Accounts in Drug Discovery
Case Studies in Medicinal Chemistry

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CHAPTER 1

The Discovery of the Dipeptidyl Peptidase-4 (DPP4) Inhibitor Onglyza™: From Concept to Market

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1.1 Introduction

The prevalence of diabetes in developed and now emerging countries represents a significant health burden to a large portion of the world's population. Type-2 diabetic patients, characterized in part by elevated fasting plasma glucose of $>125\,\mathrm{mg\,dL^{-1}}$ ($7.0\,\mathrm{mmol\,L^{-1}}$) and glycosylated hemoglobin (HbA1c) $\geq 6\%$, are at increased risk for the development of both microvascular (retinopathy, neuropathy, nephropathy) as well as macrovascular complications (myocardial infarction, stroke). As such, diabetes is the leading cause of blindness, kidney failure, and limb amputation worldwide.[1] Diabetes is a progressive disease, with morbidity and mortality risk increasing with both duration and severity of hyperglycemia. Additionally, diabetes is also now impacting different population sectors (adolescents, developing countries) not typically associated with the disease 30 years ago. Consequently, the continually increasing diabetes prevalence is placing greater strain on both health care systems and economies on a global scale. In 2007 alone, studies have shown that diabetes cost the US

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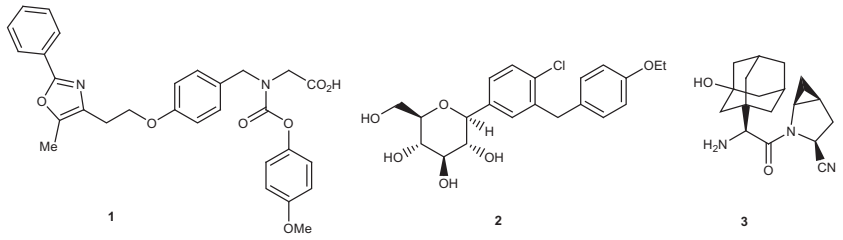

Figure 1.1 Late-stage development candidates from the Bristol-Myers Squibb diabetes research portfolio.

economy $174 billion in medical expenses and lost productivity.[2] While death rates related to heart disease, stroke, and cancer have all decreased since 1987, the death rate due to diabetes has increased by 45% during this same period.[3] Thus, the discovery and development of new therapies for treating and preventing diabetes continue to be a major emphasis of health care companies.

In response to this landscape, the Discovery organization at Bristol-Myers Squibb (BMS) made the strategic decision to refocus efforts in the late 1990's towards identifying and progressing novel targets for the treatment of diabetes. This was in part aimed at building upon BMS's already established presence in the anti-diabetes market through the Glucophage™ franchise and in recognition of the significant unmet medical need for novel, more efficacious, and well tolerated treatments for the disease. It was from these efforts that advanced clinical candidates such as muraglitazar (**1**, Pargluva™, dual PPAR agonist),[4] dapagliflozin (**2**, SGLT2 inhibitor),[5] and saxagliptin (**3**, Onglyza™, DPP4 inhibitor)[6] were discovered within the BMS Discovery organization (Figure 1.1).

1.2 Modulation of GLP-1 in the Treatment of Diabetes

At the start of this effort, several oral anti-diabetic agents (OADs) were available to patients suffering from type-2 diabetes. These included hepatic glucose suppressors (*e.g.* metformin), insulin secretagogues (*e.g.* sulfonylureas), glucose absorption inhibitors (*e.g.* acarbose), and insulin sensitizers (*e.g.* thiazolidinediones or TZDs such as rosiglitazone and pioglitazone). While all have shown utility in lowering HbA1c levels in diabetic patients, current OADs come with a variety of safety and/or tolerability issues. The biguanindes such as metformin, currently the most widely prescribed therapy for diabetes, have issues related to gastrointestinal (GI) tolerability and lactic acidosis.[7] Sulfonylurea treatment is often accompanied by higher incidences of hypoglycemia and weight gain,[8] while glucose absorption inhibitors exhibit modest efficacy and GI disturbance.[9] Finally, TZDs have been associated with edema, wor-

With this background in mind, we sought to identify new targets which would not only provide an efficacious alternative mechanism for lowering blood glucose and HbA1c levels, but would also present an opportunity for achieving a superior safety and tolerability profile when compared to current standards of care. Ideally, such a drug would be suitable for combination with existing agents, as poly-pharmacology with multiple OADs is emerging as the standard treatment paradigm for type-2 diabetes therapy.

Glucagon like peptide-1 (GLP-1) is a 30-amino acid peptide incretin hormone derived from processing of pro-glucagon and is secreted by the L-cells of the intestinal mucosa in response to glucose stimulation. Since the early 1990's, GLP-1 had been known to be a potent insulin secretagogue and glucagon suppressor, with robust anti-diabetic and pro-satiety effects in diabetic humans,[11,12] but efforts to advance GLP-1 itself as a pharmaceutical agent were hampered by its extremely short pharmacokinetic half-life *in vivo* (plasma $t_{1/2} \approx 2$ min). As a result, considerable effort in the drug discovery community was expended toward the identification of small-molecule GLP-1 receptor agonists that would capture the beneficial effects of GLP-1 while exhibiting oral bioavailability and a superior pharmacokinetic duration of action. Unfortunately, efforts to identify such small-molecule agonists have to date been unsuccessful, due in part to a dearth of viable *bona fide* screening hits.[13] In light of this shortcoming, a number of pharmaceutical and biotech companies have advanced subcutaneously administered, peptide GLP-1 receptor agonists with superior duration of action *in vivo*. Among the most advanced agents are exenatide (Byetta™)[14] and liraglutide (Victoza™),[15] both of which have been approved by regulatory agencies for the treatment of type-2 diabetes. While these drugs are effective in lowering HbA1c and demonstrate a net beneficial effect on weight gain and other CV risk factors, they require parenteral administration (once or twice daily dosing), and patient uptake of these agents has been limited despite their robust efficacy and promising safety profile.

1.3 Dipeptidyl Peptidase-4 as a Target for Diabetes Treatment

While the advancement of orally active, small-molecule GLP-1 receptor agonists remains elusive, another opportunity to modulate GLP-1 receptor activity *in vivo* focused on preventing the degradation of endogenous GLP-1 with small-molecule inhibitors of the primary peptidase responsible for the *in vivo* degradation of GLP-1, dipeptidyl peptidase-4 (DPP4), a non-classical serine protease.[16] Our initial interest in DPP4 inhibitors was piqued by a report from Holst and Deacon, wherein the authors outlined a compelling argument for the utility of DPP4 inhibition in the treatment of diabetes, primarily *via* the potentiation of endogenous GLP-1.[17] DPP4 belongs to a family of aminodipeptidases and is both a cell surface and circulating enzyme. Historically, it had

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