Press release
January 8, 2025

In the Biology and Biomedicine category

The Frontiers of Knowledge Award goes to the four researchers who laid the biological foundations for the revolutionary new treatments in diabetes and obesity

- **The work done by Daniel Drucker, Joel Habener, Jens Holst and Svetlana Mojsov** uncovered the biological function of the GLP-1 hormone, with an essential role in both the maintenance of glucose levels and the regulation of appetite

- **Their discoveries have spurred development of a new generation of drugs** that are effective both for the treatment of type 2 diabetes and for achieving substantial weight loss in obese patients while reducing their vulnerability to cardiovascular problems

- **Treatments based on the GLP-1 hormone have also shown exciting potential** to combat neurodegenerative conditions, like Parkinson's and Alzheimer's, and addiction disorders, with studies now under way to gauge their effectiveness

The BBVA Foundation Frontiers of Knowledge Award in Biology and Biomedicine has gone in this seventeenth edition to Daniel Joshua Drucker (Mount Sinai Hospital, Toronto, Canada), Joel Habener (Harvard University, United States), Jens Juul Holst (University of Copenhagen, Denmark) and Svetlana Mojsov (The Rockefeller University, United States) for fundamental biological discoveries that have driven the development of new generation drugs against diabetes and obesity.

The combined work of the four laureates elucidated the biological function of the hormone known as GLP-1, produced in the small intestine after food intake, and playing a fundamental role in both the maintenance of glucose levels and the regulation of appetite. "These findings have been exploited to develop novel therapeutics for treating type 2 diabetes and obesity," in the words of the committee deciding the award.

"The awardees' discoveries laid the biological foundations for what is nothing less than a

January 8, 2025

pharmacological revolution. Their work has mapped the pathway to a new generation of drugs that are effective both to treat diabetes and to achieve significant weight loss in obesity sufferers while helping to combat the cardiovascular problems associated with this disease," said committee member Dario Alessi, Director of the MRC Protein Phosphorylation and Ubiquitylation Unit at the University of Dundee (United Kingdom).

Not only that, treatments based on the GLP-1 hormone have shown exciting therapeutic potential in neurological conditions, like Parkinson's and Alzheimer's, and addiction disorders, with studies now underway to gauge their effectiveness.

In the exploration of the biological roots of obesity, the laureates' findings intersect with the insights of Douglas Coleman and Jeffrey Friedman on the role of another hormone, leptin, in regulating appetite and body weight, distinguished in 2013 with the 5th Frontiers of Knowledge Award in Biomedicine.

The discovery of a fundamental hormone

In the 1980s, three scientists at Massachusetts General Hospital in Boston set out to explore the potential of the newly discovered hormones known as glucagon-like peptides. When Joel Habener succeeded in cloning the gene that coded for these hormones, Svetlana Mojsov, then working in another lab in the same hospital, began looking at their chemical properties to determine which of their forms might have biological activity in living beings. She managed to identify and synthesize one such form, the GLP-1 peptide, and to show that, in small quantities, it stimulated insulin production in the pancreas of rats.

At the same time Daniel Drucker, a postdoctoral fellow in Habener's laboratory, was striving to get a more precise handle on the function of GLP-1. After multiple experiments, he finally deduced that insulin production only occurred in very short forms of the peptide, and only when blood sugar levels were high.

Meanwhile, in Copenhagen, Jens Juul Holst was examining how gut hormones were able to stimulate insulin secretion. He knew from his experience as a surgeon that the blood sugar levels of some patients could fall dangerously low after their time in the operating theater, causing hypoglycemia. It seemed clear that the reason for this was the gut overstimulating insulin production, but the question remained as to what was triggering the process.

January 8, 2025

Holst made this the subject of his PhD thesis, and in the early 1980s, together with his team, made the independent discovery that GLP-1 stimulated insulin release in the pancreas. Although other hormones were known to perform this function, what the team observed was that GLP-1 also inhibited production of glucagon, a hormone secreted by the pancreas that increases levels of sugar in the blood. It was this second property that drew their attention, as it was precisely the effect sought in type 2 diabetes patients, and they immediately got to work on exploring its potential as a therapeutic agent. "We did this seminal study administering GLP-1 via blood infusion to type 2 diabetes patients, and found that in four hours we could lower glucose to completely normal levels. It was a real turning point," the awardee recalls.

Encouraged by these experimental results, they launched a large-scale clinical trial – published by *The Lancet* in 2002 – in which, over a six-week period, they replaced insulin with GLP-1 in the drug infusion pumps used daily by diabetes patients. "The results were remarkable," Holst says today. "Not only did we almost cure diabetes, but in those six weeks our patients lost weight, and all of this without side effects." In 2005 the first GLP-1 drug was approved for the treatment of type 2 diabetes, and several more have followed based on the same underlying principles.

From bench to bedside: effective drugs for diabetic and obese patients

The weight loss Holst had observed in his experiment was more than fortuitous. In 1996, Drucker had found that GLP-1 suppressed appetite in the animals to which it was administered and led them to shed weight. In parallel, Holst was able to confirm the satiating effect of GLP-1 in human subjects, paving the way for the 2014 approval of the first anti-obesity drug based on the peptide.

In the past two decades, GLP-1 has marked a game-changing advance in the treatment of both type 2 diabetes and obesity. Various diabetes treatments were already in use, but the advantage of GLP-1 was that it only stimulated insulin production when blood sugar levels were high, dramatically reducing the risk of them dropping below the safe limit. For the first time, patients were freed of the need to continually measure their blood sugar, since the drug itself would regulate its level.

In addition, being overweight can worsen outcomes with type 2 diabetes. Yet most previous treatments caused weight gain, diminishing their overall effectiveness. With GLP-1, this side effect not only disappears, but the drug actually helps patients lose weight, providing a two-way improvement in the disease prognosis. Recently, moreover, these new medications have been observed to reduce the risk of other complications of type 2 diabetes, including blindness, kidney

January 8, 2025

disease and heart attacks.

On the obesity score, they have achieved first-time reductions in body mass ranging from 15% to 20%, beyond anything witnessed with existing treatments. And, as with diabetes, GLP-1 drugs also reduce obesity-related risks, among them cardiovascular disease.

Exciting potential for the treatment of neurodegenerative and addiction disorders

The committee stressed that the impact of the four scientists' fundamental discoveries is not confined to the development of novel therapeutics for diabetes and obesity. They have also spawned a new research field exploring their treatment potential for other disorders like degenerative diseases and addictions. Indeed right now, as Mojsov states, "the pharmacological use of GLP-1 analogs for treatments of addiction and neurological disorders are being evaluated in clinical trials."

GLP-1 based treatments have also been shown to have a powerful anti-inflammatory effect, and as such hold out considerable promise in neurodegenerative conditions. Drucker is currently exploring this avenue with his team at Mount Sinai Hospital in Toronto. "We are taking an in-depth look at the drugs' effects against inflammation processes, a line of research that I am particularly excited about. We want to understand this mechanism to see, for example, whether it could be effective in reducing inflammation in the brain as a way to combat Alzheimer's disease. The science here holds great promise and we have a large number of trials underway studying whether GLP-1 medicines will be potentially useful in these conditions. I'm really looking forward to the results."

Holst believes that GLP-1 drugs may find use in treating drug addiction disorders, since "they have quite a pronounced effect on the reward center in the brain." So "just as these treatments inhibit food reward as a means to suppress appetite and achieve weight loss, they might also serve to reduce dependence on alcohol and other addictive substances."

Says Drucker, "what I'm most excited about going forward are new innovations in the field that will bring GLP-1 drugs to many millions of people who currently can't access these medicines, enabling the health benefits to be extended not just to rich countries that can afford them, but to people all over the world."

Laureate bio notes

January 8, 2025

Daniel Joshua Drucker (Montreal, Quebec, Canada, 1956) completed his MD at the University of Toronto in 1980. After working at the Johns Hopkins Hospital and Massachusetts General Hospital, in 1987 he took up simultaneous appointments at the University of Toronto and Toronto General Hospital, combining teaching and research as he continues to do today. Currently a University Professor at the University of Toronto and Senior Scientist at the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital in the same city, he has participated in more than 60 peer-reviewed research projects and serves on the editorial boards of the *Journal of the Endocrine Society, Molecular Metabolism* and *Cell Metabolism*, and as Consulting Editor of *Diabetes*. Drucker is the holder or co-holder of some thirty patents in the United States alone, and has authored more than 300 publications in scientific journals.

Joel Habener (Indianapolis, Indiana, United States, 1937) received his MD from the University of California, Los Angeles in 1965. After two years at the Johns Hopkins Hospital, he worked for the National Institutes of Health in Bethesda (1967-1969) before moving to Massachusetts General Hospital (MGH), where he remains to this day, combining his work as Physician Investigator with the leadership (since 1979) of the Laboratory of Molecular Endocrinology. He has also held a professorship of medicine at Harvard Medical School since 1989. Habener was a Howard Hughes Medical Institute investigator from 1976 and 2006. He sits on the editorial boards of several scientific journals and has served on numerous advisory committees for pharmaceutical companies and the National Institutes of Health.

Jens Juul Holst (Copenhagen, Denmark, 1945) received an MSc in Medical Sciences from the University of Copenhagen, where he went on to earn a PhD in the same subject in 1978. Professor of Biomedical Sciences at the University of Copenhagen since 1996, he also spent ten years (2010-2020) as Scientific Director of the Novo Nordisk Foundation Center for Basic Metabolic Research - based at the same university - where he is currently a Senior Group Leader. He heads the research cluster on Endocrinology and Metabolism in the Faculty of Health Sciences and from 1995 to 2002 was Vice-Chairman of the Biotechnology Center for Signal Peptides. He is co-founder of the startups Antag Therapeutics and Bainan Biotech and author of over 2,000 publications, almost 1700 of them in PubMed. A former visiting professor at Guangdong Pharmaceutical University (China), he currently gives more than 30 presentations a year across the Americas, Asia and Europe.

Svetlana Mojsov (Skopje, North Macedonia, 1947), now an American national, graduated with a BS in Physical Chemistry from the University of Belgrade (Serbia) in 1971, then went on to complete a PhD in Biochemistry seven years later at The Rockefeller University (New York). After doing postdoctoral research at the same center, in 1983 she took up a position in the Endocrine Unit and as an Assistant in Biochemistry at Massachusetts General Hospital, where she also headed the

January 8, 2025

Howard Hughes Medical Institute peptide synthesis facility, at the same time working as an Instructor in Medicine at Harvard Medical School. In 1990 she returned to The Rockefeller University, where he has held the position of Research Associate Professor since 2002. Mojsov's research has resulted in five patents, four of which she obtained after Massachusetts General Hospital amended an initial registration that failed to recognize her contribution.

Nominators

A total of 157 nominations were received in this edition. The awardee researchers were nominated by Rikardo Bueno Zabalo, Director General of the Basque Research & Technology Alliance (Spain); Meric S. Gertler, President of the University of Toronto (Canada), on behalf of this institution; Anne-Claude Gingras, Director of the Lunenfeld-Tanenbaum Research Institute and Vice President of Research of Sinai Health (Toronto, Canada) and Bente Merete Stallknecht, Dean of the Faculty of Health and Medical Sciences at the University of Copenhagen (Denmark).

Biology and Biomedicine committee and evaluation support panel

The committee in this category was chaired by **Ali Shilatifard**, Robert Francis Furchgott Professor of Biochemistry and Pediatrics at Northwestern University (Chicago, United States). The secretary was **Óscar Marín**, Professor of Neuroscience and Director of the Centre for Developmental Neurobiology at King's College London (United Kingdom). Remaining members were **Dario Alessi**, Director of the MRC Protein Phosphorylation and Ubiquitylation Unit at the University of Dundee (United Kingdom); **María José Alonso,** Professor of Biopharmaceutics and Pharmaceutical Technology at the University of Santiago de Compostela (Spain); **Lélia Delamarre**, Director and Distinguished Scientist in the Department of Cancer Immunology at Genentech (United States); **Robin Lovell-Badge**, Principal Group Leader and Head of the Laboratory of Stem Cell Biology and Developmental Genetics at the Francis Crick Institute (London, United Kingdom); **Ursula Ravens**, Professor Emerita in the Carl Gustav Carus School of Medicine at the Technical University of Dresden and Guest Scientist in the Institute of Experimental Cardiovascular Medicine at the University of Freiburg (Germany); and **Bruce Whitelaw**, Director of the Roslin Institute and Professor of Animal Biotechnology in the Royal (Dick) School of Veterinary Studies (RDSVS) at the University of Edinburgh (United Kingdom).

January 8, 2025

The **evaluation support panel** was coordinated by **Elena Cartea**, Deputy Vice-President for Scientific-Technical Areas at the Spanish National Research Council (CSIC), and **José M. Mato**, General Director of CIC bioGUNE and CIC biomaGUNE, and formed by: **Edurne Berra**, CIC BioGUNE Associate Principal Investigator in the Hypoxia Lab; **Arkaitz Carracedo**, CIC bioGUNE Principal Investigator in the Cancer Lab; **Dolores González Pacanowska**, Research Professor at the Lopez Neyra Institute of Parasitology and Biomedicine (IPBLN, CSIC); **Óscar Millet**, CIC bioGUNE Principal Investigator in the Precision Medicine and Metabolism Lab; **Jordi Pérez-Tur**, Coordinator of CSIC's LIFE Global Area and Scientific Researcher at the Institute of Biomedicine of Valencia (IBV, CSIC); **Liset M. de la Prida**, Research Professor at the Cajal Institute (IC, CSIC); **James D. Sutherland**, CIC BioGUNE Associate Principal Investigator in the Developmental Biology Lab; and **Isabel Varela Nieto**, Research Professor at the Sols-Morreale Biomedical Research Institute (IIBM, CSIC-UAM).

About the BBVA Foundation Frontiers of Knowledge Awards

The BBVA Foundation centers its activity on the promotion of world-class scientific research and cultural creation, and the recognition of talent.

The BBVA Foundation Frontiers of Knowledge Awards, funded with 400,000 euros in each of their eight categories, recognize and reward contributions of singular impact in science, technology, humanities and music, privileging those that significantly enlarge the stock of knowledge in a discipline, open up new fields, or build bridges between disciplinary areas. The goal of the awards, established in 2008, is to celebrate and promote the value of knowledge as a global public good, the best instrument we have to confront the great challenges of our time and expand individual worldviews. Their eight categories address the knowledge map of the 21st century, from basic knowledge to fields devoted to understanding the natural environment, by way of other, closely connected domains like biology and medicine, economics, information technologies, social sciences and the humanities, and the universal art of music.

The BBVA Foundation is aided in this endeavor by the Spanish National Research Council (CSIC), the country's premier public research organization. CSIC appoints evaluation support panels made up of leading experts in the corresponding knowledge area, who are charged with undertaking an initial assessment of candidates and drawing up a reasoned shortlist for the consideration of the award committees. CSIC is also responsible for designating each

January 8, 2025

committee's chair across the eight prize categories and participates in the selection of remaining members, helping to ensure objectivity in the recognition of innovation and scientific excellence.

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