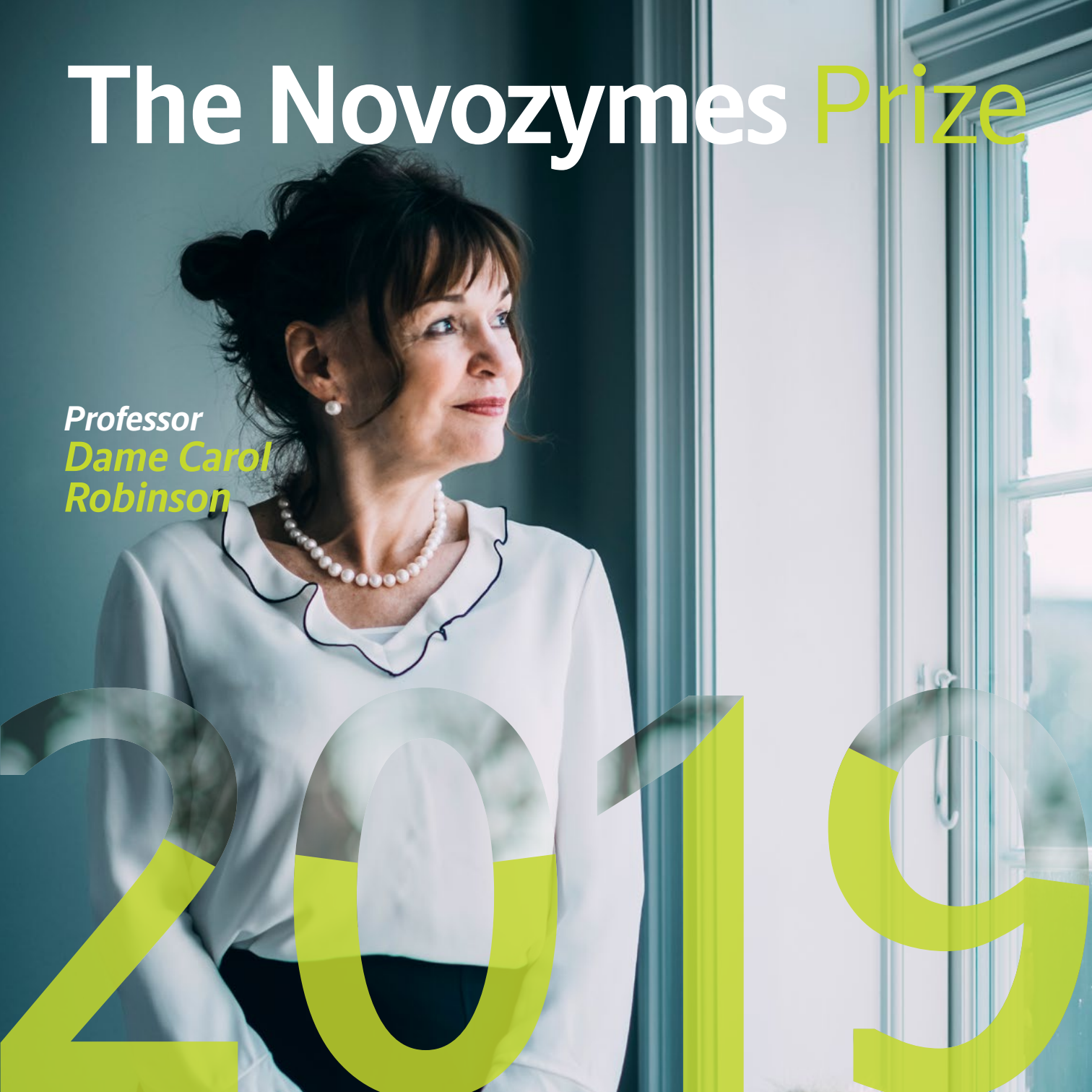
The Novozymes Prize



Professor
Dame Carol Robinson

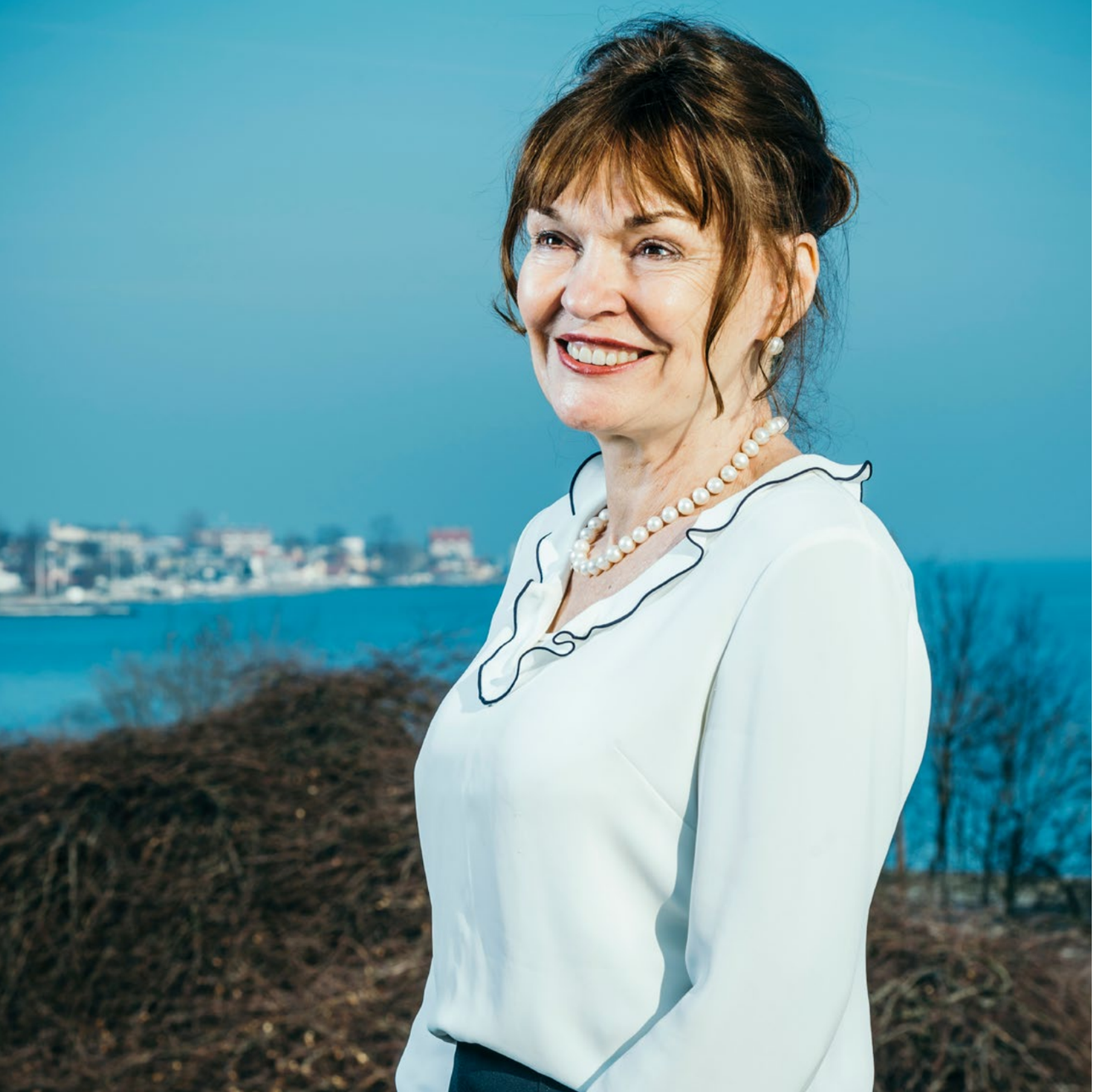
2019

Nomination of Carol Robinson

The 2019 Novozymes Prize is being awarded to Professor Dame Carol Robinson for her scientific breakthroughs in using mass spectrometry for proteome analysis, especially her pioneering work on using mass spectrometry for analysing protein complexes. Her methods are today widely used in the biotech industry and have contributed to identifying both new protein drugs and new drug targets.

Carol Robinson has followed a somewhat unusual career. After high school, she started to work on mass spectrometry as a laboratory technician at Pfizer in Kent, UK. By attending evening classes, she obtained a Higher National Degree in Chemistry and became a Graduate of the Royal Society of Chemistry. This led her to leave Pfizer to take an MSc degree in Chemistry at the University of Swansea. Following her MSc, she obtained a PhD at the University of Cambridge and thereafter pursued a one-year postdoctoral fellowship at the University of Bristol. She then took an 8-year career break to concentrate on her family and raise her three children. At the age of 35 years, she returned to science through a junior position to work on mass spectrometry in the group of Professor Dobson at the University of Oxford. Carol Robinson was encouraged to enter into the new field of proteomics that emerged at that time. However, when everyone in the proteomics field went for high-throughput analysis, she went for analysis of protein complexes. In 1999, she was appointed as a titular professor at the University of Oxford. Two years later, she returned to her alma mater, as Professor of Chemistry at the University of Cambridge, the first female professor in chemistry at the University. In 2006, she became a Royal Society Research Professor and, in 2009, she returned to the University of Oxford as Dr Lee's Professor of Chemistry, hereby becoming the first female chemistry professor also of this university.

Carol Robinson has pioneered using mass spectrometry for analysing protein complexes. She started to work on structural proteomics very early after the electrospray ionization technology itself became available. This enabled the introduction of intact proteins from solution to vacuum, motivating her to monitor protein-folding reactions by means of mass spectrometry. She developed a hydrogen–deuterium exchange method that could detect contact surfaces on proteins and applied it to study the folding of proteins. With this technique, protein structures could be preserved in vacuum, and this laid the foundation for studying large protein structures as well as protein–protein interactions using mass spectrometry. Following her initial work, she has now clearly established that protein complexes can retain their subunit stoichiometry in the mass spectrometer and that subunit organization and the binding of co-factors and other proteins can be studied using mass spectrometry.



Carol Robinson's research catalysed the development of tandem mass spectrometers with improved ion transmission and a higher mass-to-charge range than before, enabling intact protein ions with a mass-to-charge ratio in the range of 5000 to 50,000 daltons to be detected and characterized. This was necessary for detecting intact protein complexes with a molecular mass beyond 500,000 daltons. Such instruments are now available from several mass spectrometry manufacturers and are widely applied in the pharmaceutical industry to investigate intact protein biologics, such as antibodies and membrane receptors.

The methods developed by Carol Robinson have influenced biotechnology significantly. Thus, they have enabled studies of how large protein complexes assemble and how proteins interact with co-factors and other proteins. In pioneering work, she determined the conformation of GroEL, which is an important protein chaperone in the bacterium Escherichia coli that is conserved in humans. GroEL is a tetradecamer of a 58,000-dalton monomer with a total molecular weight of about 800,000 daltons, and it was only through the use of Carol Robinson's new method that it was possible to study this large protein and, more importantly, how it assists in folding other proteins. Of especially great biotechnological relevance, she was the first to demonstrate that her mass spectrometry technique could be used to determine the stoichiometry and binding interactions within an antibody–antigen complex, and the pharmaceutical industry now uses this routinely for characterizing antibodies. Her methods have hereby enabled more rapid antibody characterization and hence assist in advancing the use of antibodies for treating cancer and many other diseases.

Another significant technological breakthrough by Carol Robinson was her discovery of the crucial role lipids play in the assembly and structure of protein complexes. In a series of studies, she unravelled how lipids play a central role in the structure and function of rotary ATPases consisting of up to 29 subunits with a membrane-embedded rotor. In these studies, she demonstrated that the entire intact assembly can be projected into the gas phase, and from the mass spectra she discovered discrete tailored lipid plugs within the membrane rotors. Further, by discovering a novel nucleotide-binding site, she managed to uncover mechanistic details that underlie cooperativity and regulation in the context of this complex holoenzyme. Her more recent work on the role of lipids in membrane protein complexes has led her to study G protein–coupled receptors, a broad class of membrane proteins that are targets for many drugs. She demonstrated that it is possible to maintain drug binding to G protein–coupled receptors and hereby identify endogenous ligands to these proteins. This enables new drugs to be identified that can bind to G protein–coupled receptors and thereby target specific cellular processes.

Carol Robinson's production of scientific articles is truly impressive. She has a long list of scientific articles published in leading journals, including many in Nature and Science, and her more than 400 articles have been cited almost 40,000 times. She has received numerous awards, including the Rosalind Franklin Award from the Royal Society and the Sir Hans Krebs Lecture and Medal. She has been awarded at least 13 honorary doctorate degrees and has been elected a Foreign Associate of the United States National Academy of Sciences and a fellow of the Royal Society. She currently serves as President of the Royal Society of Chemistry. In 2013, Carol Robinson was appointed Dame Commander of the Order of the British Empire.

In conclusion, Carol Robinson is creative, innovative and fearless. She pioneered the use of mass spectrometry for analysing protein complexes and hereby showed that protein interactions can be studied using this analytical technique. She thereby almost single-handedly founded a subfield of mass spectrometry proteomics that has turned out to be of great importance. She is a role model for all scientists in her fearless pursuit of an initially controversial notion that has now turned into a new and highly productive mainstream. She also serves as an inspiration for many female scientists looking for role models, as her own road to success challenges the notion that a career cannot be interrupted for family reasons. Her work represents outstanding research contributions that have benefitted the development of innovative biotechnological solutions, and Carol Robinson is therefore clearly a worthy recipient of the 2019 Novozymes Prize.

How life's building blocks got their freedom of movement

By Morten Busch

The myriad processes that take place in our body's cells are the basis of life as we know it. Since cells are filled with fluid, Carol Robinson created a lot of attention by setting out to investigate life's processes in a vacuum. Despite massive resistance, she persevered. Now she is receiving the Novozymes Prize for founding a new subfield of mass spectrometry to investigate the shape of proteins and how they interact. Today, this technique is used to identify brand-new targets for drugs.

Some of the most important proteins in our bodies are on the surface of all cells. The membrane proteins control the transport in and out of cells and are key to how cells communicate. This makes membrane proteins hugely important drug targets. However, since the proteins are situated inside hydrophobic membranes, researchers have had great difficulty in figuring out how the proteins assemble and interact with other molecules.

Carol Robinson is receiving the 2019 Novozymes Prize for her scientific breakthroughs in using mass spectrometry – especially her pioneering work on using mass spectrometry for analysing protein complexes.

"The membrane proteins are the really critical complexes and are incredibly hard to study, because of this whole phase issue, where they sit in the oily phase. What we did was to coat them in detergent – effectively in soap bubbles – and then we release them into a mass spectrometer. Miraculously, they stay intact in a folded stage, so we can examine their 3D structure but also how they bind to other proteins or lipids," explains Carol Robinson, Professor Dame, Department of Chemistry, University of Oxford.

"I am still hugely fascinated with seeing a beam of ions fly through a mass spectrometer and what you can learn from the spectra. A mass spectrometry spectrum is a bit like a sudoku puzzle. You start to get all possibilities and then you can solve the problem and you feel tremendously satisfied."

An unusual path to success

Mass spectrometry was originally developed to determine the mass of small molecules. In a mass spectrometer, the molecules are ionized and deflected in a magnetic field during their flight. Heavy molecules are hardly affected in their flight, whereas lighter ones are deflected more. Measuring how far the ions fly can determine how much they weigh. The molecules are sorted based on their mass-to-charge ratio.

"I am still hugely fascinated with seeing a beam of ions fly through a mass spectrometer and what you can learn from the spectra. A mass spectrometry spectrum is a bit like a sudoku puzzle. You start to get all possibilities and then you can solve the problem and you feel tremendously satisfied."

Carol Robinson ending up as the first woman chemistry professor at Oxford was not a given, and her journey has been quite unusual. After leaving school at 16, she joined Pfizer as a technician working in the mass spectrometry laboratory. One day, one of Carol's colleagues recognized that she had very special potential.

"They encouraged me to do seven years of part-time study. It was the long haul, and then I was delighted to be accepted at the University of Cambridge to do a PhD. Traditionally, mass spectra were just used to determine mass. In my PhD project, I was looking at how we could also use the mass spectrometer to determine the sequence of small fragments of a protein."

Molecular elephants with wings

Since proteins are built from specific sequences of the 21 amino acids – 21 different building blocks with different masses – the researchers managed to identify the protein sequences by looking at the distance between the peaks in the spectra. Carol Robinson's career was on track, but then something happened.

"I did something that was considered unusual. I took a career break for eight years, which was bit unconventional in those days. I really enjoyed the time at home with my three children and then went back to Oxford."

At 35 years old, she returned to science through a junior position working on mass spectrometry in Chris Dobson's group at the University of Oxford. While she was away, some revolutionary things had happened in mass spectrometry.

"I was encouraged to enter the new field of proteomics that emerged at that time. But we were not just looking at peptides and sequencing the amino acids along small chains. We were now looking at whole proteins, which are huge in terms of mass spectrometry."

Instead of being just a few hundred mass units (daltons), the proteins are between 20,000 and 30,000 daltons.

"The challenge was how to make these huge molecules fly in the mass spectrometer. John Fenn, one of my science heroes who received part of the Nobel Prize for discovering electrospray mass spectrometry, tried putting it like this: 'Well, I gave molecular elephants wings'."

Spray-painting the proteins

Although Fenn got the very large protein molecules to fly, Carol Robinson wanted more – much more. She wanted to use the mass spectrometer to determine the very shape of the protein. She started to work on structural proteomics very early after the electrospray ionization technology became available. This enabled intact proteins to be introduced from solution to vacuum.

She got a crazy idea: if she could spray-paint the molecules, she could separate them based on how much paint they were covered by. The ultimate goal was to monitor protein-folding reactions by using mass spectrometry.

"Spray-painting an unfolded protein would take a lot of paint. But if it is folded into a very compact structure and then painted, I would not use so much paint, and that is exactly what we do. We spray it with deuterium, which weighs more than hydrogen. If an area of a protein is unfolded, hydrogen atoms are exposed and exchanged with deuterium. But if it is tightly folded, it won't, so it weighs less."

Carol Robinson developed a hydrogen-deuterium exchange method that could detect contact surfaces on proteins and applied it to study the folding of proteins. With this technique, protein structures could be preserved in vacuum, and this laid the basis for studying the structure of large proteins as well as protein–protein interactions using mass spectrometry.

A damning commentary

Carol Robinson used this technique to determine the folding state of a protein. However, her scientific colleagues thought she was crazy. At the molecular level, life as we know it occurs in water. A mass spectrometer has a vacuum.

"So it was really quite a damning commentary, and it was in a very respected journal: *Proceedings of the National Academy of Sciences* in the United States, so actually it was very hard to publish, because I would always have this cited when I submitted my research papers. People would say, 'Well, haven't you read this, it is a crazy idea.' I would say: 'Yes, I know, but I really believe it'."

In her quest to prove that mass spectrometers could be used to detect even large intact proteins, Carol Robinson had to break the existing mould of what was possible. This required developing a tandem mass spectrometer with improved ion transmission and a higher mass-to-charge range than before.

"At that time, the spectrometers typically took particles up to about 4000 mass-to-charge ratio. We thought we would be a bit revolutionary and go up to 32,000. That is a huge jump, and I remember people sort of cautioning me against that. They said just go to 8000. I said: 'No, 32,000 would allow us to do so much,' and I got one made and I bought it."

The new mass spectrometers proved Carol Robinson's point that protein complexes retain their structure in a vacuum; they also enabled researchers to detect intact protein complexes with a molecular mass above 500,000 daltons and to study subunit organization.

"Our experiments clearly established that protein complexes retain their subunit stoichiometry in the mass spectrometer. Today, these instruments are available from several mass spectrometry manufacturers and are widely applied in the pharmaceutical industry to investigate intact protein biopharmaceuticals, such as antibodies and membrane receptors, but at that time it was a small revolution."

A big breakthrough

Rather than just trying to show that they could do clever things with a mass spectrometer, Carol Robinson chose to take things to a new level.

"We thought maybe we can now answer some really key questions: for example, how the proteins come together in complexes. If we disrupted them, maybe they would fall apart in pairs, in threes or any other combination. And we could then tell from these interactions how they were assembled."

This new method enabled Carol Robinson and her colleagues to study how large protein complexes assemble and how proteins interact with co-factors and other proteins. In a pioneering work, she determined the conformation of GroEL, an important protein chaperone in the bacterium *Escherichia coli* that is highly conserved in humans.

"Chaperones protect other proteins while they are folding, creating a sort of protective environment. Our technique enabled us to examine its amazing structure. It has 14 copies of the same protein that form these two rings, and inside is the folding protein, and we started to look at how this protected environment would change folding."

Ever since then, Carol Robinson's group has studied even more important and complex structures such as binding interactions within an antibody–antigen complex, and this method is now used routinely for characterizing antibodies in the pharmaceutical industry.

"This has enabled more rapid characterization of antibodies and has advanced their use for treating cancer and many other diseases."

Giant soap bubbles

These methods have established Carol Robinson as a true pioneer in using mass spectrometry for analysing protein complexes. She has almost single-handedly founded a subfield of mass spectrometry proteomics, despite fierce criticism. This has required being fearless, innovative and creative. The latter became obvious when she decided to study some of the most challenging and important structures in biology – membrane proteins.

"Membrane proteins are incredibly hard to study, because one part of the protein exists inside an oily hydrophobic membrane, whereas the parts inside and outside of the cell are hydrophilic. We got the idea to coat them in detergent and then send them into the mass spectrometer in a giant soap bubble. And miraculously, this bubble shield really protects them, so they are released into the gas phase intact in a folded state."

In a series of landmark studies, Carol Robinson unravelled the structure of the proteins synthesizing our cell's energy currency, ATP, and how lipids play a key role in the structure and function of rotary ATPases, molecular motors involved in converting biological energy in our cells. Her more recent work on the role of lipids in membrane protein complexes has led her to study G protein–coupled receptors.

"These membrane proteins are targets for many drugs. We demonstrated that it was possible to maintain drug binding to the receptors and thereby identify natural ligands to these proteins. This enables new drugs to be identified that can bind to the receptors and thus target specific cellular processes."

Freedom of movement

Carol Robinson's group is now making exciting inroads into how fields related to mass spectrometry can dictate how drug discovery is performed. Once more, she has proved her critics wrong, who suggested that she had to use other techniques such as nuclear magnetic resonance or electron microscopy to study the structures of proteins.

"But if you think about a mass spectrometer, it is not in solution and it is not in a solid as a crystal would be, so it is not constrained. If you try to run through a swimming pool, it is really hard work. But if you want to express yourself, you want to be out in the air, so I think you could have your protein molecules in the gas phase rather than seeing it as a disadvantage."

Her critics claimed that protein folding in a vacuum is madness, but Carol Robinson sees it as an advantage, because the proteins maximize their freedom of movement. They can express themselves, and something can be learned from that movement. However, as always, scientists need to accept that, though they find their ideas exciting, others might not.

"Sadly, if you do something for the first time, a lot of people do not believe it. So there was criticism of the first experiments, because people said: 'How can you measure folding in a mass spectrometer?' I always wanted to be able to do something for human health, and everybody would say to me: 'Well, that's really never going to happen,' but I think you just need to have the belief that it will."

So most importantly – according to Carol Robinson – you need to believe in your own ideas and follow your passion.

"I have had a great career in science, but I like to think that anyone can do this. I want to dispel the myth that you have to be a genius. You need imagination and creativity. Drive and energy. These are the most important things."

The 2019 Novozymes Prize was awarded at a ceremony on Friday, 15 March 2019 to Carol Robinson, Dr Lee's Professor of Chemistry, University of Oxford.

Curriculum Vitae

About Professor Dame Carol Robinson

Education

1982: Doctor of Philosophy, University of Cambridge, United Kingdom

1980: Master of Science, University of Wales, United Kingdom

1979: Graduate of the Royal Society of Chemistry, Medway College of Technology, Kent, United Kingdom

1976: ONC and HNC in Chemistry, Canterbury College of Technology, Kent, United Kingdom

Latest academic appointments

2009–: Professorial Fellow, Exeter College, Oxford, United Kingdom

2009–: Dr Lee's Professor of Chemistry, University of Oxford, United Kingdom

2006–2016: Royal Society Research Professorship

2003–2009: Senior Research Fellow, Churchill College, University of Cambridge, United Kingdom

2001–2009: Professor of Mass Spectrometry, Department of Chemistry, University of Cambridge, United Kingdom

1999–2001: Titular Professor, University of Oxford, United Kingdom

Accolades and distinctions

2018: President of the Royal Society of Chemistry

2017: Foreign Associate of the National Academy of Sciences, United States

2013: Dame Commander of the Order of the British Empire

2009: Fellow of the Academy of Medical Sciences

2004: Fellow of the Royal Society

Selected medals, awards and prizes

2018: Frank H. Field and Joe L. Franklin Award for Outstanding Achievement in Mass Spectrometry, American Chemical Society

2017: Sir Hans Krebs Lecture and Medal, Federation of European Biochemical Societies

2015: L'Oreal-UNESCO for Women in Science Award

2014: Kaj Linderstrøm-Lang Prize, Carlsberg Research Center

2011: Interdisciplinary Prize, Royal Society of Chemistry

2011: FEBS | EMBO Women in Science Award

The Novozymes Prize Committee

The Novozymes Prize is a European research award instituted by the Novo Nordisk Foundation. The Novozymes Prize is awarded in the name and with the funds of the Foundation. The purpose of the Prize is to raise awareness of basic and applied biotechnology research.

The Novozymes Prize is awarded to recognize outstanding research or technology contributions that benefit the development of biotechnological science for innovative solutions. It consists of a funding amount for the Prize recipient's research of DKK 2.5 million and a personal award of DKK 0.5 million. An additional element of the Prize is an international symposium within the Prize recipient's field of research. Prize recipients must have a current position at a public or non-profit research institution in a European country. They may previously have worked anywhere and may have any nationality.

The Novozymes Prize is awarded by a prize committee that selects the successful candidate based on scientific achievements after a confidential nomination and review process.

The members of the Novozymes Prize Committee are appointed by the Novo Nordisk Foundation Board of Directors. The 2019 Committee comprised the following seven members:

- Jens Nielsen, professor, chair
- Søren Molin, professor
- Henrik Callesen, professor
- Liisa Viikari, professor emeritus
- Michael Broberg Palmgren, professor
- Gunnar von Heijne, professor
- Birgitte Nauntofte, CEO, Novo Nordisk Foundation

The award event takes place in the spring at the Novo Nordisk Foundation Prize Celebration, at which the Novo Nordisk Prize is also awarded.

In addition, in celebration of the award, the recipient gives a lecture lasting about 1 hour at his or her workplace. Before the end of the year, the recipient and the Foundation arrange an international symposium within the scientific field of the Prize recipient.

Candidates for the Novozymes Prize can be nominated by the Prize Committee and former Prize recipients. In addition, a call for nominations is published in the spring, and candidates can be nominated based on this call.

The Committee meetings thoroughly discuss the nominated candidates with regard to their research contribution and impact, and a comprehensive bibliometric report is produced. A few candidates are then selected for thorough international peer review. Based on the international peer reviews, the Committee reaches a decision about the year's Prize recipient.







Previous recipients of

The Novozymes Prize 2015–2018

2015	Professor, Director Bernard Henrissat
2016	Professor Jens Nielsen
2017	Professor Emmanuelle Charpentier
	Professor Virginijus Siksnys
2018	Professor Gunnar von Heijne

Novo Nordisk Foundation
Tuborg Havnevej 19
DK-2900 Hellerup,
Denmark
Phone: +45 3527 6600

nnfond@novo.dk
www.novonordiskfoundation.com

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nordisk
fonden