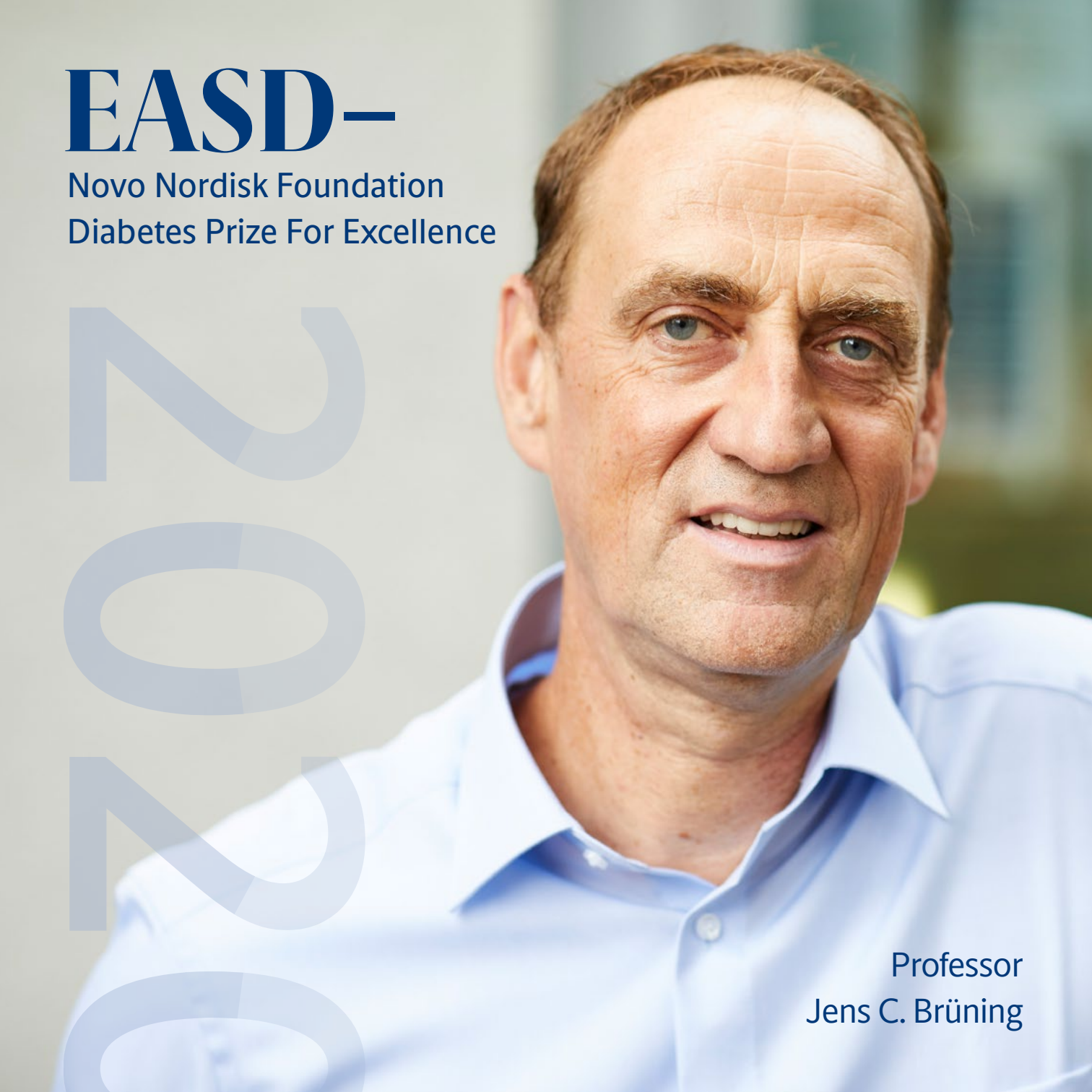
EASD–

Novo Nordisk Foundation
Diabetes Prize For Excellence

2020



Professor
Jens C. Brüning

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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 Jens C. Brüning

The 2020 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence is being awarded to Professor Jens C. Brüning

By Stefano Del Prato, President, EASD and Stephen O'Rahilly, Committee Chairperson

Jens C. Brüning is Director of the Max Planck Institute for Metabolism Research in Cologne and Professor at the Faculty of Medicine of the University of Cologne. He has been a Visiting Professor at Yale University since 2013. He started his international career as a postdoctoral fellow (1994–1997) at Joslin Diabetes Center, Harvard Medical School. He has had rapid and outstanding career development. He has systematically focused on how insulin affects the central nervous system and the role of the central nervous system in whole-body insulin resistance, a truly novel and original topic. His major scientific contributions comprise several breakthrough discoveries on the role of insulin action in the central nervous system.

He was Visiting Miller Professor at the Department of Molecular and Cell Biology of the University of California, Berkeley in 2018 and has taught a long list of successful graduate students, showing his commitment to tutoring young scientists. He has an extensive list of committee memberships and award and honours.

After training in the laboratory of Carl Ronald Kahn to use modern mouse genetics to examine various aspects of glucose and insulin metabolism, he went on to develop the first model of polygenic type 2 diabetes. His postdoctoral fellowship was very important for his scientific career and produced 14 of his approximately 175 original publications in the very top echelon of journals, such as *Nature, Journal of Biological Chemistry, Cell, Molecular and Cellular Biology, Molecular Cell, Nature Genetics, Journal of Clinical Investigation* and *Science*. This was a dream start for his scientific career, and he has been successful in maintaining this high standard in his work.

He has an h-index of 69, and his citation figure exceeds 19,000, with a rapidly raising slope since 2010, showing exceptional talent and outstanding quality. His outstanding productivity is evidenced by 27 publications between 2018 and 2020, again all in top journals, including *Nature, Nature Communications* (3), *Cell, Cell Metabolism* (2) and *Molecular Metabolism* (3) – a highly impressive achievement.

Over the past two decades, Jens C. Brüning has been a leader in using modern mouse genetics to unravel some of the most interesting and complex aspects of contemporary metabolism research. Having developed the first mouse model of polygenic type 2 diabetes, he was first to apply conditional gene targeting to the problems of diabetes and metabolism. His studies revealed that insulin resistance in muscle has a surprisingly mild effect on glucose metabolism but that insulin action has very strong effect in non-classical insulin target tissues, such as the pancreas and brain, in controlling glucose homeostasis.

This was a breakthrough in thinking and has totally changed the field. In a series of recent elegant studies, using state-of-the-art technologies in neurocircuitry mapping, his group has identified a novel obesity-associated regulator of Agouti-related peptide neurons, defined the neurocircuitry and peripheral effector mechanisms through which Agouti-related peptide neurons acutely control peripheral insulin sensitivity, defined obesity-associated impairment of brain glucose uptake as a causal factor in promoting obesity-associated systemic inflammation and unravelled the mechanism and physiological role for food perception–dependent regulation of melanocortin neurons. Finally, his group has specifically identified ceramide synthase-6-derived ceramides as a cause of obesity-induced insulin resistance and has now identified how specifically certain ceramide species contribute to lipotoxicity-induced deterioration of mitochondrial function, thus identifying new mechanistic targets for intervention in obesity-induced diabetes mellitus. His recent work has focused on the role of lipid signalling in mitochondria.

In summary, Jens C. Brüning and his team have made unique and outstanding contributions, opening new insights into the physiology of insulin action and its consequences on body glucose metabolism and obesity-associated insulin resistance. The work presents truly cutting-edge science highlighting the control of metabolism dependent on the central nervous system and its consequences in obesity. His discoveries represent breakthroughs towards opening up new avenues for understanding obesity, and there seems to be more to come. Jens C. Brüning belongs to the rarest breed of truly translational scientists who can study disease mechanisms in depth at both the cellular and animal model levels with major implementation for humans. His projects have been innovative, bold, pioneering, truly translational and successful in recognizing the challenges.

Without question, Jens C. Brüning belongs on the list of outstanding recipients of the EASD–Novo Nordisk Foundation Diabetes Prize for Excellence.

We are therefore very pleased to inform you that during the recent meeting of the committee on the EASD–Novo Nordisk Foundation Diabetes Prize for Excellence, the committee unanimously decided to award the 2020 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence to Jens C. Brüning, a highly distinguished and stimulating speaker, whom we are confident will deliver an exceptional lecture during the EASD Annual Meeting in September.

About Jens C. Brüning

2018: Paul Langerhans Medal, German Diabetes Association

2013: Outstanding Scientific Achievement Award, American Diabetes Association

2011: Director, Max Planck Institute for Metabolism Research, Cologne

2008: Minkowski Prize, EASD

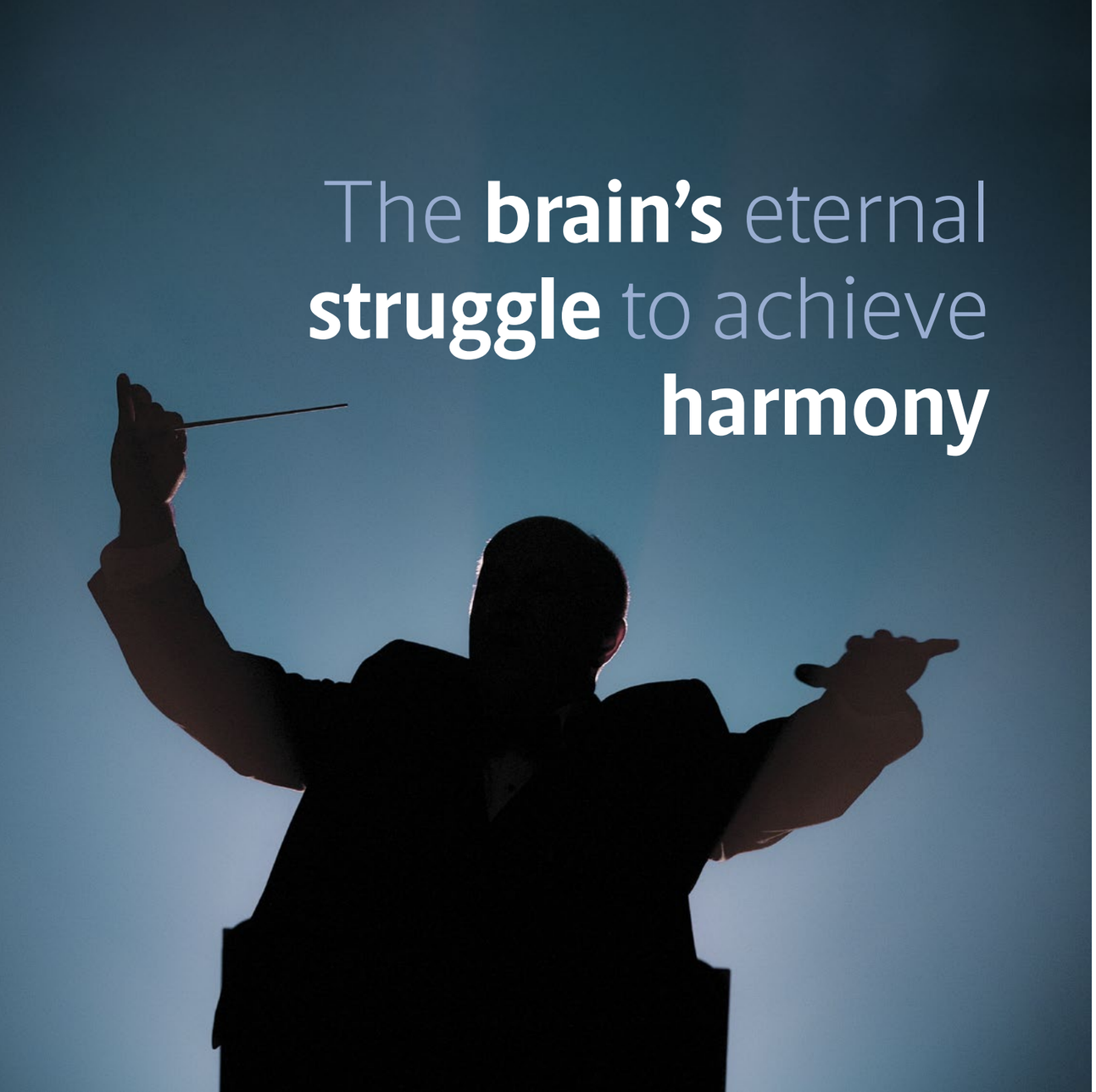
2007: Gottfried Wilhelm Leibniz Prize, German Research Foundation

2003–2011: Tenured Professor, Institute for Genetics, University of Cologne

1997–2001: Resident in Internal Medicine, University Hospital Cologne

1994–1997: Postdoctoral Fellow, Joslin Diabetes Center, Harvard Medical School

1993: Thesis (Dr.med.), University of Cologne
Jens Brüning's 175 publications have been cited almost 20,000 times.



The **brain's** eternal **struggle** to achieve **harmony**

Hunger can be one of the most urgent needs to tame. The secretion of hormones and the emission of nerve signals can be so massive that people must eventually surrender. The violent interplay between the forces of the body – especially the interaction between the stomach and the brain – has become the main focus in recent years in the struggle to understand the escalating epidemics of type 2 diabetes and obesity. Jens C. Brüning is receiving the 2020 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence for his outstanding contributions.

Like a conductor receiving input both from inside the orchestra and from the audience, the brain tries to adapt to events in various organs and to the environment. Really tuning the orchestra requires integrating all information to enable full harmony. Currently, this harmony is failing among more and more people, so the body screams for food even if it is not lacking food. This has led to explosive growth in the prevalence of obesity and type 2 diabetes in industrialized societies, but recent research has brought new hope for restoring this delicate balance.

"The overall goal of our research is to understand the basic principles of how neurons sense the nutritional signals and then adapt behaviour. We have succeeded in identifying some very crucial molecular and physiological mechanisms that fail when people develop obesity and type 2 diabetes. Understanding the molecular basis for which genetic changes are important and how metabolic disorders affect regulation has enabled us to find new goals for developing treatment related to metabolic disorders," explains Jens C. Brüning, Professor and Director of the Max Planck Institute for Metabolism Research, Cologne, Germany.

A completely different culture

Most people have no problem gaining weight. Losing weight is difficult. Many people still believe that willpower is all people need. However, the proportions of people who are overweight and who have type 2 diabetes have risen sharply in recent decades, so that every third adult is overweight globally according to WHO. Thirty years ago, when Jens C. Brüning graduated as a doctor from the University of Cologne, obesity and diabetes received far less attention.

"I finished my thesis in a completely different field, experimental haematology, investigating Hodgkin's lymphoma. Unfortunately, my experience with research was not very good since I did not think the supervision was optimal, so I planned to leave research and become a clinician."

But during the last rotation in medical school, Jens joined the Department of Endocrinology for 4 months. Here he was mentored very nicely and got really interested in the concepts and clinical questions of endocrinology and diabetes. Since a former attending physician, Professor Dirk Müller-Wieland, had worked at Joslin Diabetes Center in the laboratory of Carl Ronald Kahn, Jens was offered the same chance.

"I experienced a completely different culture in Boston. Ron Kahn is a leading figure internationally in the fields of insulin signalling and diabetes research. When I arrived, I knew very little about this field, but he was very welcoming and very open. The culture at the time in the United States was really different from what I had experienced back home. It allowed room for one's own ideas and open discussions and was clearly less hierarchical than Germany's medical system at the time. In this very stimulating environment, I quickly became fascinated with doing research."

Genetic and molecular mechanisms

Jens' entry into research proved to be a huge success, and he ended up staying from 1994 to 1997 at Joslin Diabetes Center, with as many as 14 publications in major journals such as *Nature, Science* and *Cell.* One reason for the great success was developing a polygenic mouse model to study how type 2 diabetes develops.

The level of glucose in the blood is one of the body's energy currencies. After a meal, much is absorbed into the bloodstream so it can be transported to the muscle cells that need it. The blood glucose of healthy people remains within a certain range, although it rises sharply when we eat and falls rapidly when we fast. Too much or too little glucose – as happens among people with diabetes – can lead to unconsciousness, serious permanent damage or even death.

> Insulin is the only hormone that can lower blood glucose concentrations. People with type 1 diabetes cannot produce insulin, whereas for people with type 2 diabetes, the insulin receptor is not sensitive enough."

For the vast majority of affected individuals, type 2 diabetes is not a single-gene disease. Multiple genes contribute, so mimicking and studying the human disease in mice required creating mice that did not completely lack the genes but had minor defects in the relevant genes.

"We tried to mimic this by making mice that had only one of the two copies of the insulin receptor, so they did not get very sick. Then we made mice that lacked one copy of the insulin receptor substrate gene, which are also healthy in principle, and then we crossed these two mice."

The mice did not die but became lean and highly insulin resistant, and 40% developed type 2 diabetes within 6 months. This gave researchers new understanding of the genetic and molecular mechanisms underlying type 2 diabetes and, more importantly, a method of studying it.

"By basically combining two subclinical defects in insulin signalling, many of the mice spontaneously developed an age-dependent diabetes phenotype. So this was really a polygenic mouse model of insulin resistance and diabetes."

Unconventional studies

When you knock out or inactivate the insulin receptor gene in a mouse, it dies soon after birth. So you cannot really study much in an adult mouse. By developing mice in which the insulin receptor could be inactivated in various tissues, the researchers could better understand how insulin acts in various organs.

The biochemistry textbooks at that time said that rising blood glucose concentrations cause the beta cells in the pancreas to release insulin, which then causes insulin receptors in muscle cells and fat cells to promote glucose uptake and causes the liver to suppress gluconeogenesis.

"These tissues were considered to be the major classical insulin target tissues. But if you examine where the insulin receptor is expressed, you basically find it in almost every cell. So our question was really: what is the role of insulin signalling in these unconventional target tissues, and is there more than just insulin signalling or dysregulated insulin signalling in these three classical insulin target tissues?"

By first defining what insulin can do in other tissues, Kahn and Brüning hoped to understand how this contributed to the overall clinical picture of diabetes. As they looked more closely, they wondered how metabolism is regulated by organ communication in the setting of whole-body physiology.

"Removing the insulin receptor from the liver produced the expected rising blood glucose concentration. But removing insulin signalling from skeletal muscle had surprisingly little effect on glucose metabolism. And when we examined unconventional target tissues, we were even more surprised."

Not a simple sensor

At that time, most people thought that the body's tissues – muscles, liver and pancreas – cause diabetes and other metabolic disorders. Although insulin receptors in the brain had been known for more than a decade, not much was known about the role of insulin signalling in the brain.

"The insulin receptor is clearly expressed in the brain, and some regions have more insulin receptors than the liver or adipose tissue.

> Ron would always say: the data are what they are. That was the basis to really look deeper and maybe revise ideas we previously had and then try to develop experiments based on an unexpected finding and ask questions that are off the beaten track."

We knew that adipose tissue secretes leptin in response to increased lipid storage, so we initially hypothesized that viewing leptin as a lipid sensor might make insulin a prototypical glucose sensor, communicating to the brain how much glucose is available."

However, the result differed from what they expected, leading to a paradigm shift. Lack of receptors in the brain caused the mice to eat differently, but the effect was much weaker than with leptin. Insulin receptors in the brain were far more than feeding-regulatory sensors.

"We concluded that insulin signalling in the brain seems to convey the integrated regulation of physiology. It does not solely regulate feeding but also sugar conversion in the liver, for example, so it is more an physiological regulator integrating all the information from all the various tissues and blood at a given time."

Apply or not apply?

The planned 2-year stay in the United States ended up becoming 4, so in 1997 Jens went back to Germany to continue his clinical training at the Department of Endocrinology of the University Hospital in Cologne.

"Then I added endocrinology as a subspecialty of internal medicine and became an attending physician in the Department. I was doing full-time clinical care and in parallel had built a very small research group, still pursuing basic research questions on insulin action in the brain by studying mouse models."

But in 2001, a very interesting opportunity came up. The renowned professor of genetics at the University of Cologne, Klaus Rajewsky, had retired. He had developed the technology for tissue-specific knockout mice that Jens had used. They needed a successor. The list of otherwise fully trained basic researchers included a clinician: Jens C. Brüning.

"They asked me whether I wanted to apply for this position. I like clinical practice very much, but I also like basic science very much, so I was torn as to whether to apply. Some voices advised against it: you don't have a chance, and you declare to the world that you are more interested in basic science."

The mice stopped eating

Jens ended up applying and got the position, leaving full-time clinical practice for a basic biology department. This gave him the opportunity to try to understand the neuronal basis and to identify the specific neurons that control not only feeding but also peripheral glucose metabolism – since this seemed to be the link to explore the very close association between obesity and type 2 diabetes.

"That enabled us to identify specific neurons in the hypothalamus or to clarify their function. It really showed more and more that the hypothalamus has specialized neurons that are constantly informed about the energy status of the organism and then regulate how much external energy to take in by eating or how much energy to redistribute from internal sources."

Previous studies had shown that specific neurons in the hypothalamus, called Agouti-related peptide (AgRP) neurons, which leptin targets to regulate feeding, may play an important role in feeding regulation.

"We showed that insulin inhibits these AgRP cells in the hypothalamus. So then we generated mice to determine the function of these cells, and when we killed these 3000 cells selectively in adult mice, we were really surprised that they stopped eating and eventually died."

The researchers speculated that the AgRP neurons, which were so critical for eating, could potentially also regulate glucose metabolism. So they specifically knocked out the insulin receptors in these cells.

"Indeed, we found that insulin then loses about half of its ability to suppress hepatic glucose production. That really brought us to this concept that the same neurons receive all the energy status information so that they can regulate not only feeding but peripheral glucose metabolism."

"So then we generated mice to determine the function of these cells, and when we killed these 3000 cells selectively in adult mice, we were really surprised that they stopped eating and eventually died."

Antennas of the brain

The idea that the regulatory AgRP neurons receive all the input about energy status and then try to control all aspects of physiology in relation to the energy status is key to the concept that Jens' group pursued for almost 20 years.

However, a major change in focus happened in 2010 while Jens was coordinating building an ageing centre at the University of Cologne flanked by the initiative of the Max Planck Society to establish a new Max Planck Institute for Biology of Ageing in Cologne. There was already a Max Planck Institute for Neurological Research on campus. The Max Planck Society decided that metabolism was such a key aspect of ageing that they repurposed this Institute.

"Then I was recruited to this Institute, to change the direction and build a more synergistic research community, also across traditional institutional boundaries, such as medicine versus natural science and university versus non-university research institutions, to develop a unified strategy that would benefit everyone."

Working at the molecular level in the mouse brain might answer questions about the human brain, but the researchers are still trying to find ways using functional MRI to test hypotheses they have developed for mice and for humans, both healthy and ill volunteers.

"We have been trying to identify this relay station. We can now very well map which neuron is connected to which downstream neuron, so we can understand how they function as the antennas of the brain, sensing what is happening in the periphery. We can artificially activate these neurons, including their specific projections. So we can start to functionally map how this information is related in the central nervous system and how this communication is relayed in obesity."

30% of pregnant women

The cross-disciplinary collaboration at the Max Planck Institute for Metabolism Research has progressed considerably since Jens started as a clinician 30 years ago, with the clinic and research being separate worlds. Today, special programmes free clinicians to pursue basic science and enable people to combine the two aspects of their career more efficiently.

"For me, the 4-year training in Ron Kahn's laboratory was instrumental. Without that training, I could never have done any meaningful science. Correspondingly, some people come with a very strong PhD background in either molecular genetics or neuroscience. But some physician scientists bring in different aspects, and I think this communication, even within the group, enables us to ask different questions."

One clinical question was the basis for launching a recent cross-disciplinary project on pregnancy complicated by metabolic disorders, obesity and gestational diabetes. Data show that the offspring have an increased risk of developing not only metabolic disorders but also other diseases later in life.

"We wanted to test this in mouse models. Specifically exposing mice to high fat during lactation predisposes the offspring to developing obesity and impaired glucose metabolism. Then we found that the high-fat diet compromises the signals that food intake–suppressing, anorexigenic neurons that express another neuropeptide, proopiomelanocortin (POMC), send to the downstream targets and that this metabolic dysregulation impairs the normal development of the brain in the offspring."

The offspring are born with soft-wired neurocircuitry for metabolic control, which makes them more prone to metabolic diseases themselves. More than 30% of pregnant women in the United States have metabolic alterations that predispose many of the children for metabolic diseases just through the altered maternal environment.

"Mice develop differently from people. Neurodevelopment during lactation in mice corresponds to the third trimester of pregnancy in humans. This means that the most vulnerable time for brain development predisposing for metabolic disease is probably this last trimester."

Food 24/7

Jens has not only inherited and implemented the cross-disciplinary aspects from his time in Ron Kahn's laboratory. Equally important is the open-door policy, so he is always open to discussing new ideas and unexpected findings.

"Ron would always say: the data are what they are. That was the basis to really look deeper and maybe revise ideas we previously had and then try to develop experiments based on an unexpected finding and ask questions that are off the beaten track."

Jens' group recently pursued a new conceptual question. In 2015, three independent groups in the United States reported that neurons that regulate feeding are already activated when animals are exposed solely to the sight and smell of food. Jens' group wanted to understand what this response could mean and found that the cells have a very rapid anticipatory response to food that prepares the liver for the metabolic state it would be in after a meal.

"This makes sense for a mouse in the wild, which would rarely smell food, but now food is available to people on every corner 24/7: not only food but also the smell of food. Think about how the current environment affects regulation or dysregulation."

Fighting back

With Jens' clinical background, the translational aspect of the research is always important. The most promising clinical translation came from a project focusing on insulin resistance in the classical insulin target tissues liver, muscle and fat. Jens' group had worked on the obesity-associated dysregulation of insulin action and found how specific lipids in metabolic target tissues contribute to insulin resistance.

"We got interested in the ceramide lipids, which clearly contribute to developing obesity-associated insulin resistance. These are very heterogeneous lipids, but we systematically analysed the effects and the regulation and found a very strong role for ceramide synthase 6, generating C16-ceramides in the development of obesity and insulin resistance."

The researchers strongly believe that inhibiting this specific enzyme might be a new avenue for treating people with obesity and obesity-associated insulin resistance. If this inhibitor can be successfully developed, Jens thinks that a drug is needed, because evolution is not going to fix things any time soon.

"Evolutionarily, our bodies have been optimized over millennia to survive with scarce and limited fuel sources. So why doesn't the body fight back? From a strictly evolutionary perspective, late-onset diseases occur after reproduction has taken place, so I am very sceptical of any strong evolutionary pressure. We therefore have to find alternative means to fight these diseases by developing new interventions, new drugs, to counteract how we expose our body to the current environment."

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Year and location of EASD Annual Meeting at which recipients have received the Prize.

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 25 billion (€3.3 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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