The Novo Nordisk Prize

2019

Professor
Hans Bisgaard
Nomination of Hans Bisgaard

The Novo Nordisk Foundation is awarding the 2019 Novo Nordisk Prize to Hans Bisgaard for his pioneering clinical translational studies demonstrating that newborns colonized by pathogenic bacteria in the airways by the age of 5 years have a significantly increased risk of developing asthma and for demonstrating that fish oil supplementation during pregnancy reduces the risk of asthma in the children by 30%. Hans Bisgaard’s discoveries are highly recognized internationally, and his contributions to understanding the pathogenesis of asthma have moved medical science forward.

Fetal programming of adult disease, or at least diseases that occur after some latency time, is an important and rapidly growing research field. Characteristically, Hans Bisgaard has applied new and constantly evolving tools integrating genetic, genomic, metabolomic, molecular biological and epidemiological findings to dissect the pathophysiological mechanisms essential for developing childhood asthma. In doing so, he has helped define the molecular basis of different asthma phenotypes that inform effective asthma therapies. Importantly, he has led the way in defining and evaluating biomarkers of airway inflammation and its response to therapy among people with asthma. Hans Bisgaard’s contributions to asthma research are extensive, original and groundbreaking and may be divided into the following six themes: 1) inflammation, 2) assessing lung function among young children, 3) asthma therapy for children, 4) the microbiome in the early life and asthma development, 5) genetics in atopic diseases and 6) micronutrients during pregnancy for preventing childhood asthma.

Hans Bisgaard is 64 years old and graduated as a medical doctor from the University of Copenhagen in 1981. Since medical school, his research has focused on the asthmatic young child, representing the most common chronic disorder, cause for acute hospitalization,
chronic medication and other healthcare utilization in childhood. Hans Bisgaard began his scientific carrier with a clear focus on inflammation in asthma and especially contributed pioneering studies on the role of cysteinyl-leukotrienes in asthma. This work was compiled into his doctoral thesis, entitled Sulphidoleukotrienes in human allergic diseases, and he became Doctor of Medical Science in 1988. Hans Bisgaard contributed impressively to understanding the important role of cysteinyl-leukotrienes in asthma, which provided major results in developing the cysteinyl-leukotriene antagonist, montelukast, which nowadays is a mainstay in asthma treatment, especially for young children.

In parallel with his clinical training, Hans Bisgaard continued with impressive contributions to clinical science in the 1990s, and he became a clinical professor of paediatrics in 1998. From 2003 to 2004 he was a visiting professor at the Department of Pediatrics of the National Jewish Medical and Research Center in Denver, CO, USA, where he continued his important work on the role of leukotrienes in asthma together with Stan Szefler, who is directing the United States National Institutes of Health network on asthma therapy for children. At the same time, Hans Bisgaard also established Copenhagen Prospective Studies on Asthma in Childhood (COPSAC). Hans Bisgaard’s group was the first to develop a method enabling the measurement of children’s lung function from age 2 years. Following this, they published several papers in the prestigious journal American Journal of Respiratory and Critical Care Medicine documenting a method to test the bronchial reactivity of young children as a tool for understanding the pathogenesis of asthma in early childhood. These methods have been critical for clinical evaluation of lung function among young children and to document the effect of treatment.

Randomized clinical trials provide important evidence for research-based changes in treatment concepts. Hans Bisgaard was the first to document in a double-blind randomized controlled trial the effect of topical corticosteroids inhaled via spacer among children 0–3 years old with persistent wheezing, which today remains the gold standard for anti-inflammatory treatment in this age group. This milestone study was published in The Lancet, and in a seminal study published in The New England Journal of Medicine, his group was the first to show that inhaled corticosteroids highly efficiently control symptoms but do not affect the natural course of the disease.

In 1998, Hans Bisgaard took the pioneering initiative to establish COPSAC, which has been an outstanding asset for the many exceptional scientific contributions from his group. Hans Bisgaard’s group has carried out two decades of research based on the longitudinal cohort studies COPSAC2000 and COPSAC2010. The unique combination of detailed clinical phenotyping, basic research methods and randomized clinical trials in the COPSAC cohorts has been a cornerstone of the research by Hans Bisgaard during the past 20 years. The initial programme – COPSAC2000 – involved 411 children born to mothers with asthma between 1998 and 2001. Impressively, the children in this programme have been monitored at the COPSAC research unit from birth and every 6 months for 7 years and yearly thereafter for clinical outcomes such as asthma, eczema, allergies, lung function and bronchial responsiveness, growth, puberty and all other clinical signs. The COPSAC participants have just completed the 18-year visit with an impressive follow-up rate of almost 90%.

One of the truly remarkable findings from this cohort is the discovery of reduced bacterial diversity in infants’ intestinal flora, which is associated with increased risk of allergic sensitization. In contrast to the common belief that the lungs are sterile, Hans Bisgaard and colleagues discovered that the prevalence of asthma and reversibility of airway resistance at age 5 years was increased in children who had been colonized neonatally with selected bacteria. The seminal finding published in The New England Journal of Medicine was important and surprising because childhood asthma is commonly assumed
to involve eosinophilic inflammation, but this study indicates that neutrophilic inflammation may come first. Moreover, this introduced a novel paradigm of the airway microbiome as a factor in the origin of asthma.

The successive cohort – COPSAC2010 – is more wide-reaching, following 700 unselected pregnant women and their children. It is characterized by similar standard operating procedures as the first cohort but expanded to include more extensive assessment of early exposure to an array of highly sophisticated functional methods and extensive biobanking to characterize the individual child. Impressively, Hans Bisgaard and colleagues included full-growth genome-wide scanning, gene expression, epigenetics, metabolomics of both bacteria and the virome, immune profiling and metabolomics repeatedly in pregnancy and the first 6 years of life in the COPSAC2010 cohort.

From the COPSAC2010 cohort, Hans Bisgaard’s group has contributed to the highly important discovery of the FADS genetic mutation. This study is published in Nature Genetics and is highly influential, including on current work on phenotypes for atopic diseases (asthma, rhinitis and eczema). The findings are of significant scientific and clinical importance since this remains the strongest known genetic variant leading to atopic diseases. Similarly, in another international collaboration, Hans Bisgaard’s group discovered one of the most common disease in childhood and the most common reason children are hospitalized. The 2019 Novo Nordisk Prize recipient, Hans Bisgaard, found that giving fish oil to women during pregnancy reduces the risk of their children getting asthma by 30% and significantly more if they have a certain genetic profile. His latest result shows that fish oil also influences the development of the child’s nervous system, including cognition.

The protective effect was strongest in the children of mothers with low omega-3 PUFA levels before the intervention and/or with a fatty acid desaturase genotype associated with low omega-3 PUFA levels. These groups, omega-3 PUFA supplementation caused more than 50% reduction in childhood asthma. Interestingly and of major clinical importance, the supplementation with omega-3 PUFA also led to a reduced risk of lower respiratory tract infections in childhood, improved cognitive and motor development and improved growth.

Hans Bisgaard has been honoured with several national and international prizes and awards. Further, he has attracted considerable external funding, including extensive European Union research funding and funding from the United States National Institutes of Health. He has shown great leadership and mentored many clinical scientists and numerous young researchers and PhD students who are now continuing their own research, and he has attracted numerous researchers to work in Denmark. He has an impressive scientific output of more than 300 original studies, many published in high-impact journals such as The New England Journal of Medicine, The Lancet, The Journal of the American Medical Association, Nature Genetics and Nature Communications. He has also authored several review articles in his field, and many of his reviews and original articles are highly cited. Hans Bisgaard’s research has contributed on the international scene in a leading role and with important clinical impact. Thus, Hans Bisgaard stands out as a pre-eminent scientific researcher in respiratory and allergic diseases, and his scientific work has influenced the treatment of childhood asthma beyond the general importance documented from his many highly original publications.

In summary, the Novo Nordisk Prize Committee finds that Hans Bisgaard is a worthy recipient of the 2019 Novo Nordisk Prize based on his systematic, comprehensive, clinically important and highly original international research on asthma in newborns and for the impact of this in medical science.

Asthma prevention begins before birth

Asthma is the most common chronic disease in childhood and the most common reason children are hospitalized. The 2019 Novo Nordisk Prize recipient, Hans Bisgaard, found that giving fish oil to women during pregnancy reduces the risk of their children getting asthma by 30% and significantly more if they have a certain genetic profile. His latest result shows that fish oil also influences the development of the child’s nervous system, including cognition. Children need to be able to participate in exercise and physical activity to develop their physical agility. However, children with asthma have problems breathing when they run. Most children with asthma therefore stop exercising. Today, 235 million people worldwide have asthma. It is the most common disease among children, and the physical effects of having asthma are far from the only ones.

“If you can’t participate, then you are not picked for the team. And if you’re not picked for a football team in school, you feel different than the others, so preventing the disease is crucial. We found that we can avoid 30% of all cases of asthma among children by giving pregnant mothers fish oil. Further, if we can also screen the mothers’ blood for the FADS gene, we can say specifically: you have the right genes, you do not have to take fish oil; or you do not have the right genes, so you should really take the fish oil. We call this precision prevention,” explains Hans Bisgaard, Professor, COPSAC, Copenhagen University Hospital, Herlev-Gentofte.

By Morten Busch
Unethical not to include children in research

Like many other children with asthma, Hans Bisgaard experienced the physical and psychological effects of asthma as a child. This is one of the main reasons why he has dedicated the last 35 years of his life to investigating the causes of asthma and improving the treatment of children with asthma. His lifelong dream is to prevent or cure asthma to avoid the psychological stigma he experienced as a child.

"My doctor gave me a note for the school saying that I should not play football, and I was told to sit on the line to watch the football. Clearly it is more unethical if you do not involve them. Because if you do not involve them in research, well, what you are doing in daily practice without evidence is unethical." — Hans Bisgaard

Hans Bisgaard knew from his own experience that young children with asthma were undertreated. The attitude at that time was that, since most children outgrow the disease, it was better not to treat them.

"I built my research in paediatrics for several reasons – one was that there is very little science, very little evidence in what we are doing today, and that annoyed me. We did what we usually do, and at that time it was because people thought you cannot involve children in research. That was considered unethical, but my viewpoint was that it is more unethical if you do not involve them. Because if you do not involve them in research, well, what you are doing in daily practice without evidence is unethical." — Hans Bisgaard

After finishing school, Hans Bisgaard became a medical student. He wanted to specialize in orthopaedic surgery because he was good with his hands, but jobs were lacking in that field. Instead, he started as a physician at a children’s hospital and there he found his lifelong career interest.

“I thought: ‘Yeah right, they do outgrow it’; but in the meantime I believe the obligation of a doctor is to try to cure and for certain to improve their life. I mean you could use the same argument in the emergency room: ‘You have broken your leg, but that will cure itself, if you just wait.’” — Hans Bisgaard

From firefighter to fire inspector

Hans Bisgaard began his scientific career in the late 1980s with a clear focus on inflammation in asthma, especially pioneering studies on the role of cysteinyl leukotrienes in asthma, which provided major results for developing the cysteinyl leukotriene antagonist, montelukast, which nowadays is a backbone in asthma treatment, especially for young children. Soon after, his attention was drawn to the possible use of steroids for treatment.

“When we started introducing inhaled steroids, that sparked an outcry. How can you give steroids to a young child who is growing? But we did a lot of those studies, and it was highly efficacious and safe, so because of that, this paradigm changed from giving the old treatment to using this, which is still the mainstream of treatment today.”

However, Bisgaard’s group wanted more, so although he began his research career trying to develop treatments, he now turned his attention to understanding asthma.

“I would say that treatment today is excellent, so we quickly learned how to ‘put out the fire’, but I thought it would be better to prevent the fire, so we changed the strategy from treatments – being the firefighter – to being the fire inspector who prevents the fire, and that is what we have been doing for the past 20 years. Trying to prevent this disorder from developing.”

Up against a dogma

In the mid-1990s, Hans Bisgaard and his group developed a method for measuring lung function among children older than 2 years. These methods proved critical for the clinical evaluation of lung function among young children and to document the effect of treatment. Studying the lung function of very young children also led to a big surprise.

“We collected secretion samples from the children and sent them for analysis. We found pathogenic bacteria – those typically associated with pneumonia – in 20% of the children, which was very much a surprise to me, because everybody thought that lungs are normally sterile. That has been the dogma in the textbooks, but we showed that 20% were actually carrying bacteria without having symptoms.”

Because the children had no symptoms when the sample was taken, the researchers chose not to treat them further. But 5 years later they decided to examine the children again.

“You could have had bacteria in the airways had a four-fold increased prevalence of asthma, so apparently there was a link between the bacteria and asthma. But is it the chicken or the egg? Do you have this colonization because you have asthma or do you get asthma because of the bacteria? That is still an open question.”

The results were published in the prestigious New England Journal of Medicine. Likewise, in 2011, Bisgaard’s group used DNA sequencing-based techniques to demonstrate an association between the infant gut microbiome and allergy at school age and that 1-year-old children with an immature bacterial composition of gut bacteria have an increased risk of developing asthma.

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eczema, allergies, lung function, bronchial responsiveness, growth and puberty. We take samples of urine, blood and hair, measure height and lung function, skin strips, sampling from the nose, from the airways, from faces – you name it. Everything." The initial programme – COPSAC2000 – involved 411 children born to mothers with asthma between 1998 and 2001. Impressively, the children in this programme have been monitored at the COPSAC research unit from birth and every 6 months for 7 years, and yearly thereafter. The COPSAC participants have just completed the 18-year visit, with an impressive follow-up rate of almost 90%.

"That is totally unique to Denmark. That is why they come to us from Harvard, from New York University and the University of Chicago. They come to us because we have this amazing material. This is something where we have really pushed the clinical research, and I think it is really a goldmine." Internationally unique

One valuable gold nugget the researchers dug out of the mine was genomic information. From the COPSAC2010 cohort, Hans Bisgaard's group has contributed to the highly important discovery of the filaggrin mutation, which today remains the strongest known genetic variant leading to atopic diseases such as asthma, rhinitis and eczema. This study was published in Nature Genetics.

"Similarly, in a unique design in the Danish National Patient Registry, we also found a totally new gene that is very plausible. The gene is expressed in the airways, and we know its structure." Within a relatively small group of children, in another study published in Nature Genetics, Hans Bisgaard and colleagues replicated all known asthma genes and discovered the new CDHR3 variant, which is a functional variant expressed in the airways and a functional rhinovirus receptor, suggesting this as a potential important novel target for industry in the hunt for new ways to manage asthma. Hans Bisgaard's group was also the first to demonstrate interaction between asthma genetics and airway viruses.

"Our combination of detailed and comprehensive clinical phenotyping, basic research methods and clinical trials in the COPSAC cohorts is the cornerstone of my research strategy. You can do whatever fancy DNA analysis you want to, but if you do not have the clinical foundation and know how to translate between the two, you are in trouble. Today, we are recognized internationally as unique for that specific reason." Today, translation is a buzzword and fashionable, but 35 years ago, when Hans Bisgaard started doing it, it was far from fashionable. But Hans Bisgaard knew already then, that solving the asthma puzzle required getting basic researchers and clinicians to talk to each other. "Trying to bring the two together – at least at that time – did not happen often, but I have always done it. Bringing clinicians and basic scientists together has always been part of my research, because it is so rewarding. Everybody liked it. The basic scientists said: 'Wow, a child', but the paediatricians were rewarded by finding evidence that they could not find themselves."

However, according to Hans Bisgaard, building bridges between clinical science and basic science takes more than just great data. You need to have a team with open-minded people, who do not stay in the silos they come from and who – every now and then – can accept to be stupid in the eyes of their basic or clinical colleagues. "I am an entrepreneur. So I am good at initiating projects and carrying them through to a result. Fortunately, I have great people from different scientific fields around me. It does not make sense to hire smart people and then tell them what to do. We hire smart people so they can tell us what to do. Because the people who are crazy enough to think that they can change the world are the ones who push humanity forward."

Boys catch up with girls

Lifestyle changes in Western societies have resulted in a decreasing intake of micronutrients such as vitamin D and omega-3 fatty acids. In 2016, Hans Bisgaard published a clinical trial on mothers in the third trimester of pregnancy in the COPSAC2010 cohort that turned out to be his major career breakthrough.

"In a study of 700 pregnant women, we gave fish oil to one group and olive oil to the other. We then followed the children for, now 8 years, but broke the code and published around age 5, and we saw that those kids whose mothers had fish oil had a 30% reduction in asthma, which is huge." Further, this study showed that the women who lacked one or two alleles of the FADS gene did not benefit from the fish oil. "So combining the two, we are able to do precision prevention. We can analyse the fatty acids in the blood of the mother. We can analyse for the FADS gene and, combining the two, we can say specifically: ‘You must have a supplement of fatty acids, but you do not have to, because your blood level is okay, you have the right genes, you do not have to.’"

Further, taking omega-3 fatty acids also led to a reduced risk of lower respiratory tract infections in childhood, improved cognitive and motor development and improved growth.

"Language development was accelerated by 3 weeks. Their walk and talk milestones were accelerated. They saw improved growth and respiratory tract infections in childhood, improved cognitive and motor development and improved growth."

"You must have a supplement of fatty acids, but you do not have to, because your blood level is okay, you have the right genes, you do not have to."
A canary in the coal mine
The fish oil treatment appeared to have an amazing effect, which Hans Bisgaard emphasizes is a multi-organ effect, since one intervention affected both the inflammation system in the airways, the nervous system and growth.

"Three totally independent compartments – meaning that there is some shared underlying mechanism, since taking fish oil affects three different compartments. I think this is fascinating, and it brings me to my favourite hypothesis and keeps me awake at night."

This is just one indication of a shared underlying mechanism. Another one is the fact that caesarean section increases the risk of asthma, rheumatoid arthritis, inflammatory bowel disease and leukaemia. Together with the evidence of a genetic overlap, Hans Bisgaard is convinced there is a connection.

"I believe that asthma is the canary in the coal mine. In the old days, when the canaries stopped singing in the coal mine, you better get out, because there was some gas leak. I see asthma in early life as this canary. It indicates that something is going wrong and you might have a trajectory towards various inflammatory disorders. Asthma is a good sensor, because it starts early in life and is very common."

The 2019 Novo Nordisk Prize was awarded on Friday, 15 March to Hans Bisgaard, Professor, COPSAC, Copenhagen University Hospital, Herlev-Gentofte.

About Hans Bisgaard
Senior clinical and academic positions
2003–
Chief Physician, Copenhagen Prospective Studies on Asthma in Childhood (COPSAC), Department of Paediatrics and Adolescent Medicine, Herlev and Gentofte Hospital

2003–2004
Guest Professor, Department of Pediatrics, National Jewish Medical & Research Center, Denver, Colorado, USA

1998–
Professor of Paediatrics, University of Copenhagen

1998–2002
Chief Physician, Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen

Specialist physician in paediatrics, Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen

Education
1991
Specialist Physician in Paediatrics, University of Copenhagen

1988
Doctor of Medical Science (Sulphidoleukotrienes in human allergic diseases), University of Copenhagen

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Certification by the Educational Commission for Foreign Medical Graduates, USA

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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 Directors or to 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 2019 Committee comprised the following seven members:

- Jørgen Frækier, 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 meets 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 1963–2018

1963 Professor, dr.med. Erik Warburg
1964 Chief physician, dr.med. Claus Brun
1965 Professor, dr.med. J. C. Skou
1966 Professor, dr.med. Jens Hers Thaysen
1967 Professor, dr.phil. Knud Lundby
1968 Chief physician, dr.med. Niels A. Lassen
1969 Professor, dr.phil. Erik Zeuthen
1970 Professor, dr.med. Paul Astrup
1971 Professor, dr.med. Mogens Schou
1972 Chief Physician, dr.med. J. Chr. Silim
1973 Professor, mag.scient. K. A. Marcker
1974 Professor, dr.med. Michael Schwartz
1975 Director, dr.phil. Georg Mangold-Birth
1976 Professor, dr.med. Niels Thystrup
1977 Professor, dr.med. Erik Amdrup
1978 Chief physician, dr.med. Margerita Mikkelsen and Professor, dr.med. Vilh Piotborg Petersen
1979 Chief physician, dr.med. Gerhard Salomon
1980 Professor, dr.med. Bent Fris Hansen
1981 Professor, dr.med. Flemming Kissmeyer-Nielsen and chief physician, dr.med. Anne Søvognjard
1982 Professor, dr.med. Jens F. Rehfeld
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. Sjøstrøm
1990 Professor, dr.med. Morten Simonsen
1991 Professor, dr.med. Peter Leth Jørgensen and Professor, med.dr. Arvid Maunsbach
1993 Professor, dr.med. Niels E. Skakkebæk
1994 Professor, dr.med. Hans Jørgen G. Gundersen
1995 Research professor, dr.med. Niels Boregård
1996 Professor, chief physician, dr.med. Henrik Kehlet
1997 Research professor, dr.scient. Peter E. Nielsen
1998 Professor, dr.med. Michael J. Mølby and Professor, dr.med. Christian Aalkjær
1999 Professor, med.dr. Bengt Salin
2000 Research professor, dr.med. Peter Aaby
2001 Professor, dr.med. Thue W. Schwartz
2002 Professor, dr.med. Jørgen Gliemann
2003 Professor, PhD Jiri Bartek and Senior researcher Jiri Lukas
2004 Professor, PhD Matthias Mann and Professor Peter Riisporstorp
2005 Professor, dr.med. Mads Mølbye
2006 Professor, dr.med. Henning Beck-Nielsen
2007 Professor, med.dr. Marja Jäättelä
2008 Professor, director, PhD Krestian Helin
2009 Managing director, professor, dr.med. Søren Nielsen
2010 Professor, doroctor, Henrik Clausen
2011 Professor, dr.med. Peter Lawitz Andersen
2012 Professor, dr.med. Hans Klenow
2013 Professor, dr.med. Niels Borregaard
2014 Professor, dr.med. Niels Borregaard
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