

A portrait of Professor Sir Stephen O'Rahilly, an older man with white hair, glasses, and a mustache, wearing a blue and white checkered shirt. The background is a solid dark blue.

EASD-
NOVO NORDISK FOUNDATION
DIABETES PRIZE
FOR EXCELLENCE

PROFESSOR SIR STEPHEN O'RAHILLY

2015



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 STEPHEN O'RAHILLY

**The EASD–Novo Nordisk Foundation
Diabetes Prize for Excellence 2015 is being
awarded to Professor Sir Stephen O'Rahilly.**

BY ANDREW J.M. BOULTON, PRESIDENT, EASD

Professor Sir Stephen O'Rahilly is co-Director, Wellcome Trust-MRC Institute of Metabolic Science (IMS); Director, University of Cambridge Metabolic Research Laboratories (MRL); and Director, MRC Metabolic Diseases Unit (MDU). A member of the Academy of Medical Sciences and the Royal Society, Stephen O'Rahilly is one of the United Kingdom's most renowned clinical researchers. He is widely known for combining research into the causes of obesity and insulin resistance with clinical practice.

He has a long-standing interest in the aetiology and pathophysiology of human metabolic and endocrine disease and how such information might be used to improve diagnosis, prognostication, therapy and prevention. He has a long-standing, close, collaboration with Sadaf Farooqi, Tony Coll and Giles Yeo, which focuses on Mechanisms in disorders of energy balance.

These studies use human genetic and physiological approaches, accompanied by studies in cellular and animal disease models to better understand the biological causes of highly penetrant forms of human obesity and also the mechanisms whereby more common genetic variants predispose to common forms of obesity. This work has been incorporated into a research programme at the MRC Metabolic Diseases Unit (MDU) which was formed in 2013.

Professor O'Rahilly holds a Wellcome Trust Senior Investigator Award focused on Mechanisms of Human Insulin Resistance. In this work he collaborates closely with David Savage and Robert Semple. They use human genetic and physiological approaches, accompanied by studies in cellular and animal disease models to better understand the biological causes of extreme forms of human insulin resistance and also the mechanisms whereby more common genetic variants predispose to common forms of the metabolic syndrome.

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Both of these programmes benefit greatly from extensive interactions with Ines Barroso and with Nick Wareham and colleagues in the MRC Epidemiology Unit within the IMS.

More recently he has developed an interest in canine models of metabolic disease and in certain hormones of the gastro-intestinal tract (in collaboration with Fiona Gribble and Frank Reimann).

Stephen O’Rahilly is an engaging and stimulating speaker and we are confident that the Prize Lecture will be of outstanding quality.

There are few diabetes researchers more worthy of this recognition and we are confident that his selection as the 2015 recipient of the EASD–Novo Nordisk Foundation Diabetes Prize for Excellence is a sign of the importance and exceptional quality of this highlight of the 51st EASD Annual Meeting.



THE BEGINNING OF THE END

BY MORTEN BUSCH

10 years ago Professor Sir Stephen O’Rahilly quoted Sir Winston Churchill in a Science article about genetic factors of type 2 diabetes. He stated that science was maybe at the end of the beginning in this field. Today, Stephen O’Rahilly is inclined to believe, that we have actually reached the beginning of the end.

In the 1980s Stephen O’Rahilly was among the first researchers to begin to explore the genetic basis for type 2 diabetes. Originally trained as a medical doctor he had little experience of research when he was offered an opportunity to research the physiology of type 2 diabetes at Oxford University.

“I loved it and decided that clinical academia was the career for me. The world was changing through the revolution in molecular genetics being applied to medicine and so I thought that if I was to be serious about being a clinical academic, I had to study molecular genetics,” Stephen O’Rahilly explains.

He did some of the first genetic linkage studies of type 2 diabetes and this unique combination of clinical academia and molecular genetics enabled Stephen O’Rahilly to work with patients in new ways and provide answers to unsolved mysteries of severely insulin resistant patients with very high insulin levels. He soon realized that studying extreme cases might provide an efficient route to gain a better understanding of human obesity and diabetes. A major breakthrough came via two British cousins of Punjabi origin.

A MIRACLE CURE

“We had been studying children with severe insulin resistance. We were contacted by a clinical geneticist who wanted our help in investigating two first cousins who were also extremely obese. We tried sequencing the DNA coding for leptin from the very small amounts of fat that we could get from a skin biopsy of one of the children but





the result was technically not very clean". A year later, he suggested they used a new blood assay to revisit and measure leptin levels in both the children.

"My colleague Sadaf Farooqi, who had just joined the lab, did the test, but she could not detect any leptin in the samples. As it was the first time she had run the assay, my first reaction was that the assay didn't work. But she repeated it and got the same result. When we went back to look at the sequencing gels from a year before, we could now see, that there were five instead of six bands, showing that these children had a shortened leptin molecule, which could not be secreted from their fat cells."

Leptin – known today as the satiety hormone – is made by fat cells and helps to regulate the energy balance by inhibiting hunger. By treating with leptin, Stephen O'Rahilly and his colleagues normalized the children's food intake in days and restored their body weight to normal – a miracle cure, but sadly only for a small number of patients. Since then O'Rahilly's group have found genes causing 17 extreme conditions of obesity and/or insulin-resistance.

"These extreme conditions have increased our understanding of the normal molecular mechanisms controlling human energy balance and the body's response to insulin. They have also given us clues to the basis of the more common forms of human obesity and insulin resistance. Today, we know that many obese people are obese because of how their genes are regulated in the brain. They struggle all their lives with their weight, and their appetite. They feel ashamed and are considered weak-willed and lazy. And despite developing diabetes, they just cannot get themselves to a safe weight."

A MISSING LINK

The importance of genetic imbalances for the development of obesity and diabetes is well-established today, but according to Stephen O'Rahilly one of the unanswered questions is why obesity is so strongly associated with insulin resistance. And as usual he looks to extremes to find answers – this time by looking at lipodystrophy, a



” The end goal is to provide a better molecular understanding of disease processes so improved therapy can be designed.”

rare cluster of disorders, characterized by too little rather than too much fat. These patients, however, have almost identical metabolic dysfunctionality to those with common ‘pre-diabetes’.

“The fact that the mutations are typically found in genes whose sole function is to regulate, release and store fats from the triglyceride droplet of the fat cell points very clearly to the enormous importance of lipid metabolism in fat cells to the control of glucose homeostasis in the whole body.”

The studies are now mirrored by genetic studies of insulin resistance in larger populations. The hope is that better knowledge about healthy fat storage can link the two major components of type 2 diabetes, obesity and insulin resistance, and how these two phenomena interlink to predispose metabolic diseases.

“This might indeed be the beginning of the end of the fight to find a link between obesity and diabetes. The end goal is to provide a better molecular understanding of disease processes so improved therapies can be designed,” Stephen O’Rahilly says.

STEPHEN O’RAHILLY BORN 1 APRIL 1958
 TITLE: PROFESSOR OF CLINICAL BIOCHEMISTRY AND MEDICINE
 POSITIONS: CO-DIRECTOR, WELLCOME TRUST-MRC INSTITUTE OF METABOLIC SCIENCE (IMS); DIRECTOR, UNIVERSITY OF CAMBRIDGE METABOLIC RESEARCH LABORATORIES (MRL); DIRECTOR, MRC METABOLIC DISEASES UNIT (MDU)

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 2007, the Foundation has donated more than DKK 6 billion, primarily for research within biomedicine and biotechnology 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.

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