SUMMARY AND DISCUSSION
DPP-IV inhibition is a new treatment option for type 2 diabetes. The correction of pathological changes in incretin levels as a means of re-adjusting glucose homeostasis in patients with type 2 diabetes offers advantages over current therapies. Because nausea limits the dosage of GLP-1 administered in human studies, the potential of GLP-1 agonists for long-term prevention of weight gain or, ideally, induction of weight loss versus lack of compliance from unwanted gastrointestinal side effects required scrutiny. Similarly, whether subsets of patients with type 2 diabetes will exhibit preferential GLP-1 responsivity or, alternatively, relative resistance to the glucose-lowering effects of GLP-1 is not known. As is the case with intensive insulin administration, the potent glucose lowering properties of GLP-1 agonists may increase the likelihood of treatment associated hypoglycaemia in susceptible patients concomitantly treated with insulin secretagogues such as sulfonylureas. Moreover, the current need for once or twice daily injections of GLP-1-based pharmaceutical agents’ raises acceptance and compliance issues for prolonged therapy with these agents. This new class of antidiabetic drugs can be used in early stages of the disease, including pre-diabetes or obesity combined with impaired incretin response, while the combination of DPP-IV inhibitors with metformin or thiazolidinediones as insulin sensitizers offers an additional improvement in the treatment of type 2 diabetes.

Complementary evidence supporting the importance of DPP-IV as a pharmaceutical target for lowering glucose levels is derived from analysis of rodents with inactivating DPP-IV mutations. DPP-IV knockout mice and the Fischer DPP-IV mutant rat exhibited reduced levels of glycaemic excursion after glucose loading in association with increased levels of circulating GLP-1 and insulin [71,128]. Remarkably, DPP-IV knockout mice exhibit resistance to obesity and display improved insulin sensitivity after high-fat feeding [142]. Hence, both pharmacological and genetic attenuation of DPP-IV activity is associated with enhanced incretin action, increased insulin, and lower glucose in vivo.

In the type 2 diabetic rat model, GRC 8011 produced a consistent inhibition of plasma DPP-IV activity in the OGTT. Further evidence of the pharmacologic activity of GRC 8011 was obtained by measuring levels of active GLP-1, an incretin hormone that is rapidly cleaved and thus inactivated by the DPP-IV enzyme. Although GIP is also inactivated by DPP-IV, this incretin was not measured in the present study due to
limitation of resources. Compared with STZ-vehicle control, GRC 8011 alone produced an increase in active GLP-1 levels of 1.4-fold, which increased to more than ~3-fold in acute combination treatment with metformin. This suggests the potential utility of combination therapy of GRC 8011 with metformin. Collectively, these data suggest that DPP-IV inhibition by GRC 8011 enhances incretin levels by stabilizing the active form of GLP-1.

Administration of multiple doses of GRC 8011 (10 mg/kg/day b.i.d.) over 2 months to C57BL/6J mice resulted in no visible clinical signs of adverse effects. No significant differences were observed in plasma glucose levels (both in fed state and in fasting condition) in any of the treatment groups throughout the study period. These results are comparable to those from acute dose study in normal mice where in a single-dose administration of GRC 8011 to mice fasted for 16-18 h (basal glycaemic condition) did not show hypoglycaemia. This corroborates with the literature that DPP-IV inhibitors stimulate insulin release through incretins only in response to nutrient ingestion and not under basal glycaemic conditions.

In a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes receiving metformin treatment [], concomitant treatment with LAF 237, a DPP-IV inhibitor, for up to 52 weeks, had a neutral effect on body weight. These results were in contrast to the weight gain typically found with insulin, sulfonylurea, or thiazolidinedione treatment. In addition, beneficial effects on β-cell function and mass have been reported after long-term treatment with DPP-IV inhibitors in mice and rats [74,93]. If similar effects occur in patients with type 2 diabetes, DPP-IV inhibition might improve β-cell function with long-term treatment—an important benefit given the progressive deterioration in β-cell function common in type 2 diabetic patients. Unlike GLP-1 analogues, which are also under investigation for the treatment of type 2 diabetes, DPP-IV inhibitors can be administered orally and might not cause the gastrointestinal adverse effects, such as nausea and vomiting, which have been noted with pharmacologic GLP-1 levels [143,144,145].

Whether DPP-IV inhibitors should act throughout the day is a debatable question. The broad spectrum of DPP-IV activity and the large number of potential bioactive peptide substrates pose important questions regarding unanticipated side effects
associated with the long-term use of DPP-IV inhibitors. If a non-toxic compound can be developed, it is likely to have a vast applicability. In fact, a non-toxic, orally active DPP-IV inhibitor with reasonable pharmacokinetics might actually make one of the greatest dreams of the diabetologist which is the prevention of transition from impaired glucose tolerance to overt type 2 diabetes. This is because elevated levels of active GLP-1 would be expected to restore the (mild) incretin deficiency and normalize glucose levels. The lowered glucose levels would then reduce the demand of insulin secretion from β-cell, ultimately leading to normalization of insulin sensitivity.

Following advancements in functional genomics and proteomics, scientists realized that proteins do not function alone but are interconnected in networks. Considering the number of protein-binding sites on DPP-IV and its association with regulated processes such as T-cell activation, cell migration, and invasiveness, we can only conclude that DPP-IV is tied in with several of these networks. The challenge for the future is how to unravel the roles of DPP-IV in the complexity of the cellular machinery.
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