The Novo Nordisk Prize

Professor

Jørgen Kjems
The Novo Nordisk Foundation is awarding the 2018 Novo Nordisk Prize to Professor, PhD Jørgen Kjems for his pioneering studies demonstrating how non-coding ribonucleic acid (non-coding RNA) contributes to cell maintenance and disease development.

Jørgen Kjems is 59 years old. He graduated with an MSc in chemistry and physics from Aarhus University in 1986. Subsequently, he carried out his PhD studies at the Department of Chemistry of Aarhus University and obtained a PhD degree in 1989 for work on RNA splicing in prokaryotes with Professor Roger Garrett as the supervisor. Jørgen Kjems then moved to Boston, where he spent 3 years from 1989 to 1992, first at Harvard Medical School and then at the Massachusetts Institute of Technology, to pursue his postdoctoral career in the laboratory of Phillip A. Sharp, who won the Nobel Prize in Medicine in 1992 for his discovery of RNA splicing.

During his postdoctoral career, Jørgen Kjems focused on RNA splicing and transport in HIV-1, describing the intrinsic role of the HIV-1-encoded protein Rev in regulating HIV-1 gene expression. He mapped the interaction of the Rev protein with the HIV-1-encoded RNA element RRE and showed that a short peptide in the Rev protein affects the alternative splicing of HIV-1. After returning to Denmark, Jørgen Kjems established his own laboratory at the Department of Molecular Biology and Genetics, Aarhus University and continued his research in the highly competitive HIV-1 field.

In 1994, he became an Associate Professor and, in 2003, Professor of Molecular Biology and Nanoscience at Aarhus University. In 2010, he was appointed Director of the Lundbeck Foundation Nanomedicine Centre for Individualized Management of Tissue Damage and Regeneration (LUNA) at Aarhus University. In 2014, Jørgen Kjems became Director of the Interdisciplinary Nanoscience Center (iNANO) at Aarhus University and continued his highly innovative research at the same time. In 2017, Jørgen Kjems was further appointed Director of CellPAT (Centre for Cellular Cell Patterns) at Aarhus University funded by the Danish National Research Foundation. CellPAT aims to identify how cells “talk” to each other and thereby make it possible to prevent or correct the type of communication errors that lead to disease.

Nomination of Jørgen Kjems
Living cells contain RNA, which is a polymeric molecule essential in various biological processes, including coding, decoding, regulation and expression of genes. RNA and DNA are nucleic acids, and these plus lipids, proteins and carbohydrates constitute the four major types of macromolecules essential for all known forms of life. RNA is assembled as a chain of nucleotides and usually appears in nature as a single strand folded onto itself.

Cellular organisms use messenger RNA (mRNA) to convey genetic information that carries information from DNA to the ribosome-directing synthesis of specific proteins, and many viruses encode their genetic information using an RNA genome. However, many RNAs do not code for protein, and it is estimated that more than 90% of the transcriptional output is non-coding RNA in eukaryotes. Jørgen Kjems and his colleagues have discovered many completely unforeseen ways in which RNA regulates the phenotype beyond encoding proteins. These discoveries are leading to new ways in which human diseases can be diagnosed and treated.

Jørgen Kjems started his scientific career with pioneering contributions to science. He was among the first to discover RNA splicing in prokaryotes (unicellular organisms without a nucleus or any other membrane-bound organelle such as bacteria and Archaea). Jørgen Kjems contributed to the surprising discovery that extreme thermophiles, living in hot springs at more than 100°C, were “eukaryote-like” by having large introns in their ribosomal genes, a discovery that was published in Nature in 1985.

Following this discovery, Jørgen Kjems and colleagues published a series of papers in Cell, Proceedings of the National Academy of Sciences of the United States of America and EMBO Journal describing the mechanism behind Archaea splicing. Surprisingly, they found that intronic RNA was cleaved out of the transcript by enzymes to form a circular protein RNA encoding a protein, a process with some resemblance to transfer RNA splicing in eukaryotes.

In 2011, Jørgen Kjems’s group discovered circular RNA as a highly expressed RNA specie in brain tissue and proposed that this circular RNA could regulate the expression of other genes. Further, in 2013, he published in Nature that this circular RNA could function as a microRNA “sponge”. This microRNA sponge is a sequence that sequesters the available pool of a given microRNA to reduce its capacity to act on target genes. At the same time, it became clear that the world of circular RNA is immense, with more than 10,000 species detected in brain and cancer tissue.

This adds a whole new perspective to diagnosing and preventing disease, and to highlight this, Jørgen Kjems and colleagues recently published that circular RNA expression levels can predict the chances of bladder cancer reoccurring. Evidence, pioneered from some of his previous work, also suggests that circular RNA can regulate the activity of cancer-associated microRNA and hence itself be used as a target or a novel type of gene medicine.
Along with the milestone studies in the area of basic RNA biology, his laboratory has also provided fundamental scientific contributions describing novel methods for delivery of RNA therapeutics, particularly in relation to RNA interference. RNA interference has been seen as the new killer drug in its capacity to regulate malignant genes in a highly controlled fashion. However, delivery of such large molecules was a major hurdle in exploiting RNA interference. Jørgen Kjems contributed to this by using the polysaccharide chitosan to deliver small interfering RNA, highlighting the application of this novel chitosan-based system in RNA-mediated therapy of diseases. In particular, he demonstrated therapeutic efficacy of RNA-loaded chitosan nanoparticles in preclinical rheumatoid arthritis and skin fibrosis models.

Jørgen Kjems’s scientific activities over 30 years have been technically and conceptually innovative. Throughout his career, his comprehensive, systematic and highly original research has aimed at producing groundbreaking knowledge about non-coding RNA and related areas. The wealth of scientific results obtained by Jørgen Kjems through multidisciplinary approaches is outstanding. Jørgen Kjems has focused his research on several highly original fields, which are currently hot topics. This is remarkable and outstanding. In addition to the understanding of how non-coding RNA contributes to cell maintenance and disease development with a primary aim of defining new targets for disease intervention, Jørgen Kjems has made significant scientific contributions to novel bioimaging and delivery systems for gene medicine, including silencing RNA, microRNA mimics and antisense targeting microRNAs, with a specific focus on inflammation and cancer.

Moreover, his group has provided impressive original contributions within the nanotech field with the design and construction of a functionalized self-assembled DNA box, where the lid can be opened and closed on command. Likewise, he has made nanostructures capable of complex biosensing, coupled with controlled action for drug release, enzyme activation and receptor signalling. These approaches have shown to be important in investigating the basis of diseases, including nervous system disorders, cardiovascular diseases and cancer at the molecular level.

Jørgen Kjems has participated in many collaborations with highly esteemed researchers in both Denmark and elsewhere. Jørgen Kjems has been honoured with several national and international prizes and awards. Further, he has attracted considerable external funding, including extensive research funding. He has shown great leadership and mentorship in the field of non-coding RNA, welcoming and promoting a wide range of researchers. Jørgen Kjems has led and mentored a large number of excellent scientists and numerous young researchers and PhD students who are now continuing their own research at globally leading research institutions and companies, and he has attracted numerous researchers to work in Denmark.

He has an impressive scientific output of more than 250 original studies, many published in high-impact journals such as Nature, Science, Cell, EMBO Journal and Proceedings of the National Academy of Sciences of the United States of America. He has also authored several review articles in his field, and many of his reviews and original articles are highly cited in the scientific literature.

In summary, the Novo Nordisk Prize Committee finds that Jørgen Kjems is a worthy recipient of the 2018 Novo Nordisk Prize based on his systematic, comprehensive, innovative and highly original international research on non-coding RNA and for the impact of this field on medical science.

The circles of life: birth and childhood; old age and death. By day and by season; tide and tempest. People’s cells are also propelled by this regularity. Our genes – DNA – is transcribed to RNA, which in turn is converted to proteins, the building blocks of life, before again being broken down and reused in a new cycle.

Jørgen Kjems, the recipient of this year’s Novo Nordisk Prize, has often been accused of deviating from the research cycle. Instead of focusing on one topic throughout his career, he has constantly sought out new avenues – despite being part of discovering, early in his career, an important deviation in the life cycle of cells: more than 90% of the RNA cells produce is never converted to protein. Instead, it is a key to how our body regulates itself and presumably also why humans have been so successful as a species.

"Looking, for example, at a worm and a person, both have approximately the same number of genes and the same amount of DNA. Actually, a tomato and a carp have much more DNA than a person. It is not DNA that is so important. However, if you look at how RNA is produced, then you see the complexity of a human being, and this is why our brains are so incredibly complex."
"But it is as if nature has many more structures and large molecules, many more strings to play on. Soon, my goal was to try to understand them, so I began to study molecules in nature, and it seemed natural to take account of the hot topic in the mid-1980s – DNA and how its biological cousin, RNA, is translated into proteins."

**Living at 100°C in volcanic hot springs**

At that time, Jørgen Kjems therefore focused on the key dogma that “we studied ribosomes in the Archaea microorganisms (single-cell prokaryotes similar to bacteria) living in volcanic hot springs at 100°C. What motivated me right from the start was simply understanding how such a mechanism can function at this temperature. In the midst of my studies, it was like being struck by lightning, which often happens in research when something new actually happens."

"We began to carry out my MSc project on the structure of ribosomal RNA which at those days was considered to be the skeleton of the ribosome, the machine making the proteins in the cell."

Based on his technical interest, Jørgen Kjems became interested in understanding the mechanism, but while he was investigating ribosomes, something else grabbed his attention. At that time, a discovery kick-started Jørgen Kjems’ RNA research career. At the beginning, researchers believed that the RNA that had been cleaved out was waste that had been jettisoned while the rest had been turned into useful information for protein production in the cell. However, on further investigation, it was discovered that most of the RNA produced in the cell had no apparent function.

"This process actually removed almost 95% of the RNA. At that time, it was not really understood: why do we have so much extra RNA. Why is our genome so large if we only use a small percentage of it? It was not until the late 1980s and the early 1990s that it began to dawn on people that this RNA must have some function."

**HIV hides**

In 1989, it was time for Jørgen Kjems to take the RNA a step further. After completing his PhD project, he wanted to go abroad as a postdoctoral fellow. He moved first to Harvard Medical School and later to Massachusetts Institute of Technology (MIT), working in the laboratory of Philip A. Sharp, who later received a Nobel Prize for his discovery of RNA splicing.

"It was actually an incredibly fascinating time. It was like the peak of the virus is doing. It is only when it starts to produce new virus that it suddenly produce more than 60 different proteins by splicing one small piece of information material. For a virus to thrive, it must not take too much RNA along, but it must still be capable of making a complex expression in the host. HIV can suddenly produce more than 60 different proteins by splicing one small RNA. Human cells therefore have difficulty finding out what the virus is doing. It is only when it starts to produce new virus that it first signals its presence to our immune system. But then it is too late because the virus has spread around the body."

HIV has a very simple genome comprising a small RNA that does not code for very much by itself. But then something amazing happens. The RNA is cleaved into pieces and reassembled in different ways and suddenly more than 60 proteins can be made from one small RNA, thus proving that many things can be made from one extremely small piece of information material.

"But it is as if nature has many more structures and large molecules, many more strings to play on. Soon, my goal was to try to understand them, so I began to study molecules in nature, and it seemed natural to take account of the hot topic in the mid-1980s – DNA and how its biological cousin, RNA, is translated into proteins."

**Microscopic medicine**

When Jørgen Kjems returned from MIT to Denmark in 1992, he continued to study the processes surrounding the intricate RNA splicing system of HIV. However, before long, a completely new phenomenon appeared – actually a phenomenon that had been partly discovered by his former mentor at MIT, Philip A. Sharp.

"I also got a head start on this when I heard from my old laboratory that something new was about to happen. This new phenomenon is called RNA interference, which is what happens when cells produce a tiny RNA that can regulate all the other RNA. It turns out that this tiny regulator has an incredibly important function."

Researchers called this tiny regulator microRNA, and it soon became apparent that it plays an essential role in regulating cellular metabolism and gene expression. MicroRNA can bind to other RNA molecules that the cell uses as a template when it needs to produce protein. The production of specific proteins is in this way arrested.

"We soon discovered that microRNAs have such a major effect on various diseases, so we quickly began to think about drugs, because if we could deliver these tiny microRNAs or inhibitors of microRNA into cells and thereby treat nearly any irregularity in the cells associated with a disease."

**Shrimp shells and origami boxes**

It soon became apparent, however, that getting the bloodstream microRNA to the target location, such as cancer cells, is the challenge. As on many occasions previously, Jørgen Kjems decided to pursue this specific problem. In 2008, he therefore began studying drug delivery methods. Since then, Jørgen Kjems’ laboratory has followed two tracks: basic studies of RNA and application-oriented research on drug delivery.

"We worked with waste from shrimp-processing factories. This was a large quantity of crushed shrimp shells from which we made various
compounds. We used the polymeric sugar molecule, chitosan, which was previously discarded, to envelop the tiny RNAs, and we demonstrated that we could deliver them to the diseased cells – in both the lungs and other sites in the body and demonstrated that we were able to treat some diseases in mice.”

Another breakthrough came rapidly thereafter. This relates to how our hereditary material is constructed using specific building blocks that complement one other, and so predictably that they can actually be used as components to build things from the bottom up. So the question was: could they design tiny DNA capsules into which they could place some RNA medicine?

Jørgen Kjems’ postdoctoral colleague Ebbe Sloth Andersen took a chance and purchased the necessary ingredients.

“I thought ‘this cannot possibly work... but it did’. The fascinating thing is that one just needs to mix things. This is like dismantling a car and putting all the parts into a big bag and shaking it. The car reassembles itself, and then a box emerges without one having to do anything other than watch the process. So this is why, every now and again, you should take a big chance because you can make a big breakthrough. We did that.”

The DNA origami boxes from Aarhus became world famous in the article published in Nature. Today, there are even larger copies in various museums in Germany and elsewhere. It was a major breakthrough that both the drugs and the capsule for transporting it could be made using nature’s own components, DNA and RNA.

Kidneys, liver and maybe the heart

The potential of combining tiny RNAs and physical structures became clear as early as 2010, when Jørgen Kjems received a large grant from the Lundbeck Foundation focusing on making body implants from various types of biodegradable plastic materials.

“We did this by using stem cells inserted in plastic scaffolding using a 3D printer. This method enables the body to form new tissue. We could make new bone, fat and also cartilage.”

Just like the other times Jørgen Kjems suddenly had a new discovery on his hands, he described it as being hit by lightning. In 2011, it happened again.

“We were studying these tiny RNAs, as we had done for many years. Thomas Hansen, a PhD student in my laboratory, had obtained some curious results at that time that could not be explained by normal cellular mechanisms. For me it was like déjà vu from the start of my early days as a PhD student.”

The circular RNA molecules from Archaea had suddenly reappeared. Jørgen Kjems decided to try to understand these circular RNAs. How are they made in the cell? What do they do? How do they work? What regulates them? It turned out to be a whole new and interesting world.

“These circular RNAs are very stable and are highly expressed in the central nervous system and tumours in particular. They can act as a sponge that absorbs microRNAs so that they do not influence other processes. This is a very common phenomenon in our cells: processes are regulated by taking them and preventing them from doing what they were about to do. This is therefore a new way of being able to regulate microRNA and thus our health.”

Leave without looking back

The circle was thus unbroken. Jørgen Kjems has confirmed that occasionally wandering off into different and uncharted territories is not a problem. According to Kjems, he has just had to soak up the punches that people from other fields have occasionally thrown in his direction.

“Sometimes people think that you are a dilettante because you explore several fields. Sometimes people believe that if you are not an expert, so you should stay away. But I believe that this is a totally incorrect perception, because you have to move completely ignorant into a field to understand it. And it is naturally correct to consult experts and speak with them, learn new directions.”

Throughout his career, Jørgen Kjems has taken many gambles and made some blunders in other fields. In his view, this is the only way to build bridges between fields and to determine where the boundaries are between what one knows and does not know. In any case, he has not considered stopping. The interesting horizons and advances in science usually occur between the established fields.

“If you have various tracks running in the laboratory, some of them usually to look more promising. I probably tend to move in that precise direction. So there may be other tracks that die out ever so gradually. I believe that this is an evolution of processes – similar to how nature works.”

The answer is in the borderland

The new direction Jørgen Kjems has chosen to explore is the brain, and specifically epilepsy, one way being through a major EU project discovering microRNAs that appear to trigger epilepsy. They discovered that symptoms of epilepsy can be eliminated by firing tiny antisense molecules attached firmly to the microRNAs into the brain – but currently only in mice.

“This is an example of one disease, but it sets the scene that these circular RNAs and microRNAs play a role in all other nervous system diseases. We are also looking at Alzheimer’s and amyotrophic lateral sclerosis (ALS), and the circular RNA appears to play a role –
especially in diseases of the brain – presumably because this is the most complex and fascinating organ in our body."

A new basic research centre of excellence, CellPat, headed by Jørgen Kjems and located at the Interdisciplinary Nanoscience Center (iNANO) at Aarhus University will investigate how to use nature’s building blocks such as RNA as novel medicine. The centre will focus on how the immune system can distinguish between external threats and the body itself and why the mechanisms sometimes fail and trigger such autoimmune diseases as rheumatoid arthritis, multiple sclerosis and diabetes. It will also try to improve the use of the patient’s own stem cells to restore human body parts. The recipe is the same as always – interdisciplinarity.

"Today, we know that really new things only emerge in the borderland between fields. We need to ensure that people do not get too obsessed about their small projects. They need to get out and interact and discuss the major problems and then try and solve them together because this cannot be done alone. The important thing is to bring people together so that the whole is greater than the sum of its parts."

The 2018 Novo Nordisk Prize is being awarded to Jørgen Kjems for his pioneering studies demonstrating how non-coding RNA contributes to cell maintenance and disease development. Although he has been honoured with several national and international prizes and awards, the Novo Nordisk Prize is both a surprising and long-overdue recognition of exactly this approach.

"I do not consider myself as having been too obsessed with my field. I definitely did not count on the Prize being given to someone like me who had somewhat drifted around from basic research to medical applications. So I am naturally very grateful for the recognition that interdisciplinarity and a wide-ranging vision can also be useful in medicine."

About Jørgen Kjems
Born 1958 in Gråsten, Denmark
Professor, Department of Molecular Biology and Genetics and Interdisciplinary Nanoscience Center (iNANO), Aarhus University

2017–:
Director, Centre for Cellular Signal Patterns (CellPAT), Aarhus University, funded by the Danish National Research Foundation

2014–2018:
Director, Interdisciplinary Nanoscience Center (iNANO), Aarhus University

2010–2016:
Director, Lundbeck Foundation Nanomedicine Centre for Individualized Management of Tissue Damage and Regeneration (LUNA), Aarhus University

2003–:
Professor of Molecular Biology and Nanoscience, Aarhus University

1990–1992:
Postdoctoral fellow, laboratory of Nobel laureate Phillip A. Sharp, Massachusetts Institute of Technology, Cambridge, MA, USA

1989–1990:
Postdoctoral fellow, laboratory of Cox Terhorst, Harvard Medical School, Boston, MA, USA

1989:
PhD in biostructural chemistry, Aarhus University

1986:
MSc in biostructural chemistry, Aarhus University
The Novo Nordisk Prize Committee

The Novo Nordisk Prize, which was first conferred in 1963, is awarded to recognize unique medical research or other research contributions that benefit medical science. The Prize is awarded for a predominantly Danish contribution.

The Prize is awarded annually and is accompanied by DKK 3 million – of which DKK 500,000 is a personal award, with the remaining amount as an allowance for research purposes within the Prize recipient’s field of expertise. The Prize may not be awarded to members of the Board of the Novo Nordisk Foundation or members of committees or to members of boards, directors or employees of the Novo Group. The Novo Nordisk Prize Committee awards the Prize based on suggestions from past Prize recipients or members of the Prize Committee.

The Novo Nordisk Foundation’s Board of Directors appoints the members of the Prize Committee. The Committee currently comprises 7 members:

- Jørgen Frøkiær, professor, chair
- Lars Fugger, professor
- Marja Jäättelä, professor
- Birgitte Nauntofte, CEO, Novo Nordisk Foundation
- Thue W. Schwartz, professor
- Henrik Toft Sørensen, professor
- Anne Tybjerg Hansen, professor

The Committee meetings thoroughly discuss the nominated candidates with regard to their research contribution and impact, and a comprehensive bibliometric report is produced. A limited number of 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.

The Foundation’s collaborating partners and the Prize recipient’s guests attend the award ceremony in the spring, where the research of the recipient is briefly presented. 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.

Previous recipients of The Novo Nordisk Prize 1963–2017

1963 Professor, dr.med. Erik Warburg
1964 Chief physician, dr.med. Claus Bruun
1965 Professor, dr.med. J. C. Skou
1966 Professor, dr.med. Jørn Hess Thygesen
1967 Chief Physician, dr.med. Knud Lundtæk
1968 Chief physician, dr.med. Niels A. Lassen
1969 Professor, dr.phil. Erik Zeuthen
1970 Professor, dr.med. Poul Astrup
1971 Professor, dr.med. Mogens Schou
1972 Chief Physician, dr.med. J. Chr. Sim
1973 Professor, mag.scient. K. A. Markers
1974 Professor, dr.med. Michael Schwartz
1975 Director, dr.phil. Georg Mandahl-Barth
1976 Professor, dr.med. Niels Tøstrup
1977 Professor, dr.med. Erik Amidrup
1978 Chief physician, dr.med. Margareta Mikkelsen and Professor, dr.med. Vilhe Paulsen Petersen
1979 Professor, dr.med. Gerhard Salomon
1980 Professor, dr.med. Bent Friis Hansen
1981 Professor, dr.med. Flemming Kissmayer-Nielsen and chief physician, dr.med. Arne Sveegaard
1982 Professor, dr.med. Jens F. Rohfeld
1983 Professor, dr.med. Christian Crone
1984 Head of Department, med.dr. Staffan Magnusson
1985 Professor, dr.phil. Hans Klenow
1986 Chief Physician, dr.med. Hans Henrik Holm
1987 Professor, dr.phil. Hans H. Ussing
1988 Professor, dr.med. Gunnar Bendixen
1989 Associate professor, med.dr. Ove B. Norén and Associate professor, med.dr. Hans G. Sjöström
1990 Professor, dr.med. Morten Simonsen
1991 Professor, dr.med. Peter Loth Jørgensen and Professor, med.dr. Arvid Mauersbach
1993 Professor, dr.med. Niels E. Skakkebæk
1994 Professor, dr.med. Hans Jørgen G. Gunderson
1995 Research professor, dr.med. Niels Borregaard
1996 Professor, chief physician, dr.med. Henrik Ketlet
1997 Research professor, dr.scient. Peter E. Nielsen
1998 Professor, dr.med. Michael J. Mulvany and Professor, dr.med. Christian Aukjær
1999 Professor, med.dr. Bengt Sætter
2000 Research professor, dr.med. Peter Aaby
2001 Professor, dr.med. Thue W. Schwartz
2002 Professor, dr.med. Jørgen Gilemnn
2003 Professor, PhD. Jørn Eide and Senior researcher, Jørn Løvås
2004 Professor, PhD Matthias Mann and Professor Peter Røepstorff
2005 Professor, dr.med. Mats Melbye
2006 Professor, dr.med. Henning Beck-Nielsen
2007 Professor, med.dr. Marja Jäättelä
2008 Professor, director, PhD Kristian Helin
2009 Managing director, professor, dr.med. Soren Nielsen
2010 Professor, dr.odont. Henrik Clausen
2011 Professor, dr.med. Peter Lawær Andersen
2012 Professor, dr.med. Erik A. Richter
2013 Professor, dr.med. Soren Koegh Moestrup
2014 Professor, PhD Søren Nielsen
2015 Professor, dr.med. Jens Bukh
2016 Professor, dr.med. Christian Torg-Pedersen
2017 Professor, PhD Poul Nissen