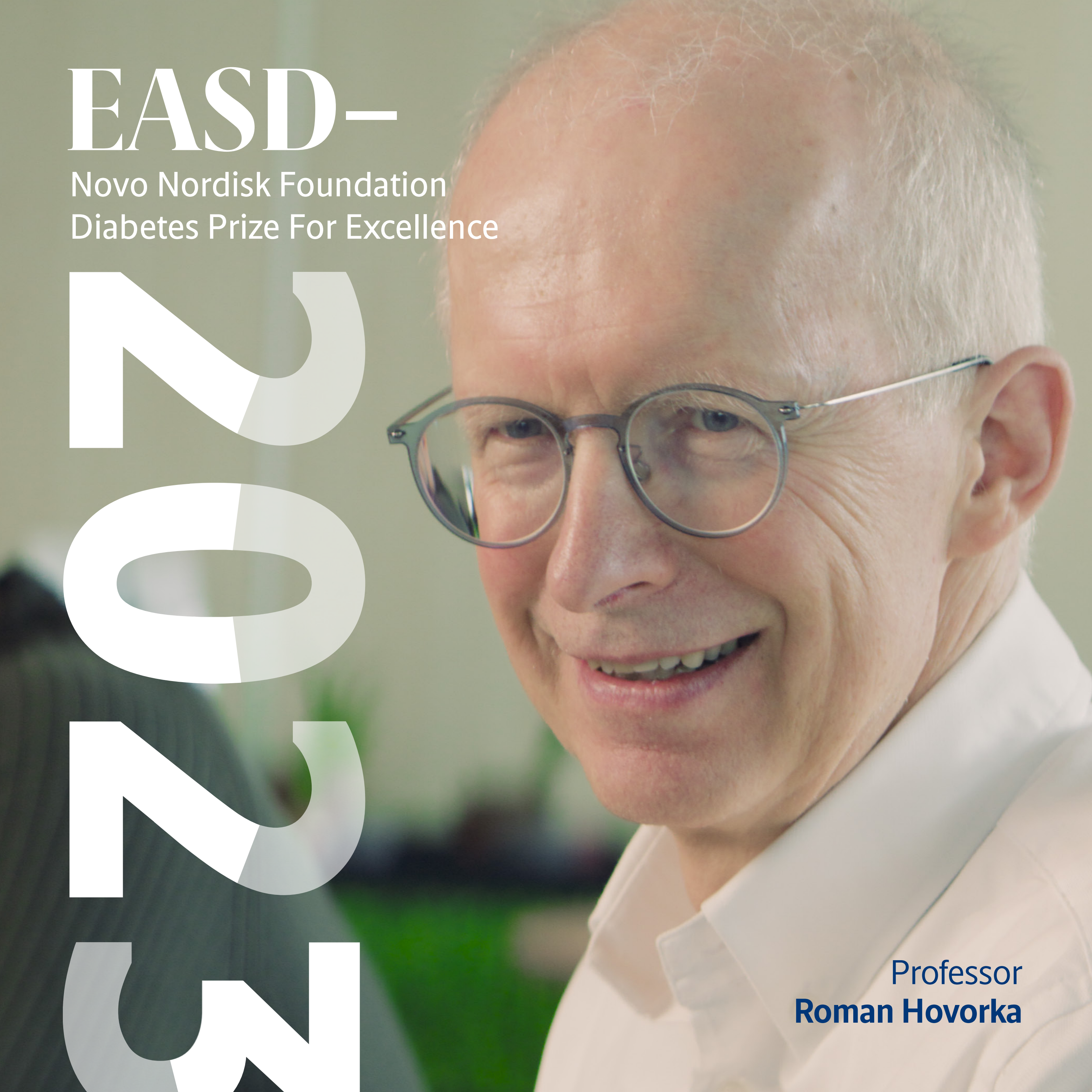

EASD–
Novo Nordisk Foundation
Diabetes Prize For Excellence
2023
Professor
Roman Hovorka

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 recognises exceptional scientists actively fighting to stop one of the defining health problems of the 21st century

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

The Prize is awarded annually to an internationally recognised 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 **Roman Hovorka**

The 2023 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence is being awarded to Professor Roman Hovorka

By Chantal Mathieu, President, EASD and Daniel J. Drucker, Committee Chairperson

Dr Roman Hovorka's research has spearheaded the development, regulatory acceptance, and clinical practice adoption of closed loop delivery (the "artificial pancreas") worldwide. His research has underpinned medical, societal, and regulatory acceptance of closed loop systems to manage type 1 diabetes.

Dr Roman Hovorka's seminal work, initiated two decades ago, focused on children and then expanded to teenagers, adults, older adults and pregnant women. Initially, his research showed that closed loop technologies are safe in controlled laboratory settings. First-of- their-kind translational randomised clinical studies under free-living conditions followed, documenting improved glucose outcomes and psychosocial benefits for the users and their families. Nowadays, closed loop systems comprising a continuous glucose monitor, control algorithm and insulin pump are changing lives of people with type 1 diabetes. Closed loop technologies are becoming the standard of clinical practice. In the UK, Roman Hovorka's research was a key contributor to the NICE guidance on hybrid closed loop systems and this has also been the case in other countries.

Dr Roman Hovorka's mathematics/informatics background, deep knowledge of physiology, insulin pharmacokinetics and pharmacodynamics, and medical device regulation enabled him to develop a glucose control algorithm embedded in a smartphone app that has now been commercialised and used in 15 countries with exponentially increasing reach. This interoperable app integrates with leading continuous glucose monitors and is the only closed loop system approved for use in very young children and pregnant women with type 1 diabetes.

His research has been presented at leading international and national diabetes conferences including the ADA, EASD, ATTD, and Diabetes UK where he has given numerous invited lectures. He has presented his research at FDA and NIDDK workshops, and represented the EASD at the European Commission's advisory body on medical device regulation. He has led numerous consortia across the UK, Europe and the US in the field of diabetes technology and the artificial pancreas funded by Diabetes UK, European Commission Framework and H2020 Programs, the JDRF, NIDDK, Helmsley Trust, and EME NIHR with a total budget in excess of GBP 25 million.

Dr Roman Hovorka has published widely in leading medical journals. He is a worldwide-recognised authority on the artificial pancreas with his work being recognised with numerous prestigious awards.

Apart from his work on type 1 diabetes, he has carried out seminal, world-leading research on the use of closed loop in type 2 diabetes both in inpatient and outpatient settings including the use of closed loop in the most vulnerable group of frail adults on dialysis. He developed an interoperable app for fully closed loop glucose control, which is undergoing implementation pilots.

Dr Roman Hovorka feels privileged to have been able to work with dedicated colleagues, collaborators, and members of his research group, many of whom have become leading researchers in the field of diabetes technology. He recognises that the multidisciplinary approach and the incisive and decisive input of many stakeholders have enabled his research to reach its potential and transform the lives of people with type 1 diabetes and their families. This has always been his mission.

Without question, Dr Roman Hovorka will be recognised as an outstanding individual joining the list of previous luminary recipients of the EASD/Novo Nordisk Foundation Diabetes Prize for Excellence. We are therefore very pleased to inform you that during the recent committee meeting of the EASD / Novo Nordisk Foundation Diabetes Prize for Excellence, a unanimous decision was taken to award the 2023 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence to Dr Roman Hovorka, a highly distinguished colleague and stimulating speaker who we are confident will deliver an exceptional lecture during the 59th EASD Annual Meeting 2023.

About Roman Hovorka

2024	Banting Named Lecture, Diabetes UK
2023	ISPAD Prize for Achievement
2018	Professor of Metabolic Technology, University of Cambridge
2017	Fellow, The Academy of Medical Sciences, UK
2017	Gerold & Kayla Grodsky Award, JDRF
2015	ISPAD Prize for Innovation
2013	Dorothy Hodgkin Named Lecture, Diabetes UK
2012	Director of Research, University of Cambridge
2004	Senior/Principal Research Associate, University of Cambridge
1989	Wellcome Trust Visiting Fellowship, City University, London
1984	Research Assistant, University Hospital, Prague

Closing the loop on diabetes: **artificial pancreas enables children to sleep tight at night**

For half a century, the notion of an artificial pancreas has tantalised researchers seeking to transform the management of people with diabetes. From scepticism to collaboration, from regulatory hurdles to clinical triumphs, the journey mirrors the resilient quest against diabetes. Unlike early backpack-sized prototypes, the new closed-loop system fuses a continuous glucose monitor with an insulin pump and a smart algorithm. Professor Roman Hovorka, the 2023 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence laureate, has spearheaded the development of this technology, marking a paradigm shift in diabetes care.

Forhalf a century, the idea of replacing a malfunctioning pancreas with an artificial one has persisted. This concept involves creating a device capable of replicating its vital function, insulin secretion, to effectively manage the blood glucose levels of individuals with diabetes, offering a potential life-changing medical solution. But developing this has been far from trivial.

"Insulin is a powerful drug. It is necessary for life. However, excessive insulin can lead to a coma or even be fatal. Therefore, we needed to ensure that the system was safe enough to progress to the next stage, where you can now take it home and incorporate it into daily life. Designing the system for children was even more challenging because food, and especially carbohydrate, affects the body more rapidly, and activity and eating patterns are less predictable," explains Roman Hovorka, a Professor at the Wellcome-MRC Institute of Metabolic Science, Metabolic Research Laboratories at the University of Cambridge, United Kingdom.

Simple in principle

Roman Hovorka's journey into the development of closed-loop systems was marked by a diverse background and a series of progressive steps. Beginning in the early 1980s, his career trajectory initially led him into the field of mathematical informatics, which he studied at Charles University in Prague, at that time in Czechoslovakia. His early exposure to the University Hospital in Prague in 1984, as the sole non-medical staff member, ignited his curiosity about the medical world, particularly diabetes.

"I was part of a group that managed diabetes, and I was a person who was quite unique within the group. While I communicated using my mathematical background, they used the medical language. We had to find a way to communicate, but they could see the potential in what I could offer them at that time, in the mid-1980s. I could also see that I was able to help them solve problems during that period. This helped us move towards the concept of closed-loop systems."

The idea of closed-loop systems is simple in principle.

"A continuous glucose monitor is a device that is placed on the skin, either on the arm or the abdomen. Through a little probe, it measures glucose levels every 1–5 minutes. These data are then transmitted to the computer algorithm, which processes the glucose values and instructs the insulin pump, which administers the required amount of insulin."

Roman Hovorka's interest led him to pursue a PhD focused on creating a decision support system for individuals with type 1 diabetes. His career path took a pivotal turn when he secured a Wellcome Trust Visiting Fellowship, which facilitated his move to City University, London, in 1989. During that time, he continued to deepen his knowledge in pharmacokinetics, pharmacodynamics, physiology, clinical trials and regulatory issues.

"I became involved in several European projects centred around diabetes management. Recognising the potential for applying mathematical approaches to improve diabetes care, I became increasingly committed to advancing the field. And then, in the late 1990s, I got a call from a company called Disetronic, a Swiss-based manufacturer of insulin pumps, that was working on developing a closed-loop system."

Finding the way

However, the journey was not without challenges. In 2003, Roman Hovorka approached the Juvenile Diabetes Research Foundation (JDRF) with his vision for closed-loop systems despite their dedicated and longstanding focus on finding a biological cure.

"Their efforts at the time were not focused on devices but on cures such as immunotherapy or cell-based therapies. So at that time I was forced to try to secure funding from other sources, which proved to be very difficult."

Up until then, the story of the closed-loop system had also been a story of broken promises.

"People kept estimating the solution will come in the next five to 10 years. And it never happened. And people were losing faith in that application and trust was also lost."

"In 2006, the JDRF radically changed its position recognising that a cure would not be immediately forthcoming, and if we have this number of people with type 1 diabetes, we need to help them. So even though the JDRF still maintains finding a cure is the ultimate goal, they appreciated the paramount importance of helping individuals who are already living with this condition and the potential of the artificial pancreas."

You cannot do everything on your own

The JDRF turned to their members, and the response was overwhelming. A substantial number of members wanted the JDRF to pursue solutions for those who already have type 1 diabetes. This prompted the establishment of the key JDRF Artificial Pancreas Consortium, which proved to be the turning point for the whole field

"A group of leaders in the field was assembled, and substantial financial and support resources were allocated, including engagement with regulatory bodies. We found ourselves privileged to become part of the Consortium and to embark on the journey from that point forward."

The new Consortium brought about an important change.

"In the early days, people tried to do everything, from the pump to the algorithm and the sensor system. I think what people also realised at the time was that you need to collaborate. You can't do everything on your own. It's usual to have a sensor from one Company and a pump from somewhere else. But the ability to put it all together was something that could accelerate progress."

In 2006, it was realised that it was more important to leave industry to handle the individual technological challenges and instead focus the new collaboration on the big gap, which was the algorithm.

Pursuit of perfection

Meanwhile, Roman Hovorka had moved from City University, London, to the University of Cambridge, where he set up his research group.

When the efforts to construct the closed-loop system had started, several people said that the researchers could never mimic the physiology of the pancreas – of delivering insulin to the portal vein and sensing glucose in the blood – and instead insulin should be administered and glucose levels measured in subcutaneous tissues.

"There were people aiming for perfection. Initially, people actually tried to do an implantable system, where you implant the insulin pump and the sensor, but that was too difficult. This pursuit of perfection hindered progress. When I saw how people's diabetes was being managed, while it may not be ideal, it would be better to use an imperfect closed-loop system compared with what was available."

> "In the early days, people tried to do everything, from the pump to the algorithm and the sensor system. I think what people also realised at the time was that you need to collaborate."

Feedback and motivation

Roman Hovorka and colleagues talked to many people in the early stages of their research, including parents. They asked them whether they would trust a closed-loop system that injects insulin automatically for their children.

"We told them that, in principle, this is potentially dangerous, because it can be life-threatening if the system fails. So we had this focus group with mothers and children, and many simply said, 'We need anything. We're just tired. The burden of disease is too much on the family. We just need our lives back.'"

The feedback became the motivation and driver for the hard work to come. And probably in the same way that many people perceive mathematicians as highly theoretical individuals, Roman Hovorka approaches challenges differently.

"I have always been a problem-solving person who tries to see the problem and break it down into smaller problems. So it was a sort of stepwise process that benefitted from lots of things I had learned in my early career. And, again, the motivation came from seeing a problem, being able to solve it, but also getting the feedback from people when they came back to us to say that what we are offering was life-changing."

No two nights the same

The research, which started at the University of Cambridge in 2006, was divided into two main parts. One included safety studies carried out in a controlled environment in the clinical research facility of Cambridge Addenbrooke's Hospital. People were closely monitored while the researchers tested the early version of the algorithm, which controls the insulin infusion.

"We were testing when study participants were running on a treadmill. We were testing big meals and small meals. We really pushed the system into the corners, which are difficult to manage. We were gaining confidence that the system could cope. We even had one study where adults drank three quarters of a bottle of wine, because alcohol strongly affects glucose control, so we wanted to make sure that it worked even then."

The many tests were also necessary because insulin is such a potent molecule, so they wanted to be sure that the system was safe enough to move to the next step, where they could confidently say that it was safe to use at home, on vacation, at school, skiing or travelling.

"My main role was developing the algorithm, the computer program. And what it aims to do is basically describe how insulin affects glucose and, of course, other aspects like how meals affect glucose. And we aimed to create a model so we can better forecast glucose levels. We looked at the data coming from the individual patient to see which model would fit better to this person. And then we used all these models to optimise and time the insulin infusion."

The second stage of the development started with shorter home studies: first three weeks, then three months, and eventually years, in which Roman Hovorka and his team tested various populations.

“We studied the closed-loop system in pregnancy; we tested it on very young children. And in those longer studies, we learned that every day and every night is even more different than we thought it would be. Therefore, we had to make the system more adaptive and more responsive. Because there’s a week and a weekend. There’s school and there’s a holiday. No two nights are the same.”

Adapt 24 hours a day

The research showed that models could even change over time – and sometimes quite rapidly, so Roman Hovorka and his team had to figure out ways to jump from one model to another very quickly. The extensive tests taught them which parameters they had to change and how these parameters change.

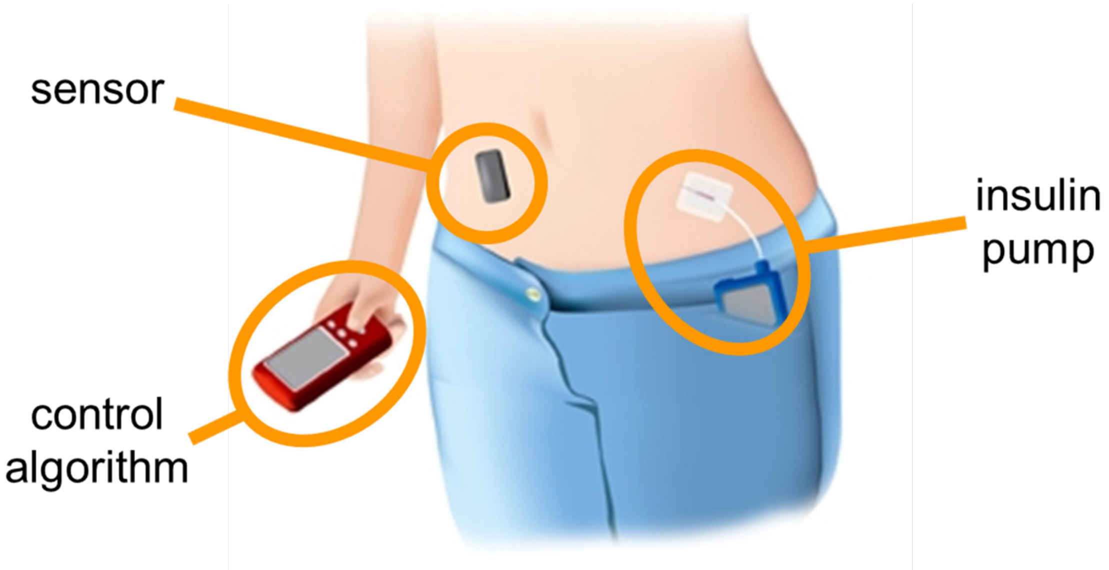
“We were helped tremendously by also doing computer simulations. The keyword turned out to be adaptivity. So, we have developed a system that can adapt to people throughout the 24-hour cycle. The system continuously adapts; it never stands still.”

Overnight glucose control is one of the major benefits of the artificial pancreas, especially for parents, who normally get up two to three times every night just to check that their child’s glucose levels do not get too high or too low.

“Every day and every night is, in principle, different. So what is good on one night is not good another night. And the closed-loop system, where the system is monitoring what’s happening regardless of the events of the day, can run on its own. This is where the closed loop kicks in: it will give the right amount of insulin every night, around the meals, throughout the 24-hour cycle. It is really the way forward before that illusive cure is found.”

The greatest life improvement with the closed-loop system is overnight.

“With a closed loop, your blood glucose is better controlled with fewer long-term side-effects, but it is the psychosocial benefits



that are also important to families, both for the children and the parents. If you have better control, you have better sleep, mood and concentration, and you feel safer – both as a child with diabetes and as a worried parent."

Decided to set up his own company

With the development of a well-functioning closed-loop system, there would be no more guessing about how much insulin to give. The researchers did lots of studies, published widely and carried out randomised controlled trials, which clearly showed the benefits. But despite the unanimous positive feedback from the users, one important hurdle was left: the regulatory approval of closed-loop systems to manage type 1 diabetes.

national diabetes conferences including the American Diabetes Association, the EASD, Advanced Technologies & Treatments for Diabetes and Diabetes UK.

"So we were able to work with the healthcare professionals and show them the system: this is what it can do. We were also preparing regulatory bodies: this is what's likely to come in your direction."

The initial intention from the researchers was to license the developed closed-loop system to established companies to take it to the market. There were positive discussions, but these failed to materialise. In 2018, Roman Hovorka and colleagues decided the only option was to set up a company, CamDiab Ltd.

> "With a closed loop, your blood glucose is better controlled with fewer long-term side-effects, but it is the psychosocial benefits that are also important to families, both for the children and the parents."

"So what happened quite often in our clinical trials was, despite having bulky devices and not ideal usability for these devices, people were still willing to use them. And we did actually have some problems getting the devices returned because the participants had felt the positive change in their quality of life. But we couldn't do it at the time because these devices were not regulatory approved and were still only usable under the Clinical Trials Directive."

Roman Hovorka presented his research to the United States Food and Drug Administration, FDA, and United States National Institutes of Health, NIH, and to the European Commission's advisory body on medical device regulation. His research was also presented on numerous occasions at leading international and

"We started commercialising what we had done; it was a pretty big challenge at the time. But right now, we are in 15 European countries and Australia. We have over 16,000 users, and we are growing by about 1,300 users per month."

Life changing

Today, there are several commercial closed-loop systems, so the 60-year-old dream of creating an artificial pancreas is no longer just a dream, and Roman Hovorka is getting amazing feedback from people on their improved quality of life.

"Some people are saying that being on a closed loop is like taking a bit of a diabetes holiday. They can step back and not think about it.

For some people, it is a life-changing experience. So the differences are huge, especially for those people who are conscious about the parents who really care about their children and feel burdened by diabetes we can take part of this burden from them, so they can spend more positive time on family life."

The journey has been long in getting to where the field is today. But Roman Hovorka feels privileged to be part of it.

"When I started working in this field, it was not something I could have imagined. I came with my mathematical informatics background. What was really crucial is that at my first job in the university hospital, I was dealing with people with the real problems."

Roman Hovorka has been along for the ride from the early safety studies, and later clinical studies, all the way to commercialisation.

"We were able to go through the whole journey. I could see the world that was developed on paper, then on a computer, going all the way to reaching tens of thousands of people in real life. The motivation came from seeing a problem, being able to solve it but also getting feedback from people who come back to you and say that this is life-changing."

Roman Hovorka is receiving the 2023 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence, accompanied by DKK 6 million (€806,000), for his outstanding contributions that have improved the knowledge and the treatment of diabetes.

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

The European Association for the Study of Diabetes

The EASD Annual Meeting is the largest diabetes-related conferences in the world and EASD is an active player in postgraduate education, having trained over 40,000 healthcare professionals through training courses and online education activities.

In 2000, EASD increased its commitment to stimulate diabetes research in Europe by creating the European Foundation for the Study of Diabetes (EFSD). Since its inception, the EFSD has committed over €120 million to diabetes research in Europe by various funding means.

EASD is the publisher of *Diabetologia*, a major monthly international diabetes journal with an impact factor of 8.2 (2022).

For more information, please visit: www.easd.org

The Novo Nordisk Foundation

Established in Denmark in 1924, the Novo Nordisk Foundation is an enterprise foundation with philanthropic objectives. The vision of the Foundation is to improve people's health and the sustainability of society and the planet. The Foundation's mission is to progress research and innovation in the prevention and treatment of cardiometabolic and infectious diseases as well as to advance knowledge and solutions to support a green transformation of society.

www.novonordiskfonden.dk/en

Novo Nordisk Foundation

Tuborg Havnevej 19
DK-2900 Hellerup
Denmark

Phone: +45 3527 6600

nnfond@novo.dk
www.novonordiskfonden.dk/en

novo nordisk
foundation
Benefitting people and society