

Emerging Drug Candidates of Dipeptidyl Peptidase IV (DPP IV) Inhibitor Class for the Treatment of Type 2 Diabetes

Rajesh Gupta, Sameer S. Walunj, Ranjeet K. Tokala, Kishore V.L. Parsa, Santosh Kumar Singh and Manojit Pal*

New Drug Discovery, R & D Center, Matrix Laboratories Limited, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Andhra Pradesh, 502 325, India

Abstract: Dipeptidyl peptidase IV (DPP IV) is a key regulator of insulin-stimulating hormones, glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), thus it is a promising target for the treatment of Type 2 Diabetes mellitus (T2DM). Inhibition of plasma DPP IV enzyme leads to enhanced endogenous GLP-1 and GIP activity, which ultimately results in the potentiation of insulin secretion by pancreatic β -cells and subsequent lowering of blood glucose levels, HbA_{1c}, glucagon secretion and liver glucose production. Various classes of structurally different DPP IV inhibitors are currently being explored and few of them such as Sitagliptin and Vildagliptin were successfully launched. These drugs have been approved as a once-daily oral monotherapy or as a combination therapy with current anti-diabetic agents like pioglitazone, glibenclamide, metformin *etc.* for the treatment of T2DM. Several other novel DPP IV inhibitors are in pipeline. The present review summarizes the latest preclinical and clinical trial data of different DPP IV inhibitors with a special emphasis on their DPP8/9 fold selectivity and therapeutic advantages over GLP-1 based approach.

Key Words: DPP IV, GLP-1, T2DM, developmental progress, sitagliptin, vildagliptin, alogliptin, selectivity.

1. INTRODUCTION

T2DM is a metabolic disorder characterized by impaired control of blood glucose level. T2DM is prevalent worldwide affecting almost 6% of the population. It is predicted that 366 million people will be affected by T2DM in the next 30 years if preventive measures are not taken [1]. Med Ad News projects that an aging and increasingly obese population will spur the market for T2DM drugs to \$20.5 billion by 2012. The current oral pharmacological treatments against T2DM include metformin, sulfonylurea (SU), thiazolidinedione (TZD) and glycosidase inhibitors. These anti-diabetic agents are associated with adverse events like gastrointestinal toxicities, weight gain, edema, hypoglycemia *etc* and thus, there is a need to develop novel therapeutic agents. Over recent years, therapies that increase the circulating insulin levels proved to be beneficial for the treatment of T2DM. Low molecular weight reversible inhibitors of DPP IV were studied for several years [2] and were found to lower glucose level, increase glucose tolerance and improve insulin response to oral glucose challenge in patients with T2DM [3].

DPP IV is a serine aminopeptidase that inactivates incretins, especially GLP-1 and GIP, which are gut hormones released in response to food intake. GLP-1 has several glucoregulatory activities as outlined in Fig. (1). This spectrum of glucoregulatory actions of GLP-1 underscores its importance in T2DM therapy. As soon as released from the gut during meals, the incretin hormones (GLP-1 and GIP) serve

as enhancers of glucose-dependent insulin release from pancreatic β -cells [3]. As GLP-1 is rapidly eliminated (within 1 min) because of its cleavage by DPP IV into an inactive metabolite, several strategies were explored including the use of exogenous GLP-1, GLP-1 fusion proteins and DPP IV resistant GLP-1 analogs for the treatment of T2DM. Chronic infusion of GLP-1 to T2DM patients resulted in a significant decrease in both blood glucose and plasma HbA_{1c} levels [4-5]. However, the requirement of parenteral route of administration and potential for development of auto-antibodies are the major drawbacks associated with this therapeutic approach. In addition, sustained GLP-1 infusion induced nausea and vomiting in clinical studies [6]. Thus, DPP IV has emerged as a potential therapeutic target for the treatment of T2DM. The proof of concept for the efficacy of DPP IV inhibitors was provided by DPP IV deficient mice that were healthy, fertile and displayed improved glucose homeostasis [7-8]. Further evidence for efficacy in humans was provided by clinical studies carried out with Sitagliptin and Vildagliptin as monotherapy or in combination with other existing anti-diabetic agents. The mechanism of action by which DPP IV inhibitors lower blood glucose is distinct from existing class of oral glucose-lowering agents. They control elevated blood glucose by potentiating pancreatic insulin secretion, increasing circulating GLP-1, reducing glucagon secretion, and signaling the liver to reduce glucose production [9]. This review summarizes the developmental status of different DPP IV inhibitors with an emphasis on their preclinical and clinical findings. It covers the potential advantages of current DPP IV inhibitors over GLP-1 mimetic based therapy. Finally, as two clinical candidates of this category have been successfully launched, the review also provides an overview of preclinical and clinical efficacy data of selected DPP IV inhibitors.

*Address correspondence to this author at the New Drug Discovery, R & D Center, Matrix Laboratories Limited, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Andhra Pradesh, 502 325, India; E-mail: manojitpal@rediffmail.com

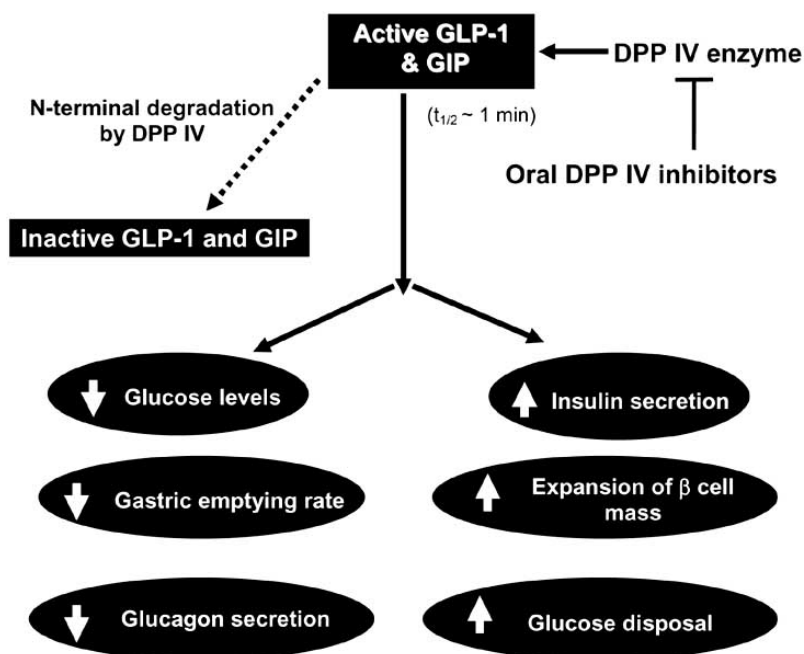


Fig. (1). Physiological actions of GLP-1 and GIP and their modulation by oral DPP IV inhibitors. Schematic representation of the effect of oral DPP IV inhibitors on GLP-1 and GIP is shown. Half life of GLP-1 and GIP is increased upon inhibition of plasma DPP IV by oral DPP IV inhibitors.

2. DPP IV ENZYME (EC 3.4.14.5): STRUCTURE, CATALYSIS REQUIREMENTS AND SUBSTRATE SPECIFICITY

DPP IV is a 766 amino acid long aminopeptidase. The crystal structure of DPP IV revealed that it is a tetramer with each sub-unit comprising of two structural domains, N-terminal β propeller domain and C-terminal catalytic domain [10]. The β -propeller domain consists of eight blades with 4 anti-parallel strands and harbors an ellipsoidal and continuously open tunnel. The catalytic domain adopts a typical α/β hydrolase fold with a central eight-stranded β sheet sandwiched by several α helices. The active site of the enzyme is covered by the β -propeller domain thus restricting access to the substrate. Therefore, there are two possible routes for substrate access: tunnel through the β propeller domain [10] or a side opening formed at the interface of β -propeller domain and catalytic domain [11].

DPP IV is a glycosylated protease belonging to the subset of proteins that are capable of cleaving post-proline bond two amino acids downstream of the N-terminal of protein. It has preference for X-Pro over X-Ala, where X is any amino acid other than proline [12]. It is generally believed that glycosylation of an integral protein is required for its enzymatic activity. However, in the case of DPP IV it appears to be controversial [11, 13].

Based on *in vitro* studies, a wide range of potential substrates including growth hormone-releasing hormone, bradykinin, certain chemokines, neuropeptide Y, eotaxin, *etc* (Table 1) have been identified but only few of them such as GLP-1 and GIP are reported to be the endogenous substrates [14-15]. Although DPP IV has a preference for proline in the second position but GLP-1, the endogenous substrate of DPP IV, has alanine in this position. A high expression of this

enzyme is observed in kidneys, where it is localized in the glomerular basement membrane and proximal convoluted tubules. However, there are reports demonstrating that DPP IV is expressed in other tissues as well and widely distributed in the body [16].

3. PHYSIOLOGICAL ACTIONS OF INCRETIN HORMONES, THEIR USE AND LIMITATIONS

In the recent years, approaches targeting elevation of GLP-1 have emerged as a promising area for T2DM therapy. Physiological actions of GLP-1 and GIP are described in Fig. (1). Briefly, they stimulate glucose dependent insulin secretion, inhibit glucagon secretion, delay gastric emptying, suppress appetite, stimulate differentiation and proliferation and inhibit apoptosis of β -cells thus they increase the β -cell mass and improve peripheral glucose uptake and disposal. Extrapankreatic actions include the reduction of hepatic insulin clearance [17] and an apparent "insulin mimetic" effect on skeletal muscle [18], liver and adipose tissues. But the half life of these hormones is very short ($t_{1/2} = \sim 1 \text{ min}$) as they are rapidly cleaved by circulating DPP IV enzyme to produce an inactive product, GLP-1 (9-36 aa) amide [19]. Inhibition of circulating DPP IV enzyme by DPP IV inhibitors prolongs the half life of GLP-1 leading to increased levels of active endogenous GLP-1 and GIP. The two forms of GLP-1 secreted after the meal ingestion, GLP-1 (7-37) and GLP-1 (7-36) amide, differ from each other by single amino acid. Both peptide forms are equipotent and exhibit identical plasma activities [18, 20-21]. GLP-1 contributes more towards maintenance of glucose homeostasis than GIP [21]. Another approach to increase the circulating levels of active GLP-1 is the use of GLP-1 analogs which are resistant to cleavage by DPP IV. GLP-1 mimetics such as Liraglutide, NN2211, Exenatide (ByettaTM), AC2993LAR (Exendin-4 long acting)

Table 1. Physiological Peptides/Hormones Identified as Substrates of DPP IV and Subject to Modulation by DPP IV

Physiological Process	Peptide/Hormone
Nutrient metabolism and glucose homeostasis	GLP-1 (7-37*) & GLP-1 (7-36*) amide
	GIP (1-42) & Glucagon
Growth and development	Insulin-like growth factor-1 (IGF-1)
	Growth hormone releasing factor (GHRF)
	Growth hormone-releasing hormone (GRH (1-29)
	GRH (1-44)
Digestive & Vascular system	GLP-2 (1-33)
	Trypsinogen & Trypsinogen pro-peptide
	Gastrin releasing peptide (GRP)
	Pro-colipase & Enterostatin
	β -Casomorphin, Aprotinin & Bradykinin
Reproductive system	Human chorionic gonadotropin α (hCG α)
	Leutinising hormone α chain (LH α)
	Prolactin
Neuroendocrine & Endocrine system	PACAP (1-27) & PACAP (1-38)
	Thyrotropin α & Vasostatin-1
Nervous system	Substance P & Peptide YY (1-36)
	Neuropeptide Y & Enkephalins
Immune system	Interleukin-2 & Interleukin-1 β
	α_1 -Microglobulin (GCP-2) & RANTES
	Stromal cell-derived factor-1 α (SDF-1 α) & SDF-1 β
	Macrophage-derived chemokine (MDC)
	Interferon- γ -inducible protein-10 (IP-10)
	Monocyte chemotactic protein-1 (MCP-1&2)

* Circulating GLP-1 peptide forms in the plasma.

and AVE-10 had showed substantial increase in insulin secretion in preclinical animal models. Exenatide is the first incretin mimetic drug approved for clinical use by the US Food and Drug Administration (FDA). In phase 3 clinical trials, Exenatide reduced HbA_{1c} by ~1% and body weight by ~2 kg in T2DM patients who were unable to achieve glycemic control with metformin and/or a sulfonylurea. Exenatide is a 39 amino-acid peptide that exhibits gluco-regulatory activities similar to GLP-1 [22-23]. Unlike SU and meglitinides, Exenatide increases insulin synthesis and secretion in the presence of glucose only. Since the actions of Exenatide on insulin secretion and glucagon suppression are glucose dependent, the risk of hypoglycemia can be minimized to some extent except when used in combination therapy with agents that induce hypoglycemia, such as SU. The major drawback with GLP-1 peptide analogs is the lack of orally bio-available dosage forms. It was observed in clinical trials

that administration of GLP-1 analogs caused nausea and vomiting. In rodents, it was reported that GLP-1 led to adverse effects such as increased heart rate and blood pressure; however the same were not observed in humans [24]. In addition, it was recently observed during post marketing surveillance that two out of six patients receiving Byetta™ succumbed to death because of hemorrhagic pancreatitis [25].

4. TREATMENT OF T2DM: DRUGS IN USE AND UNDER DEVELOPMENT

A list of existing class of drugs for treatment of T2DM and associated adverse events is shown in Table 2. The major side effects observed with existing anti-diabetic therapies were hypoglycemia, weight gain, edema and GI disturbances. Promising dual PPAR α/γ agonists such as Ragaglitazar (Dr.Reddy's/Novo Nordisk) and MK-0767 (Merck &

Table 2. Different Classes of Antidiabetic Drugs for Treatment of T2DM other than DPP IV Inhibitors

Drug Class	Molecular Target	Site of Action	Adverse Events	Expected HbA1c Reduction (%)
Insulin	Insulin receptor	Liver muscle	Hypoglycemia, wt gain, edema	1.5-2.5
Sulphonylurea	SU receptors	Pancreatic Beta cells	Hypoglycemia, wt gain	1.5
Biguanides	Unknown	Liver	GI problems, lactic acidosis	1.0-1.5
Acarbose	α -glucosidase	Intestine	GI problems	0.5-0.8
Thiazolidinediones	PPAR γ	Adipose tissue, liver, muscles	Wt gain, edema, anaemia	0.5-1.4
PPAR α/γ dual agonists	PPAR α/γ	Adipose tissue, liver, muscles	edema, hepatotoxicity, cardiac risk	0.5-1.3
GLP-1 analogs	GLP-1 receptor	Pancreas	GI problems, nausea, abdominal pain, wt loss	0.5-1.0

Co./Kyorin) were discontinued in phase 3 trials in 2003 because of the occurrence of malignant tumors in long-term mice studies. Muraglitazar (Bristol-Myers Squibb) exhibited major adverse cardiovascular events and increased incidence of death in phase 3 trials compared with placebo or pioglitazone (Takeda). Liraglutide, a DPP IV resistant GLP-1 analog, reduced fasting and postprandial glucose, was weight neutral but caused nausea and diarrhea upon administration.

5. DPP IV INHIBITORS: PROOF OF CONCEPT STUDIES

Extensive evidence suggests that therapeutic benefits in treatment of T2DM can be realized by selective DPP IV inhibition. DPP IV null mice which are healthy and viable showed no significant N-terminal degradation of GLP-1. Consistent with this, these mice displayed increased levels of insulin and improved glucose tolerance even on a high fat diet, which could be due to the persistent activity of the insulin-stimulating hormone GLP-1 and perhaps due to active GIP as well [7-8]. In agreement with the DPP IV-deficient mice data, a strain of rat with a natural point mutation in DPP IV displayed similar glucose lowering effects [9].

Increasing number of studies involving different animal models such as Zucker fatty rats, *db/db* mice and streptozotocin induced diabetic rats, revealed that administration of small molecule inhibitors of DPP IV led to decreased plasma DPP IV activity, enhanced insulin levels and reduced glucose levels along with the restoration of β -cell function and islet neogenesis [26-28].

Available data indicate that the oral administration of DPP IV inhibitors led to a sustained reduction in HbA_{1c} to a clinically meaningful level with weight neutrality and minimal hypoglycemic events [15,29]. These agents can compete with the existing oral anti-diabetic agents like pioglitazone, SU *etc*, particularly because of their weight neutrality and lower hypoglycemic risk. However due to higher cost of medicine and lack of familiarity, it is likely that they may be used mainly as a combination therapy with other agents for a few years. Thus, DPP IV inhibition is a therapeutically proven and effective strategy to treat a multifactorial and complex disease like T2DM.

6. STRUCTURE OF DPP IV INHIBITORS IN CLINICAL TRIAL AND DISCOVERY PHASES

While development of inhibitors possessing selectivity towards DPP IV over DPP-8 and DPP-9 is a major challenge, extensive Structure activity relationship (SAR) work however, has indicated that desired selectivity for DPP IV inhibition can be achieved *via* introducing appropriate substituent or group. Moreover, in addition to focusing on potency and selectivity, development of long acting inhibitors is also desirable because they could potentially provide maximal efficacy, particularly in severe diabetic patients (e.g., HbA_{1c} > 9%). Until recently, a diverse class of DPP IV inhibitors has been reported in the literature and the lead molecules in various stages of clinical development are listed in Tables 3 and 4. Based on their structural features these inhibitors can be divided into two classes e.g. *peptidomimetic* and *non-peptidomimetic series*. The *peptidomimetic* series can be subdivided into (a) glycine-based inhibitors or α -series and (b) β -alanine-based inhibitors or β -series.

In the case of α -series, the pyrrolidine derivatives have been widely explored as DPP IV inhibitors due to DPP IV's specificity for substrate having an amino-terminal proline at C-2. Depending on the presence of a substituent (Z) at the C-2 of the pyrrolidine ring, the α -series can be further divided into two classes e.g. (a) irreversible {when Z = diphenylphosphonate ester [-P(O)(OPh)₂] or O-acylhydroxamic acid (CONHOCOR')} and (b) reversible {when Z = boronic acid [B(OH)₂], nitrile (CN) or hydrogen} inhibitors. 2-Cyano pyrrolidine based inhibitors that belong to the reversible class of α -series have been studied most extensively because apart from behaving as a proline mimic, the presence of nitrile on the five-membered ring provided (i) nanomolar inhibition of DPP IV and (ii) chemical stability adequate for oral administration. Vildagliptin (Table 4), a potent, selective, and orally active inhibitor of DPP IV, is the most advanced compound in this series [30]. Despite the advancement of Vildagliptin in clinical trials, one of the key issues encountered with the use of 2-cyano pyrrolidine derivatives was its stability in solution due to the participation of cyano group in an intramolecular cyclization process thereby generating inactive products. This problem was addressed by introducing a cyclopropyl ring fused on the pyrrolidine moiety leading to

Table 3. DPP IV Inhibitors in Discovery and Clinical Trial Phases

DPP IV Inhibitor	Generic Name/ (Proprietary Name)	Company	Clinical Phase	DPP IV IC ₅₀ or Specificity	Type of Inhibition & Duration	Status
MK-0431	Sitagliptin (Januvia™)	Merck & Co	3	IC ₅₀ = 18 nM Ki = 9 nM	Reversible inhibitor & Long acting	Launched ^a
LAF-237	Vildagliptin (Galvus)	Novartis	3	IC ₅₀ = 3.5nM Ki = 17 nM	Covalently bound & reversible inhibitor	Launched ^b (Europe)
BMS-477118	Saxagliptin (Onglyza)	Bristol-Myers Squibb/Astra Zeneca/Otsuka Pharma	3	IC ₅₀ = 3.37 nM Ki = 0.6 nM	Covalently bound and reversible inhibitor	Pre-registration, An NDA was filed with FDA in June'2008
SYR-322 (TAK-322)	Alogliptin	Takeda Pharmaceuticals, San Diego	3	IC ₅₀ = 7 nM	Reversible inhibitor	Pre-registration, A US NDA was accepted for filing in Feb'2008
GSK-823093C	Denagliptin	Glaxo Smithkline	3	Ki = 22 nM	-	Discontinued
BI 1356	Ondero	J Dondero & Boehringer Ingelheim Pharma GmBH	3	IC ₅₀ = 1 nM Ki = 1 nM	Competitive inhibi- tor, reversible & Long-acting	Studies ongoing
NVP DPP728		Novartis AG	2	IC ₅₀ = 22 nM Ki= 11nM	Slow-binding inhibi- tor	Discontinued
P32/P98	Isoleucine thia- zolidide DPP IV	Probiodrug AG	2	IC ₅₀ = 420 nM Ki = 80 nM	Reversible inhibitor	Discontinued
MP-513	IDDBCP161883	Mitsubishi Tanabe Pharma	2	IC ₅₀ = 1.35 nM	-	In progress
GRC 8200	Melogliptin	Glenmark pharmaceuticals Ltd	2	IC ₅₀ = 1.61 nM	-	\$
AMG-222 (ALS-2-0426)		Alantos Pharmaceuticals & Amgen Inc	2a	-	-	-
PSN-9301 (P93/01)		Prosidion & Probiodrug AG	2	-	Reversible inhibitor & Short acting	Discontinued
Des-fluoro- sitagliptin	Sitagliptin analog	Merck & Co	Discovery	-	Reversible inhibitor	-
PHX-1149	Dutogliptin tartrate	Phenomix Corp	3	-	Reversible inhibitor	-
R-1438	Aminomethylpyri- dine derivative	Roche	2	Ki= 0.1 nM	Reversible inhibitor	Discontinued
KRP-104		ActiveX Biosciences Inc	2	-	-	-
R-1579	Carmegliptin	F Hoffmann-La Roche Ltd & Chugai Pharma	2	-	Reversible inhibitor	Phase 2 completed
SK-0403		Sanwa Kagaku KenKyushu	2	-	-	-
RO-0730699		Roche Holding AG	2	-	-	-
DP-893	Sulfonamide derivative	Pfizer Inc	Discovery	Not available	Reversible inhibitor	-
LC-150444		LG Life Sciences Ltd	1	Not available	Reversible inhibitor	-
IP-10.C8		IMTM GmbH	1	-	-	-
BMS-686117		Bristol-Myers Squibb Co	1	-	-	-
TAK-100		Takeda Pharmaceutical	1	-	-	-

(Table 3) contd....

DPP IV Inhibitor	Generic Name/ (Proprietary Name)	Company	Clinical Phase	DPP IV IC ₅₀ or Specificity	Type of Inhibition & Duration	Status
E-3024		Eisai Co Ltd	1	-	-	Discontinued
ABT-279		Abbott Laboratories	1	Ki = 1 nM	-	Pre clinical data were presented at the 67 th ADA Sessions in Chicago IL
ARI-2243		Arisaph Pharmaceuticals Inc	1a	-	-	-
TS-021		Taisho Pharmaceutical Co Ltd	1	Not available	-	-
SSR-162369		Sanofi-Aventis, Deutschland GMBH	1	IC ₅₀ = 18nM	Reversible inhibitor & Long-acting	-
K-579		Kyowa Hakko Kogyo Co Ltd	Discovery	-	Reversible inhibitor & Long lasting	-
GW-1853		Glaxo Smith Kline Co	Discovery	-	-	Pre clinical studies completed
LY-2463665		Eli Lilly & Co	Discovery	IC ₅₀ = 34nM Ki=7nM	Reversible inhibitor	Pre clinical studies completed
TRC-XXXX		Torrent Pharmaceuticals Ltd	Discovery	-	-	-
DPP IV inhibitor		National Health Research Institutes, Taiwan	Discovery	-	-	-
ER-319711-15		Eisai Co Ltd	Discovery	IC ₅₀ = 89nM	-	-
CR-14025		Nuada Pharmaceuticals Inc	Discovery	-	-	Discontinued
ASP8497		Astellas Pharma Inc	Discovery	IC ₅₀ = 5.30 nM	Reversible inhibitor & Long-acting	-
DPP IV inhibitor		Graffinity Pharmaceuticals AG & Santhera	Discovery	-	-	-
S-40010		Servier	Discovery	-	-	Pre clinical studies completed & presented at the 67 th ADA Sessions in Chicago IL
PT-630		Point Therapeutics	Discovery	-	-	-

Key: FDA = American Food and Drug Administration; NDA= New drug application; '-' = not available. "\$" = Looking for potential partners for licensing and co-development. a = Sitagliptin was launched in Mexico in 2006, and in USA, UK and several other European countries in 2007. b= Launched in Europe.

the identification of *cis*-4,5-methanoproline nitrile-containing inhibitors. Saxagliptin [31] (Table 4), a highly efficacious, stable, and long-acting DPP IV inhibitor showed robust glucose-lowering effects in a dose-dependent manner in the Zucker^{fa/fa} rat OGTT model and efficacy in reducing post-prandial glucose AUC in *ob/ob* mice. This compound was effective in elevating insulin levels after an OGTT in *ob/ob* mice and is currently undergoing phase 3 clinical trials. Incorporation of a fluoro substituent at C-4 position of the 2-cyanopyrrolidine ring in a *cis*-fashion provided a new and stable series of inhibitors. This is exemplified by the identification of Denagliptin [32] (Table 4), though the phase 3 clinical study on this molecule has been suspended.

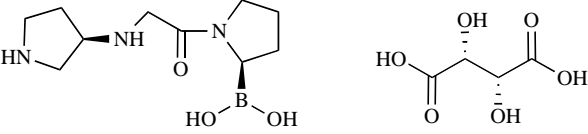
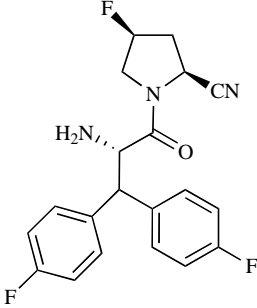
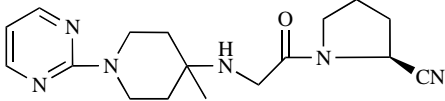
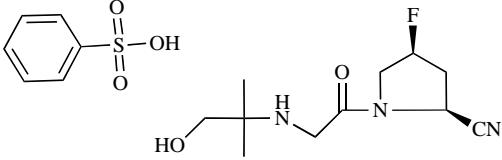
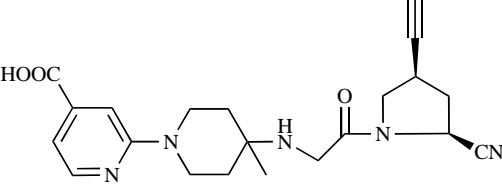
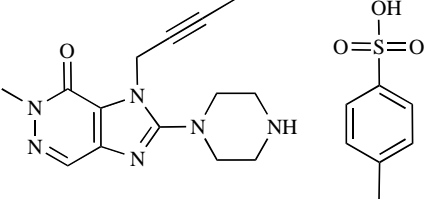
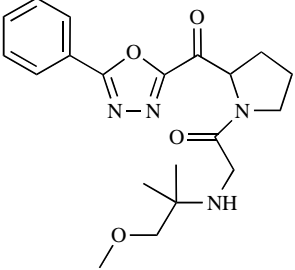
In contrast to the α -series that was mainly developed by using information and data available in the literature, the β -series was generally developed from a lead obtained *via* high-throughput screening (HTS). A number of inhibitors based on β -amino amide backbone have been reported. A triazolopiperazine-based inhibitor Sitagliptin [33] (Table 4) that belongs to this β -aminoamide series was found to be highly selective inhibitor of DPP IV and was launched in 2007.

Non-peptidomimetic inhibitors are distinctly different from the traditional α - or β -series in terms of their structures and an impressive number of compounds that belong to this

Table 4. Structure of Current DPP IV Inhibitors in Clinical Trial and Discovery Phases

DPP IV Inhibitors	Structure	References
MK-0431 (Sitagliptin)	<p>Piperazine derivatives</p>	[33, 36-38]
LAF-237 (Vildagliptin)	<p>Cyanopyrrolidine derivatives</p>	[29, 30, 39]
BMS-477118 (Saxagliptin)	<p>Methanoproline derivative</p>	[31]
SYR-322 (Alogliptin)	<p>Pyrimidine derivatives</p>	[34]
NVP DPP-728		[40-42]
P32/98		[43]
GRC-8200 (Melogliptin)		[44, 45]
MP-513		[46]

(Table 4) contd....

DPP IV Inhibitors	Structure	References
PHX-1149 (Dutogliptin tartrate)		[47]
Denagliptin (GW823093)		[48]
K-579		[49, 50]
TS-021		[51]
ABT-279		[52]
E-3024		[53, 54]
LC-150444		[46]

(Table 4) contd....

DPP IV Inhibitors	Structure	References
DP-893		[55]
R-1579		[56]
BI-1356 (Linagliptin)		[57, 58]
ER-319711		[59]

class have been reported. In most of the cases X-ray crystallography studies showed that in spite of their distinct structural features these inhibitors interacted well with the DPP IV active site. The most advanced compound in this series is Alogliptin [34] (Table 4) that is presently undergoing phase 3 clinical trial.

It is important to mention here that depending on their nature of interactions with DPP IV active site all the inhibitors can be classified as covalent and non-covalent inhibitors. For example, as indicated by the X-ray studies on DPP IV bound inhibitors, Vildagliptin and Saxagliptin belong to the class of covalent inhibitors whereas Sitagliptin and LY 2463665 [35] belong to the non-covalent class.

7. DEVELOPMENTAL PROGRESS OF DPP IV INHIBITORS

The launch of Sitagliptin and Vildagliptin for the treatment of T2DM validated the therapeutic potential of this category of anti-diabetic agents. In this section, we present the developmental status, preclinical and clinical findings of different DPP IV inhibitors that are listed in Table 3. PK data of selected DPP IV inhibitors are described in Table 5.

P32/98

This compound was developed by Probiobdrug and was found to reduce the glucose levels significantly in diabetic

Table 5. Comparison of Pharmacokinetic Properties of DPP IV Inhibitors

DPP IV Inhibitors	C _{max} (μM)	CL _p (l/kg/h)	AUC (μM.h/mg/kg)	T _{1/2} (h)	F (%)	Species	References
NVP DPP728	0.80	1.3	-	0.55	>90	CM	[40]
Vildagliptin	0.29	1.5	-	1.5	>90	CM	[41]
Sitagliptin	0.33*	3.6	0.52	1.7	76.0	Rat	[36-37]
Sitagliptin	2.2*	0.36	8.3	4.9	100.0	Dog	[36-37]
Sitagliptin	0.33*	1.68	1.0	3.7	68.0	CM	[36-37]
Melogliptin (GRC 8200)	0.54 [#]	6.40	1.48	1.28	60.1	Rat	[105]
Melogliptin (GRC 8200)	6.72 [#]	0.98	12.64	4.31	90.0	Dog	[105]
Melogliptin (GRC 8200)	3.83 [#]	0.98	16.35	2.15	93.7	CM	[105]
Alogliptin	0.39 [@]	-	-	2.77 [^]	45.0 [^]	Rat	[88]
Alogliptin	0.66 [@]	-	-	3.04	68.0	Dog	[88]
Alogliptin	0.46-9.6 [@]	-	-	5.46	72.0-88.0	CM	[88]
ABT-279	0.37 [@]	-	-	4.70 [#]	28.0	Rat	[52]
ABT-279	0.30 [@]	-	-	5.30 [¶]	35.2	Dog	[52]
ABT-279	0.14 [@]	-	-	2.00 [¶]	11.2	CM	[52]
Saxagliptin	-	-	-	2.1 [^]	75.0	Rat	[31]

Note: CL: plasma clearance, C_{max}: maximum plasma concentration, F (%) :oral bioavailability, CM :cynomolgus monkeys, ** = orally administered as 2 mg/kg dose. # = orally administered as 5 mg/kg dose. @ = expressed in μg/ml. - = not available. ¶ = orally administered as 2.5 mg/kg dose. ^ = orally administered as 10 mg/kg dose.

rats after acute and subchronic treatment. In an OGTT study in VDF rats, P32/98 improved glucose and insulin kinetics after 12 weeks of administration [43]. Studies in Wistar rats with P32/98 showed a dramatic increase of active GLP-1 (13.4%-90%). Further studies in lean and obese Zucker rats demonstrated inhibition of DPP IV activity (65%) and a 150% increase in insulin levels compared to controls. Long-term treatment with this compound improved the glucose tolerance, insulinemia, peripheral insulin sensitivity and β-cell glucose responsiveness. In clinical studies, P32/98 showed a significant postprandial improvement in glucose tolerance in diabetic patients [60]. Although P32/98 was the first molecule that showed efficacy in animal studies, but it was not considered for further development due to the observed toxicities. Another compound P93/01 demonstrated a dose-dependent reduction of prandial glucose in patients with T2DM and was evaluated further in phase 2 trials. No further development has been reported so far.

NVP DPP728

NVP DPP728 is an orally active selective and extensively studied DPP IV inhibitor discovered by Novartis AG. This compound reduced DPP IV activity in plasma and improved glucose tolerance in diabetic Zucker rats [27]. In a randomized, double-blinded, placebo-controlled, multicentre 4 week study, NVP DPP728 (100 mg t.i.d or 150 mg b.i.d) showed a marked improvement in glycemic control (0.6% reduction in HbA_{1c}) to a similar extent in both the dosing

regimens. This compound was safe, tolerable and weight neutral with low incidence of hypoglycemia (4 treatment Vs 1 placebo) [42]. However, it did not enhance insulin levels. In fact mean 24 h insulin levels were decreased in both the treatment groups.

Vildagliptin (Galvus)

Vildagliptin is a potent, selective, reversible and orally bioavailable DPP IV inhibitor with better anti-hyperglycemic properties, being developed by Novartis AG for the treatment of T2DM [30]. In healthy human volunteers, Vildagliptin was rapidly absorbed with 85% bioavailability [61] and a half-life of about 90 minutes. However, sustained DPP IV inhibition was observed for more than 10 h [62-66]. In a preclinical study it was observed that this agent expands β-cell mass [20-21]. PK data in cynomolgous monkey is provided in Table 5.

In different clinical trials Vildagliptin was tested both as monotherapy and in combination with other anti-diabetic agents like metformin, TZD, SU or insulin, and was found to improve glycemic control (0.7% reduction in HbA_{1c}) [29]. It improved GLP-1 and GIP levels, reduced plasma glucose and glucagon concentration without the risk of adverse effects that are commonly associated with pioglitazone or metformin therapy [67]. In meal tolerance tests, single dose of Vildagliptin augmented insulin secretion in T2DM patients and inhibited hepatic glucose release, leading to increased suppression of endogenous glucose production [21, 67]. Vil-

dagliptin may be used as a prophylactic therapy in subjects that are prone to T2DM as it was found to improve postprandial glycemia through increased insulin sensitivity and β -cell function in subjects with impaired fasting glucose [68].

Vildagliptin, at 50 and 100 mg, is safe and tolerable with incidence of adverse events similar to placebo group [29]. The most common adverse events associated with Vildagliptin are headache, nasopharyngitis, cough, constipation, dizziness, and increased sweating [62]. Hyperinsulinemic hypoglycemia and nesidioblastosis due to increased circulating concentrations of GLP-1 observed after gastric bypass surgery are other possible adverse effects that were reported [21, 69].

Vildagliptin did not show any significant effect on the pharmacokinetic profile of commonly used anti-hypertensive drugs [70-73]. Even a high fat meal did not interfere with Vildagliptin pharmacokinetics and thus, it could be recommended for taking along with meals [74-75]. Vildagliptin bioavailability in patients with mild, moderate or severe hepatic impairment was unaltered as compared to healthy subjects [76].

Vildagliptin, a once-daily oral treatment for patients with T2DM, was approved by European Union in Sep' 2007 [77]. Further studies are being carried out on Vildagliptin to evaluate its long term efficacy, safety and tolerability in comparison with other anti-diabetic agents and results are awaited [39, 21, 78]. Extensive studies are required to assess advantages of this agent over current anti-diabetic therapies in T2DM patients, particularly in terms of effects on pancreatic β -cell restoration and potential weight loss [21, 79].

Sitagliptin (JanuviaTM)

Sitagliptin, an oral once daily and highly selective DPP IV inhibitor, was evaluated in clinical trials as a monotherapy, or as an add-on therapy with existing anti-diabetic agents like metformin [80]. Sitagliptin provided effective fasting and postprandial glycemic control in a wide range of patients with T2DM. Markers of β -cell function also improved with Sitagliptin treatment [81]. Sitagliptin may also have several advantages over currently available insulin secretagogues such as SU agents. It was generally well tolerated with an overall incidence of adverse experiences comparable to placebo, a low risk of hypoglycemia or GI disturbances, and a neutral effect on body weight [80, 82, 83]. Good bioavailability following the oral administration of Sitagliptin (2 mg/kg) in a number of animal models was reported (61% in mice, 76% in rats, 100% in dogs and 68% in monkeys). Details of AUC, $t_{1/2}$, clearance, C_{max} etc are provided in Table 5. A recent report disclosed that adverse effects such as nausea and vomiting were associated with Sitagliptin following a single oral dose in an OGTT study [84]. In lean mice, an oral dose of 1 mg/kg resulted in a plasma drug concentration of 190 nM at 80 min post-dose with a 69% plasma DPP IV inhibition. The corresponding values following a 3 mg/kg dose were 600 nM and 84%. It was noted that the extent of DPP IV inhibition determined in the *in vitro* assay underestimated that obtained *in vivo*. This discrepancy was due to the competitive, rapid and reversible inhibiting properties of Sitagliptin and the fact that the activity assay requires plasma (and hence inhibitor) dilution, and

the presence of a substrate, which competes with the inhibitor for enzyme binding. Preclinical data suggests that Sitagliptin may have a longer duration of action than Vildagliptin, as its $t_{1/2}$ in monkeys is 2-fold higher than that of Vildagliptin [80]. Sitagliptin is superior to Vildagliptin in terms of DPP IV selectivity, and if any resulting off-target effects with the inhibition of other DPP subtypes prove to be associated with adverse events, then Sitagliptin may have a competitive edge over Vildagliptin. However, the absence of serious side effects in clinical studies of Vildagliptin indicates that the difference in selectivity between various inhibitors may likely be more of academic than clinical importance. Other reported side effects associated with the use of Sitagliptin include stuffy or runny nose, sore throat, upper respiratory tract infection, stomach pain, diarrhea and headache [85]. Sitagliptin was generally well tolerated and provided effective glycemic control in patients with T2DM and moderate to severe renal insufficiency, including patients with end stage renal disease (ESRD) on dialysis [86].

K- 579

Treatment with K579 at a dose of 1 mg/kg inhibited the plasma DPP IV activity even 8 h after the administration and significantly suppressed the blood glucose elevation in glibenclamide-pretreated Wistar rats without marked hypoglycemia, and it was observed that the combination treatment of K-579 and SU was more effective than glibenclamide alone [49, 50].

BI 1356 (ONDERO)

Ondero is a long acting DPP IV inhibitor that showed approximately 90% inhibition of DPP IV at doses of 3 and 10 mg/kg and 70% inhibition at a dose of 1.0 mg/kg throughout a 7 h study period. Even 24 h after dosing, it showed $\geq 50\%$ inhibition of DPP IV [57]. Long lasting effect of Ondero was also observed during OGTT. Glucose excursion was significantly reduced by $\sim 50\%$ and 20-30% when challenged with glucose at 45 min or 16 h respectively after dosing with Ondero (1 mg/kg). This long lasting effect on glucose tolerance, distinguished Ondero from the other DPP IV inhibitors under investigation and/or in clinical trials. In comparison with other inhibitors of this class, Ondero exhibited a persistent DPP IV activity over a period of 24 h [57]. OGTT studies in Zucker fatty rats with Ondero (3 mg/kg), showed an elevation of GLP-1 levels. Furthermore, active GLP-1 levels were found to remain same at elevated basal levels after glucose-induced peak. This observation was not consistent with insulin levels, where administration of Ondero did not increase basal insulin levels before glucose challenge. This effect was due to the tight binding and long lasting inhibition of DPP IV by Ondero, which leads to accumulation of minor amounts of GLP-1 soon after dosing and before glucose stimuli. Overnight fasted animals, showed that the concentration of active GLP-1 in the plasma remained elevated in animals pretreated with Ondero as compared to control animals in all prandial and postprandial phases throughout the day. It was postulated that increasing basal GLP-1 levels may provide the conditions for β -cell regeneration [87]. Thus a drug of this class which causes increased basal levels of GLP-1 even 24 h after dosing could be more beneficial to T2DM patients.

SYR-322 (Alogliptin)

Alogliptin, (2-[[6-[(3R)-3-amino-1-piperidinyl]-3,4-dihydro-3-methyl-2,4-dioxo-1(2H)-pyrimidinyl] methyl] benzonitrile monobenzoate) is a potent and highly selective (>10,000 fold selective for DPP IV over other closely related proteins) and is currently being evaluated in phase 3 trials [34, 88]. In studies with monkeys it was shown to reduce plasma DPP IV activity with a half-life of 5.7 h and a bioavailability of 72-88% (dosed at 2, 10 and 30 mg/kg). Assessment of mean peak inhibition of plasma DPP IV administered orally with a dose of 10 mg/kg (in rats), 3 mg/kg (in dogs) and 2-30 mg/kg (in monkeys) showed that the inhibition was greater than 85, 95 and 80% in rats, dogs and monkeys, respectively. A sustained DPP IV inhibition (80%) at 24 h post dose was observed in monkeys. It was also found to reduce glucose excursion following an OGTT in C57BL/6 mice [89]. PK profile of Alogliptin in rats, dogs and monkeys is described in Table 5.

In a clinical study, the drug displayed good efficacy in reducing glucose levels throughout the day. In a 4 week *ob/ob* mice study, Alogliptin at 2.8, 14.1 or 42.2 mg/kg/day, showed a dose dependent (24%, 62% and 80%, respectively) reduction of plasma DPP IV activity and an increase in GLP-1 levels [92]. In another 4 week study carried out in n-STZ (neonatal- Streptozotocin) rats with Alogliptin, pancreatic insulin content was elevated by 1.5 fold and HbA_{1c} was reduced by 0.2% with a minimum effective dose of 3 mg/kg [90]. Safety results for this multi-dose study showed that Alogliptin was well tolerated in patients with T2DM, with an incidence of hypoglycemia similar to placebo. No serious adverse events were reported, and no dose-limiting toxicity was observed over the entire dose range of 25 to 400 mg [90]. Takeda Pharmaceuticals, began the phase 3 trial for this drug in Jan'2006. The results of a single-dose (50 mg) pharmacokinetic study in patients with renal impairment demonstrated an increase in Alogliptin exposure compared to healthy volunteers [91]. The increase in exposure to Alogliptin was approximately 1.7, 2.1, 3.2, 3.8 fold in patients with mild, moderate, severe renal impairment and ESRD patients respectively. The safety and efficacy profiles of Alogliptin as monotherapy and in combination with metformin, pioglitazone, glyburide, and insulin in patients with T2DM were evaluated in phase 3 clinical trials and results were presented at the 68th Annual Scientific Sessions of the American Diabetes Association (ADA) in 2008. Co-administration of Alogliptin with pioglitazone, glyburide, or metformin in healthy volunteers resulted in no significant drug-drug interactions [92-94]. In clinical trials, Alogliptin was well tolerated across a variety of doses and no dose-limiting toxicities were observed in 2 published trials. No patients were withdrawn from these studies because of adverse events [95, 96]. It is claimed that Alogliptin may provide some specific advantages due to distinct chemotype over other DPP IV inhibitors currently under advanced developmental stages. In February 2008, a New Drug Application (NDA) was submitted and a response from FDA is expected by the year end.

Saxagliptin (BMS-477118)

Bristol-Myers Squibb (BMS) developed a pyrrolidine-based, oral DPP IV inhibitor, BMS-477118 (Saxagliptin), for

a potential once-daily treatment of T2DM. Earlier BMS investigated a series of DPP IV inhibitors with methanoprolinonitrile dipeptide mimetics and observed that these compounds had the highest degree of β -branching and greater stability [31]. In August 2004, preclinical data on Saxagliptin were presented at the 228th ACS meeting in USA. Saxagliptin does not inhibit T-cell activity *in vivo*. The ED₅₀ values after 0.5 and 6 h post-dose were 0.1 and 0.5 μ M/kg, respectively. In an oral glucose challenge in normal rats treated with 3 μ M/kg, Saxagliptin administration resulted in much higher GLP-1 levels than in the control group. It showed several beneficial effects in some of the clinical studies. In another clinical study, Saxagliptin was found to be safe and tolerable in a single (100 mg oral dose) or in combination with metformin (100 mg saxagliptin + 1000 mg metformin) with side effects similar to placebo group [97]. It significantly improved glycemic control (0.7-0.9% reduction in HbA_{1c}) and was weight neutral [98]. In another 24-week phase 3 trial, Saxagliptin, showed significant reduction in all key measures of glucose control studied like HbA_{1c}, fasting plasma glucose and postprandial glucose when added to a SU or a TZD in patients with inadequately controlled T2DM [99]. The combination of Saxagliptin with SU or TZD was well tolerated over the course of the studies, and significantly more number of patients were able to achieve the ADA recommended target (HbA_{1c} < 7 %). A NDA was submitted to the U.S. FDA and a Marketing Authorization Application to the European Medicines Agency (EMA) in 2008. Phase 3 trials assessing the safety and efficacy of Saxagliptin involving more than 4,000 patients revealed minor adverse effects like urinary tract infection, nasopharyngitis, upper respiratory tract infection, influenza, diarrhea, back pain, headache, cough and hypertension. BMS and Astrazeneca have proposed the name ONGLYZATM and await the approval from FDA and EMA [99].

AMG-222

AMG-222 is a DPP IV inhibitor and is being evaluated for the treatment of T2DM. The molecule is currently in a phase 2a study in collaboration with Servier Pharmaceuticals, which owns the rights outside the United States [www.amgen.com]. Amgen acquired the rights of this compound in 2007 through acquisition of Alantos and is developing this molecule along with Servier. Although, information on *in vitro* and preclinical data of AMG-222 publicly available is less but, latest studies revealed the drug to be highly selective and to be suitable for once-daily administration [100].

ARI-2243

It is a potent DPP IV inhibitor that possesses an additional DPP IV independent beneficial mechanism which contributes to improved glucose control [101]. ARI-2243 produced a 29% reduction in glucose excursion during OGTT studies in DPP IV knock-out mice. In multiple animal models for diabetes, ARI-2243 consistently produced dramatic efficacy results, including a 2.5% reduction of HbA_{1c} in Zucker diabetic rats [101].

ARI-2243 showed improved insulin sensitivity following 14 days of dosing in Zucker^{*fa/fa*} animals whereas Sitagliptin had no effect on insulin sensitivity in this diabetic animal

experiment [101]. In mice, ARI-2243 showed maximal glucose lowering of approximately 85% with a dose of 0.1 mg/kg compared with about 55% reduction of glucose excursion with Sitagliptin at 10-100 times higher doses. Moreover, at 18 h post dose, ARI-2243 lowered plasma AUC 25%, whereas with no effect was observed with Sitagliptin, demonstrating its long duration of action and the feasibility of once-daily dosing with ARI-2243.

GRC 8200 (Melogliptin)

Melogliptin was originally developed by Glenmark Pharmaceuticals Ltd. Preclinical data suggest that this compound is very potent with an IC_{50} of 1.61 nM against human recombinant DPP IV enzyme and with a selectivity of 10,000 fold over DPP2, PPCE and other proteases tested [44-45]. Melogliptin has an excellent pharmacokinetic profile with a reported oral bioavailability of 50-95% [102]. PK data of Melogliptin is described in Table 5. Structure (www.thomson-pharma.com; CAS RN, 868771-57-7) is described in Table 4. Oral administration of Melogliptin at a dose of 3 mg/kg/day in *db/db* mice resulted in 30% reduction of AUC in OGTT. Also, insulin levels were doubled [45]. In overnight fasted beagle dogs (5 mg/kg po) Melogliptin produced a peak concentration of 2.15 μ g/ml, plasma clearance of 1.17 l/h/kg. Further, plasma DPP IV was inhibited by more than 90 % until 6 hours post administration of the drug [103]. The results of phase 1 trial suggest that both single ascending and multiple ascending doses of the drug were well tolerated with a linear pharmacokinetic profile, supporting once-daily dosing [104-105]. The inhibition of plasma DPP IV was more than 90% within an hour of dosing. Currently, melogliptin is in phase 2 trials.

R-1579 (Carmegliptin)

Both Roche and Chugai are co-developing R-1579, a small molecule based DPP IV inhibitor as a back up for another DPP IV inhibitor R-1438 which was discontinued by Roche [106]. The results of a single center, double-blinded phase 1 trial suggest that both single ascending and multiple ascending doses of R-1579 were tolerated with more than 50 % reduction in DPP IV activity observed even after 10 hours of dosing [107]. Further, this compound has successfully completed Phase 2 trials in July 2008 and data obtained in this study suggest that the drug is safe and efficacious and there was no evidence of weight loss [107].

PHX-1149

PHX-1149 of Phenomix Inc. was the lead from a series of orally active DPP IV inhibitors for the potential treatment of T2DM. In preclinical studies, this compound showed excellent safety and efficacy profile [108]. Pharmacokinetic and pharmacodynamic profile of PHX-1149 in a double-blinded, placebo controlled studies in healthy subjects revealed comparable results [109]. In August 2007, preclinical data on PHX-1149 were presented at the 12th annual Drug Discovery and Development of Innovative Therapeutics meeting in Boston, USA. PHX-1149 exhibited a half-life of 6 to 7 h in monkeys, 4.1 h in rats, and 3.8 h in dogs with a T_{max} of approximately 2.5 h. The compound demonstrated good microsomal stability, no substantial CYP inhibition,

low-protein binding and good metabolic stability. In monkeys (45 mg/kg) PHX-1149, inhibited DPP IV upto 24 h. PK and PD studies carried out in dogs and monkeys supported once-daily dosing regimes in humans. A dose of 9 mg/kg in dogs and monkeys showed a 50% and 80% DPP IV inhibition respectively even after 24 h. PHX-1149 exhibited a half-life of 6.3 h, time to C_{max} was 0.8 h and C_{max} was 555 ng/ml and an AUC concentration of 2030 h.ng/ml [110]. A 28-day phase 2a clinical trial of PHX-1149 in 174 T2DM patients, demonstrated that drug was well tolerated and met its primary endpoint of reduction in postprandial glucose levels.

In April 2007, a 12-week phase 2b clinical trial study was initiated and in May 2008, positive results were reported. In this combination therapy study with PHX-1149 + metformin or TZD or placebo, 422 patients received 200 or 400 mg of PHX-1149 or placebo once daily plus an optional constant dose of metformin or a TZD or both [111]. PHX-1149 significantly reduced HbA_{1c} levels in both dose groups with significant effects on fasting and post-meal blood glucose levels and also achieved HbA_{1c} levels of <7% [112]. The drug was also safe and well tolerated.

8. SELECTIVITY ISSUES OF DPP IV INHIBITORS

DPP IV is a member of a family of serine peptidases that includes other related members like quiescent cell proline dipeptidase (QPP/DPP2), DPP6, DPP8, DPP9, and DPP10. The catalytic regions of these enzymes show similarity to each other and therefore a DPP IV inhibitor may also inhibit the related enzymes in body to a certain extent. For example, the DPP IV inhibitor Val-boro-pro appears to be relatively nonselective for DPP IV as it may also inhibit FAP, DPP8, DPP9 and DPP2 [113]. Functions of other family members and their clinical importance are unclear at present. Lankas *et al.* [113] found that administration of DPP8/9 inhibitor produced alopecia, thrombocytopenia, reticulocytopenia, enlarged spleen, multiorgan histopathological changes, and mortality in rats and GI toxicities in dogs. The QPP inhibitor was found to produce reticulocytopenia in rats, but selective DPP IV inhibitor exhibited no toxicities in these species. Moreover DPP8/9 inhibitor attenuated T-cell activation in human *in vitro* models. Based on the above preclinical study data, it was perceived that selective inhibitors of DPP IV may be a safe clinical candidate for T2DM [113].

While selective inhibition of DPP IV over DPP8/9 is desirable it is however not clear what should be the degree of selectivity towards DPP IV inhibition for a compound to become a pharmacologically safe drug? The fold selectivity data of few DPP IV inhibitors is summarized in Table 6. A recent study carried out in rodents with Vildagliptin (a less selective DPP IV inhibitor over DPP 8/9) revealed no toxicities that were reported earlier with selective DPP 8/9 inhibition [114]. It may be concluded that the observed toxicities may be due to a mechanism other than DPP 8/9 inhibition. Thus, very high selectivity for DPP IV over DPP 8/9 may not be an absolute prerequisite for developing efficacious DPP IV inhibitors with acceptable safety profiles and further extensive studies should be performed to understand the importance of DPP 8/9. Comparison of *in vivo* efficacy of selected DPP IV inhibitors is summarized in Table 7.

Table 6. Potency of DPP IV Inhibitors Against Closely Associated Enzymes

Compound	IC ₅₀ (nM)					Fold Selectivity		Ref.
	DPPIV	DPP8	DPP9	DPP2	FAP	DPP8	DPP9	
Sitagliptin	18	48000	>10000	>100000	>100000	2667	>5550	[37]
Vildagliptin	3.5 (Ki=3)	Ki= 810	Ki= 95	> 500000	NA	270	32	[30]
BI 1356 (Ondero)	1.0	>40000	>10000	>100000	89	40000	10000	[57]
Alogliptin	7.0	>100000	>100000	>100000	>100000	14285	14285	[88]
Saxagliptin	3.37	244	104	>30000	NA	72	31	[117]
Melogliptin (GRC 8200)	1.61	NA	NA	NA	NA	>2500	>2000	[106]
ASP8497	5.30	2830	436	NA	NA	530	82	[117]
ABT-279	Ki= 1	Ki >30000	Ki >30000	Ki >30000	Ki >30000	30000	30000	[52]
ABT-341	Ki= 1.3	Ki >30000	Ki >4000	NA	NA	>20000	3000	[118]
LY 2463665	7.0	>100000	>100000	>100000	>70000	>10000	>10000	[119]

Note: NA, Not available.

Table 7. Comparison of *In Vivo* Efficacy of DPP IV Inhibitors

Time (h Post Dose)	ED ₅₀ (mg/kg)				
	Ondero	Saxagliptin	Alogliptin	Vildagliptin	Sitagliptin
7	0.3	0.1	0.1	0.5	2.3
24	0.9	2.7	10	14	>30

ED₅₀ values for inhibition of plasma DPP IV activity in Han Wistar rats at different times after dosing.

9. SHORT-ACTING VERSUS LONG-ACTING DPP IV INHIBITORS

A number of DPP IV inhibitors are now in the late stages of clinical development. They have different properties, in terms of their duration of action and hence anticipated dosing frequency. Considering that active GLP-1 is short lived ($t_{1/2} < 1$ min) and DPP IV enzyme that inactivates GLP-1 is involved in regulating other physiological functions, short acting DPP IV inhibitors maybe preferred over long acting DPP IV inhibitors to minimize any potential side effects. However, the duration of DPP IV inhibition should be long enough to reduce the post prandial glucose excursion, yet sufficient enough to allow time for the activities of other endogenous DPP IV substrates to restore to their normal levels [115]. To overcome this limitation short acting DPP IV inhibitors maybe administered along with meals (b.i.d./t.i.d). However, issues such as cost and dosing convenience may outweigh the benefits of short acting over long acting DPP IV inhibitors, provided that long term inhibition of DPP IV does not lead to toxicities. Further studies should be conducted to better understand which type of drug would be beneficial to treat T2DM with minimal side effects.

10. CURRENT OPINION ON DPP IV INHIBITORS VS GLP-1 ANALOGS

Both DPP IV and GLP-1 based therapeutic approaches have been approved by FDA for T2DM. So the emerging question is that which one of these two approaches is more beneficial? Current evidence suggests that both DPP IV inhibitors and GLP-1 analogs may exhibit beneficial actions on the pancreatic islets, acting to preserve β -cell mass *via* opposing effects on proliferation and apoptosis. However, DPP IV inhibitors are small, orally bioavailable low-molecular-weight compounds but they are without any inherent anti-diabetic activity of their own and hence their therapeutic effect is reliant on enhancing the activity of GLP-1 and GIP whereas all GLP-1 analogs are based on a naturally occurring, relatively large peptide with inherent anti-diabetic activity. Currently there are no small-molecule GLP-1 mimetic drugs available for oral administration and thus they must be given parenterally. Researchers in many industries and academic labs are working on development of oral small molecule agonists of GLP-1 receptor to overcome the existing limitation (injectable and less stable) of GLP-1 based therapy. Although GLP-1 based therapy offers physiological

benefits, but it is also associated with adverse events like hypoglycemia, nausea *etc* as observed in human clinical trials. Further, modified GLP-1 peptide based analogs are potentially immunogenic. However, none of the compounds under investigation were reported to elicit any antibody response and thus the potential side effects of GLP-1 mimetics need to be evaluated further in long term studies. The anti-hyperglycemic effects of DPP IV inhibitors is glucose-dependent meaning that the stimulation of insulin release by these compounds depends upon elevated ambient blood glucose levels and hence there may not be a potential risk of hypoglycemia. However, long-acting DPP IV resistant GLP-1 analogs may cause hypoglycemia and thus dose regimen to be administered should be monitored carefully. Moreover, in rodents it was reported that, sustained GLP-1 elevation leads to undesirable effects like increased heart rate and blood pressure, however the same was not observed in human trials in studies with DPP IV resistant GLP-1 analogs [24]. Although both GLP-1 and DPP IV inhibitor based therapies have been approved to be clinically efficacious as monotherapy but DPP IV inhibitor combination therapy (with TZD's, SU or biguanides) may be a safer therapeutic approach. GLP-1 analog based therapy causes reduction in body weight, which has not been observed in DPP IV inhibition based therapy. Considering all the above facts, DPP IV inhibitors possess more advantages (orally bioavailable, small molecular weight, low hypoglycemic risk, weight neutral *etc*) over GLP-1 analogs, but the long-term effects of DPP IV inhibitors in T2DM patients need to be explored because of its role in regulation of other physiological hormones, neuropeptides, chemokines and many other substrates listed in Table 1.

An important thing to mention here is that metformin (a drug with multiple anti-diabetic mechanisms) was reported to inhibit DPP IV, this strengthens the long-term safety of DPP IV inhibitors as metformin is available as a therapy for treatment of T2DM since 1950s [116]. Currently, Sitagliptin is the only FDA-approved DPP IV inhibitor. However, the market may get crowded with other DPP IV inhibitors that are near approval, including Saxagliptin and Alogliptin suggesting that DPP IV inhibition is a safe and effective therapy for T2DM.

11. CONCLUDING REMARKS

In general, the safety profile of most of the DPP IV inhibitors under evaluation and those for which studies have been completed are encouraging. While they do not lower glucose to a greater extent (as monotherapy) than existing therapies, they are more effective in combination with other drugs like TZD, SU or biguanides and thus in a combination therapy adverse effects associated with existing therapies can be avoided to a certain extent. DPP IV inhibitors like Vildagliptin [78] and Sitagliptin [80] are well tolerated and have demonstrated the ability to cause sustained reductions in HbA_{1c} with negligible risk of hypoglycemia. Older therapies for T2DM do not prevent β -cell apoptosis and thus newer agents with complementary modes of action and the potential to prevent β -cell damage could be of great interest. There is enough evidence based on animal studies that DPP IV inhibitors can preserve and even reverse the progressive loss of insulin secretion capacity, although this has not yet

been demonstrated in humans [120]. Moreover, DPP IV inhibitors are weight neutral and have a negligible risk of hypoglycemia. Thus DPP IV inhibitors have an advantage over other anti-diabetic agents like long-acting GLP-1 analogs, TZDs, SUs, biguanides *etc*.

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ABBREVIATIONS

DPP	=	Dipeptidyl peptidase
GLP-1	=	Glucagon-like peptide-1
GIP	=	Gastric inhibitory peptide
T2DM	=	Type 2 Diabetes mellitus
HbA _{1c}	=	Glycosylated hemoglobin A1c
FDA	=	US Food and Drug Administration
AUC	=	Area under curve
OGTT	=	Oral glucose tolerance test
EMEA	=	European Medicines Agency
ESRD	=	End stage renal disease
TZDs	=	Thiazolidinediones
SUs	=	Sulphonylurea's
PPCE	=	Post-proline cleaving enzyme
STZ	=	Streptozotocin
BMS	=	Bristol Myers Squibb

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