Innovative molecules and delivery technologies enabling the future of GLP-1-based therapies

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Abstract

The multiple physiological effects of gut hormones in different metabolic tissues make them attractive therapeutic targets for the treatment of metabolic diseases. Currently, only GLP-1 receptor-based agonists and oral DPP-4 inhibitors are available on the market. Despite their positive clinical outcomes across a range of indications these treatments present several clinical challenges, including high costs, the need for peptide injections, and requirements for repeated administration. These limitations have driven research into improved GLP-1-based therapies, such as oral small-molecule agonists and novel drug delivery strategies based on emerging GLP-1 medicines. This article describes the challenges in clinical application and development of GLP-1-based pharmacotherapies. We review the development of oral small-molecule agonists and various drug delivery technologies, including ultralong-acting injectable technologies, continuous-acting implantable pumps, smart-acting electronic devices, nutrient-induced cell therapies, and noninvasive delivery systems. We discuss the current state of research, challenges to overcome, and opportunities to improve patient compliance and clinical outcomes. Additionally, we explore how endocrinological effects and patient-oriented needs can guide the development of advanced GLP-1 medicines.

Key words

Innovative technologies; glucagon-like peptide 1 (GLP-1); GIP; diabetes; obesity; weight loss; metabolic disorders

Essential Points

- Gut hormones are involved in a wide range of metabolic processes, making them an attractive therapeutic target for the treatment of metabolic diseases.
- Most GLP-1 medicines currently require weekly injection.
- Innovative technologies enable the development of advanced GLP-1 medicines, with an increased therapeutic efficiency and improved patient compliance.
- Small molecule GLP-1RAs may increase the supply and ease of use of GLP-1 therapies
- Innovative delivery systems such as oral lipid nanoparticles and ingestible electrical devices may provide new options for GLP-1 therapy.
- Smart electronic devices combined with programmed engineered cells may provide advanced options and personalized technology for GLP-1 delivery.
- Most innovative strategies, such as ultralong-acting injection technologies, noninvasive drug delivery technologies, smart electronic devices, implant pumps, and cell therapy, are still in their infancy and need to be validated in large animal models and humans.

1. Introduction

Incretins, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are secreted by enteroendocrine cells and classically potentiate meal-stimulated insulin release. GLP-1 and to a lesser extent, GIP, also coordinate a range of physiological processes, including the reduction of glucagon release, gut motility and food intake, as well as a reduction in glycogen synthesis, lipid deposition, and systemic inflammation (1-5). The potential beneficial effects of gut hormones on different metabolic processes and the specific understanding of these effects on the physiological regulation of different tissues has sparked interest in the development of GLP-1-based pharmacotherapies for the treatment of different metabolic diseases, such as type 2 diabetes mellitus (T2DM) and obesity. There are two types of incretin-based pharmacotherapies: oral dipeptidyl peptidase-4 inhibitors (DPP-4i) (6,7), which prevent proteolytic breakdown and inactivation of natural incretin hormones, and GLP-1 medicines (including GLP-1 receptor agonists (GLP-1RAs) and GLP-1/GIP receptor co-agonists) (8-10), which provide a supraphysiological concentration of ligands that stimulate the targeted receptors.

Over the past two decades, incretin-based pharmacotherapies have provided significant benefits for patients with T2DM (6,10). Among them, DPP-4i have modest benefits for blood glucose control and have no meaningful effect on weight loss. As a result, more potent GLP-1 medicines have gained increasing attention, not only for their effective role in the treatment of obesity and T2DM (11) but also for the clinical evidence of their benefit in cardiovascular disease, metabolic dysfunction associated steatotic liver disease (MASLD), diabetic kidney disease, sleep apnea, and osteoarthritis (12-17). However, most GLP-1 medicines, with the exception of oral semaglutide, are injectable. The injection route is a source of inconvenience and discomfort for some patients,

who may experience pain, local allergic reactions, and rarely, scarring and infection (18-20). These harmful effects can lead to poor adherence by patients, especially those with chronic diseases that require long-term therapy. Therefore, extensive research efforts have explored the feasibility of improving patient compliance, optimizing therapeutic efficiency and reducing administration frequency through various innovations, including development of oral small molecule agonists and a variety of delivery techniques for GLP-1 medicines, including sustained release (21), controlled release (22), or gene therapy strategies (23), as well as the possibility of alternative delivery routes, including transdermal (24), pulmonary (25), nasal (26), or oral (27) administration. Innovative oral small-molecule GLP-1R agonists (GLP-1RAs) and peptide-based drug delivery technologies are emerging that may provide patients with more convenient, painless and diverse therapeutic alternatives.

In this review, we briefly describe control of incretin hormone release and its multiple physiological actions. We define key physiological processes regulated by these hormones in different metabolic tissues and then outline the development and limitations of current incretin-based pharmacotherapies in patients. To improve clinical benefits and patient satisfaction with GLP-1 medicines, the development, advantages and challenges of oral small-molecule agonists and various drug delivery strategies are described in detail.

2. Incretins: From discovery to physiological roles in metabolic syndrome

The most important incretin hormones are GIP (the first incretin hormone identified in 1971), which is released by enteroendocrine K cells in the upper intestine, and GLP-1 (identified in the early 1980s), which is secreted by enteroendocrine L cells located mainly in the distal intestine

(28). Both hormones are secreted from the intestine in the basal state, and secretion is increased in response to nutrients (such as carbohydrates and lipids). These hormones then interact with their receptors (GIP receptor (GIPR) and GLP-1 receptor (GLP-1R), respectively) expressed in the pancreas, leading to augmentation of insulin secretion from β-cells in a glucose-dependent manner (29). The preferential insulinotropic effect of oral vs. intravenous glucose (up to 70% better), which is also referred to as the incretin effect, reflects the actions of GIP and GLP-1 to potentiate insulin secretion following oral nutrient ingestion. Exploiting the incretin effect, the body can mitigate the development of hyperglycemia despite substantial amounts of ingested glucose (2). In addition to their insulinotropic effects, GIP and GLP-1 play key roles in a variety of physiological processes in different cells and tissues that express GIPR and GLP-1R, including the pancreas, brain, bone cardiovascular and immune systems (30) (Fig. 1). These actions have contributed to the attenuation of diseases associated with the so-called *"metabolic syndrome"* (31). However, the physiological actions of native GIP and GLP-1 are transient due to renal clearance and the enzymatic cleavage and inactivation by DPP-4 (32). The plasma half-life of native GLP-1 and GIP is very short, approximately 1-3 min, in the presence of the DDP-4 enzyme.

3. Incretin-based pharmacotherapies

Over the past few decades, interest in the use of incretin-based pharmacotherapies to ameliorate obesity, diabetes and other obesity-related metabolic conditions (such as MASLD) has increased (33). Fig. 2 shows the timeline of incretin-based pharmacotherapy development. As early as 1987, researchers demonstrated that porcine GIP did not stimulate insulin secretion in people with T2DM (34). Owing to the controversy over the physiological efficacy of GIP agonists and antagonists, and the limited efficacy of GIP alone in people with T2DM, no products have been developed that

rely on GIP alone. In contrast to GIP, GLP-1 was the first incretin hormone to be developed therapeutically. Currently, therapy with a class of GLP-1RAs, for which the half-life is increased through the use of different chemical structures (for example, by tagging a fatty acid or recombinant human albumin to the analog) (35), is well established (Fig. 2). GLP-1RAs exert metabolic benefits to lower glycemia and body weight while conferring cardiovascular protection (36). DPP-4i, a second class of incretin therapies, have been available on the market since 2006. DDP-4i are rationally designed on the basis of the therapeutic and physiological effects ensuing from potentiation of endogenous GLP-1 and GIP action. DDP-4i are all small, orally available molecules and do not exert a glucose-lowering effect by themselves. They interact with the catalytic site of the DPP-4 enzyme without affecting any of its known non-enzymatic functions, thereby increasing the active levels of GLP-1 and GIP (6).

Recently, several second-generation GLP-1 medicines have attracted particular interest, including the GLP-1RA semaglutide combined in the same delivery device with an amylin receptor agonist (cagrilintide) (37), the unimolecular GIP/GLP-1 receptor coagonist tirzepatide (38), the GCG/GLP-1 dual agonist survodutide, a human monoclonal antihuman GIP receptor antagonist antibody conjugated to two GLP-1 agonist peptides (AMG 133 or maritide) (39), and a GCG/GIP/GLP-1 triple agonist (retatrutide) (40). Compared with GLP-1RA monotherapy, these multiagonist GLP-1 medicines exhibit greater therapeutic effectiveness in clinical trials and/or in real-world use for obesity and T2DM. The development of oral small-molecule GLP-1RAs has progressed rapidly in the clinic (41-43). Furthermore, gene therapy based on GLP-1 has also attracted intensive interest. GLP-1-based gene therapy is primarily designed to provide long-term metabolic benefits with a single dose (23). Although there are no gene therapy GLP-1 initiatives

in late-stage clinical trials, gene therapy approaches have exhibited substantial efficacy in preclinical studies evaluating the regulation of metabolic disorders. Many of the new GLP-1 medicines show weight loss efficacies that are now similar to those of bariatric surgery (36). With the success of the development of highly effective GLP-1 medications with tolerable side effects, the demand for this class of drugs has increased among individuals living with metabolic syndrome (especially patients living with obesity and/or T2DM), further promoting enthusiasm for the development of new and more advanced GLP-1-based therapies.

4. Limitations to currently available GLP-1 therapies

DPP-4i and GLP-1-based peptides are well-established therapies used in the clinical setting (Table 1). The currently available DPP-4i are alogliptin (25 mg once-daily dosing), linagliptin (5 mg once-daily dosing), saxagliptin (5 mg once-daily dosing), sitagliptin (100 mg once-daily dosing) and vildagliptin (50 mg twice-daily dosing) (6,44). The currently available GLP-1-based medicines are exenatide, lixisenatide, liraglutide, dulaglutide and semaglutide (45) along with the GIP/GLP-1 coagonist tirzepatide (46,47). The chemical structures, therapeutic mechanisms, administration doses, administration frequencies, benefits and potential risks of DPP-4 inhibitors and GLP-1-based peptides have been reviewed elsewhere (6).

Substantial real-world data supports the efficacy and long-term safety of GLP-1 medicines since the first drug, exenatide, was approved in 2005. Nevertheless, some limitations exist for marketed incretin-based drugs. For example, although DPP-4i are easy to use (oral dosage), their ability to increase active levels of GLP-1 and GIP is limited (only ~2- to 3-fold), their actions to reduce blood glucose levels is modest, and they are inefficient at reducing body weight (48). To achieve

greater blood glucose control, DPP-4i are often used in combination with other glucose-lowering therapies, such as insulin, metformin and sodium–glucose transporter 2 (SGLT2) inhibitors (49-51). Owing to these limitations, the main focus of drug development is the improvement of the activity, frequency of administration and tolerability of GLP-1RAs. GLP-1-based receptor agonism has exhibited considerable benefits in glucose control and weight management; however, all the available agents are peptides and most are injectable, often contributing to suboptimal compliance for patients with chronic diseases (e.g., T2DM). Oral semaglutide, coformulated with the absorption enhancer sodium N-(8-[2-hydroxylbenzoyl] amino) caprylate (SNAC), is the first oral GLP-1RA product approved by the U.S. Food and Drug Administration (FDA), which fills the gap in the field of the oral delivery of GLP-1 medicines (52). Nevertheless, the permeation enhancer SNAC is inefficient to enhance drug absorption when it is co-formulated with other GLP-1RAs (e.g., liraglutide (52)). In addition, oral semaglutide is effective only when it is taken on an empty stomach. Specifically, the use of oral semaglutide tablets must follow a strict overnight fasting rule and require no further intake of food, liquids, or medications for 30 minutes or more after oral administration (53). Moreover, its oral bioavailability is still extremely low (0.4% to 1%) (54). Overall, the limitations (Table 1) of currently available GLP-1 medicines highlight the need for technological innovations that increase therapeutic efficiency, tolerability and patient compliance.

5. Advanced GLP-1 medicines: Development

The clinical success of drugs based on the incretin effect represents a significant advance in treatment areas such as diabetes and obesity. Despite the limitations of current clinical drugs, these findings provide an opportunity for the development of new drugs and new drug delivery

techniques to improve patient compliance and enhance drug effectiveness. Combined with the production, action and metabolic mechanism of incretin hormones, advanced incretin-based therapies currently being developed include mainly oral small-molecule agonists, new peptide based multi-agonists and novel delivery strategies based on potentiation of GLP-1 action.

5.1 Oral small-molecule agonists

Currently, most clinically used GLP-1 medicines are peptide drugs derived by modifying the sequence or structure of natural gut peptides. Peptide agonists must traditionally be injected, which has prompted researchers to develop and synthesize nonpeptide agonists for oral administration. Nutrients in the gut induce the secretion of gut hormones by stimulating G protein-coupled receptors (GPCRs) (e.g., GPR40 and GPR119) expressed in intestinal endocrine cells (55,56) and then act on the corresponding receptors (e.g., GLP-1 receptors (57,58)) in different tissues and organs to mediate different metabolic activities (Fig. 1). With the help of artificial intelligence and structural biology, the discovery of active protein pockets in targeted receptors and the design and screening of active small molecules continues to progress (59,60). The development of oral small-molecule drugs based on GLP-1 has focused on agents directly targeting the GLP-R, as well as on drugs acting on the receptors expressed on enteroendocrine cells to promote the secretion of endogenous gut peptides. Notably, several oral small-molecule GLP-1RAs have shown effective blood glucose reduction and weight loss (Table 1). Several drugs have also demonstrated reasonable safety and tolerability profiles, unlike other oral small-molecule agonists based on potentiation of GLP-1 secretion (e.g., GPR40 and GPR119 agonists). Compared with injectable peptide GLP-1RAs, small-molecule GLP-1RAs are more convenient for oral administration and

have no fasting restrictions (45,61). Therefore, in this section, we introduce the development of oral small-molecule GLP-1RAs.

5.1.1 Orforglipron (LY3502970)

Orforglipron (LY3502970) has a half-life of 29 to 49 h and is taken orally once daily to improve blood glucose control and promote weight loss (42,62,63). Orforglipron is highly selective and acts only on GLP-1 receptors and not on other GPCR class B receptors (62). Unlike the mode of action of the peptide GLP-1RAs, orforglipron is a biased agonist of GLP-1R and has a greater effect on cyclic adenosine monophosphoric acid (cAMP) signaling than on β-arrestin recruitment (62,64). Clinical trials have demonstrated that orforglipron reduces glycemic levels by stimulating insulin secretion and inhibiting glucagon secretion and can also delay gastric emptying and act on the CNS to reduce appetite and food intake, showing promising therapeutic effects in the treatment of T2DM and obesity/overweight (42,63,65-67). In phase 2 clinical trials (NCT05048719, NCT05051579), assessing up to 36 weeks of dosing, 12 mg or more of orforglipron was found to significantly reduce hemoglobin A1C (HbA1c) (by up to 2.1%) and body weight (by up to 10.0%) compared with weekly GLP-1RA dulaglutide (1.1% and 4.0% for reduced HbA1c and body weight, respectively) (42,63). The safety profile of orforglipron was reported to be similar to that of dulaglutide (63). Multiple phase 3 clinical studies of orforglipron are studying its efficacy and safety in the treatment of obesity, overweight and T2DM in adults (NCT06584916, NCT06192108, NCT06109311, NCT06010004, and NCT06045221), as well as in adolescents (NCT06672939).

5.1.2 Danuglipron (PF-06882961)

Danuglipron (PF-06882961) is an oral small molecule GLP-1RA, with a molecular weight of 555.6 Daltons (61,68). The action of danuglipron on the binding pocket of GLP-1R requires a primate-specific tryptophan 33 residue, enabling the molecule to activate GLP-1R in primates and humans (68). Danuglipron also has good therapeutic effects on reducing blood glucose and weight loss. Its mechanism of action is similar to that of orforglipron, which has a strong and potent effect on cAMP signaling (the half-maximum effective concentration (EC50) is 13 nM) (61). Danuglipron was initially administered twice daily, with patients receiving the highest dose (120 mg twice daily) experiencing a 1.16% reduction in HbA1c and 4.17 kg weight loss after 16 weeks of treatment (43). Doses of 40 mg or less (twice daily) were not effective for weight loss after 16 weeks of therapy (43). However, tolerability was poor with twice daily danuglipron, prompting assessment of extended-release formulations of danuglipron suitable for once daily administration. The pharmacokinetic profile of the preferred modified release formulation has been shown to support once-daily dosing, and its safety is consistent with that of the previous phase 2b clinical study of danuglipron, (NCT06153758). Dose optimization studies have been conducted for optimizing a modified release formulation of danuglipron (69).

5.1.3 Other oral small-molecule GLP-1RAs

More than a dozen oral small-molecule GLP-1RA drug candidates have entered clinical trials. These molecules act in a similar manner at the GLP-1 receptor, mainly potentiating cAMP signaling (70-73). Phase 2 trials have studied orforglipron, danuglipron, as well as HDM1002 (NCT06481085, NCT06500299), GSBR-1290 (NCT05762471, NCT06693843), TTP-273 (NCT02653599), and RGT001-075 (NCT06277934, NCT05297045).

5.2 GLP-1 medicine drug delivery strategies

Short-acting GLP-1 medicines (e.g., exenatide) or orally administered DPP-4i do not exert sustained GLP-1R activation sufficient to produce robust reductions in HbA1c and body weight. Over the past decade, modifying the chemical structure of GLP-1 has resulted in several long-lasting GLP-1RAs (albiglutide, dulaglutide and semaglutide) (74,75). However, these drugs still need to be injected weekly. Long-term injections of drugs for chronic diseases, such as cardiometabolic disorders can pose a challenge to medication adherence, even for once-a-week therapies (76). Typical adverse effects include aversion to injections, concerns about discomfort at the injection site, cost, and more rarely, infections (18). Currently available GLP-1RAs with extended half-lives are effective for up to a week following one single dose and improving on pharmacodynamic activity by structural modification of GLP-1 analogs alone may not be easy to achieve (77) (Fig. 2). In many fields, drug delivery technological developments have facilitated the development of new drugs to improve patient health by maximizing therapeutic efficacy and promoting patient compliance (78). At present, emerging GLP-1 medicine release technologies are based on controlled release, smart release or endogenous simulation release, which are accomplished mainly through nanotechnologies, microneedle-based technologies, implantable materials, gene therapies or noninvasive delivery technologies (Fig. 3).

5.2.1 Ultralong-acting injectable technologies

Injectable microspheres and nanoparticles

Drug carriers, such as polymeric and lipid-based particles, have been exploited to extend drug action time by improving their pharmacokinetic and pharmacodynamic properties (79-83).

Currently, exenatide once weekly (EX-OW) is the only sustained-release GLP-1RA formulation on the market that extends the action of exenatide by subcutaneous controlled release, from two daily injections to one weekly injection, by encapsulating exenatide within polylactic acid-glycolic acid (PLGA) microspheres (84). While the once-a-week PLGA microsphere injection form is much more effective than exenatide alone, EX-OW which was developed in 2012, is not currently an ultralong-acting form that is clinically advantageous, as numerous once-a-week GLP-1 medicines are now available that show better therapeutic outcomes in reducing blood glucose levels and body weight (46,47,85,86). The sustained release effect observed with PLGA microspheres also extended the actions of liraglutide and semaglutide in preclinical studies. The pharmacokinetic release profile of PLGA microspheres prepared by ultrasonic spray drying increased from one day to one week (liraglutide) and from one week to four weeks (semaglutide) in rats (87). Liraglutide-loaded injectable microspheres prepared via a double emulsion method provided controlled release of the incorporated drug for up to ~ 30 days (88). In addition to PLGA microspheres, other drug carriers have also been explored. For example, a polyphenol–metal nanoparticle platform was designed for tunable release of liraglutide. Hydrogen bonds were formed between liraglutide and tannic acid, thereby forming a complex coordination interaction between tannic acid and Al^{3+}, which resulted in the sustained release of liraglutide for over 8 days, maintaining a lower blood glucose level for over 6 days in a T2DM *db/db* mouse model (89). Sustained-release nanotechnology can be used to package drugs in well-ordered hexagonal mesoporous silica structures or PLGA microspheres containing lecithin nanoparticles, which have shown highly prolonged hypoglycemic effects with exenatide that could last for 25 days in mice (90) and 30 days in rats (91), respectively. These drug carriers improve pharmacokinetics primarily by controlling drug release and avoiding rapid drug clearance in the body.

Injectable gene therapy approaches

Gene therapy can correct or compensate for disease symptoms caused by mutated genes by introducing exogenous wild-type genes, which has been proven to be a promising approach in multiple fields of medicine, such as coronavirus infection (92), cancer (93) and cystic fibrosis (94). One of the greatest advantages of gene therapy is that some diseases can potentially be cured with a single treatment, which is undoubtedly promising for patients with chronic diseases. Experimental viral and nonviral gene delivery strategies are under development to provide constant GLP-1 release to regulate glucose homeostasis, increase insulin secretion and reduce weight gain (95-99). Nonviral GLP-1-based methods for gene delivery, such as the polyethylenimine/plasmid GLP-1 complex system (100) or plasmid GLP-1-loaded chitosan nanoparticles (96), have shown promising results in controlling blood glucose levels and increasing insulin secretion but only for approximately two weeks in a diet-induced mouse model. Viral gene delivery methods, especially adeno-associated virus (AAV) vectors, have been widely applied owing to their advantages in terms of high *in vivo* efficacy, non-pathogenicity and immunogen evasion (101). A single injection of a GLP-1_{7-37}-encoding double-stranded AAV vector increased both insulin and circulating GLP-1 levels in mice for up to 4 months in *db/db* obese mice (102). Notably, the preclinical data of GLP-1-based pancreatic gene therapy candidate (GLP-1 PGTX, a novel AAV gene therapy) was recently released (103,104). GLP-1 PGTX was developed for pancreatic islet delivery, in which islet cells are terminally differentiated, making AAV suitable for durable effect. GLP-1 PGTX was well tolerated in two obese/diabetic animal models (*db/db* mice and mice with diet-induced obesity). The therapeutic efficiency of single-dose GLP-1 PGTX was greater than chronic semaglutide administered by non-gene therapy approaches in these rodent

studies. Specifically, in *db/db* mice, the group treated with repeated daily injections of semaglutide for 10 weeks had a 64% reduction in fasting blood glucose and a 3.5-fold increase in fasting insulin levels, while the group treated with a single dose of GLP-1 PGTX had a 70% reduction in fasting blood glucose and a 1.9-fold increase in fasting insulin levels after 10 weeks. A single dose of GLP-1 PGTX produced 27% weight loss on day 28 after treatment, compared with 21% after daily semaglutide administration. While GLP-1 gene therapy has demonstrated promising results in small rodent disease models, there are still significant challenges to overcome, including efficiently delivering therapeutic genes to target tissues (e.g., the pancreas and brain), ensuring precise control of gene expression, pharmacokinetics of systemic GLP-1 delivery and minimization of off-target effects. A goal of current efforts in the research and development of GLP-1-based gene therapy remains sustained, potentially lifelong control pf blood glucose or body weight with a single dose. However, drawbacks in complexity, risk, efficacy, safety and high cost limit rapid progress toward this goal (105).

Injectable hydrogels

Hydrogels are soft, water-swollen three-dimensional structures with remarkable biodegradability and adjustable physiochemical properties; in addition, hydrogels are injectable and can serve as drug reservoirs to deliver drug loads or drug-loaded micro- or nanoparticulate systems (106). Many studies have employed hydrogels for delivery of GLP-1-based therapies (107-114). Compared with systemic administration, injectable hydrogels have the advantages of sustained release and controlled biodistribution, thereby achieving long-term maintenance of the effect of the loaded incretin. For example, thermosensitive biopolymers, such as elastin-like polypeptides (ELPs), have gel-like properties that improve the pharmacokinetics and bioavailability of their fused therapeutic

proteins (115,116). A single subcutaneous injection of a first-generation GLP-1-ELP achieved blood glucose level control for 2–3 days in *ob/ob* and *db/db* mice (116). In the second step, the ELP molecular weight and phase transition temperature were optimized. This second-generation GLP-1-ELP was slowly released in monkeys for up to 17 days upon a single dose, and a monthly dosage form could be achieved in humans (116). By mixing long-acting GLP-1RAs (liraglutide or semaglutide) into a polymer–nanoparticle (PNP) hydrogel formed by a strong dynamic physical interaction between poly(ethylene glycol)-b-poly(lactic acid) (PEG–PLA) nanoparticles and dodecyl-modified (hydroxypropyl)methyl cellulose (HPMC−C_{12}), a longer-acting insulin–hydrogel system was obtained (107). A single dose of this semaglutide-loaded injectable hydrogel product resulted in consistent exposure over 42 days in rats. The pharmacokinetic model is affected by differences in typical subcutaneous dosing between rats and humans, which directly affects the time frame for hydrogel erosion and drug release. In addition, the elimination half-life of GLP-1RAs in rats (semaglutide $t_{1/2}$, serum ~ 0.29 days) is much shorter than that in humans (semaglutide $t_{1/2}$, serum ~ 7 days), suggesting that this 6-week continuous treatment in rats could provide more than 4 months of continuous treatment in humans (107). Alternatively, hydrogels might be engineered as local delivery carriers that can deliver high concentrations of payloads to functional tissues highly involved in metabolic activities, such as different adipose tissues.

5.2.2 Continuous-acting implantable pump technologies

The pharmacology and pharmacodynamic activity of short-acting and long-acting GLP-1RAs is different (10). Long-acting GLP-1RAs, which are less frequently injected, cause more rapid tachyphylaxis of side effects (10). While short-acting GLP-1RAs require frequent injections, administration of short-acting GLP-1RAs (such as exenatide) before each main meal is considered

a reasonable treatment strategy for control of postprandial glucose (10). A matchstick-sized miniature GLP-1 RA pump, ITCA 650, is classified as a continuous-acting exenatide-based product (117-119). Continuous subcutaneous delivery of exenatide via ITCA 650 resulted in glycemic control and weight loss lasting up to 1 year in people with T2DM (117-119). The application of ITCA 650 was initially accepted for review by the FDA in 2017, and it was predicted to be the first injection-free GLP-1 therapy. However, the ITCA-650 application for T2DM treatment was unanimously rejected by the FDA committee in September 2023 because of concerns surrounding device issues and safety. ITCA-650 was also not designed to achieve on-demand exenatide delivery. Thus, the development of an implantable pump capable of delivering short-acting GLP-1RAs on demand might be advantageous. A pump driven by magnetism was developed for exenatide delivery before meals. Equipped with a secure patterned magnet, a flexible biomaterial reservoir and an intermediate container, the pump offers several advantages, such as preventing accidental infusion due to household magnets, negative reservoir pressure buildup, and fluid penetration around the implanted pump, and reducing frequent refilling processes. Exenatide can be administered after implantation of the pump, and the pharmacokinetic profiles and pharmacodynamic effects (such as body weight reduction, plasma glucose levels and insulin levels) in Goto-Kakizaki rats was found to be similar to those of conventional subcutaneous injection (twice per day) at 7-days post-injection of the same dose (22). The main limitations of using these pumps include i) the need for invasive subcutaneous surgery to place, replace, and remove the pump and ii) the inevitably high cost.

5.2.3 Smart-acting electronic devices

Smart electronic devices that combine on-demand drug delivery and sensing systems could provide minimally invasive personalized medicine approaches for metabolic disease. Current research focuses on closed-loop insulin therapy devices. The MiniMed 780G is an easy-to-wear hybrid closed-loop insulin system that was approved by the FDA in 2023. As the world's first insulin pump with nutrient detection technology, it enables automatic, real-time insulin correction every five minutes (120). There are currently no smart electronic devices that combine a GLP-1RA-loaded pump and an electronic sensing system. Nevertheless, the field of GLP-1 medicine and metabolism would greatly benefit from harnessing the potential of this technology. Smart control of GLP-1RA release (especially short-acting GLP-1RAs and endogenous GLP-1 release) at physiologically required levels could not only help to reduce the incidence of gastrointestinal adverse events but also achieve appropriate endocrine and metabolic regulation.

Programmed engineered cells for precise therapeutic correction of various metabolic diseases, especially diabetes, have been validated in preclinical and clinical studies (121-123). Personalized healthcare with smart electronic devices combined with engineered cells (e.g., GLP-1 secretion is initiated by light or electrical stimuli) for glucose management has expanded the potential of cell therapy (124,125). Subcutaneous implants containing light-induced transgenic cells combined with wireless light-emitting diodes have shown promise for reducing glucose drift in preclinical T2DM models (126). An implantable hydrogel microcapsule (alginate-poly-L-lysine-alginate) that contains far-red light-controlled engineered cells that can be remotely controlled via a smartphone to automatically trigger far-red light activity and the production of the short variant of human GLP-1 was tested in diabetic mice on the basis of user-defined blood glucose level thresholds (127).

Under the control of a specific app in the smartphone and an all-wireless system, glucose sensing can be digitized to control insulin and human GLP-1 production. This engineered cell-regulating electronic interface can also be used to regulate release with high precision via threshold-dependently triggering of blood samples on a glucose meter (127). The green glow of smart wearable electronic devices such as the Apple Watch has been specifically used to record health parameters (128). Engineered human cells implanted within hollow fiber macrocapsules under the skin could be controlled by a green light-operated smartwatch, enabling a transdermal strategy for the remote release of human GLP-1, which can reduce postprandial hyperglycemia, insulin resistance, and obesity (128). Fussenegger and his team have also developed a versatile bioelectronic interface that can differentiate insulin and GLP-1 levels in serum samples from wild-type mice and mice with type 1 diabetes mellitus and T2DM, which could facilitate the deployment of this interface in implantable devices to sense and control physiological states via cell therapy (such as sensing and precisely regulating the release of physiological and pathological levels of GLP-1 medicines) (129). Despite advanced and personalized intelligence, challenges remain for current programmed engineered cells in combination with smart electronic devices for glucose monitoring and smart release solutions, such as the effectiveness, availability, and widespread adoption of these devices (124,130).

5.2.4 Nutrient-induced cell therapies

Although cellular metabolism and artificial electronic devices share similar working principles in terms of input perception, information processing, and output production, the core information transfer and processing functions of living systems and electronic systems differ, which limits their interoperability (131). Electronic devices combined with programmed cells do not enable real-

time intelligent regulation of hormones in the body, requiring implantation and maintenance of a bioelectronic device. Moreover, electronic transmission devices require a considerable amount of energy to operate, and the light source involved in the long-term use of chronic disease control may cause phototoxicity to the human body (132). To address these issues, researchers have explored a bioengineering approach that induces gene expression in mammalian engineered cells through controlled ingredients in the diet, such as noncanonical amino acids (133) and caffeine (134). Capitalizing on a persistent rise in blood glucose levels after meals, an intraperitoneal implant encapsulating programmed cells designed with caffeine-stimulated advanced regulators to precisely control the synthesis of human GLP-1 was generated, which could fine-tune *in situ* production and systemic delivery of GLP-1 in response to the intake of coffee or other caffeine-containing beverages in diabetic mice (134).

5.2.5 Bioacting microneedle patches

A microneedle patch is a hybrid between a hypodermic needle and a transdermal patch, as it contains micron-scale needles (from tens to thousands of micrometers) attached to a baseplate (135). From the patient's perspective, microneedle patches present many advantages: they are painless, easy to use, minimally invasive, safe, effective, and especially suitable for patients who need frequent injections of potent drugs (for example, proteins and peptides) (136-138). Microneedles can not only administer payloads directly into the skin space but also achieve the sustained release of active compounds. To achieve different payload release profiles, various microneedles have been developed, including solid microneedles, dissolving microneedles, nanoparticle-loaded or coated microneedles, hollow microneedles and hydrogel-forming microneedles (139). Many long-acting microneedle patches loaded with GLP-1 medicines have

been developed to eliminate the need for frequent injection of clinical products (24,140-145). For example, a dissolving microneedle loaded with liraglutide-loaded PLGA nanoparticles achieved long-acting liraglutide delivery to control blood glucose levels in obese and diabetic mice for up to 15 days (146). Importantly, although GLP-1 medicines are less likely to cause hypoglycemia because of their glucose-dependent action, the sudden release of high doses of long-acting drugs may cause an overdose that may result in adverse effects, such as vomiting (147,148). In another example, dual mineralized particles that separately integrate exendin-4 and glucose oxidase were loaded onto an alginate-based microneedle-array patch that triggered the release of drugs under high blood glucose levels, providing on-demand and long-term GLP-1 drug administration for glucose regulation in T2DM mice (143). Additionally, an ultrarapid-acting microneedle patch for the immediate delivery of a GLP-1 drug was developed by incorporating effervescent agents into a microneedle tip. The ultrarapid-acting microneedles quickly produced carbon dioxide bubbles upon insertion into the skin, instantly powering the rapid release of the encapsulated liraglutide within minutes, which helped avoid the need for frequent syringe-based injections and showed good biocompatibility for long-term treatment (149). Notably, a microneedle patch can transport an active compound to desired sites (e.g., skeletal muscles and adipose tissues in different areas of the body), potentially improving therapeutic effectiveness. Another key benefit of using the microneedle patch approach is the ability to bypass the harsh gastrointestinal environment encountered via the oral route.

5.2.6 Pulmonary delivery

The delivery of bioactive molecules via inhalation presents certain advantages, such as noninvasive administration, a large absorption surface area of the lung, extensive vascularization

and relatively low metabolic activity, and this method is ideal for the rapid systemic delivery of macromolecules (150,151). The feasibility of pulmonary delivery of incretins (such as GLP-1RAs) has also been investigated (152-154). Inhalation of biomacromolecules depends on the selection of excipients. After spray drying GLP-1 without excipients, the particle size range of GLP-1 powder (less than 5 μm) was suitable for pulmonary administration. However, the efficacy of excipient-free GLP-1 dry powder-inhaled formulations is still poor, with most of the drug deposited in the throat and at all impactor stages (25). The *in vivo* fate of pulmonary delivered excipient-based particulate systems depends on their composition and physicochemical characteristics, such as particle size, charge, and hydrophobicity. Although several studies have investigated the inhalation of GLP-1 medicines in animals (152,153,155), few studies have investigated the inhalation of GLP-1 in humans. MKC253 inhaled powder (Technosphere®) delivers the active agent human incretin hormone GLP-1 (7-36 amide) deep into the lungs, and fumaryl diketopiperazine is used as the carrier. In patients with T2DM, GLP-1 inhalation leads to plasma GLP-1 levels comparable to those when GLP-1 is given intravenously and at sufficient therapeutic doses to induce insulin secretion, thereby attenuating postprandial glucose drift (156). However, over the past decade, not only have there been no clinical trials on the administration of GLP-1 medicines via inhalation, but preclinical research on this topic is also scarce. This might be attributed to the negative experience with earlier insulin inhalation products on the market (Exubera® and Afrezza®) due to safety concerns, among other issues (157,158). Although inhaled delivery could represent an alternative noninvasive route of administration for GLP-1 medicines, further studies are needed regarding long-term safety, currently limiting enthusiasm in this area of research.

5.2.7 Intranasal delivery

The nose-to-brain pathway is a noninvasive approach that enables peptide-based therapeutics to bypass the blood–brain barrier (BBB) and enter the brain directly via the olfactory and trigeminal pathways, facilitating drug delivery to the central nervous system (CNS). This would allow rapid onset of action and increase drug bioavailability in the brain while potentially minimizing adverse reactions (159). GIP and GLP-1 receptors are highly expressed in the brain and are promising targets for cognitive enhancement, neuroprotection, and appetite control (30,160). Accumulating evidence indicates that intranasal administration is considered an ideal route for delivering GLP-1 medicines to the CNS, as GLP-1RAs or GLP-1/GIP receptor co-agonists mitigate progressive cognitive dysfunction and lead to weight loss when delivered intranasally in preclinical studies (161,162). More studies of GLP-1 therapy via nasal delivery are needed to advance the commercialization of products to the market, including improving the stability of these drugs during formulation, manufacturing and delivery; increasing the efficiency of drug transit to precise cerebral sites; and understanding the mechanisms of nanoparticle movement along neurons.

5.2.8 Oral delivery

There is broad enthusiasm for developing orally administered GLP-1 medicines owing to the cost of goods, easy of manufacturing, simple administration for patients, increased comfort, ideally associated with decreased cost, and lack of additional training for the use of the drugs or surgical implantation of devices. This might lead to higher rates of initiation and better compliance for long-term administration in patients with chronic diseases (163-167). There is currently only one oral GLP-1 medicine (oral semaglutide tablet), and current dosing or oral semaglutide up to 14mg daily has limitations, not least that its oral bioavailability remains extremely low. Before the oral

dosage form of semaglutide was introduced, it was generally believed that oral GLP-1 medicines could physiologically mimic the functional route taken by native GLP-1 *in vivo*, recapitulating the intestinal secretion and the first-pass effects of peptides on the liver, and the active gradients of GLP-1 in the portal vein and systemic circulation (168,169). Overgarrd and colleagues compared the changes of HbA1c, body weight, cardiovascular biomarkers and side effects in thousands of people with T2DM treated with oral or subcutaneous semaglutide, showing the route of semaglutide administration does not affect pharmacodynamic outcomes when corrected for circulating level of semaglutide (170). These findings indirectly suggest that oral peptide GLP-1RAs absorbed through the stomach do not result in better clinical outcomes than subcutaneous GLP-1RAs in T2DM patients independent of their circulating drug levels. Orally administered peptide GLP-1 medicines face obstacles related to the structural organization and physiological function of the gastrointestinal tract (GIT), resulting in poor oral bioavailability. The purpose of this section is not to comprehensively discuss the gastrointestinal physiological barriers and pathological features faced by orally administered GLP-1 medicines; readers can refer to other recent reviews (163,171-175). A variety of strategies to facilitate the oral delivery of GLP-1 medicines have been pursued, including permeation enhancers (PEs) (176,177), micro/nanoparticulate delivery systems (178-180), live bacteria-mediated gene therapy (181-183), and physical methods (e.g., capsules, oral microrobots, and buccal patches (184-186)).

Permeation enhancers

To date, the most extensively studied and most successful oral peptide strategy continues to be the use of PEs to increase the permeability of the epithelial barrier in the GIT. The effectiveness of PEs for oral peptide delivery depends on the ability of the PEs to rapidly and sufficiently but

transiently disrupt the GIT epithelial barrier (transcellular or paracellular enhancement). This would help promote systemic absorption of macromolecules while also being reversible and exhibiting minimal local and systemic toxicity (187-189). PEs are a class of heterogeneous substances, ranging from small chemical molecules (such as sodium caprylate) to biologic agents (such as cell-penetrating peptides (CPPs)) to nanoparticles with different physiochemical properties (such as anionic 50 nm silica nanoparticles), which can instantly alter the GIT epithelial barrier and promote the penetration of large biomolecules (176,188,190,191). This section focuses on increasing the oral absorption of GLP-1 medicines through the use of different PEs.

A myriad of chemical PEs have been evaluated in preclinical studies, which have shown increased intestinal permeability, but few have progressed to clinical trials owing to evidence of local and systemic toxicity (187). To date, after decades of effort, only two oral peptide drug therapies based on chemical PE strategies have been approved (52,192). These therapies include an oral semaglutide tablet, which was approved in 2019; the first oral GLP-1 tablet, which uses sodium polyethylene glycol sulfonate (SNAC) as an absorption enhancer (52); and the only oral GLP-1 medicine currently approved. In recent years, no serious unanticipated adverse events have been reported in the long-term use of oral semaglutide in the clinical treatment of T2DM patients, confirming the long-term safety of oral semaglutide when it is combined with SNAC (193). The co-formulation of semaglutide with SNAC still has several limitations. The therapeutic effect of semaglutide is influenced by food ingestion; the oral bioavailability of semaglutide is less than 1%, and this co-formulation is selectively efficient for semaglutide (194,195). The landmark approval of oral semaglutide and its clinical success (even with bioavailability values of ~1%), as well as the excellent performance of several other absorption enhancers in clinical trials, have

stimulated further research on the use of PE strategies to deliver GLP-1 medicines. Sodium caprate is one of the most widely studied PEs and has also been used in clinical trials for the oral delivery of macromolecules (196). Compared with semaglutide, the combination of sodium caprate with a GIP/GLP-1 co-agonist peptide results in better drug penetration in minipig intestines because of the favorable physicochemical properties of the orally administered co-agonist particularly its greater proteolytic stability in pancreatin. When the concentration of sodium caprate in the intestinal lumen of minipigs was greater than 100 mM, the oral bioavailability of the GIP-GLP-1 peptide reached 2% without the use of peptidase inhibitors (197). Sodium caprate and SNAC are commonly used for the intestinal and gastric delivery of macromolecules, respectively. A single oral dose (an erodible tablet containing 300 mg of PE) administered to nonhuman primates resulted in similar oral GIP-GLP-1 peptide bioavailability of 5.7% and 4.2%, respectively (198). Sodium chenodeoxycholate (NaCDC) has also shown marked effects in the oral administration of GLP-1 medicines. MEDI7219 is a bis-lipidated GLP-1RA that is specifically designed for oral use and has a bioavailability of approximately 6% when taken orally in tablets containing 20 mg of peptide and 300 mg of PEs (100 mg NaCDC and 200 mg propyl gallate) (199). Despite the promising results obtained with the use of PEs for the oral delivery of macromolecules, the dosing of PEs still limits their use in oral drug delivery. Moreover, the oral bioavailability of GLP-1 medicines through traditional chemical PE techniques is difficult to scale from rodents to large animals and even to humans in most examples because of the narrow absorption windows of PEs *in vivo*.

CPPs are powerful transepithelial PEs that can increase the intracellular delivery of hydrophilic macromolecules without causing significant damage to the biological membrane (200-202). CPPs themselves are relatively small functional peptides, typically cationic or amphiphilic polypeptides

containing 5-30 amino acids, which are often combined with nanotechnology-based approaches for the effective oral delivery of GLP-1RAs (203). Owing to the limited concentration-detection methods for GLP-1 medicines in blood, most studies involve only *in vitro* cell studies. In *in vivo* studies (rats or mice), mostly small-molecule fluorescence-labeled drugs have been used (203), which cannot truly reflect the real systemic absorption of GLP-1 medicines *in vivo*. No large animal studies or clinical trials have evaluated the oral delivery of incretins via CPP-based strategies.

Nanoparticles, such as small negatively charged silica nanoparticles, can act as PEs to open tight junctions to increase the oral bioavailability of GLP-1 medicines rather than as delivery systems to protect cargos (176). Pretreatment with anionic nanoparticles can increase intestinal permeability and enable protein drugs to be absorbed orally. The relative bioavailability of exenatide enteric-coated capsules after 2 hours of particle pretreatment reached 10% in mice, which meets the needs for the development of next-generation PEs (188). In addition, this permeation-enhancing effect of the nanoparticles was reversible and non-toxic. Importantly, the absorption of peptides is affected by the pretreatment concentration of silica nanoparticles; therefore, pretreatment with high oral doses of nanoparticles (greater than 100 mg/kg) is necessary to increase intestinal permeability before each dosing (176). For chronic disease patients, long-term oral administration of very high amounts of silica nanoparticles raises safety concerns. The lack of data in nonhuman primates also adds uncertainty to the clinical translation of 50 nm silica nanoparticles as PEs.

Nano- and microparticulate delivery systems

Nanoparticles or microparticles can act as carriers, providing cargos with protection from the harsh GIT environment, allowing mucosa penetration and transport across epithelial cells. These drug delivery carriers have been widely explored for the oral delivery of GLP-1 medicines (155,180,204-206) and GLP-1 plasmids (207,208). On the basis of the advantages of formulation materials, excipients, and preparation methods, several types of particle delivery systems (such as polymeric particles (209), lipidic particles (210), metal–organic frameworks (MOFs) (179), and hybrid vesicles (206)) have been tested in rodent animal models for the oral delivery of GLP-1-based drugs with success. A detailed introduction to oral particle delivery systems (e.g., particle materials (173) and formulation techniques (211,212)), along with their biological interactions in different regions, cells and organelles in the GIT under healthy and pathological conditions, has been reviewed elsewhere (171). Particle delivery systems provide stability as well as increased uptake, and targeted delivery of GLP-1 drugs is enabled by regulating the physicochemical properties of the particles (such as size, shape, and surface charge) (176,180,204,206) or tuning the surface of the particles (e.g., with the use of mucoadhesive coatings, muco-penetration coatings or ligand coupling) (178,213-216). Additionally, the combined application of physical approaches (e.g., bubble-generating reagents (179)) can further increase particle motility, optimize the intestinal motility trajectory of particles in mucus and increase the oral absorption of GLP-1RAs (e.g., exenatide and semaglutide). Notably, in terms of improvements in the oral bioavailability of GLP-1RAs, particle-based approaches are generally superior to PE strategies for overcoming multiple delivery barriers, with some particulate strategies achieving astonishing bioavailability values (even exceeding 20%). However, multiple challenges are encountered in the commercial translation of these particle systems, and to date, no formulated particles have been successfully

approved for clinical trials of oral GLP-1RAs owing to the complex formulation at preclinical stages of development. Sophisticated multicomponent systems also present safety concerns and scale-up issues and are costly, which adds regulatory hurdles and complicates clinical translation. Nevertheless, owing to the recent nanomedicine revolution, research and development on micro/nanocarriers for the oral delivery of GLP-1 medicines are still in full swing, and most current efforts are aimed at keeping formulation strategies simple.

Live bacteria-mediated gene therapy

In recent years, with the progress of genetic engineering technology and in-depth study of the gut microbiota, genetically engineered probiotics have emerged as promising oral delivery strategies (217-220). Intestinal commensal bacteria are ideal carriers of genes for the *in situ* expression of proteins (217,221), including the *in situ* production of intestinal hormones such as incretin hormones (182,183,222,223). Engineered gut bacteria, such as plasmids expressing GLP-1 transformed into *Escherichia coli* Nissle 1917 and *Lactobacillus gasseri*, have shown beneficial effects on increasing the circulation GLP-1 and insulin level, improving the glucose tolerance and alleviating the insulin resistance, body weight gain and hepatocyte steatosis after daily gavage for several weeks in obese/diabetic mice or rats *in vivo* (182,183,222,223). This strategy can not only avoid the inactivation of peptide drugs (GLP-1 analogs) by direct contact with the harsh acidic gastric environment but also follow the physiological pathway of GLP-1 secretion, i.e., with increased portal vein GLP-1 levels (182). Long-term oral gavage of these reprogrammed bacteria was not found to inhibit other normal functions of the body, supporting the concept that engineered commensal bacterial signaling to mediate enteroendocrine cell function *in vivo* (221). Nevertheless, there is a long way to go before live bacteria-mediated GLP-1 biotherapies are

brought to the clinic. Compared with current clinical drug formulations, bacteria engineered for oral administration are often difficult to customize, are quickly cleared, and require long-term daily administration, making them not particularly advantageous. In addition, substantial issues such as the development of solid dosage forms of live bacteria, the control of production costs and safety investigations remain to be solved.

Physical methods

Some techniques utilize physical forces, including mechanical, magnetic and acoustic forces, to increase the oral absorption of GLP-1RAs (184,224). Compared with other oral delivery strategies, physical GLP-1-related peptide delivery, with submucosal delivery via oral microrobots, buccal patches, and others, has the potential to achieve higher oral bioavailability at a lower cost (225,226). While the currently available strategies are in the early stages of development, some of these physical approaches have shown promising results in preclinical evaluation in large animals. More recently, the first human trial investigating the safety, performance and gastrointestinal transit of a physical device concept in healthy participants showed that DV3395 device can self-activate in the stomach as planned and be safely excreted from the body after being swallowed by healthy participants (NCT05314283).

Oral microrobots consist of macromolecular drugs (such as GLP-1RAs) encapsulated in small devices with microneedle injectors or patches (226). These microrobots are designed so that gravity, intestinal fluid, or an intestinal peristaltic thrust is used to trigger an elastic mechanism to push the microrobots to a specified position in the GIT. Alternatively, they can be designed so that remote control, such as a magnet, can be used to orient the microrobots to a specified position in

the GIT, thus achieving accurate penetration of the tissue wall for drug delivery. The design transcends the diffusion process of traditional strategies with the ability to deliver, locate, and release drugs, achieving higher oral adsorption efficiency. Traverso and colleagues developed an oral microrobot inspired by a leopard turtle, also known as a self-directed millimeter-scale applicator (SOMA). Once the SOMA reaches the stomach, it automatically changes direction, injecting the compressed drug millipost into the stomach wall and releasing the drug into the bloodstream at a controlled rate (227). Recently, the team upgraded the device, called liquid-injecting SOMA (L-SOMA). L-SOMA has been used to deliver an inactivated semaglutide-like GLP-1 analog that shows measurable plasma drug levels at least 3 days after administration, with an absolute bioavailability of approximately 78% in swine (184). Traverso and colleagues have also developed a smart capsule containing a dynamic omnidirectional adhesive microneedle system (DOAMS) by mimicking symbiotic thorny-headed worms in fish intestines. When triggered by the local gastric environment, tablets containing MNs in capsules are ejected and anchored to the gastric wall, increasing the systemic absorption of semaglutide without causing significant damage to mucosal tissue (228). With these technologies, the delivery of biomacromolecules is usually not limited to a specific molecule. While the developed luminal unfolding microneedle injector (LUMI) (229), mucus-clearing RoboCap (230) and intelligent magnetic-controlled microneedle robotic (MMR) (231) have been tested only for the oral delivery of insulin in swine, these technologies could theoretically be used to deliver GLP-1 medicines as well.

When buccally administered, the drug does not need to overcome the harsh GIT environment and can avoid the hepatic first-pass effect. Owing to the blockage of the oral mucosa, which has a

surface squamous stratified epithelium (50 layers of nonkeratinized cells 800 μm) (232-234), it is difficult for biomacromolecules to penetrate to achieve effective bioavailability, even with the use of PEs. Recently, inspired by the unique structural features of octopus suckers, an oral stretch patch with a suction cup orifice design (SCOD) was developed to help peptide drugs, including the GLP-1RA semaglutide, pass through the buccal mucosa (185). SCOD shows strong adhesion and mechanical deformability in the oral mucosa, disrupts the mucosal barrier through mechanical stretching and synergizes with PEs to further promote drug diffusion to deeper cell layers (185). The application of the patch achieved systemic absorption comparable to that of approved oral semaglutide tablets. The acceptability and safety of SCOD were validated in 40 healthy subjects. The oral stretch patch (free of drug and PE) did not affect the participant's talking, walking, or gargling for 30 minutes and did not cause damage to their oral mucosa or show signs of use. While 12.5% of the patches fell off prematurely due to improper handling, subjects still had a higher acceptance of the device compared to injection administration, demonstrating the high degree of clinical translation of this simple and effective platform technology (185).

Other physical techniques for oral biologic delivery, such as ultrasound and needle-free jets, have also shown promising results in large animal preclinical evaluations (186,224,235,236). Unlike traditional chemical strategies (e.g., nano- and microparticulate delivery systems), these technologies have recently been shown to significantly improve the delivery of different biomacromolecules, including peptides, nucleic acids and vaccines, without the need for any formulation or encapsulation procedures (186,224,235,236). Owing to the similarity of the physiochemical properties of the tested drugs, such as insulin, these technologies should not present technical limitations in delivering GLP-1 medicines.

6. Advanced GLP-1-based therapies: Challenges and opportunities

It has been nearly 20 years since the first incretin-based drug (exenatide, a twice-daily injection) came on the market. Over the past 20 years, the development of GLP-1 medicines has led to considerable advances in the treatment of T2DM and its complications. The first breakthrough was the successful development of long-acting GLP-1 analogue injections, including exenatide once weekly, liraglutide, dulaglutide and more recently, semaglutide. Compared with short-acting GLP-1 analogues, they can not only effectively prolong the action time on GLP-1R but also communicate with central GLP-1Rs to enable greater weight loss. The launch of tirzepatide (GLP-1R/GIPR co-agonist) marks another key development, combining the actions of GIP and GLP-1 for the first time, and showing better pharmacological outcomes vs. semaglutide in head-to-head trials in people with T2DM or obesity (46,237-239). Given that semaglutide and tirzepatide were only approved in 2017 and 2022, respectively, the rapid development of GLP-1 medicines is quite remarkable. Indications for GLP-1 drugs are not limited to T2DM and obesity. In March 2024, semaglutide also received an extended label for cardiovascular risk reduction (240). This marked the arrival of a new era in the treatment of metabolic diseases.

In this paper, we conduct an in-depth review and discussion on the innovative molecules and delivery technologies based on GLP-1 therapy for metabolic diseases (Fig. 4). Despite the increasing market share of peptide GLP-1 agonists, their high cost is still beyond the reach of many patients (8). The multiple nonpeptide small molecule GLP-1RAs under development may have great potential, perhaps reaching more patients, hopefully with reduced cost (241,242). The emergence of oral small-molecule GLP-1RAs is certainly not the last step in the evolution of GLP-

1 medicines (45). With the in-depth understanding of GLP-1 metabolic mechanism and the
2 revelation of key receptor structures involved in GLP-1 pathway, the development of drug
3 candidates is in full swing. Importantly, whether newer GLP-1 medicines will exhibit comparable
4 or greater efficacy, with the same safety and tolerability profiles as established products, while still
5 improving outcomes, remains to be determined.
6
7 Patients challenged by metabolic diseases need long-term or even lifelong medication. Innovative
8 GLP-1 technologies centered on improving patient satisfaction with use are also highly sought
9 after. This article reviews in detail the opportunities and development of innovative strategies for
10 patient-oriented GLP-1 drug delivery. Table 2 summarizes the advantages and limitations of these
11 innovative delivery strategies. Representative strategies include the use of ultralong-acting
12 injection technologies to improve efficacy; the combination of noninvasive drug delivery
13 technologies (including transdermal, pulmonary, intranasal and oral routes) to increase patient
14 adherence; and the introduction of smart electronic devices, implant pumps, and cell therapy to
15 achieve on-demand drug delivery. Most of these strategies have been validated in small animal
16 models, but further validation in large animal models, such as pigs and dogs, is needed for their
17 translation to the clinical setting. Moreover, the complexity of some of these sophisticated
18 strategies hampers their clinical application and presents safety issues, a poor cost–benefit ratio or
19 difficult scale-up, among other disadvantages. In addition, when GLP-1 medicines are designed
20 for sustained delivery over long periods, such as in the case of ultralong sustained-release
21 implantable pumps or injectable gels, the stability of GLP-1 medicines over months or even years
22 remains challenging. For technologies such as cell therapy and live-bacteria delivery, developing
23 solid formulations and increasing peptide stability are among the challenges that must be overcome

to be successfully translated into the market. Furthermore, despite oral physical devices based on gastrointestinal microneedle injections can provide the same bioavailability as the subcutaneous injection of GLP-1 medicines (184,228,243), these devices may cause adverse medical events, such as partial intestinal obstruction, perforation, or infection, when used clinically.

Although the described delivery strategies in this review are all under development, and most of them are still at a preclinical stage, each strategy has its own unique advantages (as summarized in Table 2). Metabolic diseases are influenced by various factors in various metabolic tissues, such as adipose tissue, liver, brain and skeletal muscle. Injectable hydrogels are not only beneficial for patients with oral dysphagia, but also can be used for local treatment, such as in adipose tissue and skeletal muscle. When GLP-1 producing bacteria can exhibit prolonged colonization in gut, this method can reduce the frequency of administration. Furthermore, GLP-1 producing bacteria can theoretically be genetically modified to achieve personalized medical treatment, such as controlling the secretion of GLP-1 according to the physiological state and dietary conditions of the body. Altogether, each strategy could be beneficial in a different pathological context, at different stages of the disease.

GLP-1-based therapy is closely related to the endocrine system (244). Its physiological and pathological effects are not controlled by a single organ but rather by a complex biological system involving various organs, tissues, receptors, signaling pathways, and intricate feedback mechanisms (244,245). However, perhaps due to the immaturity of current technologies, most of those innovative drug delivery strategies for GLP-1 are aimed at improving patient compliance or prolonging and enhancing a therapeutic effect, without fully considering the complex feedback

mechanisms of metabolic diseases. It is promising to integrate complex disease regulation mechanisms into the design of innovative drug delivery strategies of GLP-1 to realize intelligent regulation and meet the actual needs of patients for drugs. With the cross-application of technologies such as synthetic biology, wireless interfaces and electronic control, GLP-1 personalized medicine and precision medicine are gradually established, such as the development of on-demand drug delivery strategies based on GLP-1.

GLP-1 is mainly secreted by enteroendocrine L cells under nutritional or electrical stimulation. In addition to secreting GLP-1, the gut also secretes more than 20 other hormones that together regulate different physiological functions of the human body (244,246-248). In recent years, the use of new techniques to regulate the secretion of endogenous intestinal hormones has been studied. Traverso team used electrical stimulation to increase the secretion of endogenous ghrelin through ingested electronic devices (249). Xu and Beloqui reported lipid nanocarriers could induce the GLP-1 secretion by simulating endogenous lipid ligands, which have also been shown to be effective in synergically treating metabolic or gastrointestinal diseases when encapsulating peptides such GLP-1RAs or GLP-2RAs via oral route (180,205,213,250). Notably, the team recently reported that fine-tuning of the release of multiple gut hormones, including GLP-1, GIP, and PYY, can be achieved by altering the composition and particle size of lipid-based nanocarriers via an oral pathway (251). While achieving endogenous regulation of gut hormones using a drug delivery system is still at a very early stage, the development of this strategy is promising, not only to effectively improve patient compliance, but also to synergistically leverage the enteral and parenteral physiological effects of targeted gut hormones such as GLP-1, potentially expanding their multi-tissue metabolic benefits and ultimately meeting patient needs.

In addition, GLP-1 is secreted from the gut where hosts a vast population of gut microbiota. Some rodent models and human studies have shown that the gut microbiota is associated with the efficacy of GLP-1RAs (252-255). Gut microbiota is closely responsible for GLP-1 function (253). In some small human studies, the benefits of GLP-1 therapy was linked to a normal gut microbiota, and gut microbiota dysbiosis impaired GLP-1 responsiveness (254). In a human study, different gut microbiota compositions associated with different responses to GLP-1 RA (256). The beta diversity of gut microbiota was significantly differed between GLP-1 RA responders and non-responders, as well as some bacteria, such as *Bacteroides dorei* and *Roseburia inulinivorans* (256). Another human study reported liraglutide significantly increased the diversity and richness of the gut microbiota, especially *Bacteroidetes*, *Proteobacteria*, and *Bacilli* (252). In addition, many studies have demonstrated that microbial metabolites such as short-chain fatty acids (SCFAs) can increase GLP-1 secretion (257-260). However, there is no study on whether the therapeutic effect of GLP-1 RAs is partially mediated by microbial metabolites. The link to gut microbiota and the potential efficacy of GLP-1 medicines in the clinic is fascinating but insufficiently developed to make clear conclusions at this time.

Although the development of GLP-1-based therapies is ongoing and significant progress has been made, several side effects of the marketed GLP-1 medications, especially those of chronic GLP-1 RAs, have been reported. The most common side effects are gastrointestinal adverse events, including vomiting, nausea and diarrhea (9). GLP-1 can delay gastric emptying (retaining the food in the stomach for a longer time), and reduce intestinal transit time, which contribute to increasing satiety and reducing weight, but it also promotes gastrointestinal symptoms (261). Gastrointestinal

adverse events mainly occur in the early stage of treatment or after dose increases, which may lead to serious complications such as dehydration. Furthermore, GLP-1-based medications such as semaglutide and tirzepatide are approved for weight management, but weight rebounds after drug withdrawal (262-264). Some extremely rare side effects have been reported, including intestinal obstruction, gastroparesis and vomiting during anesthesia, gallstones and cholecystitis, as well as non-arteritic ischemic optic neuropathy, and possibly age-related macular degeneration (265,266). For improving the efficacy of established and investigational GLP-1 medicines and emerging innovative technologies, more attention should be paid to investigating the optimization of concurrent lifestyle management, including aerobic and resistance exercise as well as different dietary regimens, on and off drug, to establish and maintain healthy weight loss.

7. Conclusion

GLP-1 medicines have revolutionized the treatment of several metabolic syndrome-associated diseases, such as T2DM and obesity (267-269). Such therapies also show great therapeutic prospects in many clinical trials for the treatment of other metabolic diseases, such as cardiovascular disease, MASLD and neurodegenerative diseases (12,270-273). However, the delivery route and administration frequency of GLP-1RAs pose a challenge to patient satisfaction and adherence with their clinical use. The high price of these drugs has also increased patient healthcare costs. While these limitations are challenging, they also provide a unique opportunity for the development of advanced incretin-based therapies. In this review, we focus on the development, challenges, and opportunities associated with the development of advanced incretin-based therapies. We believe that the current success of GLP-1 medicines in clinical applications will further motivate researchers and clinicians to continue developing relevant new drugs and

new technologies with enthusiasm, which are expected to continue to increase in the coming years. We expect that the landscape of GLP-1 medicines will change rapidly, providing patients and clinicians with new treatment options.

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Legends for Figures and Tables

Figure 1. Metabolic benefits of incretin hormones in target tissues and organs. The incretin hormones GLP-1 and GIP are involved in different physiological processes in different metabolic tissues and organs. The different color fonts represent the metabolic benefits of different incretin hormones on target tissues and organs (blue: GLP-1; brown: GIP). Notably, these physiological roles are related to the prevention and treatment of different metabolic diseases and their complications, which has led to the development of incretin-based therapies. GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulin peptide; NO, nitric oxide; VSMC, vascular smooth muscle cell. Created with BioRender.

Figure 2. Timeline of incretin-based therapy development. Created with BioRender.

Figure 3. Limitations of currently available GLP-1-based therapies and the development of different classes of GLP-1-based drug delivery strategies. Created with BioRender.

Figure 4. The innovative molecules and delivery technologies based on GLP-1 for the treatment of metabolic diseases. Created with BioRender.

Table 1: Clinical trials and marketed GLP-1-based therapies.

Table 2: Advantages and limitations of different delivery strategies for GLP-1-based therapies.

1 **Table 1:**

Active ingredient	Delivery Technology	Administration Frequences	Function (Chemical Type)	Advantages	Limitations	Notable clinical trials		
						Phase	Settings	Trial Registration Number
Vildagliptin	Cyanopyrrolidine	Oral Twice-Daily	DPP-4 Inhibitor (Small Molecule)	Easy to use	Limited elevation of GLP-1 and GIP levels; Modest glycemic control; Ineffective body weight reduction	Marketed	T2DM	N.A.
Sitagliptin	β-amino acids	Oral Once-Daily						
Saxagliptin	Cyanopyrrolidine							
Linagliptin	Xanthene-based structure							
Alogliptin	Pyrimidine derivatives							
Sitagliptin	β-amino acids					Phase 2	Obesity	NCT02697253
Saxagliptin	Cyanopyrrolidine					Phase 4	Prediabetes; CVDs; T2DM; Obesity	NCT0196020 NCT02583438
Linagliptin	Xanthene-based structure					Phase 3	Prediabetes; Insulin resistance	NCT04134650
TQ-F3083	N.A.					Phase 2	T2DM	NCT03986073

Exenatide	Absence of alanine or proline at position 2 for DPP4 nonrecognition	Subcutaneous Twice-Daily	GLP-1RA (Peptide)	Significant improvements in glucose and weight management	Injectable; Noncompliance with chronic disease management	Marketed	T2DM	N.A.
	Biodegradable PLGA microspheres containing exenatide	Subcutaneous Once-Weekly						
Lixisenatide	Amino acid substitution at N-terminal position 2 for DPP4 protection	Subcutaneous Once-Daily						
Dulaglutide	Modified human immunoglobulin G4 heavy chain							
Liraglutide	C16 fatty acid addition to Lys26 and Lys34-to-Arg substitution for albumin binding	Subcutaneous Once-Daily					T2DM	
							Obesity	
Semaglutide	Amino acid substitutions at position 8 for DPP-4 resistance; Lys26 acylation with C18 fatty	Subcutaneous Once-Weekly					T2DM	
							Obesity	

	diacid for albumin binding							
	SNAC as absorption enhancer	Oral Once-Daily		Easy to use	Very low oral bioavailability (less than 1%)		T2DM	
Ecnoglutide	Linker of 2-(2-(2-aminoethoxy)ethoxy)acetic acid (AEEA) and γ-glutamic acid connects the peptide lysine to C18 diacid fatty acid	Subcutaneous Once-Weekly		Significant improvements in glucose, weight management and cognitive function	Injectable; Noncompliance with chronic disease management	Phase 3	Weight management; T2DM	NCT05813795 NCT05680155
	T2026 as absorption enhancer	Oral Once-Daily				Phase 2	Obesity	NCT05111912
Exenatide	Biodegradable PLGA microspheres containing exenatide	Subcutaneous Once-Weekly				Phase 2	Parkinson disease	NCT04305002
Liraglutide	C16 fatty acid addition to Lys26 and Lys34-to-Arg substitution for albumin binding	Subcutaneous Once-Daily				Phase 3	T1DM	NCT02516657

Semaglutide	Amino acid substitutions at position 8 for DPP-4 resistance; Lys26 acylation with C18 fatty diacid for albumin binding	Subcutaneous Once-Weekly				Phase 2	Symptomatic asthma; Alcohol abuse; Alcohol addiction; Alcohol dependence; Alcohol use disorder; T2DM in obese; MASLD; Liver fibrosis	NCT05254314 NCT05895643 NCT06005012
	SNAC as absorption enhancer	Oral Once-Daily		Easy to use	Very low oral bioavailability (less than 1%)	Phase 1	Prediabetes; CVDs	NCT06446531
Tirzepatide	GIP-based structure with C20 fatty diacid to Lys20 for albumin binding; Noncoded amino acids at	Subcutaneous Once-Weekly	GLP-1/GIPRA (Peptide)	Significant improvements in multiple	Injectable; Noncompliance with chronic	Marketed	T2DM	N.A.
							Obesity	
						Phase 4	Obesity; Knee osteoarthritis	NCT06191848

	positions 2 and 13 for long half-life and high albumin affinity			physiological actions in body	disease management	Phase 1 Phase 2	MASLD; MASH; T2DM; Liver fat	NCT05751720
						Phase 2	T1DM; Overweight and obesity	NCT06180616
VK2735	N.A.					Phase 2	Weight loss	NCT06068946
DD01			GLP-1/GCGRA (Peptide)			Phase 2	Mild atrophic simple liver disease; Mixed atrophy steatohepatitis	NCT06410924
ZP7570			GLP-1/GLP-2 RA (Peptide)			Phase 1	Overweight and obesity	NCT06000891
Danuglipron		Oral Twice-Daily	GLP-1RA (Small Molecule)	Easy to use	Limited potency compared to peptides	Phase 1	T2DM	NCT03538743
						Phase 2	Obesity	NCT04707313
Lotiglipron						Phase 1	T2DM; Renal impairment	NCT05510245

						Phase 2	Diabetes mellitus; Obesity	NCT05579977
TTP273		Oral Once/Twice-Daily				Phase 2	T2DM	NCT02653599
HDM1002						Phase 2	Overweight and obesity; T2DM	NCT06500299 NCT06481085
Orforglipron		Oral Once-Daily				Phase 3	Overweight; Obesity; T2DM	NCT05869903 NCT06109311

T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; MASLD, metabolic dysfunction associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

1 **Table 2:**

Drug delivery strategies		GLP-1 therapies	Advantages	Limitations
Ultralong-acting injectable technologies	Injectable microspheres and nanoparticles	Peptide GLP-1RA	Prolong the circulation of drug in the body; reduce the frequency of injection	Invasive injection; safety issues of excipients; complex delivery systems
	Injectable gene therapy approaches	GLP-1-based genes	Potentially be treated with a single injection or markedly reduce the frequency of injection	Complexity of the systems; off-target risk; safety concern and high cost
	Injectable hydrogels	Peptide GLP-1RA	Target tissue delivery; prolong the kinetics of drug release; reduce the frequency of injection	Invasive injection; safety issues of materials in the systems
Continuous-acting implantable pump technologies		Short-acting GLP-1RA	On-demand drug delivery	Invasive subcutaneous surgery; high cost
Smart-acting electronic devices		Peptide GLP-1RA; programmed engineered cells	Personalized GLP-1 medicine	Complexity of the device; limited interoperability between living systems and electronic systems; high cost; invasive surgery; safety concern
Nutrient-induced cell therapies		Programmed engineered cells	Personalized GLP-1 medicine	Complexity of the systems; invasive surgery; high cost
Bioacting microneedle patches		Peptide GLP-1RA	High compliance; potentially be targeted delivery of skeletal muscles or adipose tissues	Complexity of the systems; safety concern
Pulmonary delivery			Noninvasive administration; high compliance	
Intranasal delivery			Noninvasive administration; high compliance; potentially be targeted delivery of brain	
Oral delivery	Permeation enhancers		Noninvasive administration; high compliance; potentially be targeted delivery via engagement of the enteroendocrine system	
	Nano- and microparticulate delivery systems			
	Physical methods			

	Live bacteria-mediated gene therapy	GLP-1-based plasmid		

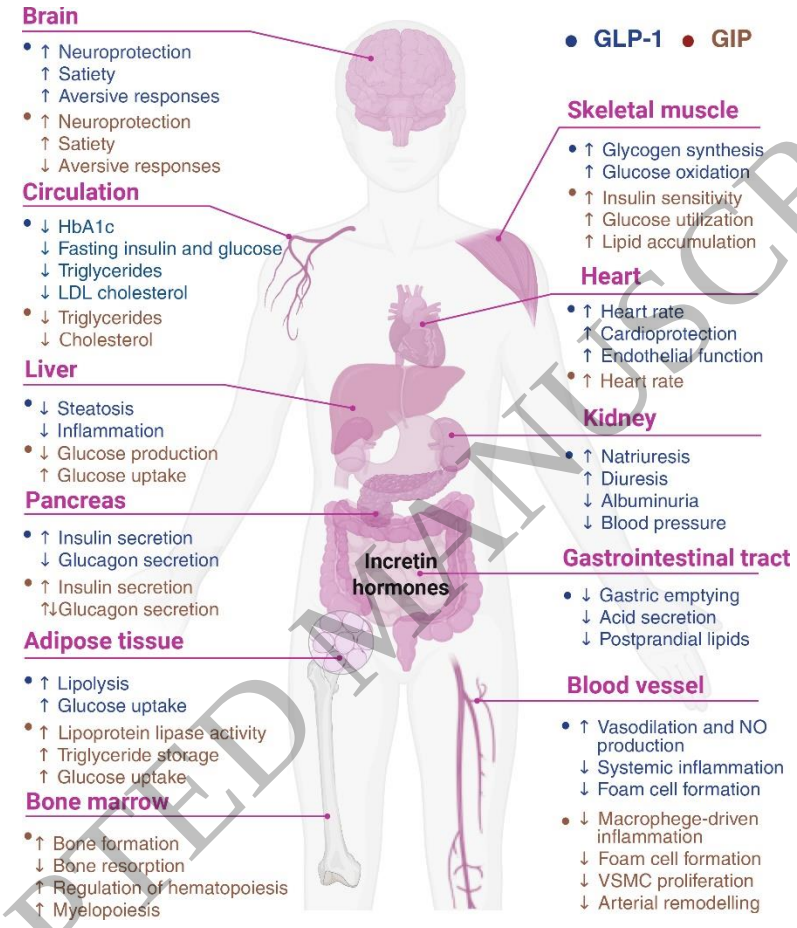

Figure 1
102x121 mm (DPI)

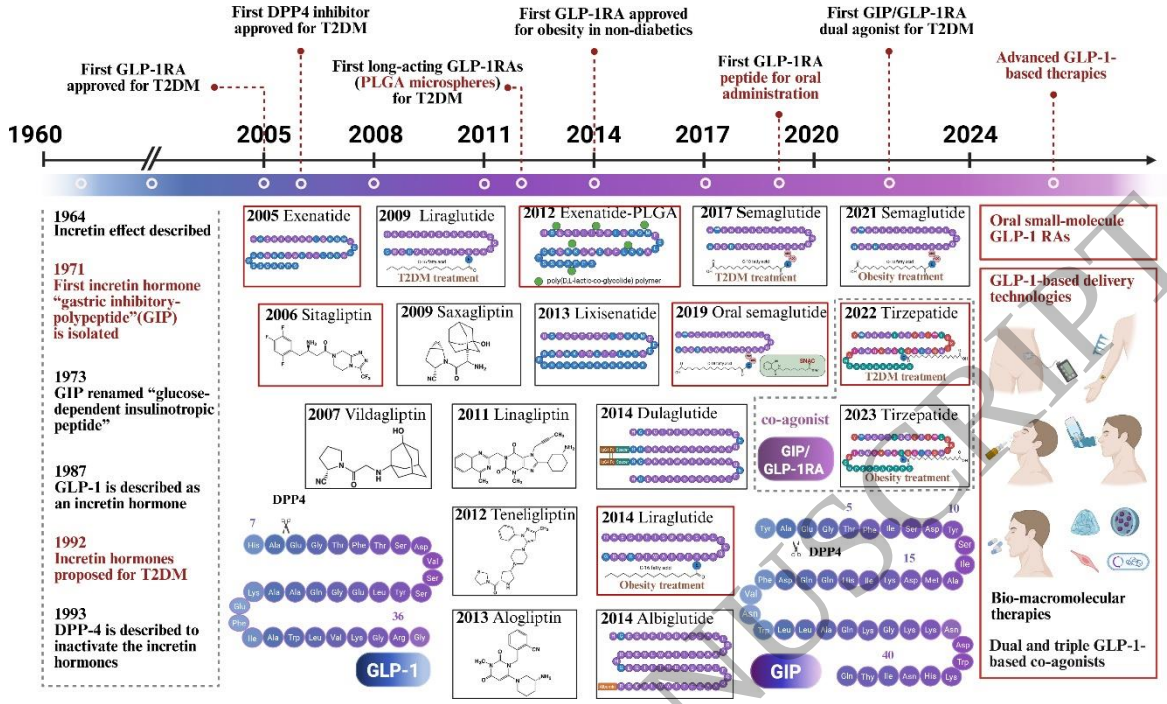

Figure 2
153x91 mm (DPI)

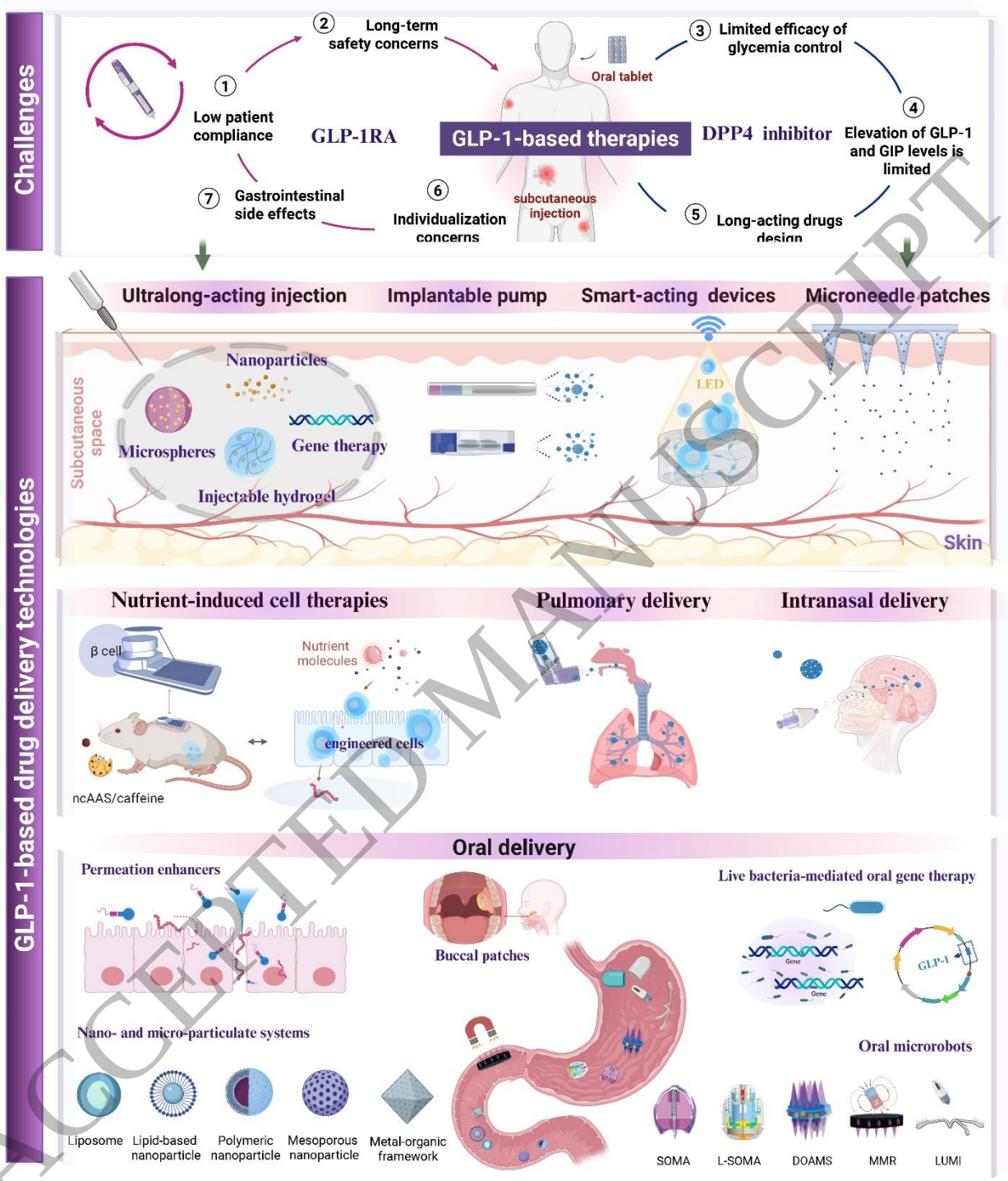

Figure 3
163x190 mm (DPI)

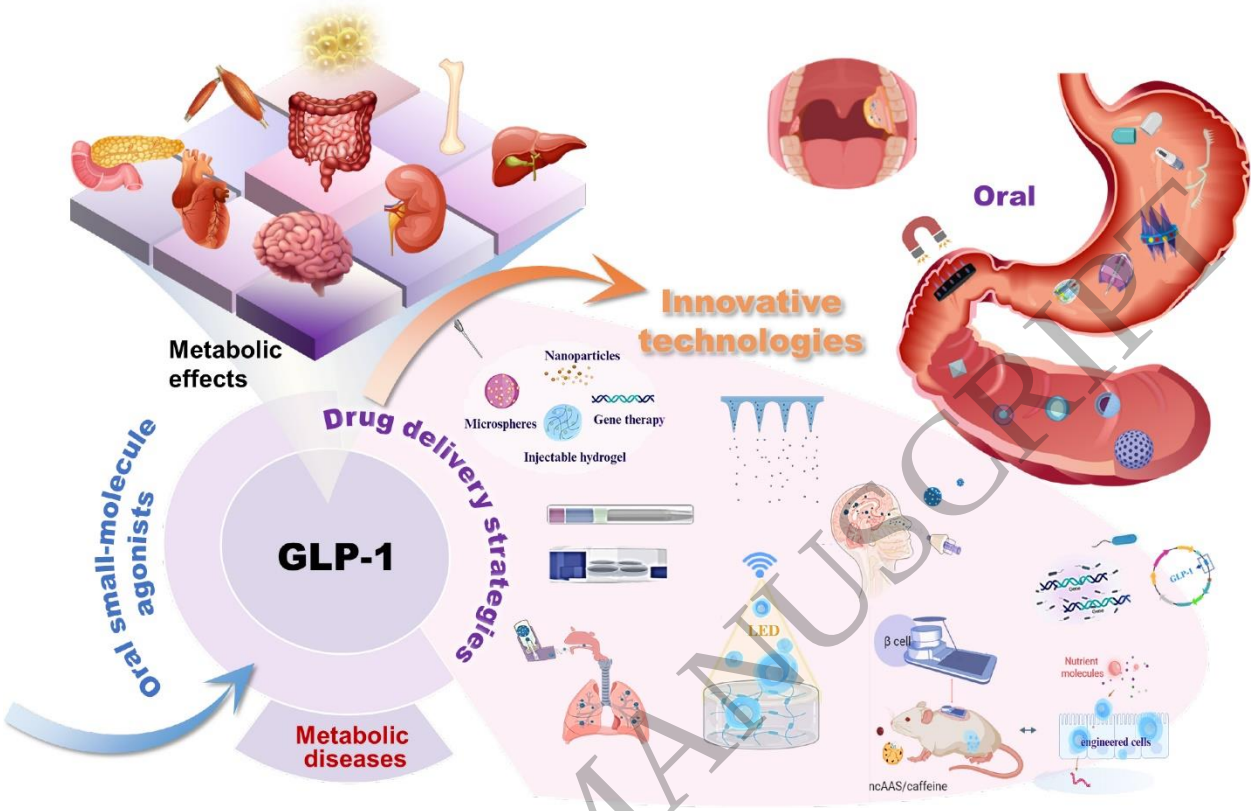

Figure 4
191x125 mm (DPI)