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NOVO NORDISK FOUNDATION
CENTER FOR PROTEIN RESEARCH

Annual Report 2019

Novo Nordisk Foundation
Center for Protein Research

COLOPHON

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Front page	Professor Guillermo Montoya and Associate Professor Stefano Stella founded the spin-out company Twelve Bio in 2019

Novo Nordisk Foundation Center for Protein Research

Novo Nordisk Foundation Center for Protein Research (CPR) was founded in 2007 at the Faculty of Health and Medical Sciences, University of Copenhagen, to promote basic and applied discovery research on human proteins of medical relevance.

The establishment, growth and continuation of the center has been possible thanks to unprecedented and repeated financial support by the Novo Nordisk Foundation as well as through significant contributions from the University of Copenhagen for the renovation and maintenance of the center facilities.

RESEARCH AT CPR IS ORGANISED INTO FOUR RESEARCH PROGRAMS:

- The Proteomics Program
- The Protein Signaling Program
- The Disease Systems Biology Program
- The Protein Structure and Function Program

The center offers state-of-the-art technological platforms for protein research, providing unique opportunities for researchers to understand biological processes underlying health and disease. The technological platforms hosted by CPR include:

- The Mass Spectrometry Platform
- The Protein Imaging Platform
- The Big Data Management Platform
- The Protein Production and Characterization Platform.

190 staff members from 39 different countries contribute to the scientific work performed at CPR. The staff comprises scientific personnel (68%), research support and administrative support.

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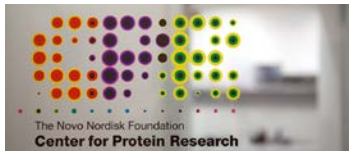

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Full overview of CPR publications

A graphic overview of how CPR research programs complement each other and a map of CPR's network of external collaborators.

The four CPR research programs, their technologies and the landmark results accomplished by the research groups in 2019.

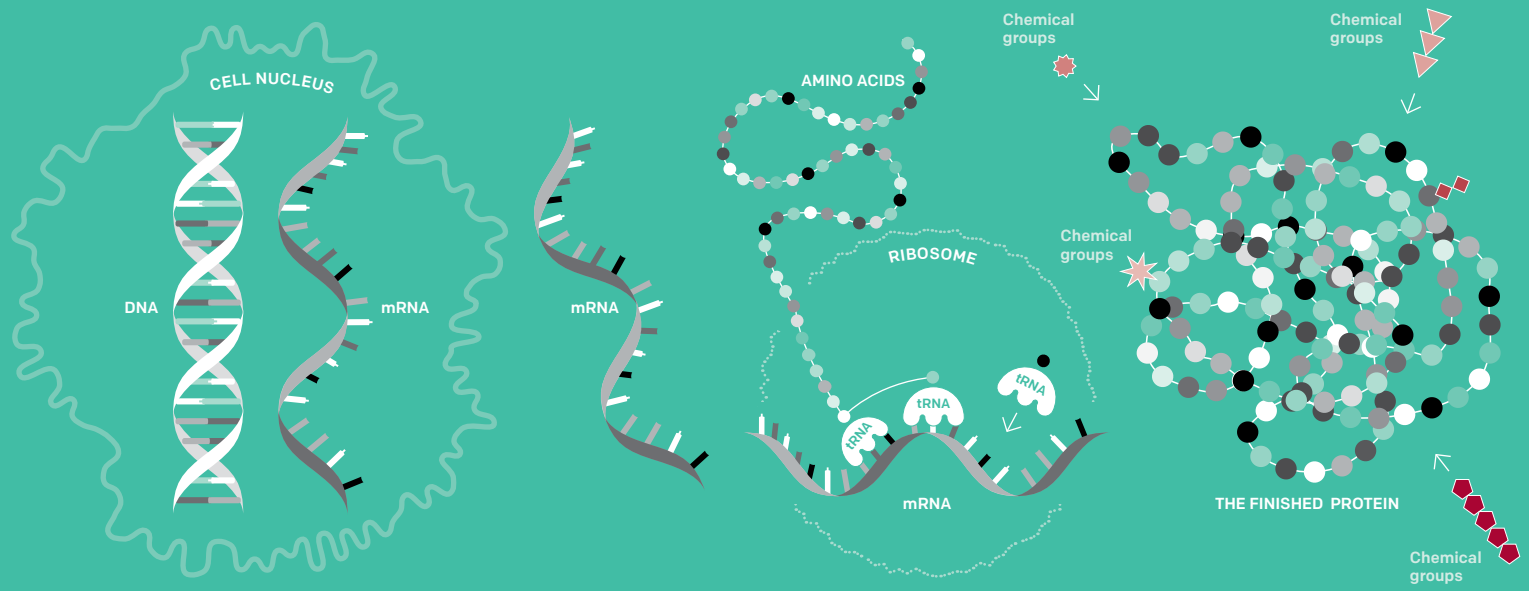
CPR has a clear governance structure tailor-made to maximize efficient governance internally and foster interactions with the Faculty of Health and Medical Sciences at the University of Copenhagen and other research organisations.

CPR researchers published 120 articles including 111 primary research articles, and 9 review articles, in 2019. Find the full reference list here.

The quest to understand the human proteome

While the basics of the human genome, the DNA, was roughly mapped in 2001, the expression of the DNA in proteins - the human proteome - is still widely unexplored. At the Novo Nordisk Foundation Center for Protein Research (CPR), researchers have taken up the challenge of understanding the protein world to lead the way for new treatments in the clinical world.

HOW PROTEINS ARE MADE IN A CELL



THE DNA HOLDS THE CODE

DNA is composed of a series of four alternating bases that define our genetic sequence. It contains around 20.000 genes that code for the expression of an unknown number - potentially more than a million - of protein variants, which regulate most functions in the human body.

→ THE mRNA TRANSPORTS THE CODE

The production of a specific protein begins when the DNA of a gene is copied into an mRNA molecule - a messenger RNA - which contains the code for the protein. The mRNA transports the protein code from the cell nucleus into the cytoplasm of the cell. It brings the code to the ribosome, the 'protein assembly line'.

→ THE RIBOSOME ASSEMBLES THE PROTEIN

The ribosome translates the code brought to it by the mRNA. Every sequence of three bases carries a signal for tRNAs – transfer-RNAs - to bring a specific amino acid to the ribosome and place it in an exact spot in the chain of acids that builds the protein like pearls on a string. Proteins are made out of a total of 20 different amino acids.

→ THE PROTEIN IS MODIFIED AND READY

In the final stage of the making of a protein, the chain of amino acids is cut, folded, and brought to a three dimensional shape. A variety of chemical groups are added by enzymes (other proteins) providing the new protein with its final distinctive features. After these 'post-translational modifications' (PTMs), the protein is ready for work. Some proteins stay in the cell, others migrate through the cell membrane.

WHAT PROTEINS DO

Proteins run the human body in myriad ways. If you look into a medium-sized cell of a human, you find billions of proteins at work. All proteins perform a job of importance for human life and health. Sometimes errors occur and cause illness. In fact, most diseases manifest at the level of proteins, and most drugs target proteins or are proteins themselves.

Proteins take care of many different functions in the body.

They are:

- **enzymes** – or socalled biological catalysts - that speed up chemical processes – such as the addition of post-translation modifications to new proteins.
- **receptors** that bind to specific ligands in their environment and forward this signal to other molecules – such as the receptors in the nose that bind to odor molecules and convey this information to the brain.
- **transporters** that take molecules from one place to another – such as hemoglobin bringing oxygen from the lungs to the muscles.
- **structure builders** that hold together cells and tissue as a scaffold – such as collagen holding together the cells of the skin.
- **hormones** that travel the bloodstream to stimulate specific cells or tissues – such as insulin from the pancreas that promotes glucose uptake in liver, muscle and fat.
- **antibodies** that detect pathogenic bacteria and viruses in our body as part of the immune system.
- **contractile proteins** that allow biological structures to contract– such as myosin and actin that make up the majority of muscle tissue.
- **storage** that serves as biological reserves - such as ferritin that stores iron inside the cell.

World-leading protein explorer

The ambition of Novo Nordisk Foundation Center for Protein Research (CPR) is to be a world-leader in exploring how proteins drive fundamental biological processes in humans. The research can ultimately lead to new ways to diagnose, prevent and treat diseases.

Post-translational modifications (PTMs) take place in the final stage of the making of proteins and affect their structure, function and activity. The modifications dramatically diversify the protein pool in the body, and hundreds of different types of PTMs are known in nature.

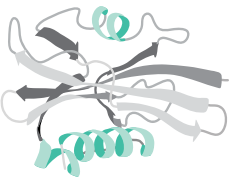
With hundreds of thousands, potentially millions of different protein variants in the human body, it is a huge challenge to decipher the function and mechanism of them all, and find the key players relevant for disease.

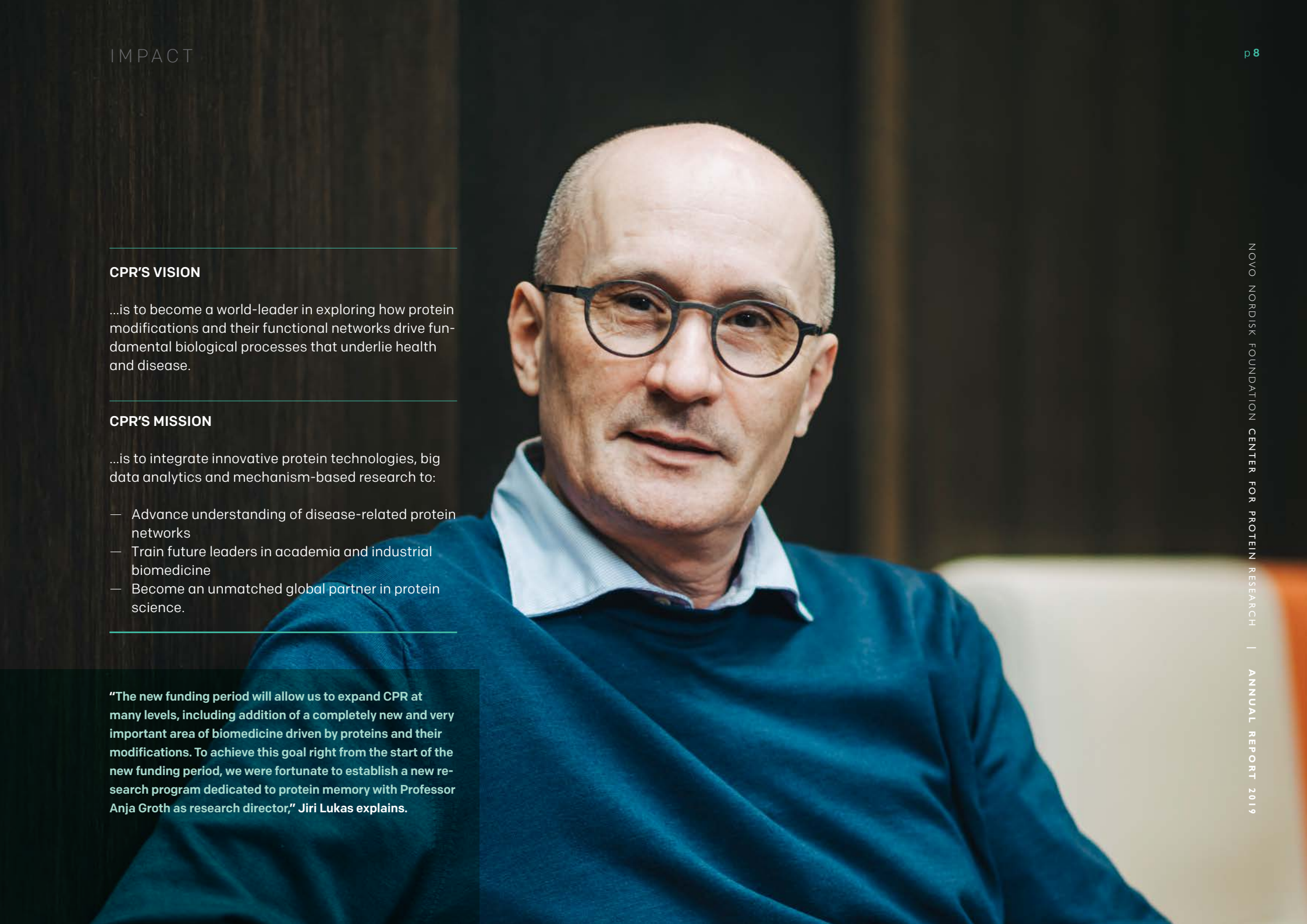
From its beginning, CPR has had a unique strategy to tackle this challenge by interdisciplinary research and the development of new technologies. The center combines three different approaches to reach its goal to become a world-leading protein explorer:

- Develop and combine under one roof the broadest possible spectrum of state-of-the-art protein technologies combined with high-end computation and big data management
- Perform highly effective technology-driven and mechanism-oriented protein research
- Translate basic discoveries to health care.

COMBINING TECHNOLOGIES TO GRASP THE PROTEIN WORLD

The technologies available in CPR span the entire spectrum from mapping all protein variants in a cell to visualising how individual proteins assemble in functional networks that drive fundamental physiological processes. This allows for a highly collaborative and interdisciplinary research environment where the different research areas cross-fertilise and bring together different approaches to explore and understand proteins.

Technology	Mass spectrometry	Big data management and analysis	Protein imaging	Cryo-electron microscopy and x-ray crystallography
	Analyses all protein variants in a sample	Predicts how proteins interact and cooperate	Investigates protein function in living cells	Deciphers the structure of individual proteins and protein complexes
				
What the technology can do?	Reveals the identity and amounts of proteins and their modifications in a biological sample by measuring the mass-to-charge ratio of ions.	Indicates how proteins function and vary across the population by generating and analysing molecular interaction networks in health and disease.	Tests the function of selected proteins /protein networks in live cells by light microscopy and image analysis. Visualises how proteins move around over time, how they interact and the effects on the cell.	Studies molecules and molecular interactions by the use of biophysical instruments. The structure and biophysical features of a protein reveal how it moves, how it interacts with other molecules, and more.
How the technologies interrelate at CPR	Mass spectrometry produces a list of proteins present in the sample for further processing by big data analysis.	Big data analysis integrates data sets collected from proteomics and other omics technologies, health data and more - and supports hypothesis generation for further testing in the laboratory.	Microscopy is used to investigate and functionally complement the results from mass spectrometry and big data analysis.	Protein characterization and structural studies contributes to the understanding of a protein's function, thus complementing all other protein technologies at CPR.



CPR'S VISION

...is to become a world-leader in exploring how protein modifications and their functional networks drive fundamental biological processes that underlie health and disease.

CPR'S MISSION

...is to integrate innovative protein technologies, big data analytics and mechanism-based research to:

- Advance understanding of disease-related protein networks
- Train future leaders in academia and industrial biomedicine
- Become an unmatched global partner in protein science.

"The new funding period will allow us to expand CPR at many levels, including addition of a completely new and very important area of biomedicine driven by proteins and their modifications. To achieve this goal right from the start of the new funding period, we were fortunate to establish a new research program dedicated to protein memory with Professor Anja Groth as research director," Jiri Lukas explains.

After the first 10 years: CPR evaluated as 'world-class faculty'

2019 was one of the most important years in the history of the Novo Nordisk Foundation Center for Protein Research (CPR) - crucial to the future of the center.

As our ten years tenure came to an end, the Novo Nordisk Foundation asked leading international experts in all main research areas covered by CPR to evaluate to which extent the money invested in the center advanced global protein research including its medical and societal implications. At the same time, the panel of experts were asked to review our strategy for moving to the next level in the coming five years.

To our delight, the experts' evaluation concluded that the center has been 'an outstanding success during its brief lifespan'; has assembled a 'world-class faculty'; and is firmly on track to become a 'world-leading institution specialising in protein research'. As a result, the Novo Nordisk Foundation decided to award 700 million DKK to support CPR in the period 2020-2024.

ONE RESEARCH CENTER UNDER ONE ROOF

Our impact on biomedical science has been achieved through the unique design of CPR: a highly interdisciplinary research center with all core expertise congregated under one roof. This fosters interactions across very diverse biomedical disciplines and the associated technologies at a level that is not seen in most other research institutes. Importantly, despite this diversity, CPR managed to develop an overarching flagship theme across all its units. This theme revolves around the mass spectrometry technology, aiming at identification of proteins with unprecedented depth and further on mapping chemical protein modifications, which can without exaggeration be seen as the main driving force of all biological processes, and whose malfunctions also often lead to diseases.

MASS SPECTROMETRY TECHNOLOGY TO A NEW LEVEL

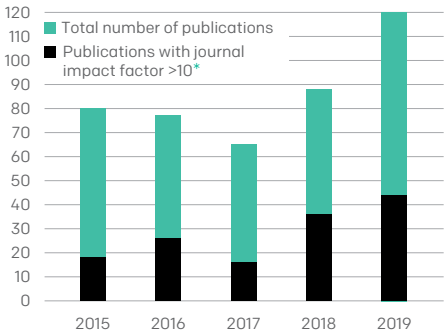
One highlight from 2019, which illustrates the power of quantitative protein research, is a study published in the prestigious magazine Cell as a result of an interdisciplinary collaboration led by Jesper Olsen and including input from three different CPR research programs. The researchers moved the mass spectrometry technology to a new level showing how mutations in growth factor receptors on the cell surface rewire the cellular signaling pathway and result in a more invasive form of lung cancer. This study paves the way to understand the genesis of this devastating disease and has a potential to launch activities to develop personalised medicine.

The impact of the center should also be measured over a longer time horizon in relation to the students and the researchers at the center. Our long-term ambition is based on an original career development concept called 'complete protein scientists', meaning that we bring our students and postdocs as close as possible to the state-of-the-art conceptual thinking in diverse biomedical disciplines and at the same time promote training in an equally diverse spectrum of sophisticated protein technologies. We believe that unless scientists really experience how the technology works, they are limited in interpreting their results. This approach fosters 'complete protein scientists' and gives a competitive advantage in generating cutting-edge science at the center level. This is probably one of the pivotal reasons for why many of our students succeed in competing for high-profile positions both in academia and pharma and biotech industries.

Jiri Lukas
Executive Director and Group Leader
Novo Nordisk Foundation Center for Protein Research

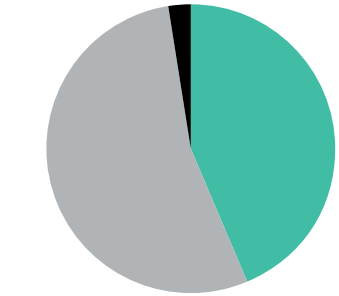
Selected numbers: CPR activities in 2019

No. of publications



* The journal impact factor (Web of Science) is an indicator calculated annually for peer-reviewed journals. The impact factor of a journal indicates the average yearly number of citations received per article published in that journal during the two preceding years.

Annual funding and distribution



- NNF center grant 69,9 mio DKK
- Competitive research grants 86,2 mio DKK
- University of Copenhagen funds 3,7 mio DKK
- Total 159,8 mio DKK

No. of courses

No. of attendees

	Under graduates	PhD students	Post-docs	Mixed Audience**
CPR organized and co-organized	4 • 107	2 • 40	2 • 22	4 • 20
Faculty of Health and Medical Sciences at UCPH	5 • 164	5 • 104		2 • 36
Outside Faculty of Health and Medical Sciences in DK and abroad	5 • 40	6 • 200		8 • 183
Total	**14 • 311**	**13 • 344**	**2 • 22**	**14 • 499**

** Mixed audience covers undergraduate students, PhD students, postdocs and academic staff.

No. of outreach events

37

events in 2019

RESEARCH OUTPUT

In 2019, CPR researchers published 120 articles: 111 primary research articles reporting on original research, and 9 review articles. Commentary and book chapters are not included in the diagram.

- More than a third (36%) of the articles were published in journals with a journal impact factor above 10.
- 37% of the CPR primary research articles were a result of a collaboration between two or more CPR research groups and of these 64% had a journal impact factor above 10.
- 35% of the primary research articles had a CPR last-author indicating that the article was conceptualised by CPR researchers.

FUNDING

In 2019, the total turnover of CPR was DKK 159.8 million.

- More than half was attracted as competitive grants, supplementing the Novo Nordisk Foundation center grant of DKK 69.9 million.
- The competitive research grants (DKK 86.2 million) stem from: 63% Danish private grants, 29% EU-grants, 7% Danish public grants, and 1% other international grants.

TEACHING ACTIVITIES

Approximately 1.176 persons attended 43 courses taught by CPR researchers in 2019. CPR's educational activities draw on the research excellence and unique opportunities associated with being a university-based research center. One example is CPR's summer school offering a 365 degree introduction to the cutting-edge protein research and technologies available at CPR to undergraduate students and other interested participants from all over the world.

OUTREACH

CPR researchers want to share the knowledge on protein research. In 2019, they participated in 37 outreach events:

- **13** media interviews
- **8** meetings with professional practitioners from health care, engineering and private businesses
- **7** activities for primary school students
- **3** events for undergraduate students
- **3** public talks – one of them a talk at the Bloom Festival in Copenhagen
- **2** visits from industry
- **1** career event for postgraduates on how to become a principal investigator.

Five more years of funding

In 2019, the Novo Nordisk Foundation awarded a new grant of 700 million DKK (EUR 94m) to Novo Nordisk Foundation Center for Protein Research (CPR).

The new grant will enable the center's almost 200 staff and management to explore the still widely unknown land of proteins over the next five years – as described in the center's strategy, CPR 2.0.

CPR's Executive Director, Professor Jiri Lukas, feels privileged by the trust shown by the Novo Nordisk Foundation. The 2019-funding is the third substantial Novo Nordisk Foundation donation to the center.

"The foundation's visionary concept of long-term funding has allowed us to take protein research to a completely new level. When building centers of excellence it is of extreme importance to have a substantial part of the funding in place as long-term grants. During the years to come, the new grant will enable us to attract and develop the expertise and technologies needed to maintain our high performance," says Jiri Lukas.

The grant followed a comprehensive performance evaluation by an independent committee of leading international researchers. The reviewers complemented the center for its successful creation of a world-class research institute in little more than 10 years, stating that CPR now ranks highly in an elite group of mid-size research institutes in Europe. They found that the center has absolutely put Denmark on the map as a cutting-edge leader in protein research.

AMBITION TO KEEP POSITION AS FRONT-RUNNER

Birgitte Nauntofte, CEO of Novo Nordisk Foundation, is impressed with the results achieved by CPR since its establishment in 2007.

"CPR has become recognised internationally for the synergy between its programs within protein research and for spearheading protein research technology", she says. "With the new grant, we want to enable the center to uncover fundamental protein mechanisms and transform new knowledge into collaborations with clinical environments to benefit patients and society."

With the funding in place, CPR has the ambition to keep its position as a front-runner in the global effort toward gaining a holistic understanding of how proteins govern essential physiological processes in humans, and how to harness this knowledge for improved disease management.

NEW EPIGENETICS RESEARCH PROGRAM

In the new funding period, the center remains dedicated to the characterisation of protein and proteome expression, modification, structure and function - with a special focus on the maintenance of genome integrity, which has major implications for human health.

In line with the center's strategy, the new grant enables the addition of a fifth research program covering the medically highly relevant area of epigenetics, which is the study of heritable changes that occur without changes to the DNA sequence. The new research program will be headed by Professor Anja Groth, an internationally acclaimed molecular biologist.

THE NOVO NORDISK FOUNDATION GRANTS

2007 - 600 million DKK (EUR 81m): CPR was established as an integrated interdisciplinary research center of excellence embedded in the Faculty of Health and Medical Sciences at the University of Copenhagen
2015 - 180 million DKK (EUR 24m) additional center grant
2020 - 700 million DKK (EU 94m) for the next five-year funding cycle

New spin-out company is in the lead to develop the sharpest and most precise DNA scissors

The CRISPR technology is known as a powerful tool for editing genomes. Now, the spin-out company Twelve Bio has discovered the molecular mechanisms behind the enzymatic activities of a variant that will allow them to develop a CRISPR tool, which is even more precise and cleaves only intended DNA sequences.

The first CRISPR enzyme - a genome editing tool – was discovered in 2012. A few years later, the CRISPR-Cas12a was acknowledged as an even more precise tool. Then, at the end of 2018, the group of Professor Guillermo Montoya at the Novo Nordisk Foundation Center for Protein Research (CPR) made a unique discovery. They revealed the molecular mechanisms behind Cas12a enzymatic activities, paving the way for new, interesting applications of the technology and a CPR spin-out company was founded by Associate Professor Stefano Stella and Group Leader Guillermo Montoya.

IMPATIENCE WITH REPETITIONS LED TO NEW DISCOVERY

Stefano Stella has a strong interest in precision but finds repetition boring. A bit of a paradox, as researchers often have to repeat their experiments numerous times. So, when Stefano repeats his experiments, he always twists the process a bit – to improve it, change it, make it more precise.

"We wanted to document the behaviour of the protein as it cuts DNA. So, Pablo (Pablo Mesa, Associate Professor in the Montoya group, ed.) used cryo-EM to obtain a series of pictures of the process, which together generated a primitive movie. When we watched it, we became the first in the world to witness a process no one knew of, and which everyone had missed, because they only had one picture. It was a completely euphoric sensation," Stefano Stella explains. The movie shows how existing CRISPR technology can have side effects on the genome. Once the DNA strand has been cut, the 'security checks' of the CRISPR protein remain open. This can cause the process to last longer than wanted, because the machinery behind gene editing continues to run and can cause genetic changes. This knowledge was used to design versions of Cas12a that put an end to the unwanted gene editing by fine-tuning the DNA cutting mechanism.

RESEARCH TURNS INTO BUSINESS

While celebrating their unique discovery and being the first to witness the behaviour of the protein, Stefano Stella and Guillermo Montoya started putting together a patent application and writing a research article on the discovery that was published in Cell in 2018 in collaboration with the group of Professor Nikos Hatzakis, Associate CPR Member since 2019. The patent was filed in August 2018 and the commercial part of their project really gained speed when the know-how was transferred to Twelve Bio.

"A driving force is probably also the competition. We are up against many other large groups with lots of resources based at the best universities in the world. They are hot on our heels. And we want to be the first to develop the most precise and sharpest DNA scissors," Stefano Stella says. "CRISPR has opened a possibility to cure diseases in a way that has not been possible before. In theory, patients can take medication that will change their DNA and permanently cure the disease. However, gene editing requires precision to not induce other diseases while changing the DNA and we are developing the most precise tool for this", explains Stefano Stella.

ABOUT TWELVE BIO

Twelve Bio is supported by pre-seed funding from Novo Seeds of DKK 3.5 million and by the Business Acceleration Academy Program from The BioInnovation Institute. The team includes three other researchers: Faizaan Mohammad (cell biologist), Nikolai Wulff (biochemist) and Zhiwei Li (bioinformatician).

"I am motivated by getting my research out into the world. I constantly feel the need to produce something and communicate knowledge to others. My end goal is not to sell a product, but to cure disease. When Novo Seeds showed an interest, it was a recognition of my research, but also very much a certainty that my discovery would actually become useful to society," tells Stefano Stella.

Read more about Twelve Bio at www.twelve.bio

Protein research cracks part of the code of tumour growth

In 2019, researchers at Novo Nordisk Foundation Center for Protein Research (CPR) together with colleagues from University of Copenhagen were the first in the world to map the protein networks that are used by cancer cells to spread in lung tissue.

Lung cancer is the biggest cause of cancer-related deaths. After seven years of in-depth analysis of signalling networks in lung tissue, the researchers have taken a big step towards cracking the code of tumour growth.

"We have developed completely new methods to map the main signalling networks in lung tissue and the proteins that control the spread of cancer in lung tissue. We have done so to understand what is actually happening in cancer mutations. This may prove to be crucial as we need to improve existing treatments for patients who often become resistant. Our findings can be used to develop new treatments that target newly identified proteins in the signalling pathway in tissue," says group leader at CPR, Professor Jesper Velgaard Olsen.

The study - published in 2019 - is the result of close collaboration between researchers at CPR, the Department of Biomedical Sciences (BMI) and the Biotech Research & Innovation Center (BRIC) at University of Copenhagen.

MAPPING IS CRUCIAL IN THE FIGHT

Cell growth and division in tissues is controlled by a specific protein - a receptor - that sits on the outer membrane of cells. This so-called EGF receptor acts as a communication channel between the environment outside the cell and it's interior. The binding of a growth factor to the receptor transmits signals to the "engine room" of the cell and dictates that the cell must grow or divide.

In case of cancer mutations, the cell receives an erroneous signal that leads to constant and unrestrained growth and division - and a growing tumour.

To prevent tumour growth in patients, a targeted drug is used to block the EGF signalling pathway. However, many patients become resistant to the treatment after about a year because particularly tough lung cancer cells will find other ways to grow.

The researchers set out to understand exactly how mutations in cancer patients lead to increased growth by so-called rewiring of signalling pathways activated by the EGF growth factor.

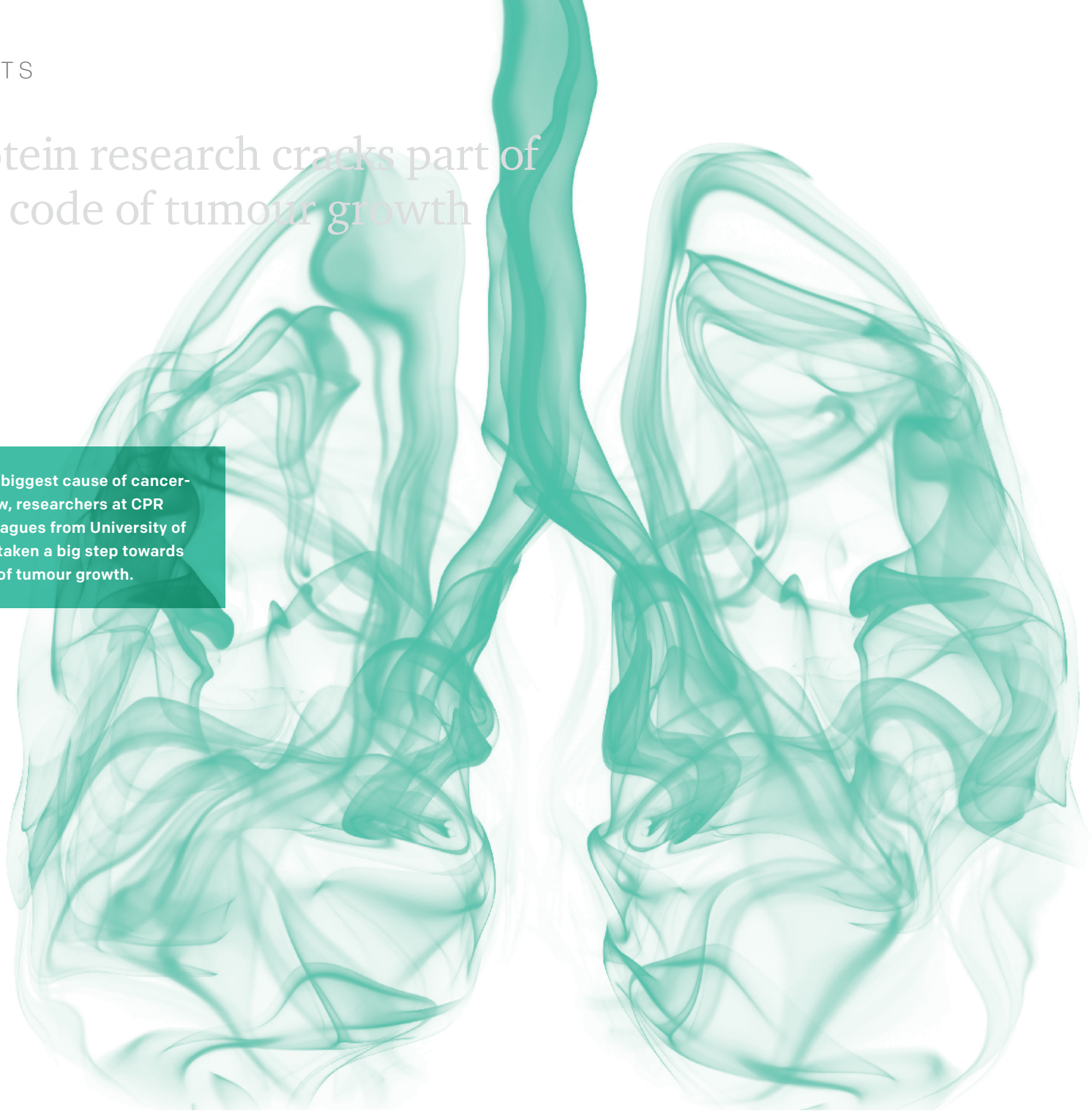
"Proteins act a bit like social networks, where they communicate with each other on the basis of mutual interest and functionality. By revealing their communications, we can understand exactly what happens when a new mutation causes uncontrolled tumour growth. This type of mapping can enable us to determine and understand how the signalling or communication between proteins goes wrong in patients" says Associate Professor Alicia Lundby from BMI and former postdoc at CPR.

MAJOR IMPACT ON ALL KINDS OF CANCER MUTATIONS

By mapping the signalling pathways in detail, the researchers were able to understand how a known mutation in lung cancer patients leads to increased tumour growth. They also identified a particular causative protein that could be a target for a new cancer drug for patients carrying this mutation.

The researchers have also looked into the protein networks that control the EGF receptors in liver tissue and the next step is to identify the rest of the body's tissues. This can have a major impact on cancer researchers worldwide who are working to crack the code of tumour growth for all kinds of cancer.

Protein research cracks part of the code of tumour growth



Lung cancer is the biggest cause of cancer-related deaths. Now, researchers at CPR together with colleagues from University of Copenhagen have taken a big step towards cracking the code of tumour growth.

New insight into how proteins build scaffolds to repair DNA damage

By the use of super-resolution microscopy, researchers at Novo Nordisk Foundation Center for Protein Research (CPR) in 2019 revealed how two proteins build a scaffold around damaged DNA, and attract other proteins to repair the damage. The discovery was published in Nature.

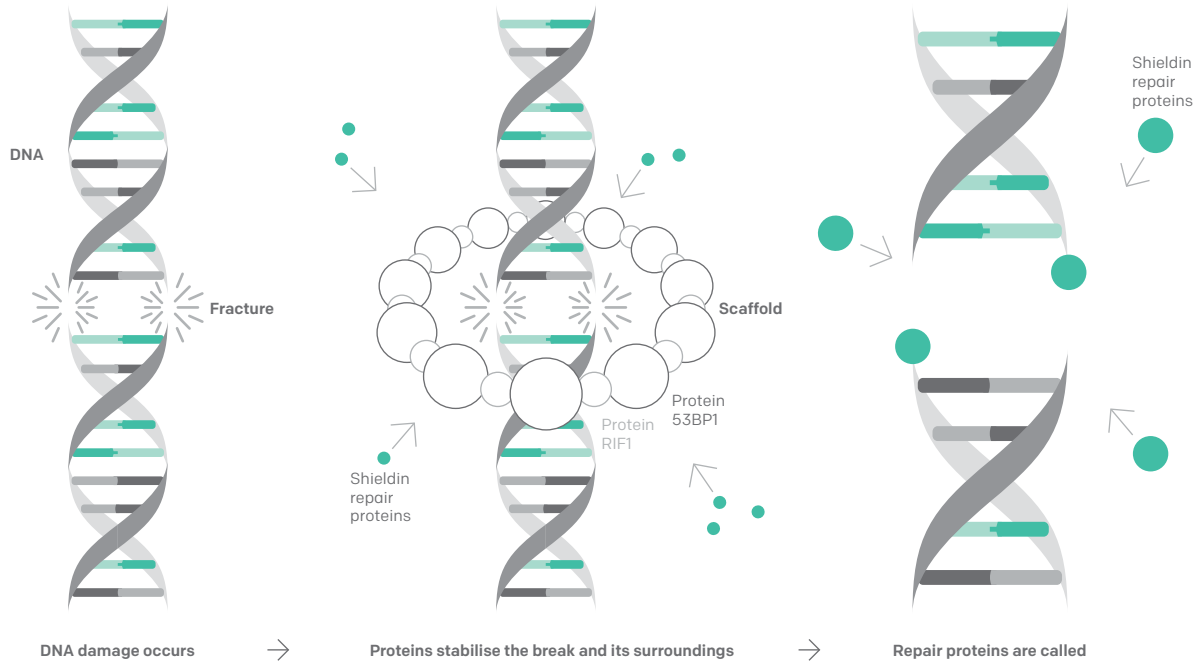
Misfortunes never come alone. This proverb applies to DNA when it is damaged and not properly repaired. Flaws in these cell mechanisms are hallmarks of diseases such as cancer, immune deficiency and dementia.

In 2019, CPR researchers published new fundamental knowledge on DNA repair that opens up previously unknown opportunities for better diagnosis or treatment of diseases caused by unstable DNA, says Claudia Lukas, Professor and Head of the Protein Imaging Platform at CPR.

"It's a unique discovery. Understanding the body's natural defence mechanisms enables us to better understand how proteins in our cells communicate and network to repair damaged DNA. This can be used to uncover new targets for drugs that improve treatment of patients with unstable DNA," she says.

By the use of super-resolution microscopy, the researchers uncovered how two proteins (53BP1 and RIF1) build a scaffold around the DNA fracture, and help attract proteins from the so-called Shieldin protein network to fix the damage. The discov-

THE DNA REPAIR PROCESS



The CRP research showed how proteins build a scaffold around a DNA fracture, and help attract proteins from the so-called Shieldin protein network to fix the damage. The network got its name because the proteins in it shield, protect and repair the DNA. In 2018, it was described by three collaborating CPR research groups in an article in the scientific journal Cell.

New insight into how proteins build scaffolds to repair DNA damage

ery was published in the scientific journal Nature in co-authorship with researchers at University of Oxford and European Molecular Biology Laboratory in Heidelberg.

ZOOMING IN ON PROCESSES IN LIVING CELLS

The researchers used two types of super-resolution imaging complementing each other: Stimulated Emission Depletion microscopy (STED) that can resolve tiny structures down to 50 nm detail, and Structured Illumination Microscopy (SIM), that allows a 120 nm resolution in all three spatial dimensions, even in living cells.

SIM and STED use different "tricks" to overcome the barrier of light diffraction, the physical phenomenon setting limits for conventional microscopy.

"This study is a wonderful example of how science benefits from cross-institutional research cooperation," says Claudia Lukas. "Suddenly we could see protein complexes around chromosome fractures with much greater detail than with conventional microscopy."

The researchers did not only see how the protein scaffold builds when things work well. They also investigated the consequences when things go wrong, which is the case in some diseases such as cancers caused by lack of scaffold proteins to repair unstable DNA.

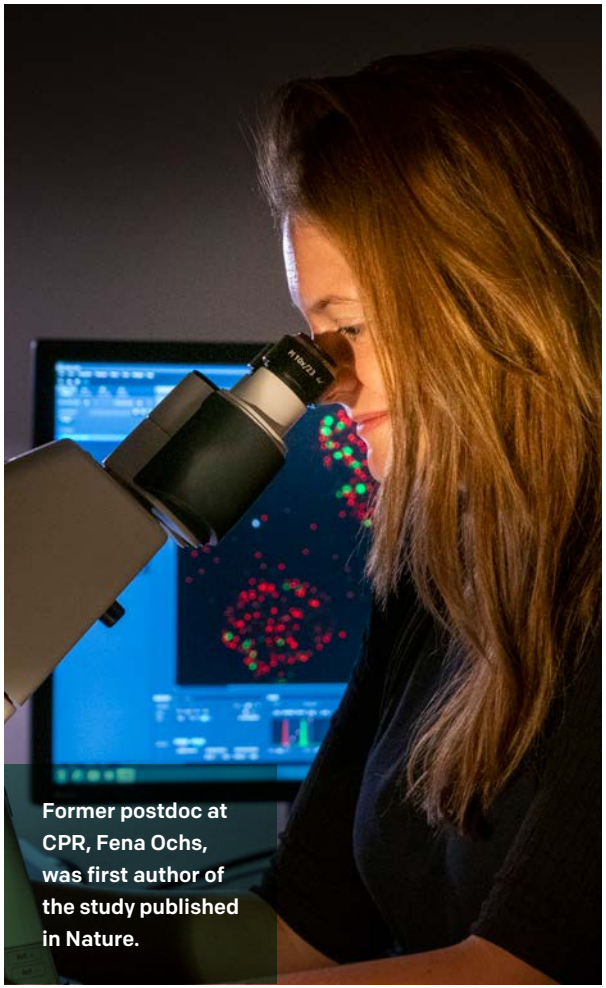
They mimicked the diseases by preventing proteins from forming the scaffold, and this really caused trouble. Large parts of the neighbouring chromosome rapidly fell apart causing DNA-damaged cells to start alternative attempts to repair themselves. This action often exacerbated the destruction of the genetic material.

MUCH LARGER SCAFFOLD THAN EXPECTED

The CPR researchers expected to find protein scaffolds only in the closest neighbourhood of the DNA fracture, but in fact the scaffold is much larger than earlier presumed by the international research community.

"Roughly speaking, the difference between the proportions of the protein-scaffolding and the DNA fracture corresponds to a basketball and a pinhead," says former Postdoc at CPR, Fena Ochs, who is the first author of the new study.

"This shows how important it is for the cell to stabilise both the DNA wound and the surrounding environment. This preserves the integrity of the damaged site and its neighbourhood and increases the likelihood of attracting the highly specialised proteins that perform the actual repair."



Former postdoc at CPR, Fena Ochs, was first author of the study published in Nature.

The researchers behind the study hope to be able to test the algorithm in clinical trials within a couple of years to prove whether, with the help of the algorithm, it is possible to predict individual patients' chances of survival in intensive care units more accurately than with the methods used today. At the same time, the next step is to further develop the algorithm so that it can make predictions by the hour.

New algorithm uses individual disease history to predict intensive care patients' chance of survival

Data from more than 230,000 intensive care patients from the past years have been used to develop a supporting tool that more accurately can predict individual patients' chances of survival in intensive care units.

Every year, tens of thousands of patients are admitted to intensive care units throughout Denmark. It is a major challenge to determine whether a seriously ill patient will benefit from intensive care or not. To make this decision, doctors and nurses rely on severity scores based mainly on acute physiology measures to predict mortality, but predictions for individual patients can be inaccurate and can be significantly improved.

To meet the need for better estimates, researchers from the Novo Nordisk Foundation Center for Protein Research (CPR) and Rigshospitalet have developed a new algorithm, which much more accurately predicts an intensive care patient's chances of surviving. Their research has been published in the scientific journal Lancet Digital Health.

The researchers have used Danish health data in a new way, using an algorithm to analyse data from the individual patient's disease history.

"The Danish National Patient Registry contains data on the disease history of millions of Danes, and in principle, the algorithm is able to draw on the history of the individual citizen of benefit to the individual patient in connection with treatment," says Professor Søren Brunak from CPR.

Excessive treatment is a serious risk among terminally ill patients treated in Danish intensive care units.

"Doctors and nurses have lacked a support tool capable of instructing them on who will benefit from intensive care. With these results we have come a significant step closer to testing such tools and directly improving treatment of the sickest patients," says Professor Anders Perner from the Department of Clinical Medicine and the Department of Intensive Care, Rigshospitalet.

HISTORICAL DATA IS COMBINED WITH CURRENT MEASUREMENTS

The researchers 'trained' the algorithm to take into account which previous diagnoses have had the greatest effect on the patient's chances of survival. No matter whether they were one, five or 10 years old.

The algorithm utilises neural networks to weigh the various factors in a patient's medical history. At first, the algorithm was not very predictive. But then the researchers included measurements and tests made in the first 24 hours of admission to the intensive care unit and this resulted in significant improvements to accuracy.

The algorithm ultimately makes three predictions:

- the risk of a patient dying in the hospital, which could be any number of days after admission
- the risk of the patient dying within 30 days of admission
- the risk of the patient dying within 90 days of admission.

OLD DIAGNOSES AFFECT CHANCES OF SURVIVAL

The researchers could tell that up to 10-year-old diagnoses affected predictions, and that young age lowered the risk of dying, even when other values were critical, while old age increased mortality risk. The algorithm is not just a useful tool in everyday practice in intensive care units, it can also tell us which factors are significant when it comes to a person's death or survival.

The algorithm was developed by the Brunak group in collaboration with researchers from the Department of Intensive Care, Rigshospitalet, and Cambio (formerly Daincare), a provider of IT solutions to improve health care and patient safety.

Professor Guillermo Montoya at the cryo-EM-facility that was used for capturing conformational changes of proteins in bacterial defence systems. The facility is coordinated by CPR and is part of the Core Facility for Integrated Microscopy (CFIM) at the University of Copenhagen.

New discoveries map defence systems in bacteria

For the first time ever, researchers have mapped at the atomic level how bacterial cells trigger their defence to eradicate outside attacks from other bacteria or viruses. Researchers at Novo Nordisk Foundation Center for Protein Research (CPR) made the landmark discoveries.

Ten years ago, the scientific community was not aware that bacteria have an immune system defence. But the idea spread that bacterial cells can fight back outside attacks from invading phages, a virus that attacks bacteria, and in 2019, researchers at CPR reached a major breakthrough when they were able to describe the mechanisms of the defence.

They uncovered the structure of a molecular switch that triggers the defence system in bacteria, and made a 'documentary' film of the process frame-by-frame showing how the system is activated. This was produced by combining the use of an advanced electron microscope at the cryo-EM facility at University of Copenhagen, and X-ray crystallography at facilities in Lund (Sweden) and Villigen (Switzerland). The landmark discoveries were published in the scientific journal Nature Communications.

REVEILING THE FIGHT BETWEEN BACTERIA AND PHAGES

The researchers showed how a bacterial cell attacked by a phage activates a messenger molecule called cOA (Cyclic Oligoadenylate). This is the switch that activates a protein complex called CSX1 to eradicate the attacker.

"The CSX1 protein complex is approximately 0.00002 mm long. We have taken 'pictures' of it and made a short film that reveals the activity inside the protein complex CSX1 that eradicates the phage," says Guillermo Montoya, Research Director and Professor at CPR. "We can see how CSX1 is activated by the cOA molecule, how it rotates and starts defending the cell by eliminating the infective material of the phage. Expressed in popular terms, the CSX1 starts cutting up the intruder."

CORNERSTONE IN FIGHTING DISEASES

The researchers expect to come up with new knowledge on the tiny world of proteins and bacteria in 2020. CSX1 is part of a larger multifaceted immune system in bacteria, and the next step for the team is to investigate how the components of this system interact to defend bacteria against intruding phages.

"The new discoveries can turn out to be an important cornerstone in fighting diseases and developing strategies against antibiotic resistant bacteria in the future. They can also be relevant as technological applications in laboratory research, such as gene silencing," says Guillermo Montoya. "Antibiotic resistance comes from this type of fight between bacteria and phages, which is why our studies may generate important knowledge for fighting antibiotic resistance."

The research took place in collaboration between CPR and the Danish Archea Center at the University of Copenhagen.

2019 Brief Highlights

CREATING SPACE FOR NEW ACTIVITIES

In 2019, laboratory and office facilities on the third floor of Novo Nordisk Foundation Center for Protein Research (CPR), were refurbished to accommodate the planned arrival of the Groth research group in spring 2020. On the first floor, office facilities were rearranged to accommodate the growing needs of the Taylor group, the arrival of staff in the Twelve Bio spin-out company, and the expected arrival of a new research group in the Protein Structure and Function Program in autumn 2020.

STRENGTHENING COMMUNICATION

CPR wants to maximise outreach and dissemination of its scientific achievements, and 2019 showed an increase in the number of high quality news stories on CPR's website, supplemented by press releases reaching out to public news media. This was a result of a 2018 agreement on partnership with the communications department of the Faculty of Health and Medical Sciences at the University of Copenhagen.

RENEWAL OF SCIENTIFIC ADVISORY BOARD

CPR succeeded in attracting three distinguished researchers to its scientific advisory board covering the research areas protein signalling, disease systems biology, and epigenetics and protein memory: Michael Yaffe, Koch Institute for Integrative Cancer Research, MIT, US, Namaa Barkai, Department of Molecular Genetics, Weizmann Institute of Science, Israel, and Steven Heinikoff, Fred Hutchinson Cancer Research Center, US. CPR wants to thank the four scientists who stepped down as a result of the natural turnover: Torben Ørntoft, Tony Hyman, Ivan Dikic, and Janet Thornton.

TECHNOLOGY BUILDING AND SHARING

The Novo Nordisk Foundation granted 100 million DKK to establish a new state-of-the-art mass spectrometry facility, Proteomics Research Infrastructure (PRI) at the University of Copenhagen in 2020. CPR spearheaded the application in close collaboration with the Faculty of Health and Medical Sciences. The aim of PRI is to give the regional research community access to the advanced proteomic technology that measures proteins in a biological sample. PRI also offers technological assistance and streamlined bioinformatics data analysis.

ALUMNI

The ability of CPR alumni to compete for positions in top international academic institutions and prominent leadership positions in the biotech/pharmaceutical industry is an important success criterion for the center. In 2019, eight PhD students completed their formal education at CPR and two of these left CPR for new positions. In the same period, eight postdocs, two assistant professors and one associate professor left CPR. CPR's young researchers have moved on to new careers within academia (4), industry (3), and other types of organisations (6), such as hospitals and research communication agencies.

SCIENTIFIC PRIZES

Research director Søren Brunak was awarded the internationally recognised 'Store Nordiska Pris' of one million SEK from Eric K. Fernström Foundation. Brunak received it for his seminal, trailblazing work that combines big data, mathematical analysis and biomedical research. Søren Brunak also received the prestigious JFK award from the Kirsten and Freddy Johansen Foundation for excellent research in health data through the years. Professor Chuna Ram Choudhary was awarded the EliteForsk-prize by the Danish Agency for Science and Higher Education.

PREPARATIONS FOR CONFERENCE

Preparations for the fifth CPR Protein Signaling conference took place with broad involvement of CPR group leaders who put together an impressive list of speakers to invite for the conference. The "Copenhagen Bioscience Conference 'Protein Signaling – from mechanism to cellular function" was planned for the autumn of 2020 but had to be postponed to 14-18 November 2021 owing to the COVID-19 pandemic.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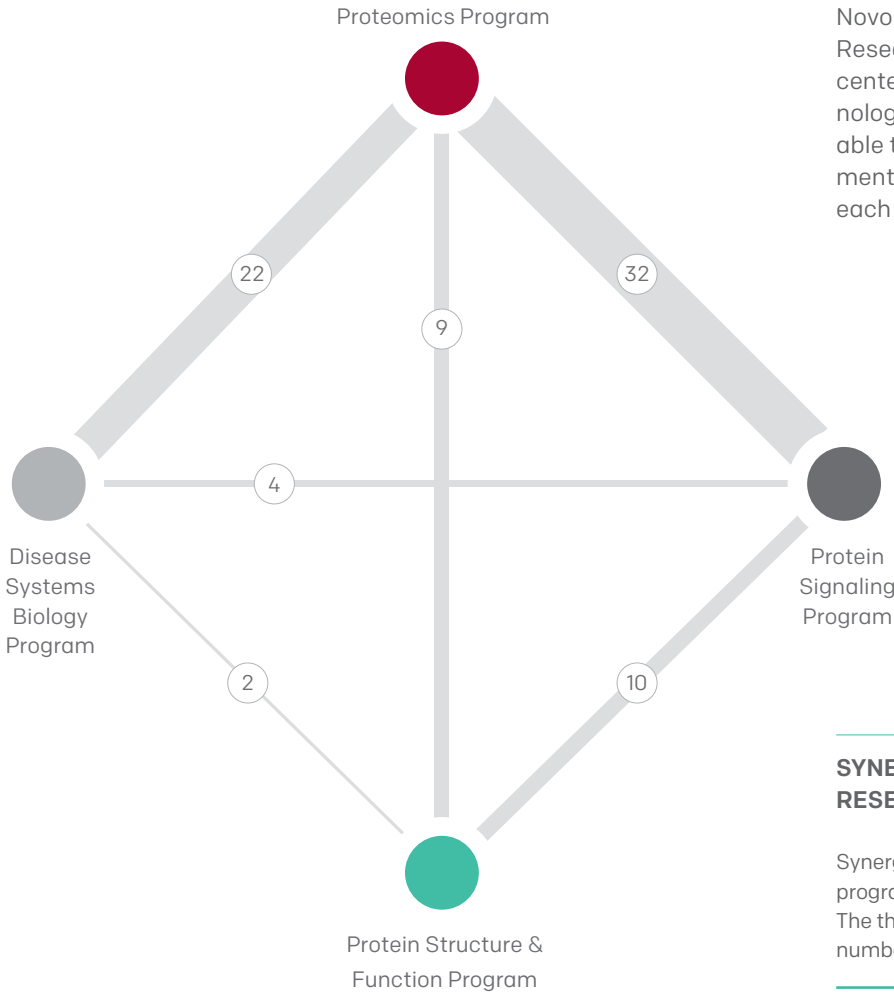
Internal and external synergy

Collaboration and exchange of ideas is high priority at the Novo Nordisk Foundation Center for Protein Research (CPR), since an open-minded and curious attitude among researchers increases the chance of generating frontier research. This applies internally in CPR as well as in collaboration with hospitals, universities and the biomedical industry in Denmark and abroad.



Novo Nordisk Foundation Center for Protein Research (CPR) is a highly integrated research center. With all research, knowledge and technology located closely together, CPR has been able to establish an interdisciplinary environment where research programs complement each other and collaborate extensively.

SYNERGY BETWEEN CPR RESEARCH PROGRAMS

Synergies illustrated by the number of program-to-program shared research publications in 2015-2019. The thickness of lines between programs represents the number of collaborative publications.

Internal and external synergy

Novo Nordisk Foundation Center for Protein Research (CPR) actively interacts with the Faculty of Health and Medical Sciences at University of Copenhagen, hospitals in the region and scientific partners from around the world. The global reach of CPR is evident in the large number of collaborations that the center has established around the world.

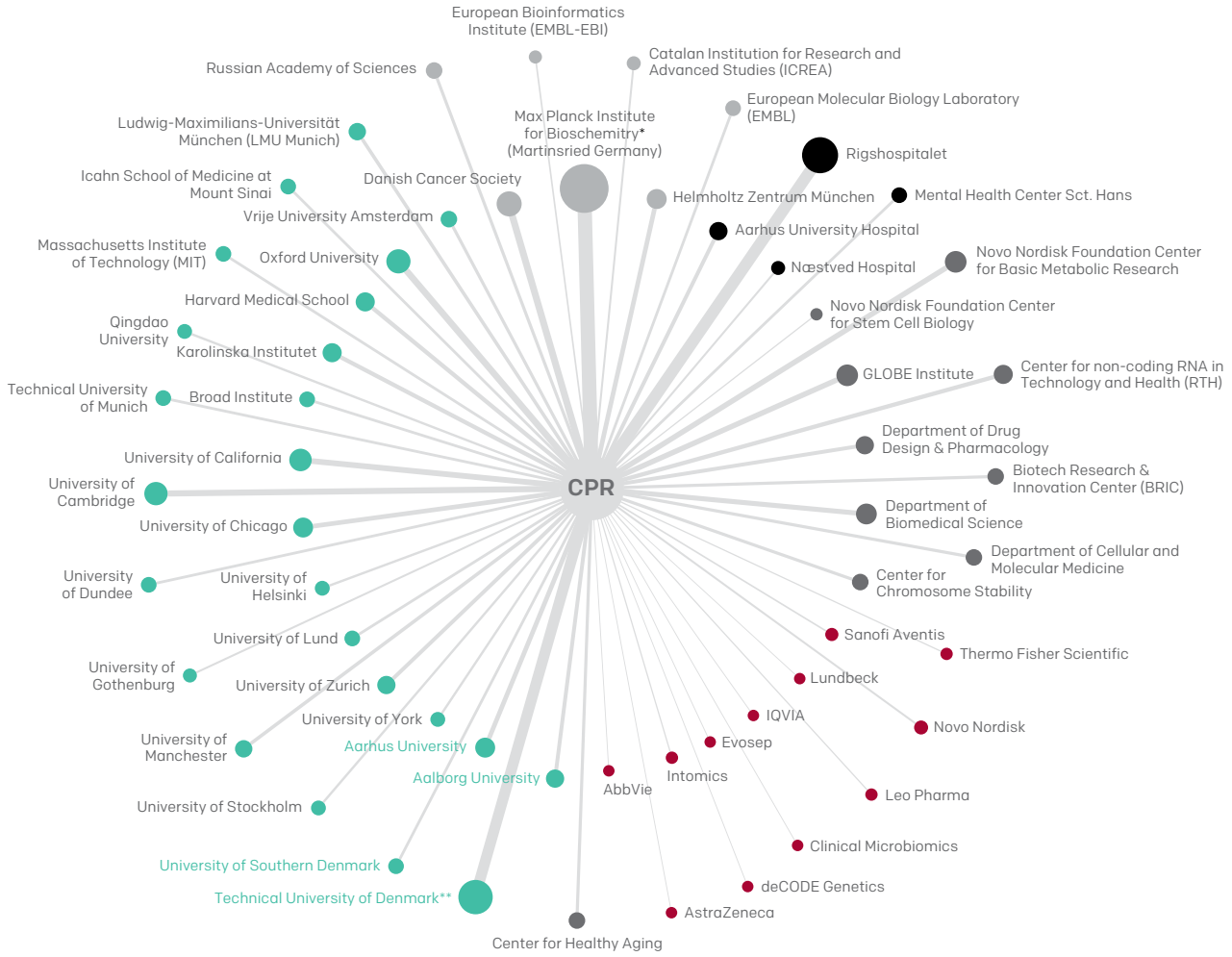
SYNERGY BETWEEN CPR AND EXTERNAL COLLABORATORS

Synergies illustrated by the number of published collaborations with external partners in 2015-2019. The number of collaborations is represented by the thickness of lines (2-46).

- Corporation
- Hospital
- Research Institution
- University
- Faculty of Health and Medical Sciences, University of Copenhagen

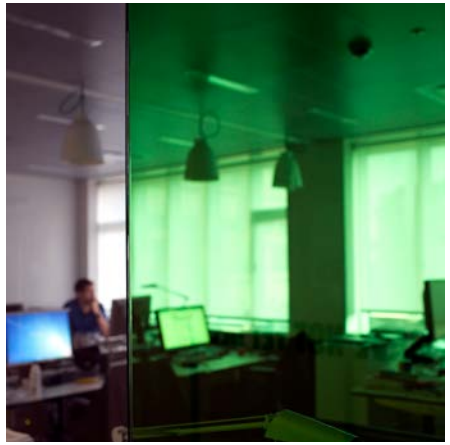
* 28 of 46 collaborations with MPI are related to Matthias Mann's appointment as Director of Department of Proteomics and Signal Transduction, Max Planck Institute of Biochemistry.

** 25 of 29 collaborations with Technical University of Denmark are related to Søren Brunak's appointment as Professor of Bioinformatics, Department of Health Technology, Technical University of Denmark.



Research programs and technologies in 2019

The research groups at the Novo Nordisk Foundation Center for Protein Research (CPR) are organised into four programs. Each program is dedicated to run a technological platform that provides state-of-the-art research resources and interdisciplinary support to fellow researchers in the center.



Disease Systems Biology Program

Professor Søren Brunak
Research Director of the Disease Systems Biology Program

The program is leading in developing innovative tools to analyse and interpret big biomedical data effectively to better understand disease development and improve treatment options. The program combines multi-omics molecular network biology data and clinical data from the healthcare sector.

THE BRUNAK GROUP

... Combines molecular and clinical data in novel ways in order to understand disease progression patterns in multi-morbidity patients. Understanding diseases in a lifelong perspective gives valuable insights for more precise treatment.

2019 landmark

“ Using data from over 230,000 patients we developed an algorithm that predicts intensive care patients’ chances of survival based on their disease history. The aim is to help doctors predict who will benefit from intensive care, which is important in order to avoid excessive treatment of terminally ill patients. ”

– Professor and Group Leader
Søren Brunak.

THE JENSEN GROUP

... Develops state-of-the-art tools for generation and analysis of molecular interaction networks from proteomics data and text mining. The tools are made freely available to the scientific community.

2019 landmark

“ We have redesigned and improved the STRING database, which we run in collaboration with an international team. The STRING database covers known and predicted protein–protein interactions for more than 5000 organisms and is used by thousands of researchers worldwide every week. ”

– Professor and Group Leader
Lars Juhl Jensen.

THE RASMUSSEN GROUP

... Focuses on computational analysis of variation in the human proteome, genome and microbiome. By applying deep learning algorithms to massive amounts of genomic, transcriptomic, proteomic and metagenomic data, they aim to increase the understanding of human diseases.

2019 landmark

“ Our group has discovered a previously unknown pandemic of plague in the Stone and Bronze Age that has shaped the genome of the modern European population. The study is a step toward understanding how pathogens evolve from being harmless to being deadly to humans. ”

– Professor and Group Leader
Simon Rasmussen.

TECHNOLOGY RUN BY THE DISEASE SYSTEMS BIOLOGY PROGRAM
The Big Data Management Platform provides a shared, scalable computational infrastructure to handle the vast amounts of data produced by the various technology platforms at CPR, such as raw mass spectrometry and imaging data.

Protein Signaling Program

The program uses cutting-edge methodologies to illuminate how proteins communicate and work together to protect cellular DNA from harmful changes. This enables a detailed molecular understanding of diseases such as cancer and paves the way for improved treatment of patients.

THE DUXIN GROUP

... Uses protein extracts from frog eggs to study fundamental mechanisms of DNA repair and DNA replication. They primarily focus on how cells repair DNA lesions known as DNA-protein crosslinks, which can cause cancer and accelerated aging if left unrepaired.

2019 landmark

“ We have discovered a previously unknown mechanism that allows cells to continue DNA replication across highly toxic DNA-protein crosslinks. The study indicates how cancer cells may continue to divide despite severe DNA damage caused by chemotherapy. ”

- Associate Professor and Group Leader **Julien Duxin**

THE LUKAS GROUP

... Explores how proteins that guard the integrity of the human genome assemble into functional pathways, how they organize themselves in the cell nucleus, and how they communicate with the external environment and cellular metabolism to shield DNA against heritable and disease-predisposing mutations.

2019 landmark

“ Using super-resolution microscopy, we have shown how proteins stabilise damaged DNA by building a 3D scaffold around it, which concentrates highly specialised and scarce proteins that are critical to restore DNA integrity without errors. ”

- Professor, Executive Director and Group Leader **Jiri Lukas**

THE NILSSON GROUP

... Investigates essential enzymes called protein phosphatases that control a vast number of signalling processes in the cell. Understanding how protein phosphatases function and select their target proteins may advance rational drug design for a range of human diseases.

2019 landmark

“ We revealed how the protein phosphatase PP4 recognises its targets. PP4 appears to be very selective, which will facilitate development of new drugs against it. This has a clinical perspective, since inhibition of PP4 is a potential treatment strategy for certain cancers. ”

- Professor and Group Leader **Jakob Nilsson**

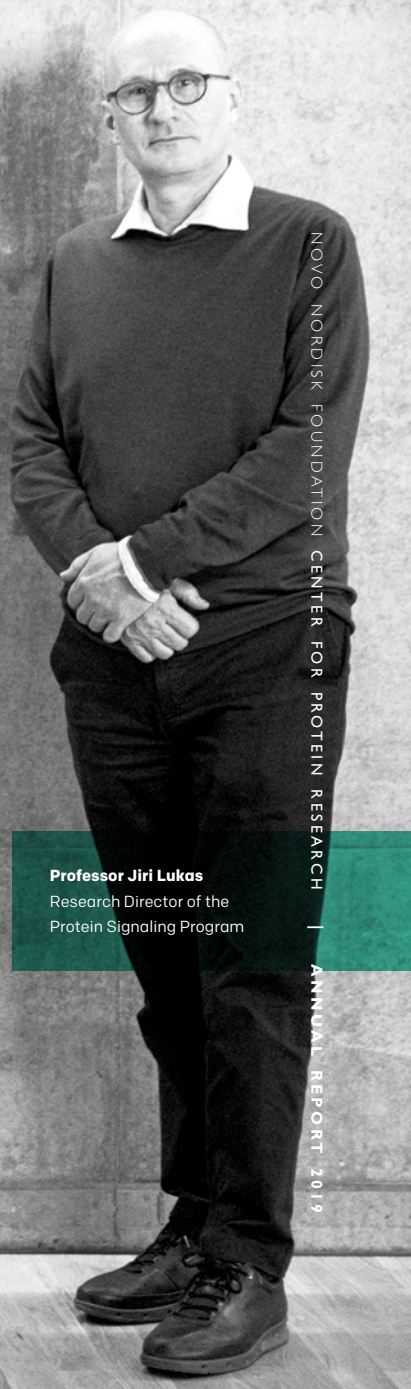
THE MAILAND GROUP

... Seeks to obtain detailed molecular insights into the processes of cellular stress management protecting cells against genetic changes, which underlie many diseases. This knowledge provides opportunities for development of new and improved treatment strategies.

2019 landmark

“ We discovered a crucial role of SUMOylation in promoting repair of DNA-protein crosslinks, which are generated by many chemotherapeutic agents. The new mechanism is essential for cells to mitigate the toxicity and disease-promoting potential of these DNA lesions. ”

- Professor and Group Leader **Niels Mailand**



Professor Jiri Lukas
Research Director of the Protein Signaling Program

TECHNOLOGY RUN BY THE PROTEIN SIGNALING PROGRAM
The Protein Imaging Platform provides cutting-edge technology and support to all researchers at CPR that use microscopy to investigate the behaviour of proteins in the cell, such as protein localisation, activity and interactions, either as a snapshot or over time.

Protein Structure and Function Program

Professor Guillermo Montoya
Research Director of the Protein Structure and Function Program

The program visualises the 3D structure of individual proteins and their assemblies to understand key biological processes. Understanding how these molecules function improves the understanding of biological mechanisms and disease development and facilitates drug development.

THE MONTOYA GROUP

Visualises the functional details of protein complexes involved in cell cycle progression and genome editing and integrity. Deciphering the mechanisms behind these important processes provides the basis for understanding disease and the possible development of treatments.

2019 landmark

“ We revealed the activation mechanism of CSX1, a genome-editing protein that provides immunity to bacteria against invading plasmids and viruses. This helps us understand bacterial immune systems and may lead to improved treatment against antibiotic resistant bacteria. ”

- Professor and Group Leader
  Guillermo Montoya

THE TAYLOR GROUP

Uncovers the structure and function of the complex molecular machines involved in transporting molecules across cell membranes. By understanding their biological role, it will ultimately be possible to adapt or modulate these systems for medical purposes.

2019 landmark

“ We have successfully set up pipelines to produce, purify and analyse the cryo-EM structure of various molecular machines, yielding promising initial results. In 2020, we aim to complete and publish our cryo-EM studies of the membrane protein complex that allows bacteria to move. ”

- Associate Professor and Group Leader
  Nicholas Taylor

TECHNOLOGY RUN BY THE PROTEIN STRUCTURE AND FUNCTION PROGRAM
The Protein Production and Characterization Platform provides CPR with purified proteins and protein complexes of the highest quality and characterizes proteins using biophysical methods. The platform is an important asset as an entry point for the cryo-EM facility.

Proteomics Program

Innovative use of mass spectrometry technology allows the program to map all protein variants in a cell (the proteome) to gain a deep biological understanding of cellular processes in health and disease. They can also identify proteins involved in disease and disease biomarkers.

THE NIELSEN GROUP
Develops novel proteomic strategies and combines this with other protein technologies and bioinformatics to understand how underexplored post-translational modifications (PTMs)* of proteins affect mammalian cell biology.

2019 landmark
“We published a technological development that greatly improves the use of mass spectrometry to measure the physiological extension of ADP-ribosylation, a post-translational modification involved in fundamental biological processes such as DNA damage repair and cell growth.”

- Professor and Group Leader **Michael Lund Nielsen**

THE MANN GROUP
Develops innovative methods for rapid quantification of proteins in body fluids and tissue. By profiling patient samples, they aim to identify novel biomarkers that can be used for patient diagnosis and possibly for prevention and treatment of metabolic diseases, such as diabetes and cancer.

2019 landmark
“We applied our proteomic profiling to patients with liver disease to identify new valuable biomarkers and drug targets. Further investigations will reveal the potential of these proteins as new and early biomarkers for liver disease.”

- Professor, Research Director and Group Leader **Matthias Mann**

THE OLSEN GROUP
Develops mass spectrometry technology towards increased speed and sensitivity while applying it to biological questions such as mapping cellular signalling via growth factor receptors on the cell surface and the study of ancient proteins (palaeoproteomics).

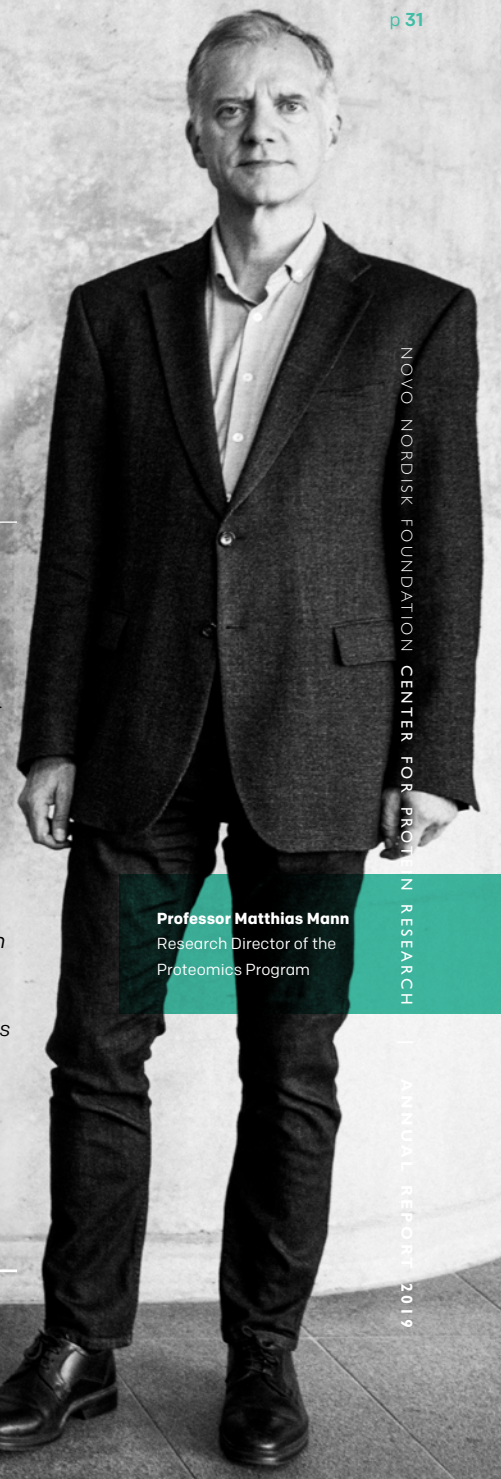
2019 landmark
“We mapped the signalling networks that contribute to tumour growth when certain genes in lung cancer cells mutate. This makes it possible to understand the functional consequence of specific cancer mutations in lung cancer and may help improve existing treatments for patients who become resistant.”

- Professor and Group Leader **Jesper Velgaard Olsen**

THE CHOUDHARY GROUP
Deciphers the regulatory effects of post-translational modifications (PTMs)* in cell signalling by subjecting engineered mammalian cell line models to state-of-the-art quantitative proteomics.

2019 landmark
“We quantified the proteome-wide stoichiometry of the post-translational modification lysine acetylation in human cells and found that most proteins are acetylated at very low levels. This resource dataset provides valuable information for evaluating the impact of individual acetylation sites on protein function.”

- Professor and Group Leader **Chuna Ram Choudhary**



Professor Matthias Mann
Research Director of the Proteomics Program

TECHNOLOGY RUN BY THE PROTEOMICS PROGRAM
The Mass Spectrometry Platform provides technical support and maintenance for research groups in the Proteomics Program to ensure that CPR retains state-of-the-art mass spectrometry technology. Additionally, the platform provides analytical proteomics support for CPR researchers.

*PTMs are chemical groups added to proteins after they are synthesised, affecting protein structure and function.

CPR organisation and leadership

Novo Nordisk Foundation Center for Protein Research (CPR) has a clear governance structure tailor-made to maximise efficient governance internally and foster interactions with the Faculty of Health and Medical Sciences at the University of Copenhagen and other Novo Nordisk Foundation-funded centers of excellence.

The governance model incorporates all leaders and principal investigators with top-down advice from the Scientific Advisory Board and bottom-up perspectives from the center's Collaboration, Health and Safety Committee as well as the Student and Postdoc Association.

All key decisions are made by the executive management headed by the Executive Director, who answers directly to the Dean of the Faculty. The CPR executive management team consists of the Faculty Dean, the CPR management, and the Research Directors. The team interacts frequently and on different levels to discuss strategic matters, scientific strategy, finances, and to streamline the day-to-day management.

CPR MANAGEMENT
Executive Director: **Jiri Lukas**
Deputy Director and Director of Education: **Jesper Velgaard Olsen**
Head of Administration and Finance: **Peter Dyrsting**

CPR SCIENTIFIC ADVISORY BOARD
Once a year, the Scientific Advisory Board evaluates the center's performance, productivity, innovation, synergy and education. The board consists of some of the most influential scientists of our time, covering world-leading expertise in all of CPR's major research fields.
Angus Lamond (Chair), Wellcome Trust Centre for Gene Regulation and Expression, Dundee University (UK). Expert in proteomics and advanced imaging.
Andre Nussenzweig, Chief at Laboratory of Genome Integrity, National Institute of Health (NIH), National Cancer Institute, Bethesda (USA). Expert in DNA damage response and mouse models of genome instability disorders.
Christoph Müller, Head of Structural and Computational Unit at EMBL, Heidelberg (Germany). Expert in cryo-EM, X-ray crystallography and advanced biophysical and biochemical approaches.
Michael Yaffe, Koch Institute for Integrative Cancer Research, MIT (USA). Expert in how signaling pathways integrate at the molecular and systems level to control cell cycle progression and DNA damage responses in cancer.
Naama Barkai, Department of Molecular Genetics, Weizmann Institute of Science (Israel). Expert in systems biology and design principles of biological circuits.
Steve Henikoff, Fred Hutchinson Cancer Research Center (USA). Expert in chromatin conformation and epigenetic inheritance.

COLLABORATION, HEALTH AND SAFETY COMMITTEE

A dialogue forum where decisions and new ideas are discussed and developed between management and employee representatives. Topics include personnel policy, work/life balance, trust, cooperation, well-being, safety, competence development and finances.

STUDENT AND POSTDOC ASSOCIATION

A bottom-up initiative created by students and postdocs to promote internal center synergy. Not a governing body per se, but the association has a direct and positive impact on the strategic decisions made by the management, and its representatives have a regular slot at group leader meetings.

CPR GOES GREEN INITIATIVE

A bottom-up initative promoting sustainability in the center's daily activities. Works to reduce the carbon footprint of CPR by implementing green initiatives related to waste, energy, water, lab reagents, consumables and daily habits.

Publications 2019

The list includes primary research papers, reviews and book chapters published in 2019 (print date). CPR authors are highlighted in bold.

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