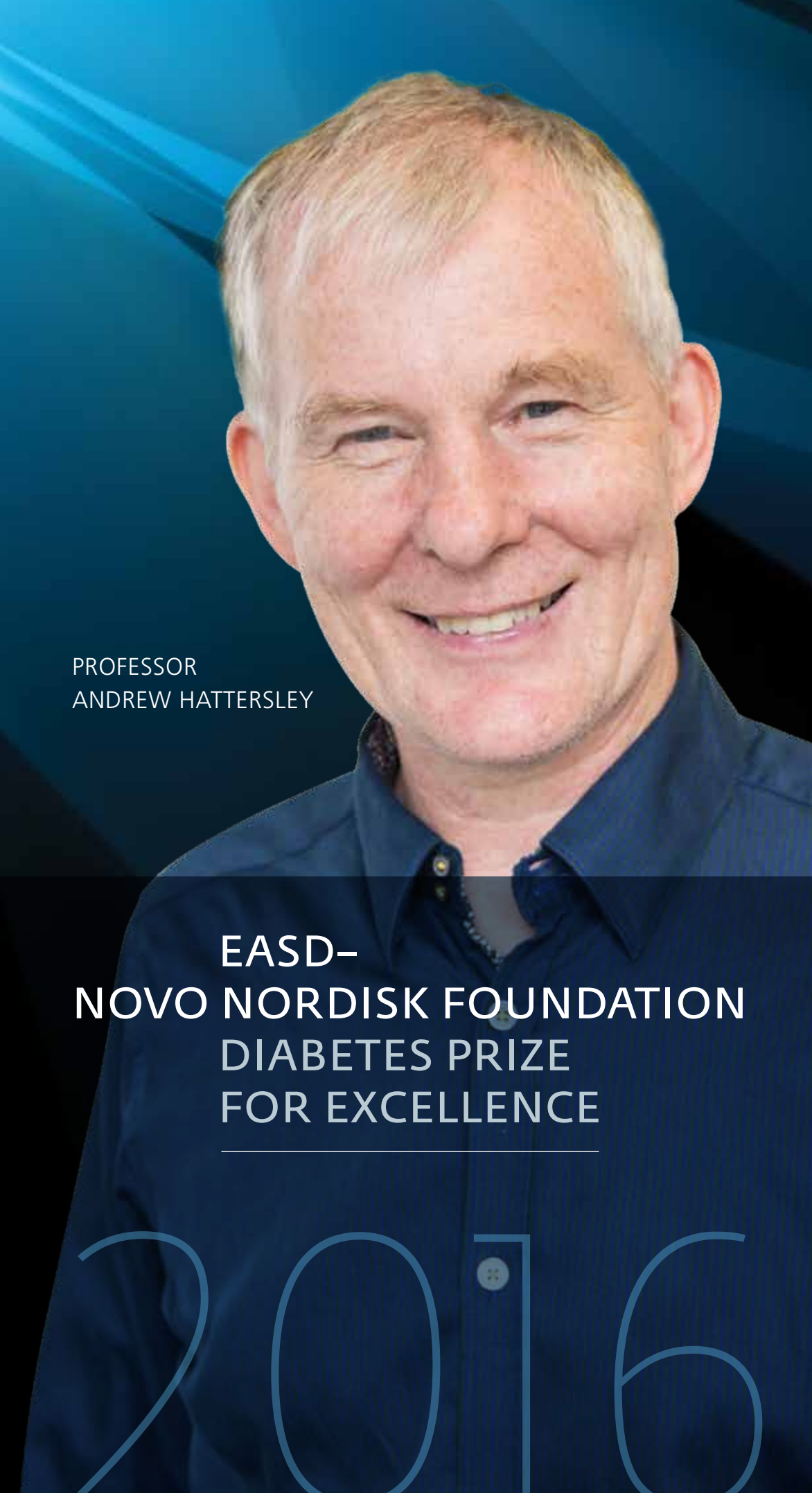


PROFESSOR
ANDREW HATTERSLEY

EASD–
NOVO NORDISK FOUNDATION
DIABETES PRIZE
FOR EXCELLENCE

2016

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 winner of the Prize, 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 ANDREW HATTERSLEY

The EASD–Novo Nordisk Foundation Diabetes Prize for Excellence 2016 is being awarded to Andrew Hattersley

BY JULEEN ZIERATH, PRESIDENT, EASD

Andrew Hattersley is Professor of Molecular Medicine at the University of Exeter Medical School. His work and outstanding scientific contributions has been recognized by election to Fellowship of the Royal Society, the highest scientific accolade in the United Kingdom. He has won 12 international awards and 11 national awards for his research.

With more than 500 peer-reviewed publications, chapters and books, including publications in *Science, Nature, Nature Genetics, Proceedings of the National Academy of Sciences of the United States of America, New England Journal of Medicine, The Lancet, Journal of the American Medical Association, PLoS Medicine, American Journal of Human Genetics, Journal of Clinical Investigation, Cell Metabolism, Diabetes* and *Diabetologia* as well as being ranked one of the most cited diabetes and metabolism researchers in Europe, Andrew Hattersley has an outstanding record or scientific accomplishments.

In addition to his personal success, Andrew Hattersley is a mentor of the highest standard. He successfully supervised 32 PhD students and 5 MD students between 1992 and 2016. The median number of papers published from his PhD students is 5. More than 65% of his students and fellows have become successful independent academics leading their own research teams, including 5 full professors and 3 associate professors. Eight of his students and fellows have won awards for top young researchers at the Diabetes UK annual meeting, five have given the RD Lawrence Lecture Award for the top United Kingdom diabetes researcher younger than 45 years and three have won the EASD Rising Star award. Others have won Albert Renold Career Development Awards for young investigators in diabetes (EASD); G.B. Morgagni Prize for the best European young investigator in diabetes, and the Minkowski Prize on 2 occasions (EASD).

Andrew Hattersley is the personification of a complete clinician scientist who has transformed the understanding, diagnosis and treatment of monogenic diabetes. He has taken research into monogenic beta-cell diabetes beyond gene discovery into fundamental insights into the development and function of the human beta cell and providing the clinical research that is the basis of clinical care of these people worldwide.

The Committee of the EASD–Novo Nordisk Foundation Diabetes Prize for Excellence has unanimously decided to award the 2016 EASD–Novo Nordisk Foundation Diabetes Prize for Excellence to Andrew Hattersley, a highly distinguished and stimulating speaker who, we are confident, will deliver an outstanding lecture during the 52nd EASD Annual Meeting.

CURRICULUM VITAE

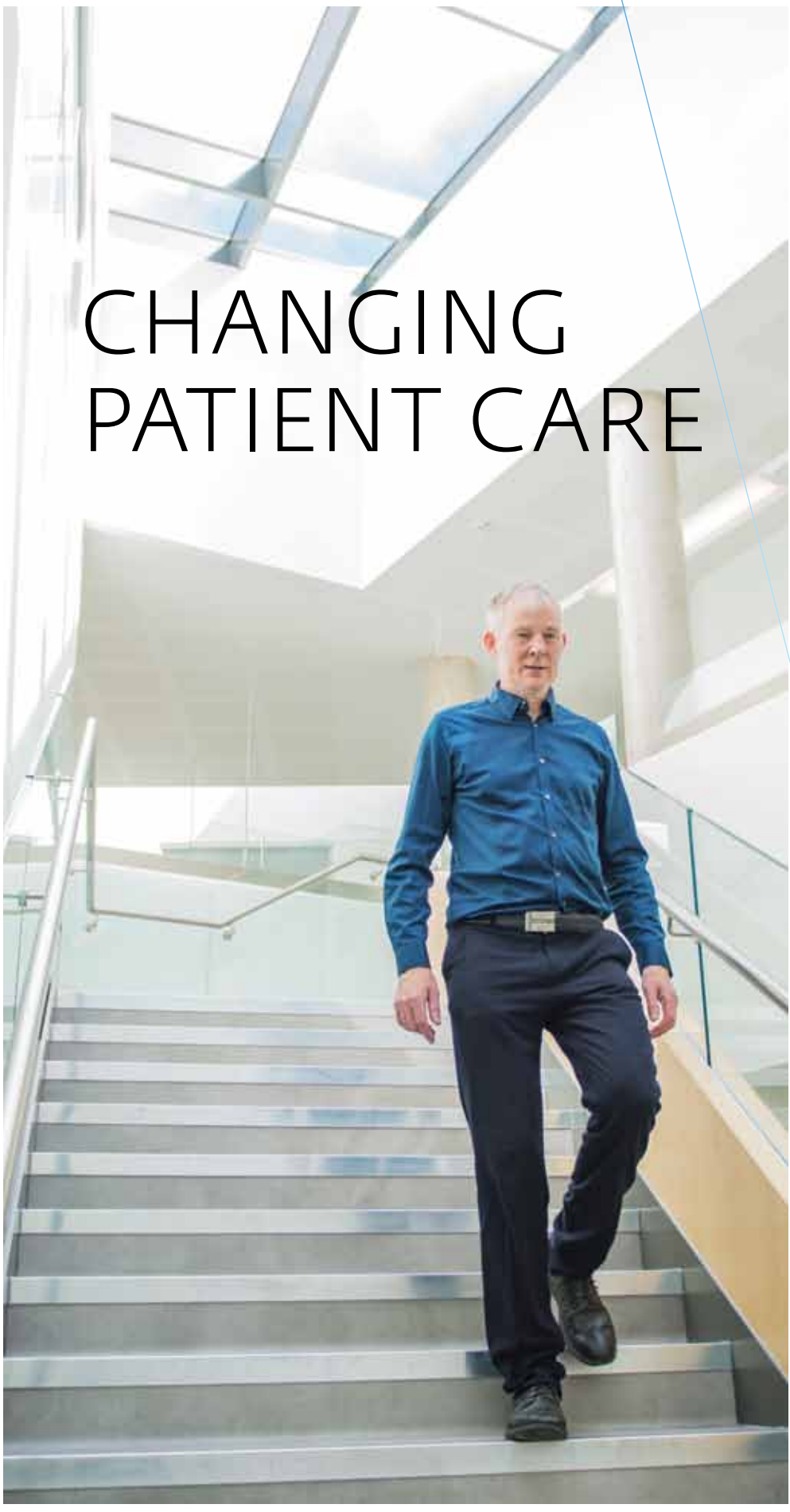
ANDREW HATTERSLEY

PROFESSOR, FELLOW OF THE ROYAL SOCIETY
BORN 1958, LONDON, UNITED KINGDOM

1999–	Professor of Molecular Medicine, University of Exeter Medical School; Clinical Director, Clinical Research Facility, University of Exeter; Consultant Physician (Diabetes), Royal Devon & Exeter Hospital; Director of Research and Development, Royal Devon & Exeter Hospital, United Kingdom
1995–1999	Senior Lecturer (Reader 1998) and Consultant Physician, University of Exeter, United Kingdom
1993–1994	Lecturer, Department of Medicine, University of Birmingham, United Kingdom
1990–1993	MRC Research Fellow, Nuffield Department of Medicine, Oxford, United Kingdom
1988–1990	Registrar, Wexham Park Hospital, Slough and Royal Postgraduate Medical School, Hammersmith, London, United Kingdom
1985–1988	Senior House Officer, Northwick Park Hospital, Harrow, United Kingdom
1984–1985	House Physician, Nuffield Department of Medicine, Oxford, United Kingdom
1984	BM BCh, University of Oxford
1981	BA, University of Cambridge

Professor Andrew Hattersley has more than 500 publications, chapters and books and more than 45,000 citations.

CHANGING PATIENT CARE



The work of Andrew Hattersley and his Exeter-based team has revolutionized diagnosis and treatment and has led to crucial insights into the development and function of the insulin-producing beta cell.

Some colleagues considered it to be academic suicide to take a post at a university not in Cambridge, London or Oxford, but Exeter's entrepreneurial spirit and geographical location appealed to Andrew Hattersley, and in 1995 he took up a post there, working mainly as a clinical diabetologist. He soon found he could not leave research behind and received support from the University of Exeter to set up a genetic laboratory in the Royal Devon & Exeter Hospital where he worked.

Sometimes starting from scratch is good, as it allows you to create an environment in which new ideas and new approaches can thrive. Andrew Hattersley and Sian Ellard, the brilliant professor of genomic medicine, had the opportunity to develop a genetics laboratory exactly as they wanted it. From the beginning, they integrated routine diagnostic testing with genetics research.

"This was a single lab with no barriers between research, making scientific discoveries and diagnostic testing for clinical care. This ensured that research findings moved rapidly into clinical care," Andrew Hattersley explains.

In many ways, the lack of a specialized genetics laboratory and established geneticists was an advantage.

"A tree growing in the middle of a field not restricted by any other trees can grow in any direction. But if the tree is growing in a forest with other trees, it is restricted and can only grow straight up in order to reach the sunlight and cannot spread out. Like the tree in the middle of the field, we were able to take our research and diagnostic service in any direction we wanted," says Andrew Hattersley.

YOUNG, SMALL AND FLEXIBLE

The genetics laboratory in Exeter rapidly established itself as the leading international centre for maturity-onset diabetes of the young, also known as MODY. Their main work was not gene discovery, which was led by Graeme Bell, professor at the University of Chicago and an excellent friend and collaborator of the Exeter laboratory. Instead, the Exeter team focused on diagnosing patients and then researching the key clinical features and optimum clinical care both during and outside pregnancy. Early work showed the impact of glucokinase mutations on foetal growth; recognized the extensive renal and multi-system phenotype of *HNF1B* mutations; and showed that patients with *HNF1A* mutations were exquisitely sensitive to sulphonylurea tablets. All this work had immediate clinical implications.

"We rapidly realized that education of diabetes specialists was needed if this new guidance for clinical care was ever going to reach patients. The education initiative was superbly led by Maggie Shepherd, a professor and diabetes nurse educator, who worked in the research team from the beginning."

"It was a plan from the very start to choose to work differently from other genetics labs and diabetes research teams. We were young, small and flexible and could react rapidly to new results. This gave us an edge. We didn't need to learn about old technology; we could jump right in and use the newest equipment," says Andrew Hattersley.

The technology in genetic testing has advanced tremendously, speeding up testing in ways that were unimaginable 20 years ago. It took 13 years to sequence the first human genome; it can now be done and analysed in 3 days. This has had a huge impact on the results from Andrew Hattersley's laboratory.

"In the past 21 years, we've been riding the waves of new technology, surfing from the crest of one technology to the next. Just when you think you can't go any further, a new technology arrives, which carries your research even further," he says.

EARLY INTEREST IN DIABETES

Andrew Hattersley became interested in diabetes as a young medical student at the University of Cambridge. His best friend had type 1 diabetes, and every day Andrew Hattersley would see his friend measure his glucose and balance his insulin, diet and exercise. This experience led him to take up clinical training in diabetes and endocrinology.

"I love the close relationship of clinical diabetes with science and physiology as well as the long-term relationship between doctor and patient."

Keen to study diabetes in depth, he moved to Oxford to do research and got excellent career advice: if you want to find genes in diabetes, it is best to look at genetic forms of diabetes!

"So I directed my scientific research towards studying maturity-onset diabetes of the young – a monogenic subgroup of diabetes. The key thing was to me to identify large families that had diabetes as the result of a single gene mutation. I was very lucky that the first gene I tested was glucokinase and we did find a mutation – this was a 1 in 20,000 chance!"

Exploring the monogenic causes of diabetes, Andrew Hattersley and his research team have developed a roadmap for the optimal clinical care of monogenic diabetes that benefits patients.

SEIZING THE OPPORTUNITIES

Similar to many other things in life, good science is about good luck – and then making use of the opportunities that present themselves. At the World Diabetes Conference in Mexico in 2001, Andrew Hattersley by chance sat next to Jan Bruining, a paediatric diabetologist from the Netherlands, at breakfast. They chatted about Jan Bruining's patients with neonatal diabetes, who were diagnosed so rapidly after birth that the cause must be genetic. They realized that the paediatricians had the patients, but not the technology, to find genes, and the geneticists had the technology but not the patient samples. They decided they could start unravelling the mystery of neonatal diabetes. Over breakfast they set up the ISPAD Rare Diabetes collection, which was a "dating agency" introducing paediatricians and molecular geneticists. The paediatricians would refer patients for a diagnosis, and the geneticists would get sample material to find the causative gene.

"Finding genes is impossible without sample material from well-characterized patients; it is pivotal to have a network of doctors who are interested in finding the genetic cause of the unusual types of diabetes of patients in their care. Without their input we could not have made any progress."

TESTING THE CANDIDATE GENE

The next decision was which of the 22,000 genes to examine first in the samples from patients with neonatal diabetes. Anna Gloyn, working with Sian Ellard in the Exeter laboratory, selected the gene encoding the Kir6.2 subunit of the beta-cell potassium channel. This choice of candidate gene was based on pioneering fundamental research conducted by professor Frances Ashcroft in Oxford, and other leading beta-cell scientists who had identified the KATP channel as playing a critical role in regulating insulin secretion.

Remarkably, this first gene tested was correct. Mutations in the KCNJ11 gene that encodes the Kir6.2 subunit were the most common cause of neonatal diabetes. With the help of Frances Ashcroft and her team, they were able to show that the mutations prevented the potassium channel from closing in the presence of ATP (the signal that the glucose

> **It was a plan from the very start to choose to work differently from other genetics laboratories and diabetes research teams. We were young, small and flexible and could react rapidly to new results. This gave us an edge."**

concentration was elevated); this meant that the insulin that was present in the beta cells could not be secreted. In 2004, these results were published with many international collaborators representing the geneticists, scientists and clinicians who had worked together on the project.

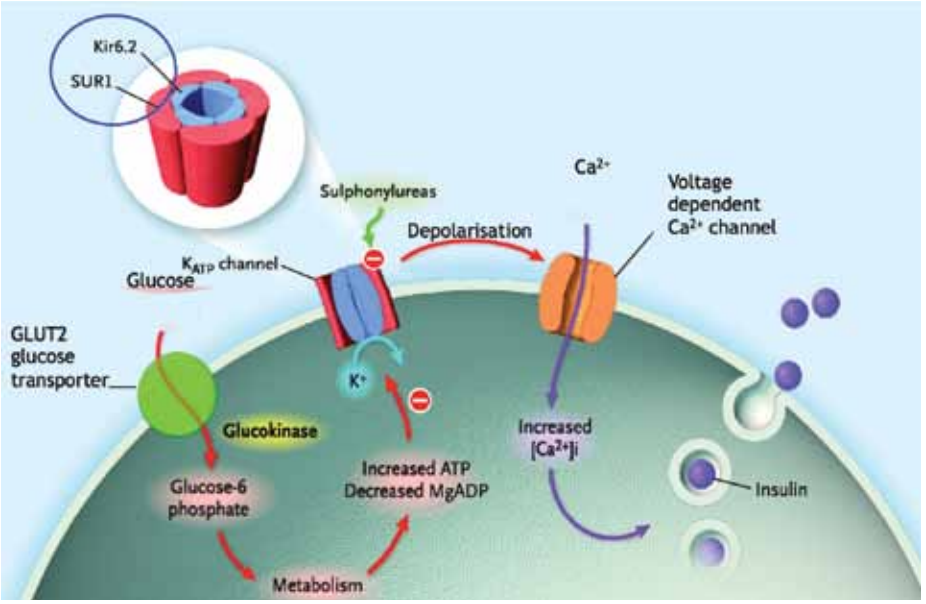
It is very rare that identifying a gene mutation that causes a disease swiftly leads to a new form of treatment, but this was an exception. Decades of research had established that sulphonylurea, a common treatment in type 2 diabetes, could stimulate insulin secretion by closing the potassium channel. As soon as the gene was found, it raised the possibility that sulphonylurea tablets might help these patients, but this treatment had never been used in patients who secreted no insulin at all.

With qualified guesswork, thorough science and knowledge of diabetes treatment, Andrew Hattersley and his team had identified a monogenic cause of early-onset diabetes. They also had a candidate for treatment. Theory is one thing, but it is a whole new ballgame to ask patients to stop taking insulin, a safe treatment that is working, and ask them to try a different medication, which they could not be sure would work at all. The team still needed to find clinical evidence that sulphonylurea could replace the insulin injections.

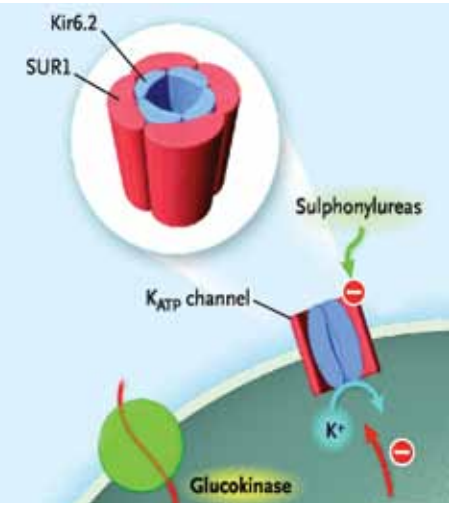
SERENDIPITY

Even one case in which a patient had successfully substituted insulin injections with sulphonylurea for a longer period would be important for Andrew Hattersley and his research team, since it would provide the much-needed empirical proof.

The answer was found in one of the earliest patients found with a mutation in the Kir6.2 subunit – a Brazilian patient diagnosed with neonatal diabetes when he was only 3 months old. His parents were unable to afford the insulin treatment so they pleaded with their doctor to find a less expensive treatment. The child's doctor tried sulphonylurea tablets, and 46 years later he was still taking these tablets and had the best glucose control of any of the patients with this type of diabetes. He was also the only one for which it could be shown that he was making his own insulin. This gave the Exeter team the empirical proof that sulphonylurea could work. Working with doctors and patients all over the world, they started to transfer patients from insulin to sulphonylurea tablets. The results



A mutation in the SUR1 or Kir6.2 gene prevents the potassium channel from closing in the presence of ATP, which signals that the glucose concentration is elevated. This means that the insulin in the beta cell cannot be secreted.



Insulin is secreted when the sulphonylurea depolarizes the hyperpolarized membrane, permitting a potassium influx.

Source: Gloyn AL, Pearson AR, Antcliff JF et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. New England Journal of Medicine 2004;350:1838–49.

were remarkable. Patients who were producing no insulin could stop their insulin injections and have better control on a high dose of sulphonylurea tablets.

Definitive proof would require large-scale testing. The Exeter team worked with Pål Njølstad in Norway and Michel Polak in France to test a consecutive international cohort of 49 patients. Ninety percent of the patients were able to stop their insulin and, remarkably, in every case their HbA_{1c} improved without an increase in hypoglycaemia. These patients now had food-responsive insulin secretion and stable blood glucose concentrations.

REMOVING THE BARRIERS BY OFFERING FREE TESTING

The discovery that mutations in the potassium genes responded to sulphonylurea treatment opened many new doors. Suddenly it was clear that, for any patient diagnosed in the first 6 months, it was crucial that mutations be tested in the Kir6.2 or SUR1 component of the potassium gene to assess who could be switched from insulin treatment.

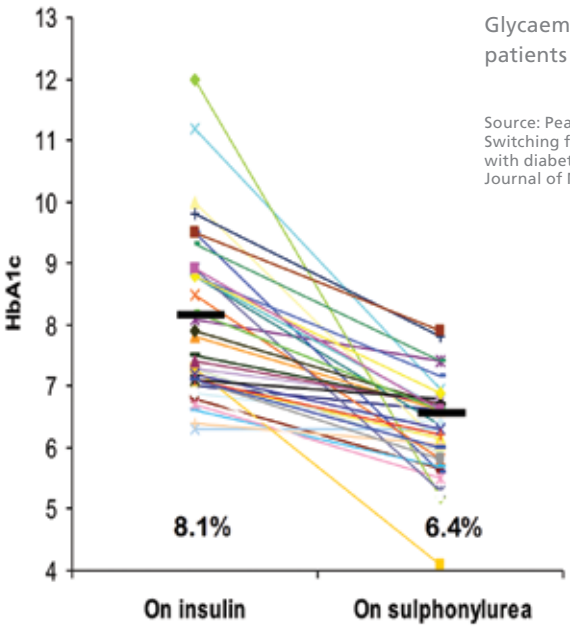
"There were many places in the world that did not have labs offering this testing, and many places that could not afford the tests. We therefore

“We will try to do what we have done within genetic forms of diabetes and see whether we can define subgroups within type 1 and type 2 diabetes that help clinical care. That’s our hope for the future."

decided to drop the patent we had taken out and offer free testing for any patient diagnosed in the first 6 months of life. Since then, the Exeter genetics lab has tested 1750 people from 87 countries. As a result, more than 800 cases were found to have a mutation in either the Kir6.2 gene or the SUR1 gene, with the vast majority able to substitute their daily injections of insulin with sulphonylurea tablets,” says Andrew Hattersley.

Another impact of receiving so many samples was that the Exeter team could now search the 50% of patients without a potassium channel mutation for new genetic causes of neonatal diabetes and start to understand how best to manage these. In this way, the Exeter team discovered 13 of the now 24 known gene mutations that cause neonatal diabetes. It also led to new understanding of the development and function of the human beta cell and allowed comparisons to be made between mice and humans.

As a result of Andrew Hattersley’s research, the international guidelines have been rewritten. It is now recommended that all children who have been diagnosed with diabetes before they are 6 months old be genetically screened. This test can be done at the Exeter laboratory free of charge thanks to grant support from the Wellcome Trust.



Glycaemic control is improved in all patients with a Kir6.2 mutation.

Source: Pearson E, Fletchtner I, Njølstad PR et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. New England Journal of Medicine 2006;355:467–77.

PRECISION MEDICINE

For Andrew Hattersley, gene discovery is only the beginning, not the end. The vision is that the gene testing will go hand in hand with the best clinical management and treatment – in the seamless and swift manner envisaged by Andrew Hattersley and Sian Ellard more than 20 years ago.

"It is in the interaction between genetic testing and clinical care where we really hope to make a difference. A lot of labs discover genes; we strive to discover the cause and find the optimal treatment."

A genetic approach has shown that the clinical condition neonatal diabetes has at least 24 genetic causes. Each subset has a very different cause and a different clinical path. Some of them also have a completely different response to therapy.

"We have seen that, if you can break down the clinical groups into defined subgroups, you can start to make far more progress than if you just look at them as one group of patients."

Andrew Hattersley is now focusing on finding different subgroups within type 1 and type 2 diabetes because he believes it does not make sense to deal with these as single disease entities.

"I am convinced that we should be looking for different subgroups within type 1 and type 2 diabetes. I hope defining these subgroups will make a similar difference as the subtypes in genetic diabetes," he says.

The team is starting to make progress in type 1 diabetes, where they are working to define the patients who still carry on producing insulin many years after diagnosis and looking at how they differ from those who make no insulin very rapidly after diagnosis.

"By defining subgroups, we're trying to bring the idea of individualization of care, an approach that has been described as precision medicine. We will try to do what we have done within genetic forms of diabetes and see whether we can define subgroups within type 1 and type 2 diabetes that help clinical care. That's our hope for the future."

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 embraces scientists, physicians, laboratory workers, nurses and students interested in diabetes and related subjects. It currently has more than 7,000 active members from over 110 countries.

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 1999, 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.

The vision of the Foundation is to contribute significantly to research and development that improves the health and welfare of people.

Since 2010, the Foundation has donated more than DKK 9 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.

PREVIOUS RECIPIENT OF
THE EASD-NOVO NORDISK FOUNDATION DIABETES PRIZE
FOR EXCELLENCE

2015 Professor, director Stephen O'Rahilly

NOVO NORDISK FOUNDATION
TUBORG HAVNEVEJ 19
DK-2900 HELLERUP
DENMARK

PHONE: +45 3527 6600

NNFOND@NOVO.DK
WWW.NOVONORDISKFOUNDATION.COM

novo nordisk fonden