However, multiple clinical programs have reported increased hepatic fat content and aminotransferase elevations, particularly in genetically susceptible individuals, highlighting a glucose–lipid trade-off.[251–252]

GalNAc-conjugated antisense and siRNA platforms enable selective hepatocyte targeting of lipid regulators. Suppression of apolipoprotein C-III markedly enhances clearance of triglyceride-rich lipoproteins and has received regulatory approval for severe hypertriglyceridemia.[253–254] ANGPTL3 silencing reduces triglycerides and atherogenic lipoproteins, while DGAT2 inhibition lowers hepatic triglyceride synthesis and lipotoxic stress.[255-257] Liver-directed thyroid hormone receptor-β agonism further exemplifies metabolic reprogramming that links steatosis resolution with improved glycemic control.[258–259]

Isolated suppression of hepatic glucose output is unlikely to provide durable benefit in diabetes. Future liver-targeted therapies will combine moderate HGP inhibition with active mitigation of hepatic lipid stress, enabling sustained glycaemic control while improving liver health and cardiometabolic risk.[75]

Receptors of fatty acids and bile acids, as emerging targets

Beyond directly agonizing GLP-1R, drug discovery has also focused on GPCRs that regulate GLP-1/PYY secretion or share overlapping metabolic pathways, notably FFARs and bile acid receptor TGR5.[260–261] Several small-molecule FFAR1 agonists, including fasiglifam/TAK-875, LY2881835, LY2922083, LY2922470, P11187, SCO-267 and others, have entered clinical trials. Fasiglifam showed promising glucose-lowering but was halted due to hepatotoxicity, illustrating off-target risks of potent FFAR agonism.[262] Newer agents (e.g., LY2881835) demonstrate insulin and GLP-1 stimulation in early trials without the same liver issues, but long-term safety and additive benefit over GLP-1RAs remain to be investigated.[263] Other FFARs (FFAR2/GPR43, FFAR3/GPR41) are activated by short-chain fatty acids, although not yet fully exploited clinically for diabetes, they are central in microbiome-gut-brain research and may yield future secretagogue-type drugs.[264–265]

TGR5 is a bile acid-activated GPCR expressed in enteroendocrine cells, brown adipose tissue, macrophages, liver, and other tissues. TGR5 has several antidiabetic actions in preclinical studies, including stimulating GLP-1 secretion, improving glucose tolerance, enhancing energy expenditure in brown adipose tissue and skeletal muscle, modulating macrophage inflammation, and potentially reducing insulin resistance.[260] These bile-acid signaling pathways are now active drug targets. Obeticholic acid and related FXR agonists, as well as FXR/TGR5 dual agonists such as INT-767, are in development for NASH and diabetic complications, aiming to correct hepatic lipid accumulation, inflammation and fibrosis.[123,266] TGR5 agonists, both steroidal and non-steroidal, are being optimized to maximize intestinal GLP-1 release and energy expenditure while limiting class-specific side effects such as gallbladder filling. The strategic direction is toward gut-restricted TGR5 agonists and intestine-biased FXR ligands that harness beneficial incretin and thermogenic effects with minimal systemic bile-acid–like toxicity.[267]

These mechanistic insights are feeding directly into an emerging therapeutic paradigm where metabolite-sensing GPCRs and nuclear receptors serve as nodal drug targets, and the gut microbiota itself is treated as a manipulable endocrine organ. New efforts target lipid-sensing GPCRs on islets and enteroendocrine cells with small molecules or engineered peptides, to integrate incretin, bile acid and SCFA pathways into single "unimolecular polypharmacology" therapies.

β-cell regeneration & protection strategies

Progressive loss of functional pancreatic β-cell mass underlies both type 1 diabetes (T1D) and late stage of type 2 diabetes (T2D). In T1D, autoimmune destruction predominates, whereas in T2D, β-cell failure reflects chronic metabolic overload, inflammatory signaling, and activation of stress pathways. Accordingly, emerging β-cell–centric therapies are organized around three interconnected axes: regeneration, rejuvenation, and replacement. Durable benefit is increasingly viewed as requiring their integration rather than reliance on a single mechanism.[28,34]

Adult human β-cells display extremely low basal replication, limiting intrinsic regenerative capacity. Among the most reproducible small-molecule strategies is inhibition of dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A). DYRK1A inhibitors, including the prototypical compound harmine, promote NFAT nuclear localization and induce proliferation of primary human β-cells *in vitro* and in transplant models.[268-270] However, the mechanism (NFAT activation) of DYRK1A inhibition has beneficial in β-cells but harmful in CNS for potential cognitive impairment. Incretin signaling further provides a pro-survival context that can potentiate regenerative responses.[26,271]

Replacement strategies provide exogenous insulin-producing cells to compensate for irreversible β-cell loss. Pluripotent stem cell–derived β-like cells capable of glucose-responsive insulin secretion have achieved functional restoration in preclinical models and early clinical studies.[272-274] However, challenges include achieving uniform maturation, ensuring engraftment and maintaining long-term identity in hostile inflammatory and metabolic environments. To avoid chronic immunosuppression, encapsulation and immune-isolation devices have been developed to shield transplanted cells while permitting nutrient and insulin diffusion. Macroencapsulation devices offer retrievability but are limited by diffusion constraints and fibrotic responses, whereas microencapsulation approaches face long-term biocompatibility challenges.[275-277] Continued advances in biomaterials and device design are critical for clinical translation.

These data indicate that β-cell regeneration, rejuvenation, and replacement are constrained by shared stress and immune barriers. Durable therapeutic benefit is therefore unlikely to arise solely from mitogenic signaling. Instead, integrated strategies that combine selective β-cell proliferation with nutrient-sensing rebalancing, senomorphic suppression of inflammatory stress and, where necessary, cell replacement supported by immune-isolation technologies are likely to define the next generation of β-cell–centric diabetes therapies.[278]

TECHNOLOGY PLATFORMS TRANSFORMING DIABETES DRUG DISCOVERY

AI/ML and computational target discovery

Artificial intelligence and machine learning (ML) are reshaping diabetes drug discovery by enabling integrative analysis of complex multi-omics data, mechanistic modeling of metabolism, generative design of small molecules and peptides, and patient stratification(Figure 5). Diabetes is a multi-tissue, systems-level disease characterized by pancreatic β-cell failure, insulin resistance in the liver, muscle, and adipose tissue, chronic inflammation, and dysregulated lipid and glucose metabolism. AI-native target discovery frameworks are uniquely suited to address this complexity.[279–280]

Deep learning–based representation learning has become the foundation of computational target discovery in diabetes. A recent identification of the NLRP3 inflammasome as a potential diabetes drug target using AI and multi-omics, via a convergent, multi-layer logic chain linking association, mechanism, and causality. First, bulk transcriptomics and proteomics from diabetic islets, adipose tissue, liver, and circulating immune cells consistently reveal enrichment of inflammatory modules, with NLRP3, PYCARD (ASC), CASP1, IL1B, and IL18 co-upregulated and correlated with clinical traits such as

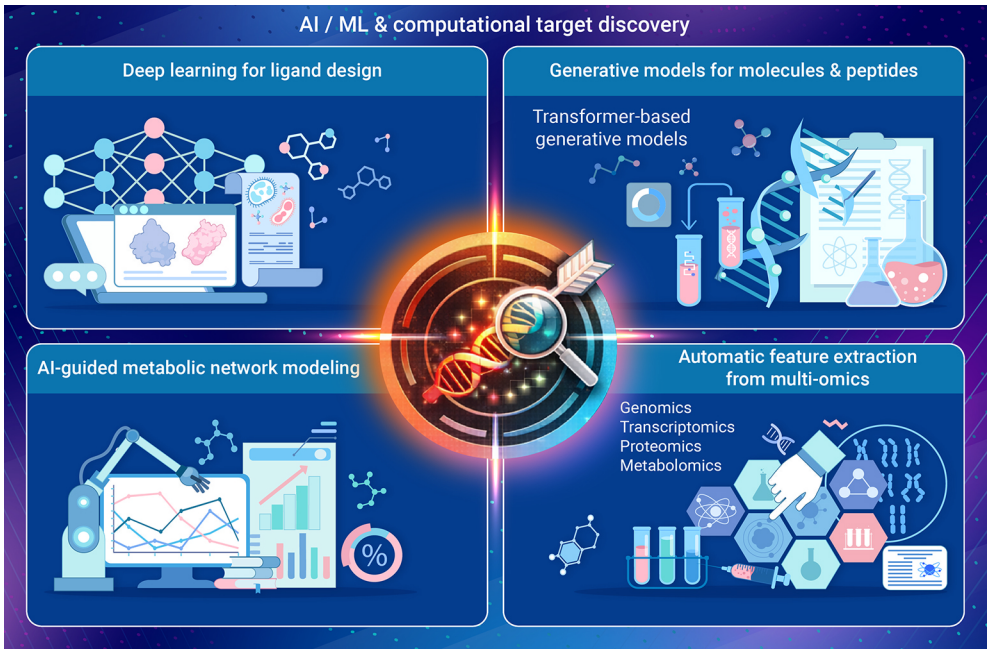

Figure 5. AI/ML and computational target discovery pipeline Artificial intelligence and machine learning enable a framework for modern target discovery and drug design. Top left, deep learning models are applied to ligand design, learning structure–activity relationships from chemical libraries and protein–ligand complexes to predict binding affinity, selectivity, and developability. Top right, transformer-based generative models enable de novo generation and optimization of small molecules and peptides, navigating chemical and sequence space to propose novel candidates with desired physicochemical and biological properties. Bottom left, AI-guided metabolic network modeling integrates pathway topology, flux constraints, and regulatory interactions to identify key control nodes and disease-relevant targets within cellular metabolic and signaling networks. Bottom right, automatic feature extraction from multi-omics data (genomics, transcriptomics, proteomics, and metabolomics) leverages representation learning to uncover latent disease signatures, biomarkers, and causal drivers. At the center, these four components converge to support data-driven hypothesis generation, target prioritization, and rational molecule design, forming a closed-loop discovery engine that links multi-scale biological data to therapeutic innovation.

HbA1c and insulin resistance.[34,281] Second, single-cell and spatial transcriptomics localize this signature primarily to macrophages and myeloid cells, linking immune activation to β-cell dysfunction.[282] Third, metabolomics provides upstream triggers—lipotoxic species, mitochondrial stress, and islet amyloid polypeptide—that activate the NLRP3 inflammasome, mechanistically connecting metabolic overload to innate immunity.[36,283] Fourth, network-based AI approaches, including co-expression modules and knowledge graphs, prioritize NLRP3 as a hub node bridging metabolic stress and cytokine release within integrated disease networks.[284–285] Finally, perturbation studies show that genetic or pharmacologic inhibition of NLRP3 reduces IL-1β production, attenuates pyroptosis, and improves insulin sensitivity, supporting causal relevance.[286–287] Together, these layers elevate NLRP3 from an inflammatory correlate to a causal, druggable regulator at the metabolic–immune interface of type 2 diabetes.

Metabolic dysregulation is central to diabetes, making genome-scale metabolic models (GEMs) a critical mechanistic layer. AI-enhanced GEMs integrate omics-derived constraints to predict tissue-specific flux states governing hepatic glucose production, de novo lipogenesis, fatty acid oxidation, and VLDL secretion.[288] Machine learning methods improve flux inference from sparse data, enable condition-specific model personalization, and link predicted flux changes to circulating biomarkers such as acylcarnitines, amino acids, and triglyceride-rich lipoproteins.[289] These hybrid ML–mechanistic models are particularly valuable for identifying metabolic intervention points that reduce hyperglycemia without exacerbating dyslipidemia or hepatic steatosis, a common liability in diabetes drug development.[226]

Once targets are nominated, deep learning accelerates ligand discovery or optimizations by predicting target engagement, selectivity, and pharmacokinetic liabilities in parallel. Multi-task neural networks evaluate potency, off-target risk, and ADMET properties simultaneously, which is essential for chronic metabolic diseases that require long-term safet.[290] Active learning frameworks further reduce experimental burden by prioritizing compounds with the highest expected information gain. Transformer architectures and diffusion models have become central to generative chemistry. For small molecules, conditional transformers generate candidate structures optimized for target affinity, physicochemical constraints, and synthetic feasibility.[291] These models enable scaffold hopping and multi-parameter optimization, critical for metabolic targets with narrow therapeutic windows. The first GLP1 receptor small molecule agonist from Lily Pharmceutics, orforglipon, demonstrates clinically measningful weigth list in phase III clinical trail up to ~11% body weight reduction over 72 weeks and significantly reduced the glycated hemoglobin (HbA1c) level up to -1.48 percentage over a period of 40 weeks.[292–293] AI identified a novel non-canonical pocket in GLP1 receptor, which orforglipon can bind and show great efficacy without mimicking peptide ligand. Another successful example that AI plaform for drug discovery is that Insilico Medicine announced the nomination of a preclinical candidate, ISM0676, a small molecule antagonist designed using Generative AI (Pharma.AI platform) targeting the GIP receptor to combat obesity (https://insilico.com/news/7niehprgd1-up-to-313-body-weight-loss-insilico-medi). For peptides, which are especially relevant to diabetes due to incretin- and hormone-based therapies, sequence-based transformers learn constraints on activity, stability, aggregation risk, and immunogenicity. Conditioning peptide generation on developability metrics, such as protease stability and half-life extension strategies, improves translational success.[96,294]

Advances in protein structure prediction, such as AlphaFold, have expanded the scope of structure-enabled target discovery.[295–296] Predicted protein structures facilitate hypothesis generation for previously intractable targets and support early-stage ligand design when combined with AI-driven chemistry approaches.[297] For example, AlphaFold2 delivers near–experimental accuracy protein structures at proteome scale, enabling rapid identification of binding pockets, domain architecture, and protein–protein interfaces. It has transformed drug discovery by expanding the druggable target space, accelerating structure-based drug design, and reducing reliance on experimental structural biology in early stages. AlphaFold supports virtual screening, target validation, and AI-integrated pipelines.[295,298]

The most effective AI-driven diabetes discovery platforms operate as closed loops: multi-omics representation learning defines disease endotypes; network and metabolic modeling identify causal targets and biomarkers; generative models design optimized ligands; and experimental feedback continuously refines the models. Although the AI-driven metabolic disease drug discovery is still in the early stage and faceles many chalelnges, such as lack of many reliable experimental data and long-time validations, this paradigm can shorten design–make–test cycles and increases the probability that discovered targets translate into durable clinical benefit when more reliable data are available.[299]

Chemical biology & screening innovations

New hits and later drugs targeting proteins or other molecules in diabetes can be significantly expanded through recent new methods and technologies, such as DNA-encoded libraries, Cryo-EM structure-guided design, high-content phenotypic screening, and PROTACs and molecular glues targeting metabolic proteins (Figure 6). These approaches can significantly increase the possibility of new drugs that are somewhat challenging for traditional drug discovery methods.

DEL couples split-and-pool synthesis with DNA barcoding to enable affinity selections across ultra-large libraries (often 10^8–10^{12} members) with modest material and time.[300-302] For diabetes programs, DEL is particularly

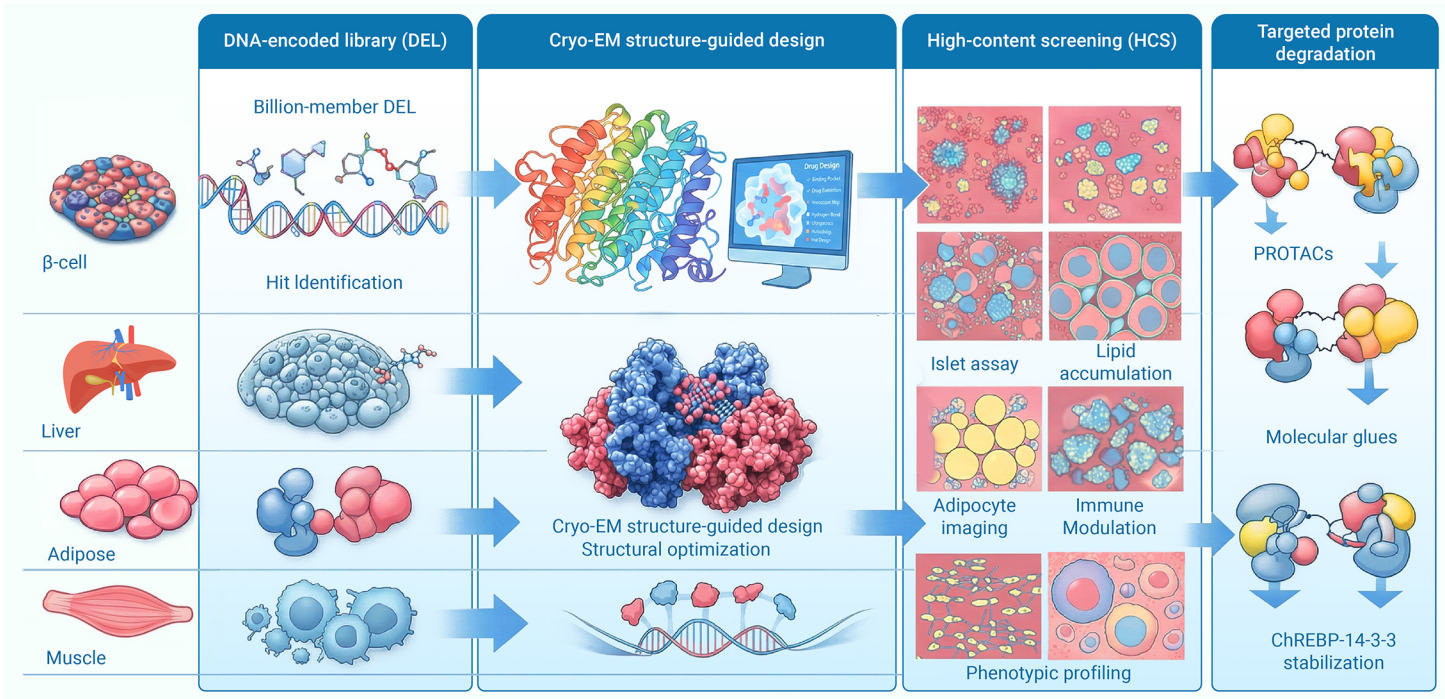

Figure 6. Chemical biology and screening innovation stack for diabetes drug discovery Overview of four complementary innovation pillars—DNA-encoded library (DEL) selections, cryo-EM structure-guided design, high-content screening (HCS) in disease-relevant cellular systems, and targeted protein degradation (TPD; PROTACs and molecular glues). The framework emphasizes tissue-anchored assay selection (beta cells, liver, adipose, muscle, and immune compartments), iterative translation from affinity hits to functional phenotypes, and modality switching when inhibition is insufficient.

useful when classical HTS struggles: dynamic enzymes and complexes; membrane proteins requiring stabilized constructs; and shallow or transient surfaces where conventional hit rates are low. Modern practice increasingly integrates DEL with orthogonal biophysics (SPR/DSF), medicinal chemistry, and cellular target engagement to rapidly convert enrichments into tractable SAR.

Cryo-EM has shifted structure-guided design from a bottleneck to an iterative engine for targets that are conformationally heterogeneous or hard to crystallize. This is especially impactful for incretin biology: Class B GPCRs (GLP-1R, GIPR, GCGR) and their multi-state activation cycles. Structures of GLP-1R bound to small-molecule agonists or ago-allosteric modulators have illuminated non-peptidic binding modes and provided templates to tune potency, bias, and receptor kinetics.[303–304]

Diabetes pathophysiology reflects networked tissue dysfunction: beta-cell stress and identity loss, hepatic glucose output, adipose inflammation and remodeling, and muscle mitochondrial deficits. HCS embraces this complexity by quantifying multi-parameter cellular phenotypes (morphology, organelle state, stress pathways) and converting them into phenoprints that can be clustered to identify MoA and de-risk toxicity.

Targeted protein degradation (TPD) encompasses heterobifunctional PROTACs and "molecular glues" that induce or stabilize productive interactions—often between a protein of interest and an E3 ligase—leading to ubiquitination and proteasomal degradation.[305-307] For metabolic biology, TPD is attractive when enzymatic inhibition is insufficient, when non-catalytic functions drive pathology, or when acute removal provides sharper target validation than genetic knockdown.

Drug delivery technologies

New developments of drug delivery technology will enable next-generation diabetes therapeutics, focusing on oral peptide platforms, long-acting injectable systems, and glucose-responsive smart-release technologies (Figure 7). Traditionally, peptide- and protein-based drugs such as insulin and GLP-1 receptor agonists require injection due to gastrointestinal degradation and poor epithelial permeability. Recent advances in peptide engineering, permeation enhancers, oral devices, and small-molecule biologic mimetics have revitalized this field.

Oral semaglutide (Rybelsus) represents the first approved oral peptide biologic for type 2 diabetes. Co-formulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, semaglutide achieves measurable systemic exposure when administered in the fasting stat.[308–309] Although bioavailability remains low (<1%), clinical efficacy has validated the concept of oral peptide delivery.[310]

Several oral insulin formulations are under development. ORMD-0801 uses enteric protection and protease inhibitors to enhance intestinal absorption and has demonstrated modest glucose-lowering effects in early trials.[311] Insulin tregopil (IN-105) is a fast-acting oral insulin analog designed for postprandial glucose control and has shown favorable pharmacodynamics in phase II/III studies.[312] Despite progress, achieving consistent exposure and avoiding hypoglycemia remain challenges.

Long-acting injectable formulations aim to reduce dosing frequency and improve adherence for peptide and protein therapeutics. Fc fusion proteins extend half-life through neonatal Fc receptor (FcRn)-mediated recycling and increased molecular size, reducing renal clearance.[313] This strategy is clinically validated across multiple biologic classes and remains attractive for incretin-based therapies for diabetes. XTEN technology employs genetically encoded, hydrophilic polypeptide chains that sterically shield the therapeutic payload, increasing hydrodynamic radius and prolonging circulation without chemical conjugation.[314–315] XTEN fusions offer precise molecular design and favorable manufacturability. Elastin-like polypeptides (ELPs) are thermoresponsive biopolymers that can form injectable depots in situ. These systems enable sustained release through temperature-triggered phase transition and have been explored for long-acting peptide delivery.[316] Additional half-life extension strategies, including fatty acid acylation, albumin binding, polymer microspheres, and crystalline depots, are often combined with these platforms to fine-tune pharmacokinetic profiles.

Glucose-responsive delivery systems aim to autonomously regulate insulin release in response to blood glucose levels, thereby reducing the risk of hypoglycemia. Three dominant glucose-sensing mechanisms are under investigation: glucose oxidase (GOx)-based enzymatic systems, phenylboronic acid (PBA)-based reversible glucose binding polymers, and lectin-based competitive binding systems.[317-319] Microneedle patches incorporating glucose-responsive vesicles or hydrogels represent a leading noninvasive approach, enabling painless administration and rapid glucose-triggered insulin release.[320–321] Injectable glucose-responsive hydrogels and nanovesi-

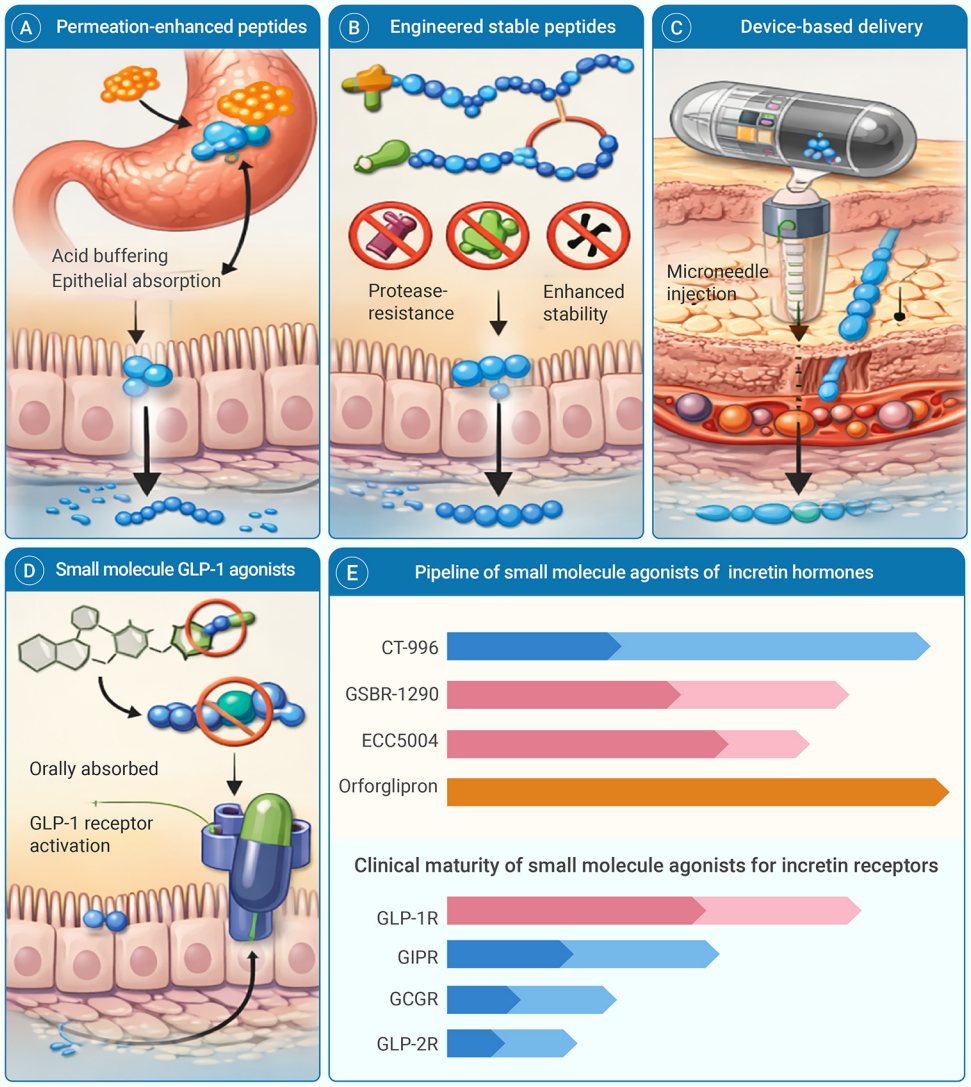

Figure 7. Strategies enabling oral delivery of diabetes medicines. Four complementary approaches are implemented to overcome gastrointestinal barriers and enable oral administration of biologic or small-molecule therapies for diabetes (A) Permeation-enhanced peptides, exemplified by oral GLP-1 receptor agonists co-formulated with absorption enhancers (e.g., SNAC), transiently buffer gastric acidity and increase epithelial permeability to facilitate transcellular uptake. (B) Engineered stable peptides incorporate chemical modifications such as lipidation, cyclization, and protease-resistant backbones to enhance stability in the gastrointestinal lumen and improve intestinal absorption. (C) Device-based oral delivery systems, including ingestible microneedles or robotic capsules, mechanically inject biologics across the intestinal wall, enabling injection-like pharmacokinetics independent of epithelial transport. (D) Small-molecule GLP-1 receptor agonists bypass peptide degradation entirely, achieving high oral bioavailability while directly activating incretin receptors, enabling once-daily or weekly oral dosing with improved gastrointestinal tolerability and clinically meaningful glycemic and weight-loss efficacy. (E) Pipeline of orally available small molecule agonists in clinical and preclinical development. Together, these strategies highlight distinct trade-offs in bioavailability, scalability, patient convenience, and translational readiness for next-generation oral diabetes therapies.

cles offer alternative depot-based strategies but face challenges in long-term stability and response kinetics. Key translational hurdles include ensuring rapid responsiveness, minimizing oxidative byproducts such as hydrogen peroxide, achieving sufficient insulin loading, and navigating regulatory pathways for combination products.

Advances in drug delivery technologies are central to the future of diabetes therapy. Oral peptide platforms promise improved patient convenience, long-acting injectables enhance adherence, and innovative glucose-responsive systems offer the potential for closed-loop control without external devices. Strategic platform selection should balance pharmacokinetics, safety, manufacturability, and clinical differentiation.

NEXT-GENERATION THERAPEUTIC CONCEPTS

Multiple gut-hormone agonists

Despite the clinical success of current incretin therapies, a substantial proportion of patients remain partial responders or experience weight-loss plateaus.[322] Multiple agonists seek to address this limitation by combining insulinotropic, anorectic, thermogenic, and gastric-emptying–modulating signals into a unified pharmacological profile (Figure 8).[322 323]

Recognition that GLP-1 and GIP act synergistically, and that glucagon, despite its hyperglycemic action, increases energy expenditure and reduces liver fat, led to the rational design of multi-agonist peptides.[324] Finan and colleagues showed that monomeric GLP-1/GIP/GCGR triagonists can reverse obesity and diabetes in rodents, inaugurating the "unimolecular polypharmacy" concept.[324] Clinical trials now show that Tirzepatide, a GLP-1R/GIPR co-agonist, outperforms semaglutide for HbA1c and weight, with structural studies revealing near-native GIPR agonism and cAMP-biased, less-internalizing GLP-1R activation.[325] GLP-1R/GCGR dual agonists such as cotadutide, IBI362/mazdutide, survodutide, pemvidutide, and efinopegdutide show superior weight loss and liver-fat reduction compared with GLP-1 monotherapy, though GCGR activity must be tightly controlled to avoid hyperglycemia and GI intolerance.[198,326] The GLP-1R/GIPR/GCGR co-agonist Retatrutide yields ≈24% weight loss at 48 weeks and strong glycemic and NASH improvements, apparently by combining GLP-1R-centric β-cell stimulation with GIPR-mediated CNS effects and GCGR-driven thermogenesis.[327] The unimolecular GLP-1R/AMYR co-agonist amycretin (NNC0487-0111) shows nanomolar potency at GLP-1R and multiple AMYRs, penetrates key brain regions, drives profound weight loss largely via reduced energy intake, attenuates the fall in total energy expenditure during weight loss, and improves MASLD and insulin sensitivity in rodents; early human data show weight loss on par with leading triagonists.[328–329] These advances reflect a shift from "GLP-1 replacement" toward engineered multi-receptor bias that distributes tasks across GLP-1R (glucose control, CV benefit), GIPR (β-cell and CNS modulation, nausea attenuation), GCGR (catabolism, liver health), and, increasingly, AMYR.

There is no fixed set of quadruple gut-hormone agonists yet. But most quad-agonist concepts involve GLP-1 receptor activation for glucose-dependent insulin secretion and appetite suppression;[89] GIP receptor activation for β–cell support and insulin sensitivity;[330] glucagon receptor activation for increased energy expenditure and lipid oxidation;[331] and a fourth satiety-focused pathway, such as amylin or cholecystokinin A receptor or FGF21 signaling.[97]

In addition to the benefits of multi-incretin receptor agonists, the multi-agonism strategy may overcome some sid-effects of GLP1R agonist drugs, such as sarcopenia. Dual and triple agonists (e.g., GLP-1/GIP or GLP-1/GIP/GCGR) may improve nutrient partitioning, promote adipose-specific fat loss rather than systemic tissue loss, and increase energy expenditure.[332] Notably, GIP receptor activation has been hypothesized to exert anabolic or anti-catabolic effects in adipose and potentially muscle tissue, partially offsetting lean mass loss.[333] In addition, development of GLP-1R agonists with reduced CNS penetration or altered signaling bias may decouple appetite suppression from excessive catabolic signaling.

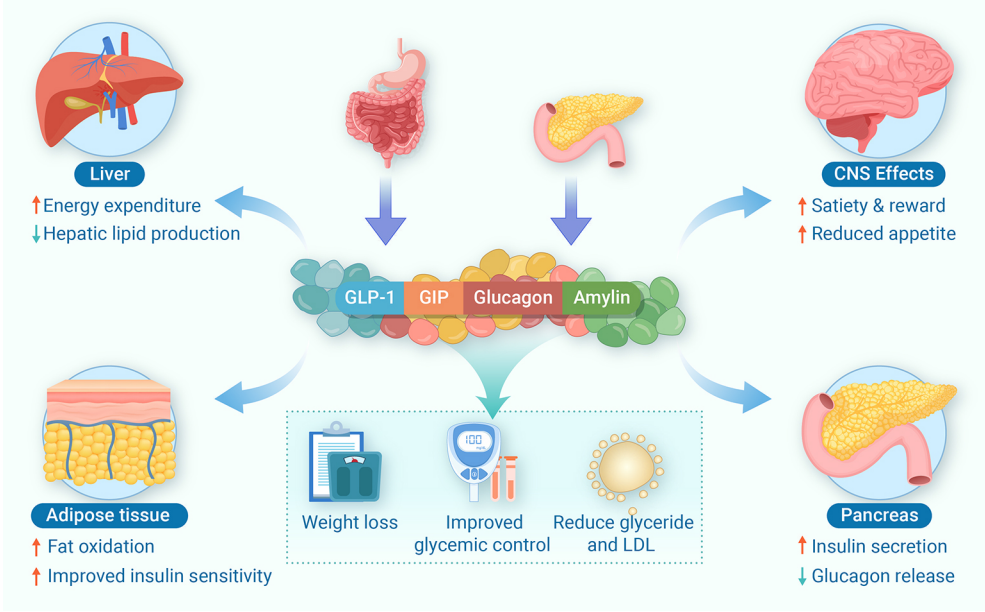

Figure 8. Mechanistic framework for quadruple gut-hormone agonists The integrated mechanism of action of a unimolecular quadruple gut-hormone agonist that engages GLP-1R, GIPR, GCGR, and a fourth satiety receptor (amylin or CCK) enables simultaneous control of diabetes and obesity. Central nervous system effects include appetite suppression, enhanced satiety, and reduced food reward. Peripheral effects include glucose-dependent insulin secretion from pancreatic β-cells, suppression of glucagon during hyperglycemia, increased hepatic lipid oxidation and energy expenditure, delayed gastric emptying, and improved triglyceride and VLDL metabolism. Balanced receptor bias is required to maximize metabolic efficacy while minimizing gastrointestinal and glycemic liabilities.

Oral small molecule agonists for incretin receptors

Orally available small-molecule GLP-1 receptor agonists represent a novel strategy in the next wave as they can provide potential favorable biased signalings and convenience of dosing. Pioneered by the non-peptide agonist Boc5 and then by the first orally available small-molecule agonist, the ARX series of compounds, for the GLP1 receptor, small-molecule GLP-1 receptor agonists are currently actively pursued worldwide.[334–335] Orforglipron is a small-molecule GLP-1 receptor agonist with oral bioavailability and no need for permeation enhancers. Phase III data demonstrate clinically meaningful reductions in HbA1c and weight, comparable to injectable GLP-1 therapy, and have just received speedy approval by the FDA.[336] However, oral small-molecule agonists face challenges related to gastrointestinal tolerability and the risk of hepatotoxicity over the long term in clinical practice. Oral small molecules may exhibit greater variability in absorption and peak plasma concentrations, which can exacerbate GI symptoms in some patients. Dose titration strategies are therefore critical to improve tolerability and adherence. While GI adverse effects are predictable and generally manageable, long-term hepatic safety requires continued monitoring in larger and more diverse populations to fully characterize risk.

Metabolism–immunity hybrid therapeutics

Diabetes, particularly type 2 diabetes (T2D), is increasingly recognized as a systemic immunometabolic disorder rather than a purely glucose-centric disease.[35] Chronic nutrient excess, lipid spillover, and ectopic fat deposition activate innate and adaptive immune pathways, leading to metaflammation, insulin resistance, and progressive β-cell dysfunction.[337–338] This evolving understanding has catalyzed the concept of next-generation metabolism–immunity hybrid therapeutics, which intentionally co-target metabolic flux and immune state as an integrated treatment paradigm.

One promising strategic direction is the development of triglyceride -first, weight-neutral cardiometabolic backbones paired with immune modulation. Therapies targeting ApoC-III or ANGPTL3 effectively lower VLDL-TG and remnant lipoproteins, thereby reducing lipotoxic stress in the liver, muscle, and pancreas.[174,238] However, lipid-lowering alone may be insufficient once immune activation is established. Hybrid strategies therefore incorporate immune-suppressing modules, such as CCR2/CCR5 inhibition to limit monocyte recruitment, NLRP3–IL-1β axis modulation to damp inflammasome signaling, or activation of resolution pathways that promote the termination of inflammation rather than chronic suppression.[339-341]

A second frontier lies in tissue-targeted immunometabolic reprogramming, where delivery specificity becomes the key innovation. Hepatocyte-directed metabolic therapies can indirectly normalize Kupffer cell activation by reducing damage-associated molecular patterns and mitochondrial stress.[342] Similarly, adipose tissue–targeted approaches aim to reprogram macrophage and T-cell phenotypes toward lipid-handling and reparative states, thereby restoring insulin sensitivity without systemic immunosuppression.[343] In pancreatic islets, localized immune modulation paired with β-cell metabolic support could preserve insulin secretory capacity, particularly in early disease stages.[344]

Borrowing concepts from oncology, immunometabolic checkpoints are emerging as attractive targets. Pathways such as mTOR, AMPK, STING, and TREM2 integrate nutrient sensing with immune activation, offering opportunities to recalibrate inflammatory tone under metabolic stress.[345-347] The gut–immune–metabolic axis further expands the hybrid concept. Modulation of bile acid signaling, gut barrier integrity, and microbial-derived immune cues can reset systemic inflammatory setpoints while supporting metabolic control.[348] Importantly, the therapeutic goal is not uniform macrophage M2 polarization but the induction of functionally appropriate immune states that support tissue remodeling and metabolic homeostasis.

Despite compelling evidence that targeting inflammatory pathways such as NLRP3 and CCR2 improves metabolic outcomes in preclinical models, translation into effective and safe therapies for human diabetes has been challenging. This discrepancy reflects fundamental differences between experimental systems and the clinical setting. Animal models often represent acute or genetically homogeneous disease states, whereas human diabetes is heterogeneous, chronic, and influenced by diverse genetic, environmental, and metabolic factors.[349] As a result, anti-inflammatory interventions that show robust efficacy in controlled models may yield only modest or variable benefits in patients. Several factors key considerations need to be considered: (i) differences between animal models and human diabetes (e.g., immune system complexity, chronicity of disease, comorbidities); (ii) the need for biomarker-driven patient stratification to identify subgroups most likely to benefit from anti-inflammatory therapies; (iii) optimization of dosing and tissue targeting to minimize systemic immunosuppression; and (iv) incorporation of translational endpoints (e.g., inflammatory biomarkers, insulin sensitivity measures) in early-phase trials. Addressing these factors will be essential for advancing anti-inflammatory therapies from experimental promise to clinical reality in diabetes.

Finally, the future of metabolism–immunity hybrids will be defined by biomarker-driven patient stratification. Distinct mechanistic subtypes—lipid-dominant, inflammasome-dominant, chemokine-driven, or fibrosis-predominant—can guide rational combination design and improve clinical success rates.[350] Collectively, these perspectives suggest that next-generation diabetes therapeutics will move beyond glucose-lowering toward integrated immunometabolic restoration with durable, organ-protective outcomes.

Personalized metabolic therapy (AI-guided)

Metabolic diseases, including type 2 diabetes, obesity, and cardiometabolic syndromes, are not unitary disorders but heterogeneous constellations of dysfunction spanning liver, adipose tissue, skeletal muscle, pancreas, immune system, and gut.[30,33,281,353] Despite this complexity, current therapeutic strategies remain largely population-averaged, optimized for mean reduc-

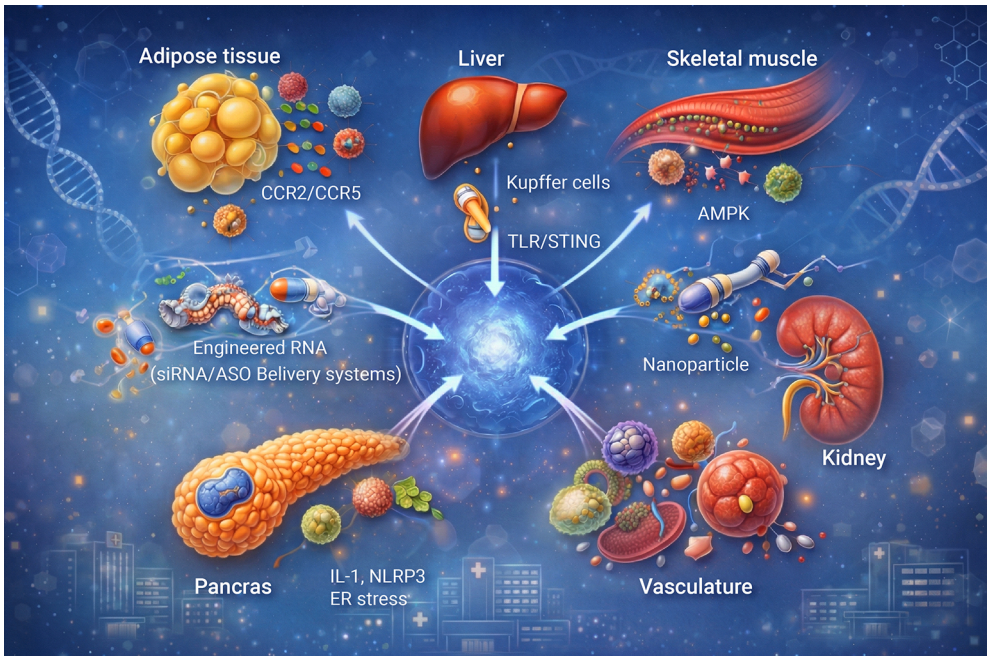

Figure 9. Future tissue-targeted immunometabolic reprogramming strategies A next-generation therapeutic paradigm of immune-state editing precisely targetes to metabolic organs to restore systemic metabolic homeostasis in diabetes and related cardiometabolic diseases. Distinct tissues—including adipose tissue, liver, skeletal muscle, pancreas, and vasculature/kidney—are shown as coordinated intervention sites connected through a central reprogramming hub. In adipose tissue, modulation of CCR2/CCR5-dependent myeloid recruitment and inflammatory signaling reduces macrophage-driven lipolysis and lipid spillover. In the liver, tuning of Kupffer cell activity and innate sensing pathways (TLR/STING) alleviates sterile inflammation and improves hepatic insulin sensitivity. In skeletal muscle, activation of AMPK–mitochondrial pathways counteracts inflammatory stress signaling to enhance glucose uptake. In pancreatic islets, suppression of IL-1/NLRP3 signaling and ER stress preserves β-cell function and identity. In the vasculature and kidney, immune reprogramming dampens endothelial and myeloid inflammation to confer cardio-renal protection. These tissue-specific effects are enabled by emerging precision delivery technologies, including engineered RNA therapeutics (siRNA/ASO), targeted nanoparticles, and biased biologics, which converge to re-establish immunometabolic balance while minimizing systemic immunosuppression.

tions in HbA1c or body weight rather than individual causal biology. This mismatch contributes to variable efficacy, adverse effects, and prolonged trial-and-error prescribing.[33,352]

Personalized AI-guided metabolic therapy represents a conceptual shift from disease-label-driven care toward mechanism-informed treatment and intervention (Figure 9). By integrating multi-omics data with dynamic physiological signals such as continuous glucose monitoring, lipid flux, imaging, and immunometabolic biomarkers, artificial intelligence can infer individualized metabolic mechanism fingerprints.[351,353–354] These latent states capture dominant drivers of disease, including hepatic gluconeogenesis, triglyceride-driven insulin resistance, adipose inflammation, or mitochondrial inefficiency, providing actionable targets beyond conventional clinical metrics.

A defining advance in this paradigm is the emergence of digital metabolic twins—computational models that simulate organ-level glucose, lipid, and energy fluxes for an individual patient (Figure 9).[354–355] Parameterized by AI-inferred mechanisms, these twins enable in silico testing of drug classes, combinations, and dosing strategies, allowing prediction of efficacy, durability, and safety before clinical deployment. This approach replaces empirical stepwise escalation with rational, hypothesis-driven therapy selection and sequencing.

Beyond individual care, this framework has major implications for drug development and clinical trials. AI-enabled stratification can enrich studies for mechanism-matched responders, reduce sample sizes, and accelerate development timelines.[356–357] Over time, regulatory paradigms may shift toward mechanism-defined indications and adaptive treatment algorithms supported by real-world evidence.

CONCLUSION

Future diabetes drug discovery will be increasingly shaped by the convergence of metabolic biology, including lipidomics, immunology, and artificial intelligence. From a metabolic perspective, effective therapies must simultaneously address hepatic glucose production, insulin sensitivity, adipose tissue, chronic inflammation, and energy balance. Multi-agonist gut-hormone therapies exemplify this systems-level approach by coordinating glucose control, appetite regulation, and energy expenditure across organs. The future diabetes drug discovery will shift from short-term glycemic control to durable disease modification, with emphasis on disease pathology improvements, β-cell preservation, insulin sensitivity, and long-term cardio–renal and hepatic outcomes.

Future diabetes drug discovery will shift from short-term glycemic control to durable disease modification, with an emphasis on improvements in disease pathology, β-cell preservation, insulin sensitivity, and long-term cardio–renal and hepatic outcomes, guided by several strategic priorities.

(1) Advance polypharmacology and multi-organ targeting, including next-generation incretin and gut-hormone poly-agonists optimized for efficacy, tolerability, and body composition.

(2) Prioritize β-cell protection, redifferentiation, and regeneration through stress-resilience pathways, senescence modulation, and cell-replacement strategies.

(3) Establish immunometabolism as a core therapeutic axis by modulating inflammatory tone, macrophage polarization, and gut barrier integrity rather than broad immunosuppression.

(4) Deploy artificial intelligence as the integrating engine for precision medicine through patient stratification, biomarker-guided intervention and therapy selection, and adaptive trial designs that reflect disease heterogeneity.

(5) Expand therapeutic modalities beyond traditional small molecules and peptides to include oral biologics, RNA-based medicines, herbs, and targeted protein degradation.

The strategy for diabetes control in the coming decades will focus on modifying disease-driving pathologies, precision interventions, and AI-driven therapy. Both interventions and therapies will employ combinatorial modalities that target multiple pathways and organs based on individual phenotypes.

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AUTHOR CONTRIBUTIONS

J.L. was responsible for the overall organization, the first draft, and correspondence during submission and revision. Z.C. and H.Q. were responsible for sections on the Gut–pancreas–liver- muscle- adipocyte- brain axis and its deficiency, GLP-1 Therapeutics, and Receptors of fatty acids and bile acids as emerging targets. F.L. and K.L. were responsible for sections on insulin and insulin analogs, DPP-4 inhibitors, and SGLT2 inhibitors. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

Jiayu Liao is an inventor for the patent *US Patent*WO2011097300A1 and a consultant for Attaisina Inc and Augusina Bioscience Inc. Jiayu Liao also is an Editorial Board member of The Innovation Drug Discovery and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.

DATA AND CODE AVAILABILITY

Not applicable.

SUPPLEMENTAL INFORMATION

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