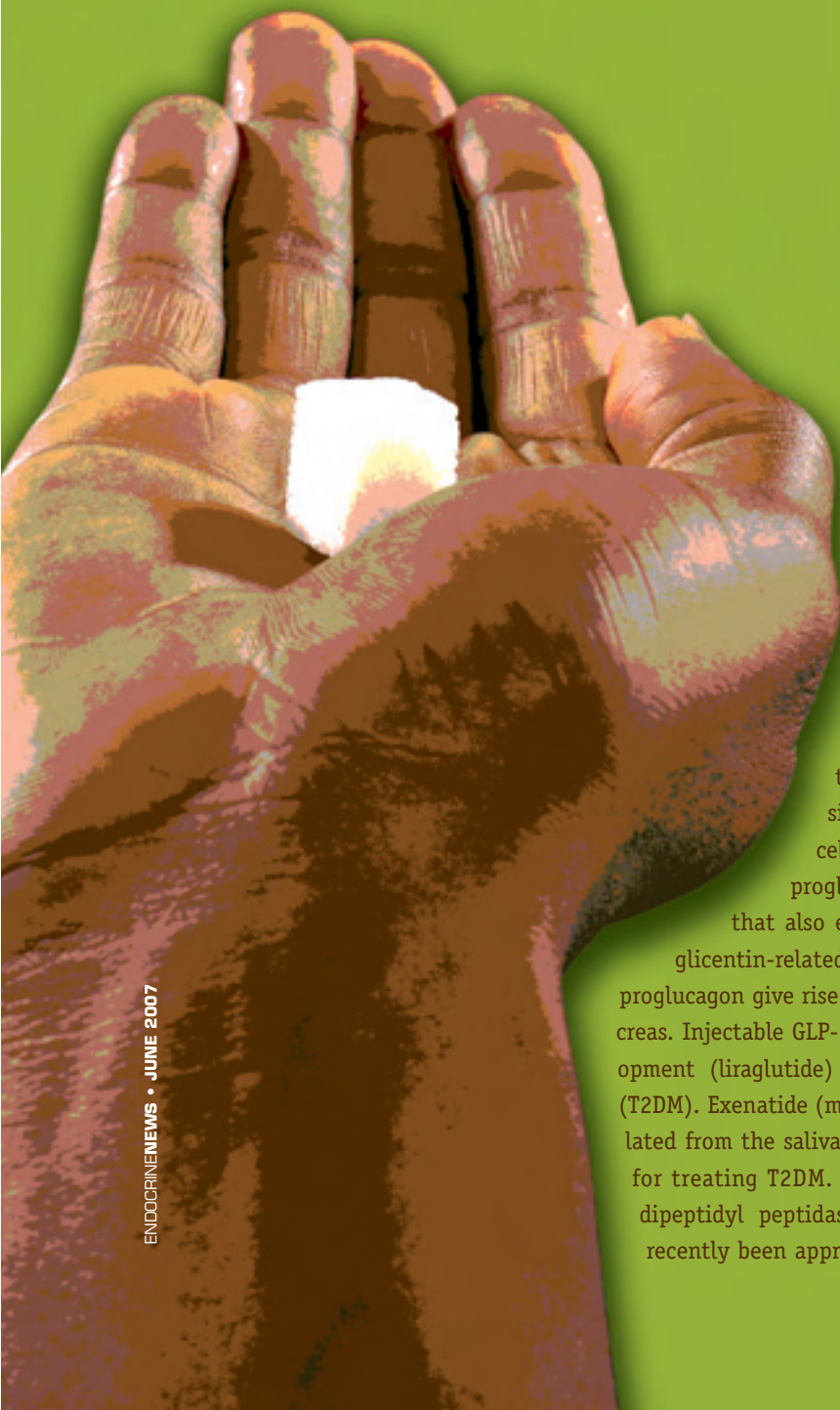


3 Perspectives

on New Type 2 Diabetes Treatments

Recent Advances in the GLP-1 Pathway



Glucagon-like peptide-1 (GLP-1) is a gut-derived incretin hormone that augments glucose-dependent insulin secretion from pancreatic beta cells. GLP-1 is insulinotropic, in that it stimulates both insulin secretion and biosynthesis, and also promotes the growth and survival of beta cells.¹ The hormone was discovered through decoding the proglucagon mRNA (cDNA), a multi-functional prohormone that also encodes glucagon, glucagon-like peptide-2 (GLP-2), and glicentin-related pancreatic peptide. Specific proteolytic cleavages of proglucagon give rise to GLP-1 and GLP-2 in the gut and glucagon in the pancreas. Injectable GLP-1 agonists are currently in use (exenatide) and in development (liraglutide) as first-line treatments for type 2 diabetes mellitus (T2DM). Exenatide (marketed as Byetta), a modified hormone (exendin-4) isolated from the saliva of the Gila monster, is the first GLP-1 agonist approved for treating T2DM. Sitagliptin and vildagliptin, oral inhibitors of aminodipeptidyl peptidase (DPP-4), the enzyme that inactivates GLP-1, have recently been approved for treating T2DM.



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Key Abbreviations

T2DM	type 2 diabetes mellitus
GLP	glucagon-like peptide
GIP	glucose-dependent insulinotropic polypeptide
DPP-4	dipeptidyl peptidase-4
PKA	protein kinase A
CD26	diaminopeptidyl peptidase-4
TZD	thiazolidinedione

From the Basic Scientist Perspective

- GLP-1 and GIP are incretin hormones (i.e., secreted from the gut in response to meals) and they augment glucose-dependent insulin secretion.
- Major antidiabetogenic GLP-1 actions include glucose-dependent insulin secretion, delayed gastric emptying that dampens prandial glycemic excursions and curtails food intake, and the suppression of glucagon secretion and lowered hepatic glucose output.
- In animal studies, GLP-1 promotes beta cell growth and survival.
- The active insulinotropic peptides, GLP-1-(7-37) and GLP-1-(7-36), amide are cleaved from proglucagon in the gut enteroendocrine L-cells and released into the circulation in response to food intake.
- DPP-4 is an aminopeptidyl peptidase that modifies the activities of many regulatory peptides by selectively removing the two amino terminal amino acids.
- GLP-1's insulinotropic activity is rapidly lost ($T_{1/2} = 1-2$ min) in the circulation by cleavage by DPP-4.

The Incretin Concept

Historically, the term incretin refers to the existence of a gut-derived factor that augments glucose-dependent insulin secretion to explain the observation that a glucose load given orally more effectively releases insulin than a comparable (isoglycemic) glucose load given systemically.² It was subsequently recognized that the incretin effect is diminished or absent in diabetic individuals. The first incretin hor-

mone discovered was gastric inhibitory peptide (GIP), subsequently renamed glucose-dependent insulinotropic polypeptide. However, GIP could only partially account for the incretin effect and its insulinotropic actions are diminished in diabetic subjects. Glucagon-like peptide 1 (GLP-1), discovered later, proved to be the missing incretin. GIP and GLP-1 account for the full incretin effect. GLP-1 also retains full glucose-dependent actions in individuals with diabetes.

Actions of GLP-1

GLP-1 has multiple actions that reflect the distribution of its receptors on islet beta and alpha cells, the nervous system, stomach and intestines, heart, kidney, and lung.^{1, 3} Insulin release by beta cells in response to GLP-1 depends directly on plasma glucose levels; insulin secretagogic activity increases with hyperglycemia and diminishes in normoglycemic conditions. GLP-1 suppresses glucagon secretion from alpha cells, inhibiting hepatic glucose output. Actions on the stomach and duodenum delay gastric emptying, dampening postprandial glucose excursions and providing a sensation of fullness that curtails food intake. GLP-1 might also have central anorexigenic actions; its receptors are located in the hypothalamus satiety center. Myocardial contractility and cardiac output are improved by GLP-1.⁴ Although GLP-1 receptors exist in the kidney and lung, little is known about their physiological actions. GLP-1 also enhances glucose disposal in the liver, apparently via neural reflexes emanating from the hepatoportal vein. GLP-1 and GIP receptor-null mice are glucose intolerant and have diminished insulin secretion in response to glucose.⁵

The GLP-1 Receptor

The GLP-1 receptor is a G-protein-coupled receptor linked to $G_{\alpha s}$, cAMP formation, and PKA activation. Cyclic AMP and glucose signaling act synergistically in beta cells to stimulate insulin secretion (exocytosis) by depolarizing the cells through the inhibition of ATP-sensitive potassium channels and the opening of voltage-sensitive calcium channels. Without cAMP signaling, glucose has little or no effect on insulin secretion and vice versa—the so-called “glucose competence effect.”⁶ The incretin hormones (GLP-1 and GIP) depend absolutely on glucose for their actions, a major distinction between them and other insulin secretagogues, such as sulfonylureas. This glucose dependency provides a low risk for hypoglycemic side effects. Another GLP-1 property that distinguishes it from other insulin stimulators is its activation of the proliferative kinase PKA and the pro-survival kinase Akt, which contribute to the proliferation and cytoprotection of beta cells.

Formation of GLP-1 from Proglucagon

The active insulinotropic GLP-1 is cleaved from proglucagon within the enteroendocrine L cells of the intestine by a subtilisin-like prohormone convertase (PC1/3) and is modified by carboxypeptidase B, amidating monoxygenase, and diaminopeptidyl peptidase-4 (DPP-4). This provides

the isopeptides, GLP-1-(1-37), -7-37, -1-36amide, -7-36amide, -9-37, and -9-36amide.^{5, 7} Insulinotropic activities are restricted to the 7-37 and 7-36 amide isoforms, which are the predominant peptides released from the L-cells of the distal intestine in response to meals. The insulinotropic activities of these peptides, however, are rapidly inactivated ($T_{1/2} = 1$ min) in the circulation by DPP-4—which removes the two amino terminal amino acids, yielding the truncated peptides, 9-37, and 9-36amide, which are devoid of insulin-releasing activity. The major circulating peptides are GLP-1-(7-37/7-36amide) and GLP-1-(9-36) amide.

DPP-4

CD26 is a large (110 kDa) protein with numerous complex regulatory functions, including immunomodulation, pain mediation, cardiovascular regulation, cell adhesion and migration, and metabolism.^{3, 8-10} The enzyme was discovered 40 years ago as a novel diaminopeptidase that removes the two amino terminal amino acids from proteins. DPP-4 was subsequently found to be identical to the CD26 antigen, a component of the T-cell receptor complex responsible for its activation. The enzyme is widely distributed throughout essentially all organs of the body as a plasma-bound ectoenzyme—cytosolic regulatory binding protein—and circulates in soluble form. CD26's best known functions are regulating development and activation of T cells in the immune system and its role in the enzymatic modifications of neuroregulatory peptides and hormones within the superfamily of glucagon-related peptides involved in metabolism. DPP-4 selectively modifies the activities of several neuropeptides, including substance P, NPY, and PYY; it also modifies to some extent all members of the glucagon superfamily of peptides, although GLP-1, GLP-2, PACAP, GIP, and GHRH are the most efficiently cleaved.

We must appreciate that DPP-4 modifies—and thereby regulates—the biological activities of peptides and does not degrade them in the sense of rapid proteolysis and disposal. Although DPP-4 abrogates the insulinotropic functions of GLP-1, some evidence suggests that GLP-1-(9-36) has insulin-like effects on the heart.¹¹ The inhibition of DPP-4-mediated processing of GLP-1 might represent a trade-off: preserving insulinotropic activities at the expense of losing insulinomimetic activities.

DPP-4 Inhibitors

The recognition that DPP-4 cleaves and modulates the functions of immuno- and neuro-regulatory peptides and metabolic hormones prompted interest in developing inhibitors of the enzyme for therapeutic use in immunomodulation, HIV infection, cancer, and diabetes. Particular attention has focused on prolonging GLP-1 and

GIP actions with DPP-4 inhibitors as a T2DM treatment. Currently, multiple pharmaceutical companies have DPP-4 inhibitors in their product pipelines. The inhibitors belong to two general classes; non-peptide heterocyclic compounds with rapid onset and duration of action, e.g., sitagliptin (Januvia), and cyanopyrrolidines, covalent modified “irreversible” inhibitors with slow onset and more prolonged actions, e.g., vildagliptin (Galvus). Sitagliptin was approved in the United States for T2DM treatment in October 2006.

From the Clinical Scientist Perspective

- GLP-1 is rapidly degraded by the enzyme DPP-4.
- DPP-4-resistant GLP-1R agonists exemplified by exenatide lower blood glucose in T2DM patients.
- DPP-4 inhibition prevents the degradation of endogenous GLP-1 and GIP.
- The DPP-4 inhibitor sitagliptin has been approved for T2DM treatment.
- GLP-1R agonists and DPP-4 inhibitors lower blood glucose by enhancing beta-cell function and inhibition of glucagon secretion.
- GLP-1R agonists also inhibit gastric emptying and reduce satiety, leading to weight loss in most treated subjects.

Because native GLP-1 and GIP are both rapidly degraded by DPP-4, degradation-resistant GLP-1R agonists and DPP-4 inhibitors have been developed to treat T2DM. The first

GLP-1R agonist approved is exendin-4 (exenatide), a 39-amino-acid peptide isolated from the venom of *Heloderma suspectum*, the Gila monster. The anti-diabetic efficacy of twice daily exenatide was initially examined in 4-week studies of T2DM subjects not adequately controlled on metformin and/or sulphonylurea agents. Exenatide therapy decreased levels of fasting and

postprandial glucose, and hemoglobin A1c (HbA1c)—a marker reflecting integrated glucose control over a period of months. Mild-to-moderate nausea was the principal treatment-related side effect. Phase 3 clinical trials assessed exenatide's efficacy over 30 weeks in T2DM subjects not achieving glycemic control on metformin and/or sulphonylurea.¹⁻³ Exenatide therapy significantly reduced HbA1c in all three studies and in the absence of concomitant sulphonylurea therapy. The drug was not associated with a significant increase in hypoglycemia—a side effect seen commonly with therapies that stimulate insulin secretion in a non-glucose-dependent manner. Moreover, exenatide-treated subjects exhibited mild-to-moderate weight loss, despite the HbA1c reduction. Although 40%–50% of

“The enzyme is widely distributed throughout essentially all organs of the body as a plasma-bound ectoenzyme—cytosolic regulatory binding protein—and circulates in soluble form.”

exenatide-treated subjects exhibited anti-exenatide antibodies at the end of the 30-week treatment period, in most patients the antibodies did not seem to be associated with any change in clinical responsiveness to the drug. Exenatide has also shown efficacy when combined with thiazolidinedione therapy—with or without concomitant metformin—with 62% of subjects achieving HbA1c less than 7% from an initial baseline of 7.9%, in association with a 1.5 kg mean weight loss over 16 weeks.

The effects of exenatide 10 µg twice daily have also been compared head-to-head with insulin administration (insulin glargine or aspart 70/30) in two different studies. The end-of-study reduction in HbA1c and rates of hypoglycemia were comparable in subjects treated with either exenatide or insulin.⁴ Subjects treated with exenatide exhibited a modest but significant weight loss versus a weight gain of several kilograms in the insulin-treated patients. In both studies, however, the withdrawal rate was significantly higher in the groups of exenatide-treated subjects.

Complementary clinical studies have examined the efficacy of DPP-4 inhibitors for T2DM treatment. Proof of concept for using DPP-4 inhibitors in T2DM human subjects was obtained in studies of 1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine (NVP DPP728). NVP DPP728 improved both fasting and meal-related glycemic excursion, and caused a significant HbA1c reduction.⁵ A subsequent 4-week study with the DPP-4 inhibitor vildagliptin (2S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl] pyrrolidine-2-carbonitrile (LAF237), 100 mg daily, demonstrated similar improvements in glycemic control and parameters of beta-cell function. Sitagliptin, the first clinically approved DPP-4 inhibitor, was well tolerated in phase 3 clinical trials, with minor gastrointestinal complaints and nasopharyngitis the most common adverse events. Both sitagliptin and vildagliptin, lowered blood glucose and HbA1c in monotherapy, but were not as potent as metformin alone in head-to-head studies.⁶⁻⁸ In contrast, addition of sitagliptin to patients not achieving adequate control on metformin or thiazolidinediones brought significant improvements in HbA1c and a greater proportion of subjects reached an HbA1c less than 7%.⁹ Moreover, in a head-to-head 52-week study of sitagliptin vs. glipizide, no significant differences in end-of-study HbA1c were noted; however, glipizide led to more hypoglycemic events and weight gain (2.4 kg). More recent data suggest that sitagliptin in combination with metformin for initial T2DM treatment results in significantly more subjects achieving target HbA1c levels than monotherapy. Sitagliptin 100 mg daily was approved for T2DM treatment.

Future Directions and Unanswered Questions

The clinical availability of two new agents that mimic and/or potentiate incretin action raises several important questions. We clearly need long-term studies of the safety and efficacy of GLP-1R agonists and DPP-4 inhibitors. Whether these agents bring about a sustained improvement

of beta-cell function more effectively than can be obtained with currently available anti-diabetic agents is unclear. Moreover, exenatide and sitagliptin have not been studied head-to-head, and the efficacy of both on diabetes prevention is unknown. Furthermore, given that GLP-1 receptors are expressed in the cardiovascular system, it is important to determine if using either of these agents reduces cardiovascular events in diabetic subjects. Clinicians also need to understand whether sitagliptin exhibits additive benefits when used with exenatide, particularly in subjects already receiving sitagliptin who are not yet achieving adequate glycemic control. Hence, the initial clinical success of these agents mandates the design of additional carefully designed clinical trials that will provide evidence-based guidance to patients and clinicians who seek to use incretin-based therapy optimally to manage T2DM.

From the Clinician Perspective:

- GLP-1 analogs/agonists enhance satiety causing weight loss, suppress glucagon, and regulate gastric emptying—novel mechanisms of action for anti-diabetic drugs.
- The incretin mimetic, exenatide, has a durable effect on lowering HbA1c and weight loss over 30 months.
- Nausea, the most common side effect with exenatide, tends to dissipate over the first few weeks of therapy.
- The DPP-4 inhibitor, sitagliptin, has not been found to interact with any other medication and to date has no significant side effects.
- Sitagliptin is excreted by the kidneys, so the dose must be adjusted in patients with renal insufficiency.

Although several new therapies for treating T2DM have become available over the past 15 years, less than one-third of diabetic patients achieve an HbA1c level \leq 6.5%, the glycemic goal recommended by the American College of Endocrinology.¹ Further, for patients who do achieve HbA1c $<$ 7%, only a small percentage can maintain this degree of control over the long term.² Therefore, a new therapeutic approach to managing T2DM is enthusiastically welcomed by both clinicians and patients.

The incretin mimetic, exenatide, and the more recently released DPP-4 inhibitor, sitagliptin, have received rapid acceptance by the clinical endocrinologist.

Incretin Mimetics

Exenatide is approved by the Food and Drug Administration (FDA) for use in combination with metformin, sulfonylureas, and thiazolidinediones (TZDs).³⁻⁶ Liraglutide, a GLP-1 analog, is currently in phase 3 clinical development.⁷

Currently, exenatide is being used therapeutically as a second or third (or occasionally fourth) medication in patients who have been unable to achieve adequate overall glucose control or in patients who have unacceptably elevated postprandial glucose levels. Although HbA1c fell about 1% in the clinical trials with the addition of ex-

natide, in those who achieved significant weight loss, the fall in HbA1c was appreciably greater, 1.7%.⁸

Exenatide is also useful in the well-controlled T2DM patient who is overweight or obese and continues to gain weight while on oral therapy. In this situation, exenatide is usually substituted for one of the patient's other oral anti-diabetic drugs. Improved diabetes control—with the likelihood of weight loss, as opposed to weight gain as seen with most other diabetes treatments—makes this a popular therapy.

Currently, exenatide is not indicated for monotherapy by the FDA, although an approvable letter for monotherapy indication was issued at initial drug approval. Treating overweight diabetic patients soon after disease onset might become very popular if the FDA approves monotherapy. In patients with relatively mild diabetes (HbA1c < 7.0%), this could potentially result in near normal blood glucose levels and probable weight loss. One important benefit of exenatide is its durability of effect. Studies up to 30 months in duration have shown a persistent 1.1% lowering of HbA1c and a maintained weight loss of 11–12 pounds in patients continuing in open label extension studies.

Also, exenatide does not have an indication for use in combination with insulin. Potentially, this combination could greatly enhance diabetes control by significantly lowering postprandial glucose levels and decreasing food intake.

Nonetheless, there are several drawbacks to exenatide use. Patients often object to initiating an injectable therapy. However, the likelihood of weight loss usually obviates that barrier. Approximately one-third of patients experience nausea when exenatide therapy is initiated, but this is usually mild to moderate, tends to diminish over the first 2–3 weeks of treatment, and tends to be lessened if the patient takes the injection just before meals. Most patients ultimately tolerate the medication well, and in the initial trials, only 3% of patients discontinued treatment because of nausea.^{3–5}

In combination with sulfonylureas, exenatide use has been associated with hypoglycemia. In trials, this has been mild to moderate and only one patient required assistance to treat it.^{3, 5} Reducing the sulfonylurea dose when initiating exenatide should be considered.

Whereas exenatide has a profound effect on postprandial glucose levels, its action on fasting blood sugar levels is modest. In 30-week trials, patients receiving exenatide 10 µg twice daily had a 10 mg/dL decline in fasting blood sugar compared to baseline and a 16–25 mg/dL decline in fasting glucose levels compared to placebo-treated patients. The smaller effect on fasting blood sugar might

be related to its relatively short duration of action. Studies with a once-weekly preparation, exenatide LAR, showed a 50 mg/dL fall in fasting blood glucose and a 2% drop in HbA1c after 15 weeks of therapy.⁹

DPP-4 Inhibitors

Sitagliptin, the first selective inhibitor of DPP-4, is FDA approved for use as monotherapy or in combination with the TZDs or metformin.¹⁰ (Vildagliptin, another DPP-4 inhibitor, is currently undergoing FDA review.¹¹) Sitagliptin is a once-a-day therapy with few or no side effects, no significant adverse reactions, and without interaction with other medications.¹⁰ The drug requires no dosage titration except in cases with renal insufficiency.

Whereas metformin and TZDs are contraindicated in patients with significant liver disease and are of limited use in patients with congestive heart failure, sitagliptin

is not. Metformin is contraindicated in patients with decreased renal function whereas sitagliptin only needs to be reduced in dose. Further, DPP-4 inhibitors do not cause hypoglycemia, whereas insulin secretagogues—such as sulfonylureas—can.

In elderly patients and others with relatively mild hyperglycemia, sitagliptin is an excellent monotherapy choice. It is also useful as initial or add-on therapy in patients with renal

insufficiency, liver disease, or congestive heart failure.

In combination therapy, addition of sitagliptin to metformin and/or TZDs results in improved control without risk of hypoglycemia or additional weight gain. Sitagliptin might also be worth considering for patients unable to tolerate or unwilling to be treated by injection with exenatide. Currently, sitagliptin does not have FDA approval for treatment with insulin secretagogues or insulin.

Sitagliptin and other DPP-4 inhibitors under investigation appear to be somewhat less potent than sulfonylureas or metformin. As has been noted with other oral therapies, the reduction in HbA1c with DPP-4 inhibitors is proportional to its elevation. The higher the HbA1c initially, the greater its absolute fall with therapy.

Sitagliptin is excreted primarily by the kidneys, and there is no significant metabolism of the drug by the liver. Gastrointestinal tolerance of the drug was similar to placebo. Since the DPP-4 enzyme has other significant actions besides inactivation of GLP-1 and GIP, and because DPP-4 inhibitors have had only limited clinical exposure, concern remains that untoward effects might eventually become apparent.

GLP-1 analogs/agonists share similar mechanisms of

“Exenatide is also useful in the well-controlled diabetic patient who is overweight or obese and continues to gain weight while on oral therapy.”

action: enhanced satiety, weight loss, and glucagon suppression. These mechanisms of action for controlling diabetes are unique. A trial of therapy with a GLP-1 analog/agonist might be very useful in both well-controlled T2DM patients and in poorly controlled patients prior to initiation of insulin therapy. DPP-4 inhibitors could also be very useful in similar circumstances. Although not currently indicated, both therapies may be very effective in combination with insulin or one another. Understanding these other uses will have to await the outcome of current and future studies. ■

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Endocrine News staff would like to thank Drs. Ellen Seely and Alan Schneyer, co-chairs of the RAC and co-editors of the tri-points, for their dedication in developing this series for our readers.

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Endocrine Society Members Who Have Made Major Contributions to the Field of GLP-1 Actions and DPP-IV Inhibitor Activity.

Tri-point Authors

Daniel J. Drucker, M.D., is Professor of Medicine and Director of the Banting and Best Diabetes Centre at the University of Toronto and a Staff Scientist at the Samuel Lunenfeld Research Institute, Mt. Sinai Hospital. While a research fellow working with Joel Habener in 1986, Dr. Drucker was a member of a team that discovered the actions of GLP-1. Dr. Drucker subsequently went on to clone and characterize exendin-4, now currently being used for the treatment of type 2 diabetes. The Drucker laboratory has defined the physiological actions of GLP-1 through generation and analysis of a series of GLP-1 receptor knockout mice. Dr. Drucker and his team have also studied the mechanisms of action of GLP-1 on islet beta cells and most recently defined the genetic determinants important for the glucoregulatory actions of the DPP-4 inhibitors.

Joel F. Habener, M.D., is Professor of Medicine at the Harvard Medical School and Associate Physician at the Massachusetts General Hospital. He is the Director of the Laboratory of Molecular Endocrinology in the Department of Medicine at the hospital. His research interests include the fields of obesity and diabetes, with a focus on the interactions of growth factors and morphogens on the expression of transcription factors during pancreas development, as well as the regulation of hormone production by the endocrine pancreas. He has authored more than 400 research articles, books, and reviews on these subjects. He has received several awards, including the Robert H. Williams Distinguished Leadership Award by the Endocrine Society in 1999.

Other Distinguished Members

John Dupré, M.D., B.M., B.Ch., F.R.C.P., F.A.C.P., Emeritus Member of The Endocrine Society, works at Roberts Research in London, Ontario, Canada. Among his

many achievements, Dr. Dupré discovered glycaemic effects of short- and long-acting GLP-1 agonists in type 1 diabetes, which are clearly independent of stimulation of insulin secretion. He has published several articles in the *Journal of Endocrinology*, *The Journal of Clinical Investigation*, *Diabetes*, and *Diabetes Care*, on endocrine and metabolic effects of GLP-1, secretin, pancreozymin, and gastrin. Dr. Dupré has demonstrated that subcutaneous GLP-1 or exendin-4 can improve glucose control in type 1 diabetes without adverse effects when self-administered before meals with usual insulin during established intensive insulin treatment programs.

Svetlana Mojssov, Ph.D., is a Research Associate Professor in the Laboratory of Cellular Physiology and Immunology at the Rockefeller University in New York. Dr. Mojssov participated in the early studies of the discovery of the insulinotropic properties of GLP-1. She was also involved in identifying two kinds of mechanisms that allow dendritic cells to induce tolerance. She is currently investigating these mechanisms in the context of autoimmunity, beginning with insulin-dependent diabetes mellitus. Dr. Mojssov has published several articles on GLP-1 in *Endocrinology* and *The Journal of Clinical Investigation*.

Michael A. Nauck, M.D., Ph.D., is the Professor of Medicine at the Diabetes Center in Bad Lauterberg, Germany. Dr. Nauck studies pathophysiology of the incretin system in T2DM and has published several articles in *Diabetes Care*. He recently published an article reporting a 52-week study comparing sitagliptin (100 mg once daily) to glipizide (a sulfonylurea) added to an ongoing metformin treatment regimen in T2DM patients. Whereas the reduction in HbA1c was identical, sulfonylurea treatment caused weight gain and hypoglycemia. This highlights specific differences in the outcome of treatment between the novel DPP-4 inhibitor sitagliptin and more traditional insulinotropic drugs.



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