EASD – Novo Nordisk Foundation Diabetes Prize For Excellence

2019

Professor
Daniel J. Drucker

EASD–
Novo Nordisk Foundation
Diabetes Prize for Excellence

The Prize is awarded to an international researcher for outstanding scientific contributions that have increased our knowledge of diabetes.

The EASD–Novo Nordisk Foundation Diabetes Prize for Excellence is being awarded to recognize outstanding research or technology contributions to the understanding of diabetes, its disease mechanisms or its complications.

The Prize is awarded annually to an internationally recognized researcher whose research may focus on prevention, treatment and/or basic research in physiological biochemistry. The research may also be clinically oriented.

In addition, the Prize may be awarded for the “discovery of the decade” within diabetes research.

Established in 2015, the Prize is awarded in collaboration between the European Association for the Study of Diabetes (EASD) and the Novo Nordisk Foundation. It is accompanied by DKK 6 million – of which DKK 1 million is a personal award and the remaining DKK 5 million is for research purposes.

A special prize committee appointed by the EASD decides the Prize recipient, and the Novo Nordisk Foundation donates the funds accompanying the Prize. Employees of universities, hospitals or other non-profit institutions are considered for the Prize.

Candidates must be highly renowned and may be of any nationality. The Prize is conferred at the EASD Annual Meeting at which the Prize recipient is invited to give a lecture.

Nomination of
Daniel J. Drucker

The 2019 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence is being awarded to Professor Daniel J. Drucker.

By David R. Matthews, President, EASD and Stephen O'Rahilly, Committee Chairperson

Canadian physician-scientist at the Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital in Toronto and a Professor of Medicine at the University of Toronto. He is universally recognized for his meritorious work on the physiology and pharmacology of glucagon-like peptides and their use for benefiting patients. Dr. Drucker earned an MD in Medicine from the University of Toronto in 1980 and completed his residency at Johns Hopkins Hospital, the University of Toronto and Massachusetts General Hospital. He has held a professorship in internal medicine at the University of Toronto since 1987. He is, undoubtedly, an internationally renowned scientist who conducts basic and translational research of the highest quality. He has been a major figure laying the scientific groundwork for developing the DPP-4 inhibitors and GLP-1 agonists. Dr. Drucker has also played a pivotal role in identifying cardiovascular mechanisms of action for incretin agents, including studies of heart rate, blood pressure, atherosclerosis, inflammation and cardioprotection, thus laying the scientific groundwork for the exemplary results of recent cardiovascular outcome studies. Dr. Drucker is widely identified as being the leading expert in delineating the underlying mechanisms linking GLP-1 receptor activation to cardioprotection.

He discovered that GLP-2 was an intestinal trophic hormone and developed the GLP-2 analogue teduglutide as an effective and licensed treatment of short-bowel syndrome. His mechanistic dissection of the compartment-specific roles of DPP-4 action for control of metabolism (Mulvihill, *Cell Metabolism* 2017) continue to illuminate how DPP-4 inhibitors work to control glycaemia and inflammation. His recent studies have demonstrated, for the first time, that DPP-4 inhibitors upregulate soluble proinflammatory DPP-4, findings that lead to important clinical ramifications (Varin et al., *Cell Metabolism* 2019).

Dr. Drucker is known for the rigour and reproducibility of his science and for his generosity. He developed and generously disseminated the GLUTag cell line, which has been a major tool for the study of entero-endocrine hormones by the international community and has provided his murine models to many external scientists. Daniel J. Drucker received the Banting Medal of the American Diabetes Association in 2014, the Harrington Prize for Innovation in Medicine of the American Society for Clinical Investigation, the Rolf Luft Award of the Karolinska Institute in 2017 and the 2012 EASD Claude Bernard Lecture. In addition, he became an Officer of the Order of Canada in 2014 and was elected to fellowship of the Royal Society in 2015. Spanning over three decades, his work has had a clear focus on the physiological role of gut hormone actions. The overarching objective of his research has been to investigate, comprehensively, the molecular mechanisms and physiological functions of the incretin system and its impact on glucose and energy homeostasis. He has been, from the start, at the forefront in this field of research, which has turned out to be a highly efficacious research path.

The important novel discoveries have had remarkable global impact on the management of people with diabetes. This field has, appropriately, become a true hot topic, and Drucker has been a major figure in driving the area forward. His publication record is both extensive and impressive, with about 350 articles published in leading high-impact journals and with high citation numbers (about 60,000, h-index 123).

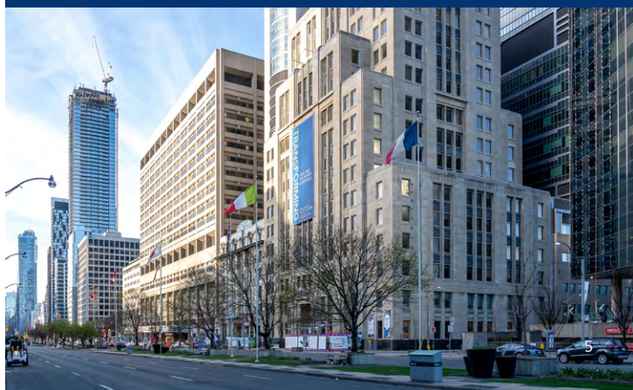
The Committee on the EASD–Novo Nordisk Foundation Diabetes Prize for Excellence is therefore privileged to announce that, during the recent Ccommittee meeting , a unanimous decision was made to award the 2019 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence to Dr. Daniel J. Drucker, a highly distinguished and stimulating speaker, who we are confident will deliver an exceptional lecture during the EASD Annual Meeting in Barcelona.

Curriculum vitae

Professor Daniel J. Drucker
Born in 1956

1980	MD, University of Toronto
1980–1987	Medical resident, Johns Hopkins Hospital and University of Toronto and postdoctoral fellow, Massachusetts General Hospital and Harvard Medical School
1987–1991	Assistant Professor, 1991–1996 Associate Professor, University of Toronto
1996	Professor of Medicine, Department of Medicine, University of Toronto and Senior Investigator, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto
2009	Clinical Investigator Award from the Endocrine Society, Washington, DC
2014	Banting Medal for Scientific Achievement from the American Diabetes Association
2015	Elected Fellow of the Royal Society of London

Daniel J. Drucker's 350 publications have been cited more than 60,000 times, and he has an h-index (Google Scholar) of 123.



Mount Sinai Hospital in Toronto »

You can't score if you don't shoot

Three decades ago, only a small number of researchers talked about gut hormones. Today, many people view these hormones as building blocks for developing new therapies to confront the obesity and diabetes epidemics that are sweeping the world. Daniel J. Drucker has studied the molecular mechanisms and physiological functions of hormones for 35 years. His studies unravelling their biological actions have led to several discoveries and the development of life-changing therapies. For his outstanding contributions, he is receiving the 2019 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence.

Everyone knows about insulin – at least by name. However, fewer people nod knowingly if you mention incretins. Although the incretin concept was established as early as 1932, incretin hormones remained obscure for more than 50 years. Daniel J. Drucker was one of the pioneers in the mid-1980s who rekindled interest in the action of incretins, principally glucagon-like peptide-1 (GLP-1). Today, the two major incretins, GLP-1 and gastric inhibitory polypeptide (GIP), have become crucial in developing new therapies for diabetes, cardiovascular diseases and obesity.

"At that time, only a few researchers, such as Joel Habener, Jens Juul Holst, Stephen Bloom and I, were interested in incretins and related gut hormones. Although I was convinced that they were important, I could not have imagined that this knowledge would be translated into multiple new therapies that help people with severe metabolic disorders today. But that's how science is. If you do enough experiments, and the science is independently validated by peers, sometimes you build a story over time and ultimately hit the translational jackpot. That scenario can be one of the most exciting rewards arising from research in the medical sciences," says Daniel J. Drucker, Professor of Medicine, University of Toronto and Senior Scientist, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada.

Today, Drucker is widely recognized for his research in the physiology and pharmacology of GLP-1 and GLP-2 – and especially his success in translating the basic science into therapies for people with obesity and diabetes by helping to develop dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists. This work is the basis for Daniel J. Drucker receiving the 2019 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence.

No room in the field

Daniel J. Drucker's family believed in working hard to achieve success in life. His parents survived the Holocaust, and this had a lasting impact not only on them but also on Daniel, who has never taken life, health and freedom for

granted. His constant motivation does reflect the gift of opportunity his parents provided for him.

“My father, Ernest, was periodically involved in inventions and patents, including solar energy, transport and constructing the modular homes of the future. His entrepreneurial spirit meant growing up in a home in which life could be fantastic, but at other times we had to move from a nice house to a small apartment because he had gone bankrupt again. So I ultimately chose a more stable career in medicine instead of a career in business.”

Daniel J. Drucker graduated in medicine from the University of Toronto in 1980 and received postgraduate training at Johns Hopkins Hospital, the University of Toronto, Massachusetts General Hospital and Harvard Medical School, where, following the advice of his mentors in Toronto, he planned to work on problems related to thyroid hormones. However, when he arrived at Harvard, he was told that there was no room for him to work on the thyroid projects in the lab.

“I was informed that thyroid research was not an option, so if I were to stay there, I had to focus on the recently cloned glucagon gene and its related hormones instead. At that time, I was not interested in that field, but I had no other options and just had to get on with it.”

A whole arsenal of incretins

Fortunately, a few years earlier a significant breakthrough had been made in the endocrinology of the digestive system. At that time, most of the interest in glucose-lowering hormones focused on insulin, with secondary importance attributed to glucagon, which raises glucose. However, in the early 1980s, when the groups of Joel Habener and Graeme Bell cloned and sequenced the genes for proglucagon, the precursor of glucagon, they got a surprise.

“The gene contained two additional glucagon-like sequences encoding two glucagon-like peptides that subsequently became known as GLP-1 and GLP-2. GLP-1 turned out to increase insulin secretion significantly, so as an endocrinologist, I quickly realized that this nascent field in which I found myself had enormous potential.”

As the researchers looked more closely, they found that the proglucagon gene is expressed in the pancreas, intestines and brain. Although the proglucagon protein produced is identical in all mammalian tissues, the profile of liberated peptides differs depending on the type of tissue. In 1987, after completing postdoctoral training, Daniel J. Drucker was appointed Assistant Professor of Medicine at the University of Toronto.

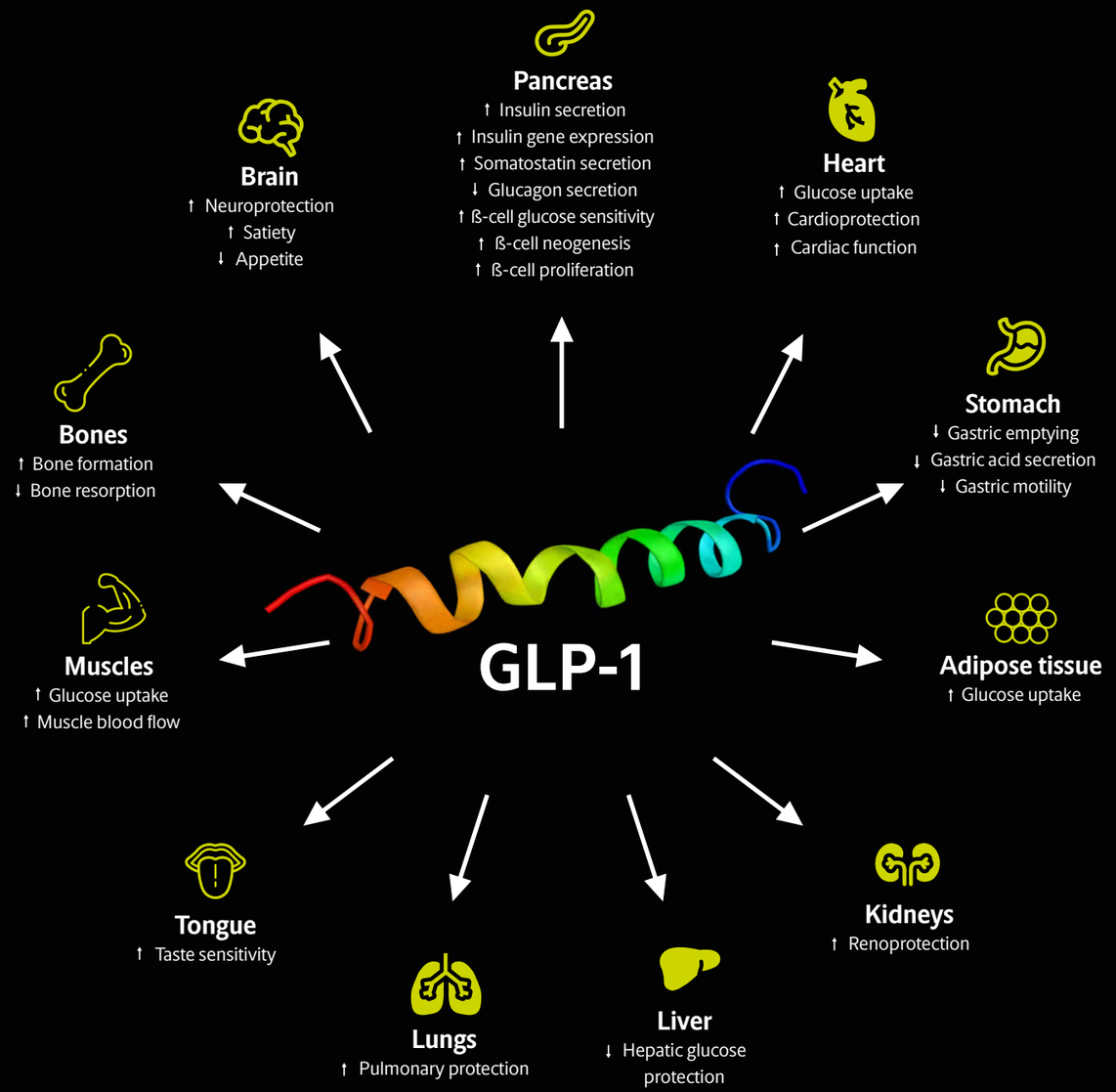
“We soon became interested in studying how GLP-1 works on our appetite and energy balance and in understanding what happens to GLP-1 action during the development of diabetes and obesity. It also became apparent that incretin receptors are expressed in multiple tissues in which incretin action was not yet clearly defined.”

A poisonous lizard helps

The researchers quickly realized the enormous potential of regulating GLP-1 and related peptide activity. However, using natural GLP-1 in therapy poses a major problem. It is not very stable and is degraded quickly by other enzymes and cleared rapidly in the body.

“This is not a problem for GLP-1 physiology in a healthy body, since GLP-1 is produced continuously. However, it needs to be much more stable for medical therapy, and there was virtually no success in developing GLP-1 therapy for many years despite its enormous potential. So even though we knew it worked, we had begun to doubt that anyone would ever crack the code of successful GLP-1 drug development.”

Help arrived more than a decade later from a somewhat unexpected quarter. At the Veterans Affairs Medical Center in the Bronx, researcher John Eng tried to develop a method for detecting new hormones. During his research, he found an interesting hormone in the venom of the Gila monster, a poisonous lizard



that lives in the southwestern United States. When he examined the venom to determine which hormones were present, he got a bit of a surprise. He discovered not only the hormone he was looking for but also a new one: exendin-4. He looked it up in a database and found that it is very similar to the human hormone GLP-1.

"The big difference was that exendin-4 is much more stable, and this was an important breakthrough in GLP-1 therapy. The pharmaceutical industry later tested and further developed synthetic exendin-4 into the drug known as exenatide. But Eng's belief, passion and thoroughness made the difference for the development of exenatide. Enthusiasts like Eng are needed to achieve key breakthroughs in research, but it is equally important that someone considers the idea and asks whether we can use this for something."

Short-bowel syndrome

Throughout his career, Daniel J. Drucker has been dedicated to translating his findings into therapies to help people. He credits both his father's interest in patents and his supervisor in Boston, Joel Habener, who both introduced him to the concept of intellectual property.

"While working in Boston, I made a very interesting discovery: GLP-1 stimulates insulin secretion and insulin biosynthesis directly in islet cells. Not long thereafter, suddenly one day when I arrived at the laboratory, my mentor, Joel Habener, had requested my notebook, containing all my experimental plans, results and data. My supervisor had become very interested in my data, and a patent had to be filed before we went further and published the work. This experience taught me that filing a patent after making an important observation in science can help lead to the development of new therapies and be critical for attracting the financial backing to develop it."

Daniel J. Drucker made another intriguing observation in 1995 while developing a new cell line for studying glucagon-like peptides. His research has always been extremely thorough, strongly focusing on how the hormones affect various parts of the body. Serendipitously, this cell line work led to the first discovery of the action of GLP-2, a hormone similar to GLP-1.

"We did not really know what GLP-2 does at that time, but we found that it is a strong growth factor that works specifically in the intestine."

With his background in medicine, Drucker knew the symptoms of short-bowel syndrome, in which people's small intestines are so short that they have difficulty in absorbing fluids and food. Many of these people need hours of life-sustaining intravenous infusions every day and have difficulty in living a normal life, since they cannot eat normally or travel very far away from home.

"We examined the effect of GLP-2, first in animals and later studies were done in humans, and found that it can restore enough functional intestine to make a difference. With the help of a local biotechnology company, we managed to develop this into a therapy so that, today, people with short-bowel syndrome only need to inject it once a day. Many of these individuals can markedly reduce or even discontinue the fluid infusions, helping them to live a near-normal life. Magical moments like this enable researchers to live with our many negative or disappointing results in research, but you can't score if you don't shoot and you need to take multiple shots at the goal."

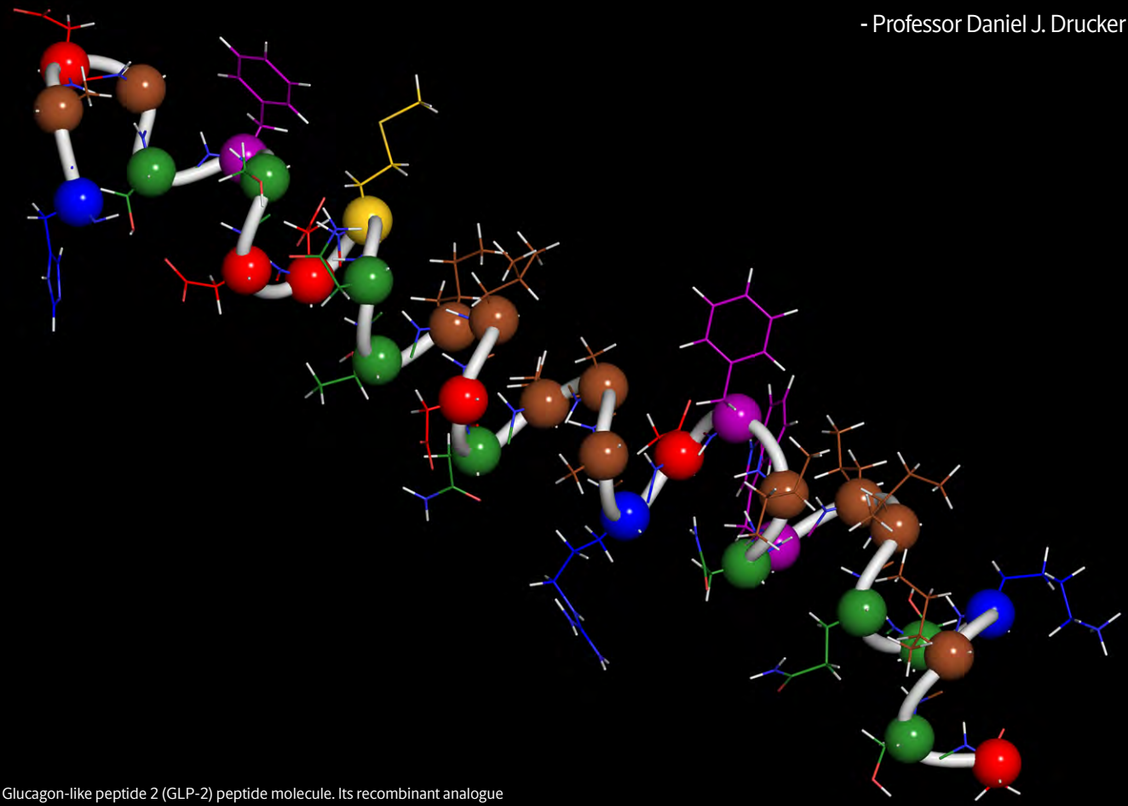
Protecting the heart

Incretins gradually took off, as more stable variants of GLP-1 emerged. The research by Daniel J. Drucker and his colleagues therefore changed from being somewhat exotic to being a centre of attention for pharmaceutical research and clinical investigation. Drucker's research was key to this trend. He showed that GLP-1 stimulates insulin secretion, cloned complementary DNA (cDNAs) for GLP-1 in the gut and brain, cloned the lizard cDNAs encoding exendin-4, developed a cell line for studying GLP-1 production and created mouse lines that did not have GLP-1 receptors.

"What caught my attention early on, however, beyond understanding how GLP-1 controls glucose, was the importance of understanding how it is

"Magical moments like this enable researchers to live with our many negative or disappointing results in research, but you can't score if you don't shoot and you need to take multiple shots at the goal."

- Professor Daniel J. Drucker



Glucagon-like peptide 2 (GLP-2) peptide molecule. Its recombinant analogue teduglutide is used to treat short-bowel syndrome, an orphan disease.

produced and functions at various sites in the body. There are incredibly large differences in how GLP-1 works in many tissues. Attempting to understand how GLP-1 works in various tissues made us realize how large and complex this field of biology is."

One advantage Daniel J. Drucker had was that he worked at a large academic medical centre with many skilled researchers, including cardiologists. Together with colleagues, his studies showed that GLP-1 proved to have yet another benefit that may turn out to be as important as its effects on diabetes and weight loss.

"We realized that GLP-1 can inhibit the development of experimental heart disease, and we therefore set out to understand the underlying mechanisms. It turned out that activating the receptor for GLP-1 strongly protects the heart." Drucker conducted comprehensive studies of heart rate, blood pressure, arteriosclerosis, cardiac ischaemia, blood flow and inflammation in the early 2000s that clarified the scientific basis for how incretins protect the heart.

"Although many of the new GLP-1-based medicines were known to be effective in reducing blood glucose or body weight, the positive cardiovascular effect, evident in large human trials, has surprised us all. The medicines reduce the number of heart attacks and strokes and decrease cardiovascular death. GLP-1 therapy seems to address inflammation, diabetes, obesity and cardiovascular complications, providing many reasons to use these GLP-1-based medicines."

Unexpected links between the incretin system and inflammation

In seeking to understand the dynamics of incretins, Daniel J. Drucker also focused in the late 1990s on DPP-4, an enzyme that degrades incretin hormones. DPP-4 inhibitors rapidly gained attention by regulating both insulin and glucagon concentrations in animals and people with type 2 diabetes. DPP-4 turned out to have a very close and interesting connection to the incretins, and Drucker's group, working with DPP-4 knockout mice and DPP-4 inhibitors, immediately saw the potential and tried to understand how the enzyme worked.

"DPP-4 was shown to be a key regulator of GIP, GLP-1 and GLP-2 by cleaving and inactivating these hormones. We and other colleagues quickly identified DPP-4 as a key to controlling the degradation of gut incretin hormones responsible for glucose control. Soon the pharmaceutical industry developed a series of DPP-4 inhibitors for treating people with type 2 diabetes."

Not surprisingly, by inhibiting DPP-4, the researchers could enhance the effect of incretins: for example, potentiating GLP-1 and GIP activity in people with type 2 diabetes. However, DPP-4 has a much more complex biology beyond glucose control and is widely distributed in various types of tissues.

"DPP-4 exercises its biological effects through multiple mechanisms. First, it is localized to cell membranes and both signals inside the cells and functions as a critical molecule for inactivating multiple proteins. However, DPP-4 also exists in a soluble form and has signalling functions at many sites in the body. For example, DPP-4 strongly affects our immune system and can act independently of its classical enzyme activity."

DPP-4 is therefore another key link discovered by researchers related to the increasingly clear connections between the immune system, inflammation in the body and diseases such as obesity, type 2 diabetes and cardiovascular diseases.

"Our most recent studies have shown that DPP-4 inhibitors can upregulate soluble DPP-4 and potentially modify inflammation in many types of tissues. This finding may prove to have many important clinical implications, and we hope to understand the importance of this finding in animals and humans."

Keep the pyramid from turning into sand

Daniel J. Drucker's work with GLP-1 and DPP-4 for diabetes, GLP-1 for obesity and heart disease and GLP-2 and short-bowel syndrome has led to new therapies at a higher success rate than the usual in science.

"I usually describe research as having good days interspersed with bad months, with real magic arising on rare occasions, often many years apart. Then, if we are really lucky, working with many colleagues in universities and companies, collectively we can transform this magic into a new therapy that can help people. Most of the time, researchers do not succeed to develop medicines and I would describe our success as being unbelievably lucky to be in the right place at the right time, allowing us to make unique observations."

Because of the increasing importance attached to understanding the scientific basis underlying these new human therapies, a few years ago Daniel J. Drucker stopped doing what he otherwise likes the most: seeing patients. Instead, he has devoted himself to searching for new even better therapies and understanding the detailed actions of peptide hormones. Today, he is more certain that these hormones play important roles in many places in the body, not only affecting blood glucose regulation but also body weight, the cardiovascular system, the immune system and the central nervous system. The science in this field is widely believed to be fundamental for the development of new therapies for metabolic disorders.

"I am sure that in the years to come, we, together with colleagues, will make more progress towards realizing the enormous potential of peptide therapy. Hopefully, this will bring more good news for people with diabetes, heart disease, liver disease and perhaps even individuals with degenerative disorders of the central nervous system, such as Parkinson's disease and Alzheimer's disease. More powerful medicines will be developed, and these will also be created in long-acting forms, which means that people with diabetes will not have to frequently monitor their blood glucose or regularly adjust the dose of their medicines. They will just need to take the medicine once a week or maybe even once a month, or a few times a year, to achieve easier, more effective and safer therapy."

Despite the enormous potential of modern science, Daniel J. Drucker believes that responsible science is best carried out carefully, not by rushing, exaggerating and publicizing new results before being completely certain of their importance and authenticity. In fact, Drucker believes that part of his success reflects the fact that, throughout his career, he has maintained very strict standards for the quality of his scientific output.

"We have to be very, very careful, to get it right. For me, the most important thing has always been to ensure that the results of my experiments can be easily replicated and to ensure that the conclusions I draw are as correct as possible. The journals always like to publish sensational 'amazing' very novel results, indirectly encouraging some researchers to emphasize aspects of their results that may actually be less robust than they would like them to be. However, I think it is incredibly important to remember that enduring science is like a pyramid. Each new research article needs to be a metaphorical brick on which others build, but if you are not careful with the quality of the bricks, the pyramid can become a sand castle that collapses far too easily."

Daniel J. Drucker is receiving the 2019 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence accompanied by DKK 6 million (€806,000) for his outstanding contributions that have increased knowledge of diabetes. His discoveries have led to several new treatments that have had remarkable global impact on the management of people with diabetes and obesity.

Previous recipients of the EASD–Novo Nordisk Foundation Diabetes Prize for Excellence

2015 Sir S. O'Rahilly, UK
2016 A. Hattersley, UK
2017 P.E. Scherer, USA
2018 Gökhan Hotamışlıgil, Turkey

The European Association for the Study of Diabetes

The European Association for the Study of Diabetes (EASD) was founded in Montecatini, Italy in 1965.

The mission of the EASD is to promote excellence in diabetes care through research and education. The aims are to encourage and support research, the rapid diffusion of acquired knowledge and to facilitate its application.

EASD membership is open to scientists, physicians, students, postdocs and fellows, allied health professionals and nurses from all over the world who are interested in the field of diabetes or related diseases. Each year, the EASD Annual Meeting brings together over 15,000 medical professionals as well as an online audience of thousands . EASD is the home of diabetes research in Europe.

The Association holds training courses and workshops to attract new talent to diabetes research and to disseminate the latest knowledge. In addition, it has established a large number of study groups focusing on different areas of diabetes research and care and has founded the journal *Diabetologia*.

In 2000, the Association created the European Foundation for the Study of Diabetes (EFSD), which operates on a non-profit basis.

The Novo Nordisk Foundation

The Novo Nordisk Foundation is an independent Danish foundation with corporate interests. Its history goes back more than 90 years.

The objectives of the Foundation are:
1) to provide a stable basis for the commercial and research activities of the companies in the Novo Group; and 2) to support scientific, humanitarian and social purposes.

Our vision is to contribute significantly to research and development that improves people's lives and the sustainability of society.

Since 2010, the Foundation has donated more than DKK 20 billion (€2.7 billion), primarily for research within biomedicine and biotechnology and diabetes treatment at universities and hospitals in Denmark and the other Nordic countries. The Foundation supports the entire research chain – from education to innovation.

In addition to awarding grants, the Foundation annually awards several honorary prizes to recognize and reward individuals for their unique efforts in research, teaching or other efforts relevant to research.

Novo Nordisk Foundation

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