ELSEVIER

The potential of incretin-based therapies in type 1 diabetes

Chen S. Suen and Paul Burn

The Sanford Project, Sanford Research, Sanford Health and Department of Pediatrics, Sanford School of Medicine of The University of South Dakota, 2301 East 60th Street North, Sioux Falls, SD 57104, USA

Finding a cure for type 1 diabetes (T1D) has been elusive. Incretin-based therapies, since their approval, have demonstrated their clinical utilities in type 2 diabetes (T2D). Yet, their potential clinical benefits in T1D remain to be appraised. GLP-1, in addition to its insulinotropic action in alleviating hyperglycemia, possesses beneficial effects in protecting progressive impairment of pancreatic β-cell function, preservation of β-cell mass and suppression of glucagon secretion, gastric emptying and appetite. Preclinical data using incretin-based therapies in diabetic NOD mice demonstrated additional effects including immuno-modulation, anti-inflammation and β-cell regeneration. Thus, data accumulated hold the promise that incretin-based therapies may be effective in delaying the new-onset, halting the further progression, or reversing T1D in subjects with newly diagnosed or long-standing, established disease.

Introduction

Annually, about 70,000 children aged 14 and under develop type 1 diabetes (T1D) worldwide. T1D involves an autoimmune-mediated destruction of pancreatic β-cells resulting in insulin deficiency and hyperglycemia. Insulin-replacement therapy is the life-saving, first-line treatment for T1D. The disease generally develops over years and involves a progressive impairment of β-cell function and a decline in β-cell mass. At the time of disease diagnosis, patients only retain about 10–20% of functional β-cell mass. In the past, it has been believed that the loss of β-cells in T1D is an irreversible process. However, recent studies [1–3] indicate that: (i) residual functional β-cells remain in T1D patients many years after diagnosis; (ii) β-cell mass can expand in response to increased metabolic demand as documented in obesity and during pregnancy; and (iii) β-cells can replicate, differentiate or trans-differentiate from various endocrine and nonendocrine cells under specific conditions. Taken together, these findings provide a strong espousal of the idea that loss of β-cell function and mass may be halted or restored by triggering endogenous repair and regeneration mechanisms. Thus, enhancing endogenous β-cell function and/or regeneration may provide a viable therapeutic approach to be considered in both, type 2 diabetes (T2D) and T1D clinical settings [4].

On the basis of studies that oral administration of glucose elicited an enhancement of the insulin secretion response compared to an intravenous administration of glucose, the phenomenon of the incretin effect was first observed almost four decades ago [5,6]. This incretin effect is attributed largely to two gut-hormones, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), which are secreted by enteroendocrine K and L cells in the small intestine and colon, respectively. GIP is a 42-amino acid peptide, and GLP-1 is a peptide present in two biologically active forms of 29- and 30-amino acid, respectively. They bind to distinct G-protein-coupled receptors (GPCRs) on target tissues. Both hormones affect glycemic control by augmenting glucose-dependent insulin secretion from β-cells of the pancreas. In addition, GLP-1 regulates glucose homeostasis by suppressing glucagon secretion from islet α-cells resulting in a reduction of hepatic glucose output; by delaying of gastric emptying; by suppressing of appetite; and by enhancing β-cell proliferation and inhibiting β-cell apoptosis; whereas, GIP promotes lipogenesis by stimulating glucose uptake by adipocytes. Both, GIP and GLP-1 are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) resulting in circulating half-life of these hormones in the range of minutes.

Corresponding author:. Burn, P. (paul.burn@sanfordhealth.org)

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2011.08.017

Please cite this article in press as: C.S. Suen, The potential of incretin-based therapies in type 1 diabetes, Drug Discov Today (2011), doi:10.1016/j.drudis.2011.08.017

In human, administration of GIP to healthy individuals begets a dose-dependent increase of insulin release. This insulinotropic effect is, however, severely diminished in diabetic subjects. By contrast, GLP-1 displays a strong insulinotropic effect on insulin release in type 2 diabetic patients when administrated intravenously. These remarkable findings embarked upon significant efforts in understanding the physiological actions of GLP-1 and its potential utility in managing diabetes. Because of the extremely short half-life of endogenous GLP-1, two pharmacological approaches have evolved: (i) GLP-1 mimetics/analogs (GLP-1 receptor (GLP-1r) agonists) and (ii) DPP-4 inhibitors. Both approaches are aimed at prolonging the biological half-life and corresponding actions of GLP-1.

Here, the utilities and various preclinical and clinical effects of US Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMA) approved GLP-1 mimetics/analogs and DPP-4 inhibitors are reviewed. Clinically relevant, short-term and long-term effects of incretin-based therapies that have the potential to provide meaningful solutions to T1D patients and thus, warrant further evaluation and assessment in T1D settings are discussed.

Incretin-based therapies

The FDA and EMA approved several GLP-1 mimetics/analogs (exenatide and liraglutide) and DPP-4 inhibitors (sitagliptin and saxagliptin and linagliptin) for the T2D indication. All medications are associated with an improvement of glucose homeostasis and lowering of fasting and postprandial glucose levels in T2D patients. Additional, clinically meaningful effects have been reported as well.

Exenatide

Exenatide, in April 2005, was the first GLP-1 mimetic approved by the FDA. It was labeled as an adjunctive therapy to control hyperglycemia in patients who have not achieved acceptable levels of HbA1c with currently available antidiabetic medications. Several recent studies provided additional clinical utilities for exenatide demonstrating increased β-cell function [7], and a meaningful reduction of daily insulin doses in insulin-treated T2D patients [8,9].

Liraglutide

The clinical efficacy of liraglutide, a human GLP-1 analog, in the treatment of T2D had been evinced in multiple LEAD trials of nearly 4000 patients [10,11]. This led to the approval of liraglutide as an adjunctive therapy to diet and exercise by the EMA in 2009 and the FDA in 2010, respectively. In addition to its glucose-lowering effects, data from clinical studies now established that treatment with liraglutide is associated with improvements of various cardiovascular risk factors, including body weight, blood pressure and lipid panels.

Sitagliptin

Sitagliptin was the first oral DPP-4 inhibitor approved by the FDA for the treatment of T2D in October 2006. In long-term clinical studies, sitagliptin demonstrated its pharmacodynamic efficacy in reducing HbA1c levels, fasting glucose levels and improving postprandial glucose excursions [12].

Saxagliptin

Saxagliptin was approved by the FDA in July 2009 as a once-daily tablet for the T2D indication, either as a monotherapy or in combination with metformin, sulfonylureas, or thiazolidinediones.

Linagliptin

Linagliptin, was approved by the FDA for the treatment of T2D in 2011. In addition to sustained reductions in blood levels of HbA1c, fasting plasma glucose and postprandial glucose improvement of β-cell function were demonstrated.

A recent study, comparing liraglutide with sitagliptin in T2D patients who have inadequate glycemic control with metformin, showed that liraglutide was superior to sitagliptin as measured by reduction of HbA1c and fasting plasma glucose [13]. In a head-to-head comparison with exenatide, liraglutide demonstrated superior efficacy in lowering blood glucose [14]. Both, liraglutide and exenatide, have been demonstrated their weight-loss effects. Unlike GLP-1 mimetics/analogs, DPP-4 inhibitors possess neutral effects on body weight and lipid profile.

As with any newly introduced drugs long-term safety will have to be monitored of both, GLP-1 mimetics/analogs and DPP-4 inhibitors in the respective patient populations and with specific combination therapies in mind. Of note, the FDA has not yet approved the concomitant use of GLP-1 mimetics/analogs and insulin. In addition, pancreatitis, as indicated in the corresponding FDA bulletins, will be a parameter to be watched. Analyzing the FDA adverse event reporting database of corresponding T2D trials, a recent report mentioned pancreatitis, pancreatic and thyroid cancer as potential safety concerns, however, the report concluded that this analysis does not establish that pancreatitis, pancreatic and thyroid cancer are caused by incretin-based therapies [15]. Similarly, another recent review of preclinical and clinical data indicated no increased risk of pancreatitis in patients with T2D treated with sitagliptin [16].

Effects of incretin-based therapies on β-cell function/mass in type 2 diabetes

Most patients with T2D display a progressive worsening of glycemic control. This is due to the gradual loss of β-cell function and mass, resulting in insulin deficiencies. Therefore, maintaining β-cell function and/or halting further loss of β-cell mass may provide a promising strategy in managing or even reversing the course of the disease. To that end, over the last decade, many studies have been carried out aimed at exploring the potential benefits of incretin-based therapies on β-cell preservation and/or regeneration.

A large body of preclinical evidence shows that activation of the GLP-1 receptor signaling pathway enhances β-cell proliferation and regeneration and diminishes β-cell apoptosis resulting in a net increase of functional β-cell mass [17,18]. The GLP-1r belongs to the class B family of seven trans-membrane GPCRs and is expressed in the β-cells of the pancreatic islets. The binding of GLP-1 to GLP-1r activates the G(s)-α protein and its downstream signaling pathways and controls β-cell function. It includes the production of cAMP and the activation of protein kinase A (PKA)-dependent and -independent pathways. Notably, β-cell-specific G(s)-α knockout mice display a marked decrease in β-cell mass due to reduced β-cell

Please cite this article in press as: C.S. Suen, The potential of incretin-based therapies in type 1 diabetes, Drug Discov Today (2011), doi:10.1016/j.drudis.2011.08.017

proliferation and increased β-cell apoptosis [19]. In addition, GLP-1 has been reported to be involved in activating several transcription factors including PDX-1; β-catenin/TCF7L2-dependent Wnt signaling pathways, which enhance proliferation and survival of β-cells [20,21]; and inhibiting β-cell apoptosis [22,23]. These data have been confirmed and extended using various GLP-1 mimetics/analogs and DPP-4 inhibitors in both, *in vitro* and *in vivo* settings [24].

Exenatide, in several independent, preclinical studies, has been shown to improve β-cell function and mass [25–27]. Reported mechanisms involve the inhibition of pro-inflammatory cytokines, β-cell apoptosis and endoplasmic reticulum (ER) stress. Similarly, studies involving liraglutide revealed an increase of β-cell proliferation and β-cell mass in *ob/ob* mice [28]. Furthermore, studies using primary neonatal rat islets showed that liraglutide, in a dose-dependent manner, inhibited both cytokine- and free fatty acid-induced apoptosis via a PI3 kinase-mediated pathway [29]. Additionally, liraglutide treatment showed reduced apoptosis of β-cells in islet transplants in streptozotocin (STZ)-induced overt diabetic BALB/c mice [30].

In clinical studies, exenatide and liraglutide have both demonstrated their beneficial effects on β-cell function as determined by glucose- and arginine-stimulated C-peptide secretion in patients with T2D [31,32].

The effects of DPP-4 inhibitor monotherapy in improving β-cell mass/function in T2D are modest. In preclinical studies [33] chronic administration of sitagliptin was reported to increase β-cell mass and insulin-positive β-cells in the islet areas. By contrast, sitagliptin showed a marginal improvement in the homeostasis model assessment of β-cell function (HOMA-β) index in T2D patients [34]. Because sitagliptin administration only modestly enhances endogenous GLP-1 levels, the magnitude of improvement of β-cell function appears to be less than what was observed in similar studies using GLP-1 mimetics/analogs. The effect of saxagliptin on β-cell function was assessed in treatment-naïve patients utilizing the hyperglycemic clamp and improved β-cell responsiveness to glucose and decreased postprandial glucagon concentrations were reported [35].

In conclusion, many preclinical and clinical studies have already provided substantial evidence that incretin-based therapies may preserve β-cell function in T2D settings. Having several FDA approved drugs at our disposal, studies exploring benefits on β-cell mass will soon shed further light on additional benefits that this class of medicines may display. Documented, beneficial effects of incretin-based therapies in T2D on β-cell function and mass are of great interest for patients diagnosed with T1D as well. Both, improving function of remaining β-cells and expansion of functional β-cell mass after disease onset are strategies that warrant further assessment in T1D patients.

Effects of incretin-based therapies in type 1 diabetes

T1D is an autoimmune disease and a metabolic disorder characterized by gradual disappearance of functional, insulin-producing pancreatic β-cells resulting in insulin deficiency and chronic hyperglycemia. Both, a T-cell-mediated destruction of insulin-secreting β-cells and a dysfunction of the remaining β-cells in processing and secreting insulin have been reported.

At the recent 2011 American Diabetes Association (ADA) annual meeting the results of several T1D clinical trials were revealed. Most trials involved immunological approaches aimed at ameliorating the autoimmune attack, inducing immune tolerance, or modulating secondary immune and inflammatory responses. Some drug candidate molecules showed promise in slowing the progression of the disease, but thus far, none have been able to halt the further progression of the disease or restore β-cell function/mass. Thus, it is imperative to consider additional approaches to complement promising immunological approaches and to sustain long-term therapeutic effects in patient with T1D.

The incretin hormone GLP-1 may be valuable in this regard, because it has been demonstrated that GLP-1 can reduce β-cell apoptosis, stimulate proliferation and enhance β-cell survival in preclinical studies. Moreover, pilot clinical studies have revealed additional, clinically relevant benefits of GLP-1 in postprandial glucagon suppression, delayed gastric emptying and weight loss secondary to increased satiety. Thus, GLP-1 receptor agonists or DPP-4 inhibitors may be clinically useful as standalone medicines or as adjunct therapies in T1D patients.

GLP-1 mimetics/analogs in type 1 diabetes

Hadjiyanni *et al.* demonstrated that exendin-4, a GLP-1 mimetic and equivalent to exenatide, administration in NOD mice exhibited a significant reduction in insulitis scores, enhanced β-cell mass and improved glucose tolerance [36]. Several additional studies addressed the hypothesis of reversing diabetes and enhancing β-cell regeneration. For example, exendin-4 in combination with anti-CD3 therapy showed a beneficial effect on β-cell mass in NOD mice [37]. As expected, this combination therapy resulted in a significant improvement of insulin response to glucose, enhancement of total islet insulin contents, and increased the remission rate of diabetes. Suares-Pinzon *et al.* demonstrated that synthetic human GLP-1 {7-36} amide restored normoglycemia in acutely diabetic NOD mice while co-administered with gastrin [38]. This effect was attributed to partial restoration of pancreatic β-cell mass. Tian *et al.* reported that exendin-4-stimulated residual β-cell replication (measured by nuclear BrdU label and cytoplasmic insulin staining) in NOD mice treated with complete Freund's adjuvant (CFA) [39]. Their data further demonstrated that the number of T regulatory (Treg) cells in spleen and pancreatic lymph node was significantly increased in both CFA- and exendin-4-treated NOD mice.

Given the observed multiple beneficial effects of GLP-1 in preclinical studies, clinical evaluation of GLP-1 mimetics/analogs were conducted in a limited number of T1D patients. Evidence from a case study [40] revealed that exenatide, used in a 40-year-old male with T1D, attenuated the patient's HbA1c from 8.7% to 7.3% after 11 months of treatment. Furthermore, his basal insulin requirements were reduced by 25% and use of short-acting insulin before breakfast and before dinner was discontinued. Another case study [41] reported on the stabilizing effects of exenatide in a patient without any detectable C-peptide. Over the treatment period of several month glycemic control improved dramatically and HbA1c levels had fallen by 2%. C-peptide levels remained undetectable suggesting that the beneficial effects were not attributable to enhanced insulin secretion but may have involved other incretin-mediated mechanisms. To that end, in other reports, it was demonstrated that administration of GLP-1or exendin-4 results in lower fasting glycemia in T1D patients, mainly by

Please cite this article in press as: C.S. Suen, The potential of incretin-based therapies in type 1 diabetes, Drug Discov Today (2011), doi:10.1016/j.drudis.2011.08.017

reducing glucagon concentrations [42,43]. Furthermore, exenatide was assessed over several months in patients with long-standing T1D and an increase in insulin secretion was reported, however, it was not considered to be clinically significant [44].

Additional clinical studies tested the hypothesis that adding GLP-1 mimetics to the treatment regimen at the time of islet transplantation would provide a benefit in preserving islet mass and function in T1D patients. To that end, a significant stabilization of glycemic control and islet transplant function was demonstrated using exenatide in islet transplant patients [45–47]. However, after discontinuation of exenatide treatment the initially observed improvement of β-cell function was not maintained.

More recently, several clinical studies aimed to discern endogenous GLP-1 response and beneficial effects of native GLP-1 [48] or liraglutide [49,50] in controlling hyperglycemia and insulin dosing regimens in T1D patients with and without residual C-peptide levels. First, the incretin response to a mixed meal test was enhanced in T1D patients with residual β-cell function. Second, both GLP-1 infusion and daily injection of liraglutide resulted in significant reduction in insulin dose; the reduction of insulin regimen was larger in C-peptide-positive patients. Of note, two C-peptide-positive patients completely discontinued insulin treatment without loss of glycemic control. Third, the levels of HbA1c significantly decreased at 24 weeks of treatment with liraglutide.

The short and long-term beneficial effects observed in T1D patients after GLP-1, exenatide, or liraglutide administration warrant further studies both, in patients with new-onset as well as established T1D. Moreover, the underlying molecular mechanisms mediating liraglutide's and exenatide's actions in T1D patients on improving glucose homeostasis and β-cell function, survival and possible regeneration, remain to be explored.

DPP-4 inhibitors in type 1 diabetes

DPP-4 is a serine peptidase that catalyzes and releases dipeptides from the N-terminus of many peptides including incretin hormones. As such, it converts biologically active GLP-1 into its inactive form. DPP-4 is also known as the cell surface antigen CD26 (DPP-4/CD26). DPP-4/CD26 is expressed in a variety of cell types, including T-lymphocytes, endothelial cells, B-lymphocytes, macrophages and natural killer cells. It has been shown to be a T-cell activation marker [51], and has a costimulatory role in T-cell activation. The expression of DPP-4/CD26 increased significantly after stimulation of human peripheral blood mononuclear cells or T-cells by mitogens [52]. In the peripheral blood, DPP-4$^+$/CD4$^+$ T-cells are involved in regulating CD14$^+$ monocyte differentiation into dendritic cells after antigen-stimulation. The activation of dendritic cells augments the T-cell-mediated immune response via a direct effect on antigen presenting cells [53]. In mice lacking DPP-4/CD26, enhanced insulin secretion and improved glucose tolerance have been reported [54]. Several groups also examined the immune system in DPP-4/CD26 knockout mice [55]. As expected, they found a reduction of CD4$^+$ T-cells in the spleen. In addition, serum levels of total IgG, IgG1 and IgG2 were markedly lower in DPP-4/CD26 null mice after a pokeweed mitogen challenge. These data revealed that DPP-4/CD26 may play a role in the regulation of CD4$^+$ T-lymphocytes, cytokine secretion and T-cell-dependent antibody production.

Furthermore, increased DPP-4/CD26-mediated activities have been reported for several autoimmune diseases [56]. Samples from patients with multiple sclerosis indicated an elevated DPP-4/CD26 activity in T-lymphocytes [57]. In the DPP-4/CD26 mutant Fischer 344 rats, the number of CD4$^+$ T effector lymphocytes was markedly reduced in a model of experimental asthma. Further analysis of these rats indicated a significantly increased influx of FoxP3$^+$ regulatory T-lymphocytes (Treg) into the lungs [58], protecting from immune attack of an airway inflammation. Of note, Treg cells play a crucial role in suppressing inessential immune response and thus, an implicit role of Treg cells in controlling the pathogenic autoimmune process in T1D had also been explored [59].

Could a DPP-4 inhibitor, in addition to prolonging endogenous GLP-1 actions, possess an immune-modulatory property thereby providing an additional benefit in ameliorating autoimmune destruction of β-cells in T1D? In preclinical studies, the DPP-4/CD26 inhibitor, isoleucine thiazolidide, was shown to improve glucose tolerance in both, STZ-induced and BioBreeding diabetic rats. Stimulation of β-cell survival and possibly islet neogenesis were suggested as the underlying mechanisms [60,61]. Furthermore, DPP-4 inhibitors demonstrated their pharmacodynamic efficacy in reversing hyperglycemia in diabetic NOD mice. However, the potential mechanisms of restoration to normoglycemia were not addressed [62]. A recent study indicated that new-onset diabetic NOD mice treated with NVP-DPP728, an experimental DPP-4 inhibitor, resulted in reducing insulitis, increasing the number of Treg cells, stimulating β-cell proliferation and leading to remission of T1D [63]. In these studies, increased β-cell replication correlated with elevated levels of plasma GLP-1.

Similar to GLP-1 mimetics, sitagliptin, in addition to effectively regulating blood glucose, was reported to have a protective effect on islet graft size after islet transplantation [64]. One of the effects of sitagliptin in preserving transplanted islets was attributed to reducing homing of CD4 T-cells into the islets [65].

Taken together, these data raise the possibility that DPP-4 inhibitors have the potential to modulate the autoimmune response and promote β-cell function in T1D.

Clinical assessment of DPP-4 inhibitors in T1D is scarce. One study, however, reported the use of sitagliptin in newly diagnosed T1D patients who received autologous nonmyeloablative hematopoietic stem cell transplants [66]. Two of the study subjects also received sitagliptin (100 mg/d). As a result, their C-peptide levels increased significantly and insulin-replacement therapy was discontinued 2 months after transplantation. Both patients remained free from exogenous insulin use for another 6 months. This impressive result may imply a sitagliptin-mediated differentiation of transplanted stem cells into insulin-secreting β-cells. Furthermore, in an intriguing recent case report it was described that the DPP-4 inhibitor sitagliptin is effective and safe as an add-on therapy to insulin in reducing blood glucose levels in patients who had no detectable postmeal C-peptide levels [67]. In other words, patients who were given sitagliptin in addition to their ongoing intensive insulin therapy displayed improved glycemic control without displaying any detectable increase in C-peptide levels suggesting that no improvement of β-cell function occurred with this particular treatment regimen. This opens up the interesting question of what else besides the described and known effects of DPP-4 inhibitors on β-cell

Please cite this article in press as: C.S. Suen, The potential of incretin-based therapies in type 1 diabetes, Drug Discov Today (2011), doi:10.1016/j.drudis.2011.08.017

function are underlying the observed reduction in glucose levels. To that end, it is of interest to note that in a study involving 11 T1D patients it was reported that the DPP-4 inhibitor vildagliptin did suppress postprandial glucagon by a β-cell-independent mechanism [68].

While the data generated from this limited number of case and small pilot studies are encouraging, it does not yet warrant clinical utility of either GLP-1 mimetics/analogs or DPP-4 inhibitors in treating T1D patients. Randomized clinical trials will have to demonstrate that these agents can attest tight control of glucose homeostasis in T1D patients and will eventually render them to become insulin-independent.

Conclusions and future perspectives

T1D is characterized by progressive impairment of β-cell function and loss of β-cell mass (Fig. 1), which results in insulin deficiencies, chronic hyperglycemia and eventually in diabetic complications. Therefore, the ultimate objective of therapeutic intervention in T1D is to normalize glucose homeostasis by preserving or restoring β-cell function and mass. To achieve this goal, to date, several strategies aimed at halting further deterioration or reversing of disease progression by modulating the autoimmune and/or secondary immune and inflammatory responses have been considered [4].

Teplizumab and otelixzumab, two anti-CD3-specific antibodies [69,70]; rituximab, a B-lymphocyte-specific, anti-CD20 antibody [71]; and an antigen-based therapy using a glutamic acid decarboxylase (GAD)-derived vaccine [72], have been investigated in newly diagnosed T1D patients in several clinical proof-of-concept studies. Data reported from these early academic studies instigated significant enthusiasm in the field and among patients. More recent studies [73,74], however, also revealed that immunological approaches targeting inflammatory responses and autoimmune attack might not be sufficient to stop further loss of β-cell function and mass [75]. Thus, β-cell regenerative approaches improving

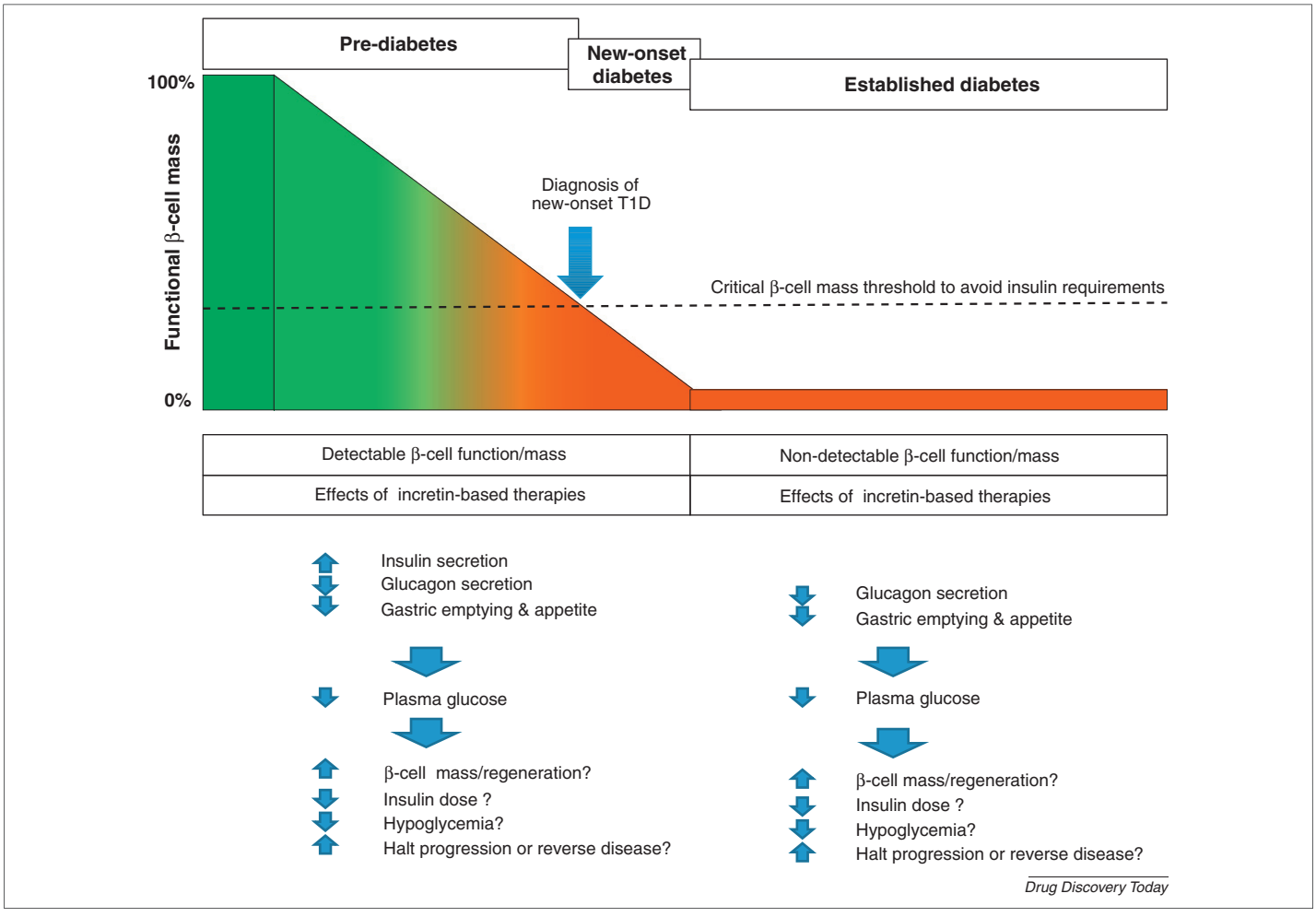

FIGURE 1

Effects of incretin-based therapies in T1D patients with and without detectable β-cell function. Demonstrated effects in humans include improved function of existing β-cells associated with a stimulation of insulin secretion; suppression of glucagon secretion from α-cells associated with reduced glucose output from liver; delayed gastric emptying; and suppression of appetite, all contributing to a reduction in fasting and postprandial glucose levels. Greatest short-term therapeutic effects are expected under conditions where functional β-cell mass is detectable (prediabetes and new-onset diabetes), while smaller short-term effects are expected in established disease where no functional β-cell mass is detectable and hence, stimulation of insulin secretion from remaining β-cells is minimal, if detectable at all. Whether incretin-based therapies display additional beneficial and clinically relevant short-term and long-term effects on residual β-cell mass, β-cell regeneration, insulin doses, risk of ketoacidosis, hypoglycemia, and long-term diabetic complications; or whether they may be effective in delaying the new-onset, halting the further progression, or even reversing T1D in subjects with newly diagnosed or established disease await further assessment in humans.

Please cite this article in press as: C.S. Suen, The potential of incretin-based therapies in type 1 diabetes, Drug Discov Today (2011), doi:10.1016/j.drudis.2011.08.017

remaining β-cell function and/or increasing remaining β-cell mass have to be considered as well [4].

β-Cell mass and function is regulated in response to metabolic demand thus, suggesting that it may be feasible to design and develop novel medicines targeting endogenous β-cells regeneration and repair mechanisms by tapping into the underlying, physiologically relevant pathways. In fact, recent clinical studies demonstrated the presence of remaining, functional β-cells in patients with established T1D as well as the existence of β-cell populations that are not fully differentiated, indicating the possibility that β-cell regeneration may occur even in subjects with long-standing disease.

Incretin-based therapies, GLP-1 mimetics/analogs and DPP-4 inhibitors, have already proven their clinical utilities in T2D. This new class of medicines has also demonstrated its beneficial effects in maintaining glucose homeostasis, anti-apoptosis, immunomodulation and β-cell regeneration in type 1 diabetic NOD mice. Are we at the prime time of translating these preclinical studies into the clinics to investigate the potential benefits of incretin-based therapies in patients with T1D? Indeed, the underlying science has evolved, supporting data have accumulated, and the patient's desire for the development of innovative, novel solutions and a cure are emerging. This, combined with the availability of several FDA and EMA approved drugs, provides a unique opportunity, allowing for safe progression and rapid assessment of incretin-based medicines in small, proof-of-concept studies in subjects with T1D. By carefully designing, executing and analyzing the data of the corresponding trials we will learn more about the effectiveness of individual incretin-based therapies in new-onset and established T1D patients and will unravel the molecular mechanisms underlying glycemic control in T1D patients. Halting further progression of the disease and restoring β-cell function and/or mass will, however, always be the ultimate, desired outcome for any trial.

Because incretin-based therapies have the potential to display their actions through multiple mechanisms including augmentation of glucose-dependent insulin secretion from β-cells, suppression of glucagon secretion, gastric emptying and appetite, or by modulating the auto-immune reaction, enhancing β-cell proliferation and inhibiting β-cell apoptosis, they may be effective both in patients with new-onset and established T1D (Fig. 1). They may proof to be clinically useful as standalone medicines or as adjunct therapies in T1D patients to aid: (i) in improving remaining β-cell function, (ii) in regenerating endogenous β-cell mass, or (iii) in regulating proper control of glucose homeostasis through β-cell-independent mechanisms thereby providing an environment that favors proper β-cell function and regeneration.

While multiple GLP-1 mimetics/analogs and DPP-4 inhibitors with distinctive PK/PD profiles are on or close to market, several small molecules aimed at augmenting the entero-insular axis by targeting novel GPCRs in the gastrointestinal (GI) tract and the pancreas, are close of entering the clinics for the T2D indication. Provided these novel medicines demonstrate effective for the T2D indication, they may also open a door for evaluating further their utility in patients with T1D.

Finally, although an attractive approach for treating patients with recent-onset or established T1D, any incretin-based therapy by itself may be hampered by the uncontrolled, ongoing autoimmune response. So, combining safe, incretin-based therapies with either emerging antigen-specific, tolerogenic approaches or with agents that modulate the autoimmune response and/or secondary immune and inflammatory responses may hold the key for the successful development of disease-modifying treatment regimens for the T1D indication. Provided successful, incretin-based therapies, both as standalone and as combination products, may emerge as safe, clinically relevant, and commercially viable solutions and cures for patients diagnosed with T1D in the near future.

References

1 Perl, S. *et al.* (2010) Significant human beta-cell turnover is limited to the first three decades of life as determined by in vivo thymidine analog incorporation and radiocarbon dating. *J. Clin. Endocrinol. Metab.* 95, 234–239
2 Keenan, H.A. *et al.* (2010) Residual insulin production and pancreatic β cell turnover after 50 years of diabetes: Joslin Medalist Study. *Diabetes* 59, 2846–2853
3 Bonner-Weir, S. *et al.* (2010) Beta-cell growth and regeneration: replication is only part of the story. *Diabetes* 59, 2340–2348
4 Burn, P. (2010) Type 1 diabetes. *Nat. Rev. Drug Discov.* 9, 187–188
5 Perley, M.J. and Kipnis, D.M. (1967) Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. *J. Clin. Invest.* 46, 1954–1962
6 Elrick, H. *et al.* (1964) Plasma insulin response to oral and intravenous glucose administration. *J. Clin. Endocrinol. Metab.* 24, 1076–1082
7 Klonoff, D.C. *et al.* (2008) Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr. Med. Res. Opin.* 24, 275–286
8 Yoon, N.M. *et al.* (2009) Exenatide added to insulin therapy: a retrospective review of clinical practice over two years in an academic endocrinology outpatient setting. *Clin. Ther.* 31, 1511–1523
9 Preumont, V. *et al.* (2010) Six-month exenatide improves HOMA hyperbolic product in type 2 diabetic patients mostly by enhancing beta-cell function rather than insulin sensitivity. *Diabetes Metab.* 36, 293–298
10 Garber, A. *et al.* (2009) Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *The Lancet* 373, 473–481
11 Buse, J.B. *et al.* (2009) Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *The Lancet* 374, 39–47
12 Dhillon, S. (2010) Sitagliptin: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 70, 489–512
13 Pratley, R.E. *et al.* (2010) Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a26-week, randomised, parallel-group, open-label trial. *The Lancet* 375, 1447–1456
14 Pinkney, J. *et al.* (2010) Selecting GLP-1 agonists in the management of type 2 diabetes: differential pharmacology and therapeutic benefits of liraglutide and exenatide. *Ther. Clin. Risk Manag.* 6, 401–611
15 Elashoff, M. *et al.* (2011) Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 141, 150–156
16 Engel, S.S. *et al.* (2010) Sitagliptin: review of preclinical and clinical data regarding incidence of pancreatitis. *Int. J. Clin. Pract.* 64, 984–990
17 Mudaliar, S. and Henry, R.R. (2010) Effects of incretin hormones on beta-cell mass and function, body weight, and hepatic and myocardial function. *Am. J. Med.* 123, 19–27
18 Schuit, F.C. and Drucker, D.J. (2008) Beta-cell replication by loosening the brakes of glucagon-like peptide-1 receptor signaling. *Diabetes* 57, 529–531
19 Xie, T. *et al.* (2010) Pancreas-specific Gsα deficiency has divergent effects on pancreatic alpha- and beta-cell proliferation. *J. Endocrinol.* 206, 261–269
20 Liu, Z. and Habener, J.F. (2010) Wnt signaling in pancreatic islets. *Adv. Exp. Med. Biol.* 654, 391–419

Please cite this article in press as: C.S. Suen, The potential of incretin-based therapies in type 1 diabetes, Drug Discov Today (2011), doi:10.1016/j.drudis.2011.08.017

21 Maida, A. *et al.* (2009) Differential importance of glucose-dependent insulinotropic polypeptide vs glucagon-like peptide-1 receptor signaling for beta cell survival in mice. *Gastroenterology* 137, 2146–2157
22 Cornu, M. *et al.* (2010) Glucagon-like peptide-1 increases beta-cell glucose competence and proliferation by translational induction of insulin-like growth factor-1 receptor expression. *J. Biol. Chem.* 285, 10538–10545
23 Quoyer, J. *et al.* (2010) GLP-1 mediates anti-apoptotic effect by phosphorylating Bad through a beta-arrestin 1-mediated ERK1/2 activation in pancreatic beta-cells. *J. Biol. Chem.* 285, 1989–2002
24 Karaca, M. *et al.* (2009) Functional pancreatic beta-cell mass: involvement in type 2 diabetes and therapeutic intervention. *Diabetes Metab.* 35, 77–84
25 Tsunekawa, S. *et al.* (2007) Protection of pancreatic beta-cells by exendin-4 may involve the reduction of endoplasmic reticulum stress; in vivo and in vitro studies. *J. Endocrinol.* 193, 65–74
26 Natalicchio, A. *et al.* (2010) Exendin-4 prevents c-Jun N-terminal protein kinase activation by tumor necrosis factor-alpha (TNFalpha) and inhibits TNFalpha-induced apoptosis in insulin-secreting cells. *Endocrinology* 151, 2019–2029
27 Kwon, D.Y. *et al.* (2009) Exendin-4 potentiates insulinotropic action partly via increasing beta-cell proliferation and neogenesis and decreasing apoptosis in association with the attenuation of endoplasmic reticulum stress in islets of diabetic rats. *J. Pharmacol. Sci.* 111, 361–371
28 Rolin, B. *et al.* (2002) The long-acting GLP-1 derivative NN2211 ameliorates glycemia and increases beta-cell mass in diabetic mice. *Am. J. Physiol. Endocrinol. Metab.* 283, E745–E752
29 Bregenholt, S. *et al.* (2005) The long-acting glucagon-like peptide-1 analogue, liraglutide, inhibits beta-cell apoptosis in vitro. *Biochem. Biophys. Res. Commun.* 330, 577–584
30 Merani, S. *et al.* (2008) Liraglutide, a long-acting human glucagon-like peptide-1 analog, improves glucose homeostasis in marginal mass islet transplantation in mice. *Endocrinology* 149, 4322–4328
31 Bunck, M.C. *et al.* (2009) One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* 32, 762–768
32 Madsbad, S. (2009) Exenatide and liraglutide: different approaches to develop GLP-1 receptor agonists (incretin mimetics) – preclinical and clinical results. *Best Pract. Res. Clin. Endocrinol. Metab.* 23, 463–477
33 Mu, J. *et al.* (2006) Chronic inhibition of dipeptidyl peptidase-4 with a sitagliptin analog preserves pancreatic beta-cell mass and function in a rodent model of type 2 diabetes. *Diabetes* 55, 1695–1704
34 Riche, D.M. *et al.* (2009) Impact of sitagliptin on markers of beta-cell function: a meta-analysis. *Am. J. Med. Sci.* 337, 321–328
35 Henry, R. *et al.* (2009) β-Cell stimulation by Saxagliptin in patients with type 2 diabetes. *Diabetes* 58 (Suppl. 1), 447
36 Hadjiyanni, I. *et al.* (2008) Exendin-4 modulates diabetes onset in nonobese diabetic mice. *Endocrinology* 149, 1338–1349
37 Sherry, N.A. *et al.* (2007) Exendin-4 improves reversal of diabetes in NOD mice treated with anti-CD3 monoclonal antibody by enhancing recovery of beta-cells. *Endocrinology* 148, 5136–5144
38 Suarez-Pinzon, W.L. *et al.* (2008) Combination therapy with glucagon-like peptide-1 and gastrin restores normoglycemia in diabetic NOD mice. *Diabetes* 57, 3281–3288
39 Tian, B. *et al.* (2009) Upregulating CD4+CD25+FOXP3+ regulatory T cells in pancreatic lymph nodes in diabetic NOD mice by adjuvant immunotherapy. *Transplantation* 87, 198–206
40 Sheffield, C.A. *et al.* (2007) Off-label use of exenatide for the management of insulin-resistant type 1 diabetes mellitus in an obese patient with human immunodeficiency virus infection. *Pharmacotherapy* 27, 1449–1455
41 Paisley, A.N. *et al.* (2009) Stabilizing effect of exenatide in a patient with C-peptide-negative diabetes mellitus. *Diabet Med* 26, 935–938
42 Creutzfeldt, W.O. *et al.* (1996) Glucagonostatic actions and reduction of fasting hyperglycemia by exogenous glucagon-like peptide I (7–36) amide in type 1 diabetic patients. *Diabetes Care* 19, 580–586
43 Dupré, J. *et al.* (2004) Exendin-4 normalized postcibal glycemic excursions in type 1 diabetes. *J. Clin. Endocrinol. Metab.* 89, 3469–3473
44 Rother, K.I. *et al.* (2009) Effects of exenatide alone and in combination with daclizumab on beta-cell function in long-standing type 1 diabetes. *Diabetes Care* 32, 2251–2257
45 Ghofaili, K.A. *et al.* (2007) Effect of exenatide on beta cell function after islet transplantation in type 1 diabetes. *Transplantation* 83, 24–28
46 Faradji, R.N. *et al.* (2009) Long-term metabolic and hormonal effects of exenatide on islet transplant recipients with allograft dysfunction. *Cell Transplant.* 18, 1247–1259
47 Froud, T. *et al.* (2008) The use of exenatide in islet transplant recipients with chronic allograft dysfunction: safety, efficacy, and metabolic effects. *Transplantation* 86, 36–45
48 Kielgast, U. *et al.* (2011) Antidiabetic actions of endogenous and exogenous GLP-1 in type 1 diabetic patients with and without residual β-cell function. *Diabetes* 60, 1599–1607
49 Kielgast, U. *et al.* (2011) Four weeks of treatment with Liraglutide reduces insulin dose without loss of glycemic control in type 1 diabetic patients with and without residual {beta}-cell function. *Diabetes Care* 34, 1463–1468
50 Varanasi, A. *et al.* (2011) Liraglutide as additional treatment for type 1 diabetes. *Eur. J. Endocrinol.* 165, 77–84
51 Ohnuma, K. *et al.* (2008) Revisiting an old acquaintance: CD26 and its molecular mechanisms in T cell function. *Trends Immunol.* 29, 295–301
52 Reinhold, D. *et al.* (2009) Role of dipeptidyl peptidase IV (DP IV)-like enzymes in T lymphocyte activation: investigations in DP IV/CD26-knockout mice. *Clin. Chem. Lab. Med.* 47, 268–274
53 Ohnuma, K. *et al.* (2001) Soluble CD26/dipeptidyl peptidase IV induces T cell proliferation through CD86 up-regulation on APCs. *J. Immunol.* 167, 6745–6755
54 Conarello, S.L. *et al.* (2003) Mice lacking dipeptidyl peptidase IV are protected against obesity and insulin resistance. *Proc. Natl. Acad. Sci. U.S.A.* 100, 6825–6830
55 Yan, S. *et al.* (2003) Deficiency of CD26 results in a change of cytokine and immunoglobulin secretion after stimulation by pokeweed mitogen. *Eur. J. Immunol.* 33, 1519–1527
56 Yazbeck, R. *et al.* (2009) Dipeptidyl peptidase inhibitors, an emerging drug class for inflammatory disease? *Trends Pharmacol. Sci.* 30, 600–607
57 Krakauer, M. *et al.* (2006) CD4(+) memory T cells with high CD26 surface expression are enriched for Th1 markers and correlate with clinical severity of multiple sclerosis. *J. Neuroimmunol.* 181, 157–164
58 Schmiedl, A. *et al.* (2010) Reduced airway inflammation in CD26/DPP4-deficient F344 rats is associated with altered recruitment patterns of regulatory T cells and expression of pulmonary surfactant proteins. *Clin. Exp. Allergy* 40, 1794–1808
59 Sia, C. and Hänninen, A. (2010) Functional alterations of proinflammatory monocytes by T regulatory cells: implications for the prevention and reversal of type 1 diabetes. *Rev. Diabet. Stud.* 7, 6–14
60 Pospisilik, J.A. *et al.* (2003) Dipeptidyl peptidase IV inhibitor treatment stimulates beta-cell survival and islet neogenesis in streptozotocin-induced diabetic rats. *Diabetes* 52, 741–750
61 Pospisilik, J.A. *et al.* (2003) Dipeptidyl peptidase IV inhibition in animal models of diabetes. *Adv. Exp. Med. Biol.* 524, 281–291
62 Suarez-Pinzon, W.L. *et al.* (2009) Combination therapy with a dipeptidyl peptidase-4 inhibitor and a proton pump inhibitor restores normoglycaemia in non-obese diabetic mice. *Diabetologia* 52, 1680–1682
63 Tian, L. *et al.* (2010) Reversal of new-onset diabetes through modulating inflammation and stimulating beta-cell replication in nonobese diabetic mice by a dipeptidyl peptidase IV inhibitor. *Endocrinology* 151, 3049–3060
64 Kim, S.J. *et al.* (2008) Inhibition of dipeptidyl peptidase IV with sitagliptin (MK0431) prolongs islet graft survival in streptozotocin-induced diabetic mice. *Diabetes* 57, 1331–1339
65 Kim, S.J. *et al.* (2010) Sitagliptin (MK0431) inhibition of dipeptidyl peptidase IV decreases nonobese diabetic mouse CD4+ T-cell migration through incretin-dependent and -independent pathways. *Diabetes* 59, 1739–1750
66 Couri, C.E. *et al.* (2009) C-peptide levels and insulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *JAMA* 301, 1573–1579
67 Kutoh, E. (2011) Sitagliptin is effective and safe as add-on to insulin in patients with absolute insulin deficiency: a case series. *J. Med. Case Rep.* 5, 117–121
68 Foley, J.E. *et al.* (2008) Effect of vildagliptin on glucagon concentration during meals in patients with type 1 diabetes. *Horm. Metab. Res.* 40, 727–730
69 Herold, K.C. *et al.* (2009) Treatment of patients with new onset Type 1 diabetes with a single course of anti-CD3 mAb Teplizumab preserves insulin production for up to 5 years. *Clin. Immunol.* 132, 166–173
70 Keymeulen, B. *et al.* (2010) Four-year metabolic outcome of a randomised controlled CD3-antibody trial in recent-onset type 1 diabetic patients depends on their age and baseline residual beta cell mass. *Diabetologia* 53, 614–623
71 Pescovitz, M.D. *et al.* (2009) Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. *N. Engl. J. Med* 361, 2143–2152
72 Ludvigsson, J. *et al.* (2008) GAD treatment and insulin secretion in recent-onset type 1diabetes. *N. Engl. J. Med.* 359, 1909–1920
73 Sherry, N. *et al.* (2011) Teplizumab for treatment of type 1 diabetes(Protégé study): 1-year results from a randomized, placebo-controlled trial. *The Lancet* 378, 487–497
74 Wherrett, D.K. *et al.* (2011) Antigen-based therapy with glutamic acid decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomized double-blind trial. *The Lancet* 378, 319–327
75 Greenbaum, C. and Atkinson, M.A. (2011) Persistence is the twin sister of excellence. An important lesson for attempts to prevent and reverse type 1 diabetes. *Diabetes* 60, 693–694

Please cite this article in press as: C.S. Suen, The potential of incretin-based therapies in type 1 diabetes, Drug Discov Today (2011), doi:10.1016/j.drudis.2011.08.017