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Addressing Unmet Medical Needs in Type 2 Diabetes: A Narrative Review of Drugs under Development

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Abstract: The global burden of type 2 diabetes is increasing worldwide, and successful treatment of this disease needs constant provision of new drugs. Twelve classes of antidiabetic drugs are currently available, and many new drugs are under clinical development. These include compounds with known mechanisms of action but unique properties, such as once-weekly DPP4 inhibitors or oral insulin. They also include drugs with new mechanisms of action, the focus of this review. Most of these compounds are in Phase 1 and 2, with only a small number having made it to Phase 3 at this time. The new drug classes described include PPAR agonists/modulators, glucokinase activators, glucagon receptor antagonists, anti-inflammatory compounds, G-protein coupled receptor agonists, gastrointestinal peptide agonists other than GLP-1, apical sodium-dependent bile acid transporter (ASBT) inhibitors, SGLT1 and dual SGLT1/SGLT2 inhibitors, and 11beta-HSD1 inhibitors.

Keywords: Antidiabetic drugs, new characteristics, new drug development, new insulins, new mechanisms of action, personalized medicine, type 2 diabetes.

INTRODUCTION

The increasing global burden of type 2 diabetes (T2D) makes this a disease of considerable concern at the individual patient level and also at the public health level given the direct health costs and indirect costs of loss of work productivity. As a country-specific example, the 2014 National Diabetes Statistics Report, released on June 10th 2014, revealed that from 2010 to 2012 the number of Americans with diabetes increased from 25.8 million to 29.1 million, and that the prevalence rate for adults aged 20 years and older increased from 11.3% to 12.3% [1]. With regard to the pediatric population in the United States, Dabelea *et al.* [2] reported that the prevalence of T2D increased from 0.34 to 0.46 per 1,000 from 2001 to 2009: when adjusted for completeness of ascertainment these figures represent a 30.5% increase. Total estimated costs of diagnosed diabetes increased 41% from 2007's figure of $174 billion to $245 billion for 2012, with $176 billion associated with direct medical costs and $69 billion with reduced productivity [3].

Consider next the global landscape. The recent International Diabetes Federation's report noted that the current figure of 382 million people with diabetes worldwide is expected to rise to 592 million by 2035: moreover, most people with diabetes live in low- and middle-income countries, which will see the greatest increase in diagnoses over the next two decades [4].

The nature of the unmet medical need for T2D is captured by the European Medicines Agency's (EMA's) 2012 guideline addressing the clinical investigation of medicinal products in the treatment or prevention of diabetes [5]:

Glucose control in type 2 diabetes deteriorates progressively over time, and, after failure of diet and exercise alone, needs on average a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good control.

DeFronzo *et al.* [6] provided a review of the natural history of T2D. The central defects in T2D are insulin resistance in muscle and liver tissue, and β-cell failure. Progressive β-cell failure is responsible for the progressive rise in HbA1c seen in T2D. However, multiple pathophysiologic abnormalities influence the condition: in addition to muscle/liver tissue and β-cells, defects in functioning in α-cells, adipocytes, and gastrointestinal tract, kidney, and brain play important roles in the development of glucose intolerance in T2D [7].

With regard to drug therapy, a given drug can become ineffective over time. The United Kingdom Prospective Diabetes Study (UKPDS) showed that, after initial declines in HbA1c, both metformin-treated and sulfonylurea-treated patients experienced progressive deterioration in glycemic control [8, 9]. The "relentless HbA1c rise observed with sulfonylureas and metformin" resulted from progressive decline in β-cell function: within 3–5 years, ~50% of diabetic patients required another drug to maintain HA1c <7.0% [6].

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Additionally, addressing the multiple pathophysiological defects noted previously requires multiple drugs to be used in combination.

Successful treatment of T2D therefore needs a constant supply of new drugs. Following a very brief recap of currently approved drugs, this paper focuses on new pharmacotherapeutic agents in development.

CURRENTLY APPROVED DRUGS AND REMAINING MEDICAL NEEDS

The life expectancy of a patient with T2D is likely to be reduced by up to 10 years as a result of having this condition [10]. At the time of writing, there are 12 classes of drugs approved by the FDA with labeling to aid with glycemic control in T2D, as presented in Table **1** [11]. However, given the need for multiple drug therapy, there is still a significant unmet medical need. Insulin is the most effective agent in reducing glucose levels: however, this efficacy does not come without the costs of increased hypoglycemia risk and weight gain. Each individual non-insulin antidiabetic agent reduces HbA1c by an average of 1% and the simultaneous use of two or more agents with different mechanisms of action can result in greater HbA1c reductions. The challenge of combination therapy is the increased treatment complexity and side effects that can affect long-term adherence.

The American Diabetes Association's (ADA's) 2014 Standards of Care Position Paper [12] recommends that metformin, if tolerated and not contraindicated, should be the preferred initial pharmacological agent for T2D (lifestyle modifications are also important components of overall therapy). These recommendations continue as follows:

- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the HbA1c target over three months, add a second oral agent, a glucagon-like peptide 1 (GLP-1) receptor agonist, or insulin.
- A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects including weight gain, comorbidities, hypoglycemia risk, and patient preferences.

Given these statements, it can be surmised that novel compounds should show an improved safety and tolerability profile focused on overcoming known or hypothesized adverse effects of marketed agents. For example, agents that have limited gastrointestinal side effects, hypoglycemic risk, weight gain, fracture risk, and edema would be desirable.

Attention now turns to new and improved versions of agents/mechanisms of action (MOA) that have already been approved, and then to new classes of antidiabetic drugs for T2D: the following review shows great promise for patients with this condition.

NEW AND IMPROVED VERSIONS OF APPROVED AGENTS/MECHANISMS OF ACTION

Dipeptidyl-peptidase 4 Inhibitors

The typical patient with T2D has a multi-drug regimen in which drugs have to be taken daily. Reducing this burden by providing once-weekly instead of once-daily tablets has the potential to improve adherence and consequently effectiveness. The once-weekly dipeptidyl peptidase-4 (DPP4) inhibitors omarigliptin (Merck - ML-3102) and trelagliptin (Takeda - SYR-472) are currently in Phase 3 development. Trelagliptin was well tolerated and produced significant dose-dependent HbA1c reductions compared with placebo in a Phase 2 trial in 322 Japanese patients. The rate of nasopharyngitis as the most common adverse event was comparable between patients on trelagliptin and placebo [13]. Dose-dependent HbA1c reductions were also found for omarigliptin in a Phase 2 study [14]: this drug is currently in Phase 3 development. The future role of once-weekly DPP4 inhibitors may depend on the equivalence of HbA1c reduction compared with established once-daily DPP4 inhibitors and their safety profile.

Glucagon-like Peptide Agonists

Glucagon-like peptide (GLP)-1 agonists are among the most potent drugs for the treatment of T2D. However, all currently available compounds are administered *via* injection, which can be a barrier for use by some patients. Alternative ways of application are therefore needed.

Several oral GLP-1 agonists in development, including: ORMD-0901 (Oramed's oral exenatide); NN9924, NN9926, NN9927, and NN9928 (NovoNordisk); Nodexen (NOD Pharmaceuticals' oral exenatide); TTP054 (Transtech); and ZYOG1 (Zydus). NN9924, ORMD-0901, and TTP054 have already reached Phase 2 development. If these compounds show good tolerability and comparable effectiveness with injectable GLP-1 agonists, they could have an important role in the future treatment of T2D.

MKC253 is an inhaled GLP-1 under development (MannKind). The rationale for this short-acting GLP-1 is that by getting into the arterial circulation by administration *via* the lungs, the compound can reach its target cells before it is degraded by DPP4. A study in T2D patients showed that MKC253 reduced postprandial glucose values significantly by increasing insulin secretion. This is in contrast to the postprandial glucose reduction achieved by exenatide which was mainly due to delaying of gastric emptying in this study [14].

Another innovative approach is continuous application of exenatide by using a subcutaneous device, DUROS® [15]. This method could lead to a once-yearly application, and could therefore improve patient adherence. This method is currently being evaluated in multiple Phase 3.

Insulins

Insulin remains the most effective blood glucose lowering agent. There is a medical need for basal insulins with a more stable profile and less hypoglycemia risk. However, administration *via* injection is a major disadvantage. Other forms of administration are therefore being investigated.

Injectable Insulins

New basal insulin analogs that lead to less glucose variability and less hypoglycemia risk and/or have a longer duration of action than currently available basal analogs are in development. LY2605541 (Lilly) is a pegylated insulin Lispro (pegLispro) that is intended for once-daily injection. The

Table 1. Marketed Drugs for T2D.

Therapeutic Class-Compound	Mechanism of Action	Date first Compound of this Group Approved	Comments
Biguanides; Phenformin Metformin	Increases insulin sensitivity, suppresses glucose production in the liver	1957 (Europe), 1995 (FDA)	Gastrointestinal side effects, lactic acidosis, contraindications in renal insufficiency
2nd generation Sulfonylureas: Glimepiride, Glipizide, Gliclazide, Glibenclamide (Glyburide), Gliquidone	Stimulation of insulin secretion by the pancreas	Glibenclamide (Glyburide): 1969 (Europe), 1984 (FDA)	Hypoglycemia risk, weight gain
Glinides: Repaglinide, Nateglinide	Stimulation of insulin secretion by the pancreas	Repaglinide: 1998 (EMA), 1997 (FDA)	Short half life – pre-prandial administration; hypoglycemia risk, weight gain
Thiazolidinediones: Pioglitazone, Rosiglitazone	Reduction of insulin resistance by activation of the PPARγ receptor	Rosiglitazone: 1999 (FDA), 2000 (EMA)	Increased risk for heart failure events, fluid retention, weight gain, bone fractures. Cardiovascular risk concerns for rosiglitazone only. Bladder cancer concerns for pioglitazone only.
α-Glucosidase inhibitors: Acarbose Miglitol Vocarbose	Reduction of glucose absorption in the gut	Acarbose: 1991 (Europe), 1995 (FDA)	Gastrointestinal side effects, no systemic effects.
DPP4 inhibitors: Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin	Stimulation of glucose dependent insulin release and suppression of elevated glucagon levels by prolonging the half-life of endogenous GLP-1 (minor effects on gastrointestinal motility and satiety)	Sitagliptin: 2006 (FDA), 2007 (EMA); (Vildagliptin only approved by EMA, 2008). Saxagliptin approved by FDA and EMA, 2009. linagliptin 2011 (FDA), alogliptin 2013 (FDA).	Concerns about risk for medullary thyroid cancer, pancreatitis or pancreatic cancer – not confirmed in clinical trials and by FDA and EMA [11].
GLP-1 agonists: Exenatide, Liraglutide, Exenatide extended-release, Lixisenatide, Albiglutide, Dulaglutide	Stimulation of glucose dependent insulin release, suppression of elevated glucagon levels, reduction of gastrointestinal motility, stimulating satiety, weight loss	Exenatide: 2005 (FDA), 2006 (EMA); Liraglutide 2010 (FDA), 2009 (EMA), Exenatide ER 2012 (FDA), (Lixisenatide only approved by EMA, 2013.) albiglutide 2014 (FDA and EMA). Dulaglutide, 2014 (FDA)	Only injectables, concerns about risk for medullary thyroid cancer, pancreatitis or pancreatic cancer – not confirmed in clinical trials and by FDA and EMA [11].
SGLT2 inhibitors: Dapagliflozin, Canagliflozin, Empagliflozin	Reduction of the renal threshold for glucose excretion	Dapagliflozin: 2012 (EMA), 2014 (FDA). canagliflozin 2013 (FDA), empagliflozin 2014 (FDA and EMA)	Genital infections, possible diuretic effects, weight reduction
Bile acid sequestrants	Possibly activation of the farnesoid X receptor/bile acid receptor	Colesevelam: 2008 (FDA); no EMA approval for treatment of diabetes	Primary a lipid lowering drug with additional glucose lowering effects
Dopamine agonists: Bromocriptine	Central modification of insulin resistance	Bromocriptin: 2009 (FDA), no EMA approval for treatment of diabetes	Orthostatic hypotension, nausea
Amylin analogue: Pramlinitide	Slowing of gastric emptying, suppression of elevated glucagon, stimulation of satiety	Pramlintide: 2005 (FDA), no EMA approval	Approved for type 1 and 2 diabetes, nausea, hypoglycemia when combined with other antidiabetic drugs (*e.g.* insulin)
Insulin: regular human insulin, NPH insulin, insulin aspart, insulin lispro, insulin glargine, insulin detemir, insulin levemir	Lowering of blood glucose	Regular insulin: 1982 (FDA); 1984 (Europe); Bovine insulin: 1922	A new administration form of inhaled insulin has been recently approved (2014) (Afrezza®) for type 1 and 2 diabetes

pegylation of the insulin is associated with slower absorption and reduced clearance, resulting in a longer duration of action. It has shown lower glucose variability, less nocturnal hypoglycemia, and better weight control than insulin glargine in T2D patients [16]. Phase 3 studies for PegLispro showed increased triglycerides, LDL-cholesterol, and alanine amino transferase, and decreased HDL-cholesterol [16, 17].

Another once-daily basal insulin analogue currently in Phase I development is Insumera (PhaseBio). The South Korean company Hanmi and NovoNordisk have once-weekly insulin analogs (HM12460A and LAI287/NN1436) in Phase 1 development.

Ultra-rapid-acting insulin analogs that have a quicker onset and shorter duration of action than rapid-acting insulin analogs [18] are currently in Phase 1 and 2 studies (*e.g.*, BIOD-123 [Biodel] and FIAsp [NovoNordisk]). Linjeta™ (Biodel) made it to Phase 3 development, but did not get approval from the FDA due to questions about efficacy, tolerability, and stability. The company, therefore, decided to go forward with BIOD-123, the follower product.

Oral Insulins

Delivering insulin orally is a promising approach for improving glycemia in patients with T2D. In addition to the advantage of avoiding needle sticks, the insulin effect from oral insulin is more physiologic than that from parenteral insulin. Endogenous insulin is subject to a first-pass effect in the liver, which also leads to a 65-80% suppression of basal glucose production [19, 20]. Oral insulin would similarly pass through the liver first, thereby reducing hepatic glucose production and glycogenolysis. This contrasts with injected insulin, which immediately exerts systemic action. Thus, oral insulin treatment might be a way to smooth the glucose profile and reduce the risk of hypoglycemia compared with parenteral insulin. A favorable benefit-risk profile still has to be shown in larger clinical studies, but currently available human data suggest that this might be a valuable approach for treating diabetes [21, 22].

Several oral insulins are in development. Short-acting oral insulins that are currently in Phase 2 development include ORMD-0801 (Oramed) and Capsulin (Diabetology). A Phase 3 study of IN-105 (Biocon) has already been conducted in India. Basal oral insulins are in earlier stages of development, *e.g.*, OI287GT (NN1956) (NovoNordisk) is in Phase I development.

Inhaled Insulins

Despite drawbacks, inhaled insulin is still in development. Exubera (Pfizer), withdrawn from the market, was taken over by another company (Dance Pharmaceuticals) to be delivered in a different application device (DANCE-501): Phase 2 trials with this preparation have been completed and the company is planning a pivotal Phase 3 trial. Afrezza® (Mannkind) is an ultra-rapid inhaled insulin, and its clinical development program has already included more than 6500 participants. This agent showed good postprandial blood glucose control with a low risk of hypoglycemia [23]. Phase 3 data are not yet published, but according to a press release from its sponsor presenting preliminary data from a Phase 3 study in T1D patients, this inhaled insulin achieved non-inferior HbA1c reductions, better post-prandial glucose control, and fewer hypoglycemic events compared with insulin lispro [24]. In June 2014, the FDA approved Afrezza® for use in diabetes mellitus as a meal-time insulin.

Challenges for inhaled insulin are that its effect is influenced by conditions that affect the lungs. Afrezza® is not approved for smokers and has a boxed warning that bronchospasms have been observed in patients with asthma and chronic obstructive pulmonary disease. The FDA required post-marketing studies in pediatric patients, further pharmacokinetic-pharmacodynamic studies, and CV and pulmonary safety studies.

NEW MECHANISMS OF ACTION

Although modifying drugs that have well-know mechanisms of action is important to increase adherence and comfort for diabetes patients, there is great need for drugs with new mechanisms of action that can be added to, or replace, currently available drugs.

PPAR Agonists/modulators

Peroxisome proliferator-activated receptors (PPAR) are transcription factors belonging to a family of low affinity lipid-binding nuclear receptors involved in glucose and lipid metabolism and inflammatory regulation [25]. There are 3 members, PPAR-α, PPAR-δ, and PPAR-γ. Although they are expressed ubiquitously, they have differential expression levels. PPAR-α is prominently expressed in tissues with high fatty acid oxidation, namely liver, heart, and kidney, and is the molecular target of fibrates, including fenofibrate, bezafibrate, and gemfibrozil. PPAR-γ is highly expressed in adipocytes and involved in adipogenesis. Many studies have shown PPAR-γ to be insulin sensitizing, consistent with being the target of the antidiabetic class of thiazolidinediones (TZDs), including rosiglitazone and pioglitazone. PPAR-δ's main sites of action seem to be the skeletal muscle and adipose tissues. By regulating fatty acid catabolism and thermogenesis, its activation leads to improved lipid homeostasis, resistance to weight gain, and increased insulin sensitivity. In addition, PPARs exert anti-inflammatory effects by interacting with inflammation-modulating transcription factors such as NF-κB and AP-1 to suppress inflammatory genes such as MCP1 and IL-6. Their expression in the vasculature also makes them relevant in the process of atherosclerosis.

Although their functions at the crossroads of metabolism and inflammation make them attractive targets in treating diabetes and metabolic diseases, current pharmacologic agents targeting these molecules have safety concerns. Activating PPAR-γ by TZDs in humans has been limited by side effects including edema, weight gain, and worsening of congestive heart failure. Thus, partial PPAR-γ agonists, or selective PPAR-γ modulators (SSPARMs) are being developed in the hopes of decrease the side effects while improving insulin sensitivity. Drugs targeting PPAR-α do not affect insulin sensitivity whereas drugs targeting PPAR-δ could offer the potential to improve both glucose and lipid metabolism.

PPAR-γ Agonists/Modulators

There are currently four molecules in Phase 1 and 2 development as PPAR-γ modulators. One of the SPPARMs is

INT131. A Phase 2 study showed comparable improvement of HbA1c and fasting plasma glucose and less worsening of peripheral edema compared with pioglitazone after 24 weeks [26].

Partial PPAR-γ agonists such as a phenylpropanoic acid derivative developed by Grupa Adamed has less than 30% activity compared with rosiglitazone. Animal studies have shown decreased glucose level with minimal body weight gain [27].

PN2034 is a non-TZD PPAR-γ modulator with two completed Phase 2 trials in 2007 (NCT00110864, NCT00110851) examining the insulin dose change, glycemic and lipid parameters after 12 weeks of treatment. This molecule was exclusively licensed by Sanofi-Aventis in 2009 [28].

Several molecules are in Phase 3 development. Balaglitazone (Dr Reddys Laboratories) is a partial PPAR-γ agonist. Although NovoNordisk had terminated development in 2004 due to lack of competitive potential, the Phase 3 BALLET trial showed efficacy and tolerability with favorable effect on bone loss and weight gain compared with pioglitazone [29]. DLBS 3233/Inlacin (Dexa Medica) is in Phase 3 development for both polycystic ovary syndrome and T2D in Indonesia. The therapy is a phytopharmaceutical comprising bioreactive plant fractions extracted from *Lagerstroemia speciosa* and *Cinnamomum burmannii* [30]. A Phase 3 trial in which all subjects were given DLBS3233 in addition to background therapy was completed in 2013.

PPAR-α/γ Co-agonists

Drugs are being developed to take advantage of the structural similarities among PPARs to achieve therapeutic benefits from activating multiple PPARs. C333H is a novel PPAR-α/γ agonist in preclinical development [31]. In rodent studies, it improves glycemia with minimal weight increase. It also induces an increase of the high molecular weight adiponectin isoforms [32].

DSP-8658 is a novel selective PPAR-α/γ modulator, currently in clinical development for diabetes but also showing promise in improving Alzheimer's disease. It has been found to improve microglial Amyloid-β (Aβ) phagocytosis and spatial memory performance in mice through upregulation of CD36, a scavenger receptor [33].

Lobeglitazone/CKD-501 (Chong Kun Dang) is a potent PPAR-γ agonist with partial PPAR-α affinity being developed in South Korea. Phase 3 investigation has shown a statistically significant reduction in HbA1c and lipid profiles compared with control, with a tolerability profile similar to placebo but with slightly more weight gain [34]. It is in the approval process for T2D as monotherapy in South Korea.

PPAR-α Agonists

KRP-101 (Kyorin Pharmaceuticals) decreased visceral fat, increased adiponectin and decreased serum leptin, as well as improving hyperglycemia and dyslipidemia in dogs. In hepaRG cells, KRP-101 increases the expression of ApoA-IV and apoA-V, which might mediate triglyceride decrease and HDL-cholesterol increase [35]. It was reported in 2009 to be in Phase II development for diabetes and dyslipidemia [36].

PPAR-α/δ Agonists

GT505 (Genfit) is an oral, once-daily, liver-targeted PPAR-α/δ co-agonist currently in Phase 2 trials for treating non-alcoholic steatohepatitis (NASH), lipid disorders, and T2D. Multiple trials with insulin resistant patients have shown a good safety profile, and improved glucose and lipid homeostasis. In addition, GT505 suppresses inflammation as shown by a reduction of plasma fibrinogen, haptoglobin, and ALT, and a lack of increase in homocysteine [37, 38]. The drug is well tolerated with good safety profile with no activation of PPAR-γ. A Phase 2 trial employing participants with T2D has completed but results have not been published as of writing. In February 2014, the FDA granted GFT505 Fast Track designation for NASH.

PPAR-δ/γ Agonists

DB959 (DARA BioSciences) is a novel PPAR-δ/γ agonist that improves glycemic and lipid parameters in rodents without increased weight gain [39]. It produced EC_{50}'s of 19 and 297 nM on PPAR-δ and PPAR-γ, respectively. Phase 1 dose escalation studies demonstrated a good safety profile. In 2013, DARA BioSciences granted rights for T3D Therapeutics to develop this drug for treatment of Alzheimer's disease given the competitive landscape of metabolic diseases [40].

PPAR-δ Agonists

MBX-8025 (CymaBay Therapeutics) treatment increases fatty acid oxidation and demonstrates broad effects on metabolic parameters and markers of inflammation. Preclinical studies and Phase 2 trials showed benefits including decreased LDL-cholesterol (including small dense LDL cholesterol particles), triglyceride, liver enzymes, high-sensitivity C-reactive protein, fasting insulin and glucose, and body fat mass, as well as increased HDL-cholesterol. Although it has some hypoglycemic effects, the development seems to focus on treatment of dyslipidemia and broader metabolic abnormalities [41].

KD3010 (Kalypsys Inc.) is a very potent and specific PPAR-δ agonist (EC_{50} of 1.5 nM). Preclinical studies showed no toxicity except for a reversible decrease in red blood cell count in monkeys. Phase 1 dose escalation studies in healthy and obese participants showed no significant side effects and promising trends in glucose, lipid, and inflammatory parameters. Furthermore, unlike another PPAR-δ agonist, GW501506, KD3010 is found to be hepatoprotective and antifibrotic in liver fibrosis rodent models [42].

Two other PPAR-δ agonists in Phase 1 development are HPP 593 (NovoNordisk) and SAR 351034 (Sanofi) for treatment of dyslipidemia and diabetes. In general, the potential of PPAR-δ agonists to improve insulin sensitivity, the lipid profile, and to suppress inflammation and oxidative stress, makes them attractive drugs for not just diabetes but also kidney and liver injury, and metabolic disorders [43].

PPAR-α/δ/γ Pan-agonists

Chiglitazar/CS038 (Chipscreen Biosciences) is an orally available small molecule not in the TZD class that activates all three PPAR transcription factors [45, 46]. It is in Phase 3 development for T2D in China (NCT02121717,

NCT02173457). Phase 2 trial results were reported in a 2007 media release which stated that the drug was well tolerated, safe, and improved glucose and lipid homeostasis [46].

Glucokinase Activators

Glucokinase (GK) serves as a glucose sensor in the insulin-producing pancreatic β-cells, although 99% of the enzyme is located in hepatic cells, where it regulates hepatic metabolism. In addition, it is expressed in enteric endocrine cells, the anterior pituitary, and perhaps vascular smooth muscle [47].

Two rare inherited metabolic disorders, autosomal dominant hyperinsulinemic hypoglycemia-secondary to activating mutation of the GK gene, and autosomal dominant hypoinsulinemic hyperglycemia-secondary to inactivating mutation of the GK gene, highlight the importance of this enzyme in glucose homeostasis [48]. The counterargument for the development of glucokinase activators (GKAs) for T2D is that the activation of the enzyme in the hepatocytes could lead to increased lipid biosynthesis, resulting in hepatic steatosis, hyperlipidemia, and increased CV risk [49, 50].

Piragliatin (Hoffmann-La Roche) [51] was the first GKA to be studied in 15 individuals with T2D. Decreases in serum glucose in the fed and fasting states, and decreases in hepatic glucose output were seen [52]. However, further development of the compound was terminated after safety concerns emerged during the Phase 2 program.

A Phase 2 study of MK-0941 (Merck) in participants with T2D on insulin glargine as background medication showed that the drug was initially efficacious in reducing post-prandial glycemia, but this effect had disappeared by week 30 of the study; in addition, there was an increased incidence of hypoglycemia, elevated serum triglyceride levels, and vascular hypertension [53].

A Phase 2 study of AZD1656 (AstraZeneca) in participants with T2D on metformin as background medication showed a significant reduction of HbA1c over four months, similar to that observed with glipizide, but with less hypoglycemic events; however, the effects on glycemia were not sustained over time in the extension period [54].

Despite intensive research efforts, there is still no GKA on the market, which highlights that many issues have yet to be resolved. It would be helpful to have GKAs with liver specificity to avoid the pancreatic cell-induced hypoglycemia [55]. A greater understanding is needed of the multifaceted role of the GK enzyme in the pancreas/liver and also in the other tissues where it is expressed, its multiple interactions with other proteins and cell organelles, and the interaction between GK and its drug activator [56]. Also of interest is the recent discovery of an intravenous liver-selective GKA for the management of inpatient hyperglycemia [57].

Glucagon Receptor Antagonists

In patients with T2D, an elevated glucagon/insulin ratio and the inability to suppress postprandial glucagon are important determinants of fasting and fed hyperglycemia, respectively [58]. For these reasons, the glucagon receptor (GCGR) has been identified as a potential target for T2D management since the 1990s. Studies with GCGR knock-out mice have shown that animals maintained normal glycemia and serum lipids, with markedly elevated serum glucagon levels and normal serum insulin levels [59]. In addition, they exhibited marked α-cell hyperplasia and increased GLP-1 levels [60]. The following synopsis discusses compounds that entered human clinical trials.

A Phase 1, 1-day, placebo-controlled study of BAY 27-9955 (Bayer) was conducted in 14 healthy, lean men after somatostatin infusion (to suppress endogenous insulin and glucagon production), insulin infusion (to provide basal insulin), and glucagon infusion (to produce hyperglucagonemia) [61]. Two different doses, 75 mg and 200 mg, were tested. In the placebo group, plasma glucose concentration increased by 75% and hepatic glucose production doubled; in the active treatment group, these glucagon-mediated effects were markedly blunted. The compound was well tolerated with no clinically significant metabolic or other side effects.

In a Phase 2 study, 342 participants with T2D were randomized to one of four MK-0893 (Merck) treatment arms at different dosages, metformin, or placebo.[1] At 12 weeks, treatment with MK-0893 resulted in statistically significant, dose-dependent reductions in fasting plasma glucose, ranging from 32-63 mg/dL. Metformin reduced FPG by 37 mg/dL, and placebo reduced FPG by just 2 mg/dL from baseline. For HbA_{1c}, reductions at 12 weeks ranged from 0.6-1.5%, compared with 0.8% with metformin and 0.5% with placebo.

In a study including 146 participants with T2D employing MK-0893 40-mg/day in combination with metformin or sitagliptin, as well as sitagliptin plus metformin, the MK-0893/metformin combination was superior to sitagliptin/metformin in lowering 24-hour weighted mean glucose, with a reduction of 117 mg/dL compared with 85 mg/dL.[2] However, MK-0893/sitagliptin was statistically significantly less effective than sitagliptin/metformin, which produced a 24-hour weighted mean glucose (WMG) reduction of 100 mg/dL. All treatments were equally well tolerated. However, there was a statistically significantly higher incidence of diarrhea in the two MK-0893 groups (10% vs. 0%). In addition, ALT and AST were elevated in the MK-0893/metformin group, and total cholesterol and LDL-cholesterol were increased from baseline with MK-0893/sitagliptin, relative to reductions with MK-0893/metformin and sitagliptin/metformin.

MK-3577 (Merck) is a glucagon receptor antagonist with a shorter half-life compared with MK-0893. In a Phase 2, 5-period, cross-over study, participants were randomized to placebo, metformin, MK-3577 10 mg qd in the morning, MK-3577 6 mg qd in the evening, and MK-3577 25 mg bid. Results were presented for the 118 participants who completed at least 2 periods. An association was found between glycemic control and LDL-cholesterol increase: completed

[1] Engel S, *et al.* Efficacy and tolerability of MK-0893, a glucagon receptor antagonist (GRA), in patients with type 2 diabetes (T2DM). Abstract 309-OR: Presented at the 2011 American Diabetes Association Annual Meeting.

[2] Engel S, *et al.* Efficacy and safety of the glucagon receptor antagonist, MK-0893, in combination with metformin or sitagliptin in patients with type 2 diabetes mellitus. Abstract 191: Presented at the 2011 European Association for the Study of Diabetes Annual Meeting.

glucagon receptor blockade led to better glycemic control, but also LDL-C increases, whereas partial glucagon receptor blockade led to smaller effects on glycemic control and LDL-C.[3]

In a Phase 1, dose-finding study, 47 participants were randomized to one of four doses LY-2409021 (Eli-Lilly) or metformin. By day 28, mean reductions in HbA_{1c} were statistically significant compared with baseline in all treatment groups, ranging from 0.69-1.02%. In the placebo group, HbA_{1c} dropped by 0.49%. Fasting glucagon increased statistically significantly by 0.6- to 4.2-fold compared with baseline across the LY dose levels, and fasting active glucagon-like peptide-1 (GLP-1) rose by 59% at the highest dose. Glucagon and GLP-1 returned to baseline levels during follow-up. The agent was generally well tolerated. Reversible elevations in hepatic transaminases were seen in five of nine participants in the highest-dose group, with no clinical signs or significant elevations in bilirubin or alkaline phosphatase.[4]

In a 3-month Phase 2a study, 87 participants with T2D who were drug-naive or on metformin monotherapy were randomized to placebo or one of 3 different doses of LY-2409021. After 12 weeks, all LY doses showed a statistically significant HbA1c reduction vs. placebo. There were also dose-dependent elevations in transaminases, GLP-1, and glucagon levels, and all returned to normal after LY-washout.[5]

In a Phase 1 single ascending dose (SAD) study including 56 healthy adults and individuals with type 2 diabetes (NCT01919684), a single dose of LGD-6972 (Ligand) reduced fasting plasma glucose in both healthy adults and those with type 2 diabetes. Fasting plasma glucose was reduced by 57 mg/dL (placebo-adjusted) in participants with type 2 diabetes.[6]

GCGRRx (Isis) is an antisense oligonucleotide that reduces glucagon receptor expression. In a Phase 2 study, participants with metformin failure were administered the drug (injected once weekly) for 13 weeks. The absolute mean reductions in HbA1c at week 13 compared with baseline were >1% and >2% in the 100 mg and 200 mg cohorts, respectively [62].

Limitations of GCGR blockade include lack of long-term safety data in humans, and islet cell hyperplasia and endocrine cell proliferation. Since glucagon exerts hypolipidemic actions, blockade of GCGR can be associated with hyperlipidemia and liver steatosis. Additionally, GCGR knock-out mice exhibit increased sensitivity to experimental liver injury, implying that the GCGR is important for vital hepatocytes [63].

Anti-inflammatory Compounds

Inflammation is part of body's defense to infection, injury, or stress. However, when overactive, it often leads to progressive tissue dysfunction and destruction. T2D is a low grade chronic autoinflammatory condition [64]. Its pathogenesis involves altered function of immune cells, which leads to persistent inflammation in multiple tissues, including adipose, liver, and pancreas. This contributes to both insulin resistance and β-cell failure. Thus, efforts have been ongoing to modify the progression of diabetes by suppressing inflammation.

Some of the key mediators of the pathways of interest are signals such as glucose and free fatty acids, cytokines including interleukine (IL)-1 beta, IL-6, and tumor necrosis factor (TNF)α, chemokines including monocyte chemotactic protein (MCP)1 [also referred to as chemokine (C-C motif) ligand(CCL)2], cell surface receptors including toll-like receptor (TLR)1, TLR4, and transcription factors activator protein (AP)1 and NFκb. The benefit of targeting these mediators includes the potential to modify the progression of diabetes, decrease diabetic complications such as nephropathy and CV disease, and the ability to co-administered with existing antidiabetic medications for additive effects. Although there are theoretical safety concerns from suppressing immune mediators, trials so far have shown a relatively safe profile.

C-C Chemokine Receptor Type 2 Antagonists

C-C chemokine receptor type 2 (CCR2) is a G protein-coupled receptor (GPCR) for multiple chemokines including CCL-2, CCL-7, CCL-8, and CCL-13. CCL2 (MCP1) mediates monocyte chemotaxis and recruitment and is a key player in atherogenesis, neuropathic pain, and many other inflammatory conditions [65]. There are at least eight CCR2 antagonists in Phase 2 trials.

Interleukin-1 Modulators

The interleukin-1 (IL-1) pathway is a central inflammatory pathway involved in immune response and autoinflammatory diseases [66]. IL1-α activation initiates the pathway in multiple cell types and leads to synthesis of the more potent IL-1β. Both IL-1α and IL-1β bind to the IL-1 receptor 1 (IL-1R1). Furthermore, hyperglycemia and high circulating free fatty acids activate β cells to make more IL-1β by > 100-fold. This leads to β cell dysfunction and death.

Another medication in this pathway, canakinumab/Ilaris® (Novartis), is currently in Phase 3 development for T2D, and is already approved for cryopyrin-associated periodic syndromes, gouty arthritis, and juvenile rheumatoid arthritis. The drug has been well tolerated in multiple clinical trials for inflammatory diseases. Canakinumab was tested in a multiple-dosing trial (N=551, ~100/treatment group). After four months there was minimal nonsignificant reduction of HbA1c, no improvement in other glycemic parameters including levels of insulin and glucose pre- and post-prandially (NCT00900146). There were significant reductions of in-

[3] Engel S, *et al.* Glycemic and lipid effects of the short-acting glucagon receptor antagonist MK-3577 in patients with type 2 diabetes. Abstract 1037-P: Presented at the 2012 American Diabetes Association Annual Meeting.

[4] Kazda C, *et al.* Short-term treatment with glucagon receptor antagonist LY-2409021 effectively reduces fasting blood glucose (FBG) and HbA1c in patients with type 2 diabetes mellitus (T2DM). Abstract 305-OR: Presented at the 2011 American Diabetes Association Annual Meeting.

[5] Kazda C, et al. Short-term treatment with glucagon receptor antagonist LY-2409021 effectively reduces fasting blood glucose (FBG) and HbA1c in patients with type 2 diabetes mellitus (T2DM). Abstract 305-OR: Presented at the 2011 American Diabetes Association Annual Meeting.

[6] Vajda EG, *et al.* Pharmacokinetics of the glucagon receptor antagonist LGD-6972. Abstract 1116-P: Presented at the 2014 American Diabetes Association Annual Meeting.

flammatory biomarkers, C-reactive protein, IL-6, and fibrinogen, and statistically significant elevation of serum triglyceride [67, 68]. Currently, canakinumab is dosed subcutaneously every four to eight weeks for approved indications, which, if applicable for diabetes, would be convenient for patients. Currently, canakinumab is tested in a large CV outcome trial including 17,200 high risk patients [69].

LY2189102 (Lilly) is a weekly-dosed humanized IL-1β neutralizing antibody. In a Phase 2 study, participants were given LY2189102 weekly subcutaneously for 12 weeks at multiple doses (~20 participants per treatment group). HbA1c reduction compared with placebo was modest (0.38%), although the percentage of participants achieving an HbA1c of 7% was higher than for placebo [70]. Inflammatory biomarkers, including C-reactive protein and IL-6, were reduced.

AC-201 (TWi Biotechnology) is the only orally-available, twice-daily, small-molecule agent that inhibits production and activity of IL-1β and down regulates IL-1R. A dose-ranging Phase 2 trial showed improvement in HbA1c of up to 0.49% compared with placebo after 24 weeks of treatment. The most common side effect was mild diarrhea (NCT012761060).

XBiotech has an extensive development program for T2-18C3/Xilonix, a bi-/tri-weekly subcutaneous injection [71], covering indications including colon cancer, vascular disease, and diabetes. This IL-1α neutralizing antibody was cloned from human tissue, and therefore has the potential advantage of lower immunogenicity compared with other engineered humanized antibodies. A Phase 2 trial interim analysis showed rapid decrease of HbA1c level by 8 weeks, 16 weeks earlier than linagliptin (NCT01427699). Adverse events reported include fatigue, nausea, and proteinuria.

Other Classes

Other anti-inflammatory compounds currently in development which can be applied to diabetes include the following: GSK1070806, a monoclonal antibody against IL-18 (GlaxoSmithKline), which has reached Phase 2; and the antisense glucocorticoid receptor inhibitor ISIS426115 (ISIS Pharmaceuticals) which is selective for liver and fat tissue and is in Phase 1 development. Data for these compounds are currently not publicly available.

G-protein Coupled Receptor Agonists

There is a great need to develop new antidiabetic agents that lower glucose levels without an increased risk of hypoglycemia, as this represents a major obstacle to glucose control and a special concern for therapies that increase insulin levels. The activation of some G-protein-coupled receptors (GPCRs) present in pancreatic β-cells, such as GPR40, GPR119, and GPR142, stimulating insulin secretion in a glucose-dependent fashion may be a potentially advantageous mechanism with a lower hypoglycemia risk [72, 73].

GPR40 is a β-cell membrane receptor that is activated by long-chain fatty acids and has been studied as a potential therapeutic target for diabetes drugs. Low hypoglycemia rates have been observed for agents in development in the class of GPR40 agonists [74]. *In vitro* and *in vivo* studies in rats with LY2881835 (Eli Lilly; in Phase 1 development) showed an increased glucose-dependent insulin secretion plus increased GLP-1 secretion, indicating that this could be a good candidate for early treatment of T2D [75].

Other compounds in development include JTT851 (Akros Pharma; Phase 2 development), P11187 (Piramal Enterprises; Phase 1 development), and CNX-011-067 (Connexios Life Sciences; preclinical study). Although GPCR agonists are promising new therapeutic entities, knowledge of the pharmacological properties of this receptor is still incomplete. Recently, the development program of one of the most promising GPR40 agonists, TAK-875 [76], was interrupted due to a liver safety signal detected during the Phase 3 program. This finding indicates that signaling through GPR40 is still waiting to be fully explored, which has implications for the development of other diabetes compounds that work through this mechanism [77].

GPR119 is another pancreatic β-cell receptor activated by fatty acid metabolites leading to insulin secretion, enteric incretin secretion (GLP-1), and gastric emptying inhibition [78]. These effects are associated with decreased food intake and reduced weight gain in rodents [79]. Several GPR119 compounds have been in development: APD668 and APD597 (Ortho-McNeil/Arena; both discontinued), DS-8500 (Daiichi Sankyo; Phase 2), ZYG19 (Zydus Cadila; IND filed), MBX2982 (CymaBay Therapeutics; in Phase 2), GSK1292263 (GlaxoSmithKline; in Phase 2), and PSN821 (Astellas/Prosidion; in Phase 2) [80]. Results from Phase 2 studies indicate an additional benefit of the use of these oral agents (MBX2982 and GSK1292263) in combination with DPP-4 [81]. The results seen so far with new GPR119 agonists have suggested the potential value of this class in the treatment of T2D and associated obesity, although the CV effects of this class of compounds are still not determined.

GPR109A is another GPCR expressed mainly in adipocytes, and is activated by nicotinic acid, inhibiting lipolysis in the adipose tissue. Results from a Phase 2 study with GSK256073 (GlaxoSmithKline) in participants with T2D indicated that this selective GPR109A agonist can decrease glucose concentrations, and does so by a different mechanism related to decreased insulin concentrations and enhanced measures of insulin sensitivity [82].

Gastrointestinal Peptide Agonists other than GLP-1

Diabetes and obesity are commonly co-morbid conditions: up to 80% of subjects with T2D are either overweight or obese [83]. Guidelines released by the American Diabetes Association (ADA) and European Association for Study of Diabetes (EASD) have indicated that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are the only class of glucose-reducing drugs that have an associated modest weight reduction, however a moderate weight loss effect has also been observed with the recently approved SGLT2 inhibitors [84]. Metformin and DPP4 inhibitors are weight neutral, and insulin, TZDs, and sulfonylureas are associated with weight gain.

Improvement in glycemic control of patients who have undergone bariatric surgery seems to be somewhat independent of weight loss. The theory is that it is related to alterations in gastrointestinal hormones such as GLP-1, oxyntomodulin (OXM), and peptide YY (PYY), which are

secreted in response to food [85]. Given these findings, Phase 1 research is being conducted to mimic alterations in these hormones to identify novel therapeutic options for obese type 2 diabetic patients.

There exists the potential for increased benefits of combining GLP-1 RAs with additional gastro-intestinal hormones. GLP-1/glucagon co-agonists have been investigated. This work has been based on data in rodents and humans that demonstrate that glucagon could have positive effects on energy balance, body fat mass, and nutrient intake. Oxyntomodulin has been shown to reduce body weight compared with placebo in obese and overweight individuals [86]. Additionally, it was proven to reduce food intake after an *ad libitum* test meal and increase energy expenditure in humans [87]. This led to the hypothesis that combining GLP-1 and glucagon in one molecule such as oxyntomodulin might alleviate both the elevations in blood glucose levels and the weight-lowering effect by glucagon receptor stimulation. Data in rodents have shown that a balanced ratio of GLP-1/glucagon-receptor activation is optimal to ensure glucose control associated with optimal weight loss [88].

Additionally, co-agonists of glucagon and GLP-1 reduce cholesterol and improve insulin sensitivity. This has been independent of the effect on appetite and body weight in diet-induced obese C57 mice [89]. Phase 1 studies are being carried out. These compounds include ZP2929, a GLP-1/Glucagon co-agonist carrying a fatty acid for once-daily dosing (Zealand Pharma), and TT401, a PEGylated analog for once-weekly dosing (Transition Therapeutics).

Another combination product being examined is the GLP-1/GIP co-agonists. GIP shares a 37% amino acid sequence identity with GLP-2 [90]. Because of the similarity of interaction sites, constructing single peptides with activity of both incretin hormone receptors is possible, which could result in a more pronounced antidiabetic effect. Preclinical data for GLP-1/GIP agonists show better reduction of blood glucose and body weight in diet-induced obesity mice compared with once-daily treatment with liraglutide. In obese mice, it was found that an acylated version of an agent targeting both the GLP-1 and GIP to be better than liraglutide at lowering body weight, diminishing food intake, decreasing fat mass and improving glucose control. A novel therapeutic, MAR701 is being developed by Marcadia Biotech.

GLP-1/PYY Combination-Peptide YY (PYY), when cleaved by DPP-4, is a selective agonist for neuropeptide Y2 receptor. It has been shown to inhibit food intake in humans and improve insulin sensitivity in rodents. Deficiency of PYY has been suggested to contribute to obesity [91, 92]. GLP-1 and PYY lack similarity, thus they require being co-administered. Preclinical data from GlaxoSmithKline showed that a combination of exendin-4 and PYY fused to an albumin binding antibody fragment led to dramatic decreases in HbA1c and body weight in diabetic mice when administered subcutaneously every other day over 15 days, suggesting a synergistic effect.

Cholecystokinin (CCK) was one of the first gut peptides to demonstrate effects of food intake by controlling meal size. A large, double-blind clinical trial was conducted to evaluate GI191771X, an oral CCK analog, to induce weight loss over a 24 week period [93]. Although this CCK1 receptor agonist/CCK2 receptor antagonist has poor bioavailability after oral administration, there was reduced food intake in short-term testing. When placebo or various doses of CCK agonists were given with a hypocaloric diet, no differences were noted in the resulting weight loss.

A chemically modified DPP4-resistant, triple-acting agonist of GIP, GLP-1, and glucagon receptors (termed YAG-glucagon) showed potent glucose-lowering and insulinotropic actions in high-fat-fed mice. This compound shows promise for treating T2D [94].

Apical Sodium-dependent Bile Acid Transporter Inhibitors

Currently available treatments with GLP-1 agonists have gastrointestinal side effects that limit their use for some patients. However, stimulating GLP-1 receptors has been one of the most successful approaches for treating T2D in the recent years. Apical sodium-dependent bile acid transporter (ASBT) inhibitors make use of the GLP-1 effects, can be taken orally and could have fewer gastrointestinal side effects than currently available GLP-1 agonists.

It was recently discovered that bile salts secreted into the intestines do not only facilitate the absorption of lipids, but also act as signals on at least two receptors, the intracellular nuclear farnesoid X receptor (FXR) [95] and the cell surface Tgr5 G protein-coupled receptor (also known as GPBAR1 and M-BAR) [96]. Both the FXR and the Tgr5 receptors are involved in lipid and glucose metabolism. Bile acids stimulate secretion of GLP-1 from colonic L-cells and GLP-1, PYY, as well as neurotensin from the ileum in rat models [97, 98]. Studies in humans also found an increase in the PYY and enteroglucagon [99]. Bile acids can regulate glucose levels and stimulate the other known effects of the gastrointestinal peptides *via* these mechanisms.

Following a meal, conjugated bile acids are secreted from the gall bladder into the duodenum to facilitate digestion of fats and 90% are reabsorbed into enterocytes *via* the ASBT. ASBT inhibitors have been developed as compounds that can inhibit the reabsorption of bile acids. This stimulates both the conversion of hepatic cholesterol to bile acids (lipid lowering effect) [100], and the release from gastrointestinal peptides, which make them candidates for the treatment of T2D. ASBT inhibitors currently in clinical development include LUM001 for cholestatic liver disease and LUM002 for hypercholesterolemia (both Shire Pharmaceuticals). A Phase 2 study has recently been completed for GSK2330672 (GlaxoSmithKline), which is the most advanced ASBT inhibitor in clinical development for the treatment of T2D [101]. This is an interesting approach as it indirectly makes use of an established mechanism of action (GLP-1, gastrointestinal peptides) *via* a new approach. No data on GSK2330672's tolerability and efficacy are yet publicly available yet.

SGLT1 and Dual SGLT1/SGLT2 Inhibitors (Excluding SGLT2-only Inhibitors)

The sodium-glucose co-transporters represent new therapeutic targets to reduce hyperglycemia in diabetes. Agents that inhibit those co-transporters (SGLT inhibitors) increase glucose excretion and help control hyperglycemia through an

insulin independent mechanism, introducing a new concept to the diabetes treatment [102]. Because their action is not mediated by insulin, there is little hypoglycaemia risk with these agents which can work even in states of pancreatic β-cell failure or insulin resistance. Differently than other therapies, these agents promote a negative energetic balance and consequent weight loss, which is also advantageous for diabetes control.

Although most of the drugs in development in this therapeutic class are SGLT2 inhibitors, agents that block SGLT1 activity in the small intestine also show improvement in glucose levels due to decreased intestinal absorption of glucose. The SGLT1 transporter is responsible for glucose and galactose absorption in the gastrointestinal tract and, to a smaller extent, glucose reabsorption in the kidneys. Selective SGLT1 inhibitors are currently being developed, such as KGA-3235 (Kissei Pharmaceuticals; Phase 1), GSK1614235 (GSK; Phase 1), EGT0001442 (Theracos; Phase 2), and EGT0001474 (Theracos; Phase 1). The basis for the effect of SGLT1 inhibition in glucose control is a reduction of the post-prandial glucose excursions and increase in GLP1 and PYY secretion in the distal part of the small intestine. An additional hypoglycemic benefit can be expected by concomitant SGLT1 and SGLT2 inhibition, and this is the basis for the development of dual SGLT1/SGLT-2 inhibitors such as LX4211 (Lexicon; Phase 2) and LIK066 (Novartis; Phase 2) [103].

Results from Phase 2 studies with LX4211 over 28 days of treatment demonstrated improvement of measures of glycemic control and decreased serum triglycerides, with additional trends toward lower blood pressure and weight [103]. These effects, observed in a small number of participants and for a short duration of treatment, led to the conduct of a larger trial to assess the dose-ranging efficacy and safety of LX4211 [104]. Approximately 300 participants with T2D inadequately controlled on metformin were randomized to placebo or one of four LX4211 treatment arms in this 12-week study. LX4211 reduced HbA1c in a dose-dependent manner, with each reduction being statistically significantly greater than for placebo. Weight and systolic (but not diastolic) blood pressure were also statistically significantly reduced.

11beta-HSD1 Inhibitors

11β-Hydroxysteroid dehydrogenase types 1 and 2 (11β-HSD1 and 11β-HSD2) regulate glucocorticoid metabolism at the tissue level: 11β-HSD1 catalyses the intracellular conversion of inactive cortisone to physiologically active cortisol, whereas 11β-HSD2 catalyzes the opposite reaction, conversion of cortisol to inactive cortisone. 11β-HSD1 is mainly expressed in liver, adipose tissue, bone, lung, and CNS, whereas 11β-HSD2 is predominantly expressed in the kidney [105].

Glucocorticoid excess leads to obesity and insulin resistance and the phenotype of metabolic syndrome. Transgenic mouse models have helped clarify the role of these enzymes in metabolic syndrome and obesity. In animals with 11β-HSD1 overexpression in adipose tissue, various features of the metabolic syndrome have been observed, such as glucose intolerance and insulin resistance, dyslipidemia, truncal obesity, and hypertension [106]. In animals with hepatic 11β-HSD1 overexpression, insulin resistance, triglyceride accumulation in the liver, dyslipidemia, and marked hypertension have been observed [105]. Conversely, 11β-HSD1-knockout animals exhibit an improvement in adipose and liver function, with improved lipid profile and enhanced liver sensitivity to insulin [107]. Based on these observations, a number of 11β-HSD1 inhibitors have been considered by the pharmaceutical industry as potential therapeutic agents for T2D and obesity, and more than 170 patents have been registered [108].

A Phase 1 study found PF-00915275 (Pfizer) to be a selective 11β-HSD1 inhibitor, with no evidence of hypertension or hypokalemia, and no changes in serum levels of ACTH, DHEA-S, 4-androstenedione, and testosterone [109]. A three-month, Phase 2 study of INCB13739 (Incyte) demonstrated a statistically significant reduction of HbA1c, FPG, insulin resistance, and body weight, plus a decrease in serum lipids in hyperlipidemic subjects. There was a dose-dependent increase in serum ACTH and DHEA-S (although values remained within the laboratory reference range), and values returned to baseline post-treatment. Morning plasma cortisol and evening salivary cortisol remained unaltered at all doses. In female participants, there was an increase in serum testosterone with a concurrent rise in SHBG, resulting in a FAI similar across all doses between study drug and placebo arms [110]. A three-month Phase 2 study of MK-0916 (Merck) demonstrated a moderate decrease in HbA1c, body weight, and BP, but no change in postprandial glucose. There was an elevation of DHEA, androstenedione, and testosterone, but values remained with normal reference range [111].

Several issues remain to be addressed before these compounds are marketed [112]. There are no long-term studies available beyond 3 months. Activation of hypothalamic-pituitary axis, as evidenced by increases in serum ACTH and adrenal androgens, might be a concern. There are potential consequences with long-term administration in women (acne, hirsutism, and menstrual irregularities). There are also potentially diminished stress responses because of decrease in local tissue cortisol production, and potential effects in innate immune responses.

ADDITIONAL COMPOUNDS WITH NEW MECHANISMS OF ACTION

Table **2** [113-126] presents a summary of other compounds in development for treatment of T2D that have new mechanisms of action. An agent's presence in the table does not reflect any speculation as to whether it will be successful or not. These compounds have only been studied in a small number of studies and/or the mechanisms are represented only by a single compound in early clinical development.

POTENTIAL IMPLICATIONS: POSSIBILITIES FOR PERSONALIZED MEDICINE IN TYPE 2 DIABETES

As previously noted, treatment of T2D typically requires a multi-drug regimen. Grant et al [127] reported that T2D patients within a single community U.S. healthcare system were taking a mean of 4.1 (±1.9) medicines per patient to

Table 2. Additional Compounds with New Mechanisms of Action.

Compound	Mechanism of Action	Phase of Development	Comments
Diacylglycerol acyltransferase (DGAT)-1 inhibitors	Inhibition of DGAT-1 (enzyme responsible for final step in triglyceride synthesis) – weight loss, improved insulin sensitivity, decreased cholesterol and triglycerides [113].	DS-7250 Phase 2 P7435 Phase 1	Gastrointestinal side effects (nausea, diarrhea, vomiting)
Cannabinoids	Protection of pancreatic beta cells, increase in insulin sensitivity [114].	GWP42003 Phase 2 GWP42004 Phase 2	Good tolerability in first clinical studies
Hepatic carnitine palmitoyltransferase 1 (CPT1) inhibitors	CPT1 is a mitochondrial enzyme involved in fatty acid metabolism. Inhibition decreases gluconeogenesis [115].	Teglicar Phase 2	Only limited data available
Fibroblast growth factor (FGF) 21 agonists	Stimulation of the FGF21 receptor results in increased glucose uptake by adipocytes, reduction in glucagon, increased energy expenditure, weight loss, decrease in steatosis [116, 117].	LY2405319 Phase 1	Only limited data available
Glucocorticoid receptor antagonist	Liver specific glucocorticoid receptor antagonist; reduction of hepatic glucose production [118].	ISIS-GCGRRx Phase 1	Only limited data available
Heat Shock Protein (HSP) inducer	Increases HSPs and nitric oxide – improved mitochondrial function and insulin sensitivity [119].	BGP-15 Phase 2	Only limited data available
Melanocortin-4 receptor (MC4R) agonist	MC4R inactivating mutation causes monogenic obesity (hyperphagia). MC4R Agonists result in weight loss and improved glucose tolerance [120].	RM-493 Phase 2	Subcutaneous injection; initial indication is treatment of obesity caused by genetic deficiency in the MC4 pathway
Tetrahydrotriazin containing oral antidiabetic – glimin	Decreases hepatic glucose production, increases muscle glucose uptake and improves pancreatic glucose dependent insulin secretion [121].	Imiglimin Phase 2	Placebo corrected HbA1c reduction as add on to metformin 0.44% in T2D patients [122].
Protein tyrosine phosphatase 1B (PTP1B) inhibitors	PTP1B is linked to insulin resistance, obesity and T2D; inhibition could improve insulin sensitivity [123].	TTP814 Phase 1/2 ISIS-PTP1BRx Phase 2	
Sirtuin1 (SIRT1) activators	SIRT1 is involved in glucose and lipid metabolism, insulin signaling and pancreatic insulin secretion; SIRT1 activation improves glucose homeostasis and insulin resistance [124].	SRT3025 Phase 1	Very early development stage
Microbiome modulator	The gut microbiome plays a role in the regulation of metabolic processes and changes of this microbiome have been associated with type 2 diabetes and insulin resistance [125]; A microbiome modulator contains concentrated bioactive food ingredients that changes the gut microbiota.	NM504 Phase 2	NM504 improves glucose tolerance in individuals with prediabetes and untreated T2D [126].

control diabetes and related comorbidities. Bauer and Nauck [128] found T2D patients were prescribed 8.4 ± 3.0 different drug compounds per day (maximum, 16), 8.6 ± 3.9 tablets per day (maximum, 22), 2.6 ± 1.6 injections per day (maximum, 7), in total 11.6 ± 4.5 doses of any medication per day (maximum, 27). However, regardless of this evidence that patients are taking multiple medications for their T2D specifically, and metabolic syndrome in general, treatment targets are often not being met. A chart audit undertaken from eight family physician practices in Newfoundland, Canada revealed that 20.6% of patients were at the recommended target for blood pressure, 48.1% for HbA_{1c}, and 17.5% for LDL-C, with only 2.5% of patients achieving targets in all three areas [129].

As Gale recently commented, "Type 2 diabetes is a disease in search of a definition. It has no hallmark clinical features, is generally diagnosed by default (no other cause for diabetes being evident), has very heterogeneous pathophysiological features, and varies widely between populations in clinical presentation and consequences. Despite this obvious heterogeneity, laboratory and clinical research is typically done as if T2D were one disease entity with uniform characteristics, thus assuming standard causal mechanisms and universal treatment pathways" [130]. Endocrinologists must therefore follow the lead of our oncology colleagues and promote personalized medicine [131-133].

Personalized medicine involves determining specific information about a particular patient and prescribing a treat-

ment regimen specifically tailored for that patient [134-136]. Because both T2D and metabolic syndrome are polygenetic diseases, it is important to confirm the therapies prescribed for a patient are appropriate. As polypharmacy is common in these patients, the risk of drug-induced adverse effects increases with the number of drugs prescribed: being able to prescribe the most useful drugs to treat diabetes, to both increase quality of life and decrease microvascular and macrovascular complications, is of paramount importance.

Future studies will need to evaluate the effect of different drug combinations for the treatment of T2D. This poses significant challenges for the pharmaceutical industry as it is possible that more and more drug classes will be available for the treatment of T2D in the future. Current clinical practice recommendations allow any combinations of antidiabetic drugs (approved at the time of writing the recommendations) according to individual patient characteristics, as there is little evidence for combining antidiabetic drugs available. Providing evidence for specific combinations of new drug classes with existing ones will significantly help the formulation of clear recommendations in the future.

As so many different drug classes are in development, a given compound's burden to make it to the market will in many cases not only be of a scientific and clinical nature, but also likely due to the financial cost of bringing a drug to the market. Current regulatory landscapes require a considerable number of patients to be studied to establish safety and efficacy for new antidiabetic drugs, which is reasonable bearing in mind that multiple thousands of patients will take an antidiabetic drug for many years once it is approved. However, a question that comes to mind is: should development of a given antidiabetic drug become much more focused and targeted towards a specified subset of patients likely to benefit from it?

Such a development model would mean a smaller number of patients potentially being prescribed the drug; consequently, this could mean less financial return to the drug's sponsor compared with the high development costs. Thus, perhaps a simpler and more cost-effective approval process could be developed because the benefit for the focused patient population would be considerably greater than the mean benefit across a larger patient spectrum. This development model could lead to more drugs being available and benefiting diabetes patients worldwide. This approach, different from the “one drug for all” approach, may require specialized physicians to prescribe the respective combinations of compounds, but there are certainly precedents for this. For example, the European Society of Hypertension has established accredited Centres of Excellence in hypertension [137] and the American Society of Hypertension has designated certain centers as Hypertension Centers that are well-placed to assist patients with difficult-to-treat hypertension and their family physicians [138]. As with hypertension, a challenge of combination therapy is the increased treatment complexity and the increased likelihood of side effects that can affect long-term adherence.

The drug development landscape for T2D remains wide and interesting. Bearing in my mind the large number of antidiabetic drugs that are currently in early clinical development, it might be the case that a “one size fits all” approach for these compounds might not be feasible. Targeting specific patient groups with specified characteristics could improve the benefit-risk profile, and a simpler and more cost-effective approval process could possibly be developed.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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