The Novo Nordisk Foundation Center for Protein Research
Annual Report 2014

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Executive summary


Executive Director, Jiri Lukas

The year 2014 marked the completion of a rigorous midterm evaluation, the first in the history of the Novo Nordisk Foundation Center for Protein Research (CPR) or any other center funded by the Novo Nordisk Foundation (NNF). CPR has emerged from the evaluation as a world-class center with a strong identity and a rapidly growing influence both in terms of research output and an organizational model for next-generation centers of scientific excellence.

From the perspective of CPR management, we see five major achievements during the past year that defined the transition of CPR from the initial 'building period' to a fully established research center with high ambitions to lead basic protein science and its applications in medicine.

Extension of the NNF core funding. First and foremost, based on the positive assessment by international peer reviewers, NNF decided to award additional DKK 180 million (€24.2 million) to extend and strengthen the activity of the Center for the coming five years. This is significant in several ways: Together with the residual resources from the first funding period, the new grant will allow CPR to operate at the existing and very competitive annual core funding level and to maximally harness and further develop the intellectual and technological potential of the Center. Furthermore, encouraged by CPR's performance, NNF decided to revise their funding scheme by introducing open-ended quinquennial evaluations. The key asset of this new financial model is that it has no pre-defined expiry date and thus the future of CPR is now entirely in our hands: As long as we produce world-class science, we have a chance to maintain the financial support from NNF. We are very proud of this achievement – it is a major motivation for a lasting win-win partnership with NNF to play a major role in the premier league of international protein science.

We are equally excited about the benefits such partnership brings to the University of Copenhagen in general and the Faculty of Health and Medical Sciences in particular. This year for example, CPR organized the first practical course in 'Advanced methods for the analysis of protein disease mechanisms' with the objective to raise interest of modern protein research among undergraduate students. This resonates well with one of the key missions of CPR; to educate new generations of researchers and give them unique competences that will make them capable of competing for top jobs in academia and industry. We take this task very seriously not only at the postgraduate and postdoctoral level but also by reaching out to the Faculty as with the undergraduate course.

We have enjoyed exceptional support in reaching our scientific and educational goals from the university leadership, which is best illustrated by the quote from Ulla Wewer, the Dean of the Faculty of Health and Medical Sciences, at the official announcement of CPR's extended funding:

'It is with immense appreciation of the foundation's global outlook and great pride in The Novo Nordisk Foundation Center for Protein Research mind set and impressive results that we are now able to begin the next chapter. We will do our utmost to live up to expectations and contribute positively to the bridge building between molecular biology and clinical medicine whereby research environments, young researchers, Danish biotech businesses and not least patients will be able to reap the benefits of basic research'.

Completing CPR structure by introducing technological platforms. The second achievement in 2014 can be described as a completion of CPR structure, which now has a clear and strong leadership, and which bears unique features that are crucial for CPR's competitiveness. With the arrival of Guillermo Montoya, CPR now consists of four research programs headed by leading experts in complementary areas of protein research: Proteomics (Matthias Mann), Protein Structure and Function (Guillermo Montoya), Protein Signaling (Jiri Lukas), and Disease Systems Biology (Søren Brunak). Apart from the close integration of all four programs and a highly collaborative spirit among

all their scientific staff, the unique asset of the CPR design is that each research program supports the whole center with a dedicated technological platform. The difference from 'standard' core facilities is that top experts who are highly competitive CPR scientists head all technological platforms. Such active leadership allows not only for top-notch technological support, but encourages CPR's students and postdocs to leave their narrow analytical 'comfort zones' by exposing them to a wide range of state-of-the-art technologies. The latter aspect is crucial for identifying new cross-disciplinary projects and perhaps even more for the educational strategy that the CPR management has dubbed as 'growing complete protein scientists'. Furthermore, thanks to contacts of the platform leaders with EMBL and other innovation hubs worldwide, the CPR platform concept secures constant operation at the cutting-edge level.

The current technological platforms and their leaders include: Mass Spectrometry Platform (Michael Lund Nielsen), Protein Production and Characterization Platform (Guillermo Montoya), Protein Imaging Platform (Claudia Lukas), and Big Data Management Platform (Lars Juhl Jensen).

We would like to point out that the success of the CPR structure has been made possible thanks to inspiration and guidance provided by members of our Scientific Advisory Board who have been sharing with us their precious experience. We are really proud that we have now reached a stage, which Professor Anthony Hyman, chair of our scientific advisory board, describes as follows:

'The idea of dividing the institute up into four areas, each supported by a strong service group was seen as excellent, creating a structure that is unique in the world. All four of the programs are world class. The arrival of Guillermo Montoya is seen as an excellent recruitment'.

CPR coming of age. The third achievement in 2014 is best described as 'CPR coming of age'. Just like the whole center, individual groups at CPR undergo rigorous quinquennial evaluation by a panel of international leaders from their respective fields of science. Recommendations by the review panels are considered crucial guidance for CPR management to decide whether to extend the group and what would be the size of its core funding. Such evaluations are particularly important for young principal investigators who have joined CPR to establish their own research groups for the first time and four of those were 'at stake' in 2014. It was among the most gratifying moments to see that all four groups, headed by Jesper Velgaard Olsen, Michael Lund Nielsen, Chunaram Choudhary (all Proteomics Program), and Niels Mailand (Protein Signaling Program) presented their research and future ideas in the best possible way, passed the truly in-depth and incisive assessments, and were unanimously extended. We are very proud of this emerging generation of strong scientific leaders and would like to congratulate them on this achievement and thank them and their groups for representing CPR so well. They clearly set the bar very high, not only for starting groups but also for more 'senior' group leaders to live up to this level of scientific excellence.

Scientific output. This short synopsis of CPR achievements could not be complete without mentioning the remarkable scientific productivity during the last year, resulting in exciting discoveries, competitive external grants, and prestigious awards to CPR scientists.

Without exception, all groups contributed to this success and a considerable part of this annual report is therefore dedicated to highlighting our most important results and their biological and medical implications. Here, as an incentive for the reader to visit the group sections in this Annual Report, we will merely highlight the fact that 22 papers out of a total 78 scientific papers with CPR affiliation were published by the most prestigious publishing houses such as Cell, Nature, Science, and their sister journals. This, more than anything, demonstrates the significance of CPR-born discoveries.

Yet there were other achievements that placed CPR firmly on the 2014 scientific map of the world: Jiri Lukas received the 42nd Leopold Griffuel Prize, one of the world's most prestigious cancer research awards. In addition, CPR has always been very successful in attracting competitive external funding and 2014 advanced this positive trend by winning some of the really 'big' ones: Niels Mailand brought to CPR its first ERC Consolidator Grant and Chunaram Choudhary was awarded the prestigious Novo Nordisk Foundation Hallas Møller grant. This is a fantastic achievement and a great boost for CPR's image both nationally and internationally. Once again, the bar is high and we will strive to keep it at this level for the coming years. Another highlight in the 2014 scientific calendar was the Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' organized by four CPR group leaders: Jeremy A. Daniel, Lars Juhl Jensen, Amilcar Flores-Morales and Michael Lund Nielsen (PTMs in Cell Signaling). Like the 1st conference on the same topic two years ago, this was an extremely successful and inspiring meeting, establishing a strong niche for CPR in this exquisitely interdisciplinary field. The success of this meeting was a joint result of the extraordinary ability of the organizers to bring together world leaders from major fields

of protein science and the generous logistical and financial support from the NNF, including the wonderful Favrholm venue.

The student and postdoc association. The fifth and last achievement is particularly precious because it did not need input from CPR management but developed spontaneously on the initiative of enthusiastic CPR students and postdocs.

Speaking for CPR leaders, we are well aware that it is our young scientists who generate real scientific value in the form of results and discoveries and we were therefore thrilled to hear that they decided to organize themselves in the 'Student and Postdoc Association' (SPA).

The aim of SPA is to intensify cross-program interaction, actively contribute to shaping the center, generate new opportunities to regularly meet with principal investigators, and a number of other exciting ideas to harness the potential of CPR as a center where scientists gain from mutual interaction rather than internal competition.

CPR management is very excited by this development and went ahead to materialize some of SPA's ideas already in 2014. For instance, SPA representatives are now invited to attend group leader meetings and actively contribute to the agenda, principal investigators regularly attend the bi-weekly SPA lunches dedicated to career opportunities, and SPA has received two 'slots' in the CPR seminar series to invite and host prominent international scientists – an a area where in no time they became particularly successful! SPA has established a dedicated niche on the CPR homepage, administered and regularly updated by SPA members to share information about SPA's ongoing activities (http://www.cpr.ku.dk/about/student-and-postdoc-association-spa/). Other exciting activities will definitely follow in the coming years.

Last but not least, we see this initiative as a key asset to attract new talents to CPR and give potential candidates a valuable insight into the CPR world.

In summary, 2014 was in many aspects an exciting and very important year for CPR. We would like to thank all CPR members for actively contributing to this success.

Peter Dyrsting
Head, Administration & Finance

Jesper V. Olsen
Vice Director

Jiri Lukas
Executive Director

Student and Postdoc Association

SPA is the student and postdoc association of CPR, initiated by a group of postdocs that sought to unite young researchers within CPR.

The association provides a forum in which we can interact across floors, groups and scientific interests.

SPA aims to increase the scientific discourse and training among its members, not only to increase the transparency of the research conducted within CPR but also to promote interdisciplinary research incorporating expertise from the research programs: Protein signaling, protein structure analysis, state-of-the-art mass spectrometry and systems biology.

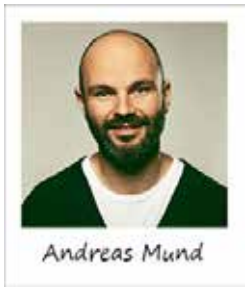
In 2014, two representatives from each floor at CPR were chosen to manage SPA activities and represent the association at CPR group leader meetings, giving students and postdocs a voice within the center management.

In the interest of improving scientific discussion, SPA has collaborated closely with the group leaders of CPR to improve the format of the CPR Research in Progress (CPR-IP) seminars. At these meetings, students and postdocs present their ongoing research with the purpose of receiving constructive feedback from other researchers at the center.

SPA also works actively to organize career planning events in order to inform students and postdocs of career possibilities outside the university. One such meeting was hosted in 2014, with more to come in 2015. In 2015, SPA will also invite world-leading scientists to present their work in the CPR Seminar Series and to meet with young researchers. SPA hopes to increase the interaction with similar student and postdoc associations from other UCPH research centers such as BRIC, in order to strengthen scientific networking and mutually benefit from each other's organized career and scientific events.

SPA Organizing Committee


Godelieve Smeenk


Andreas Mund

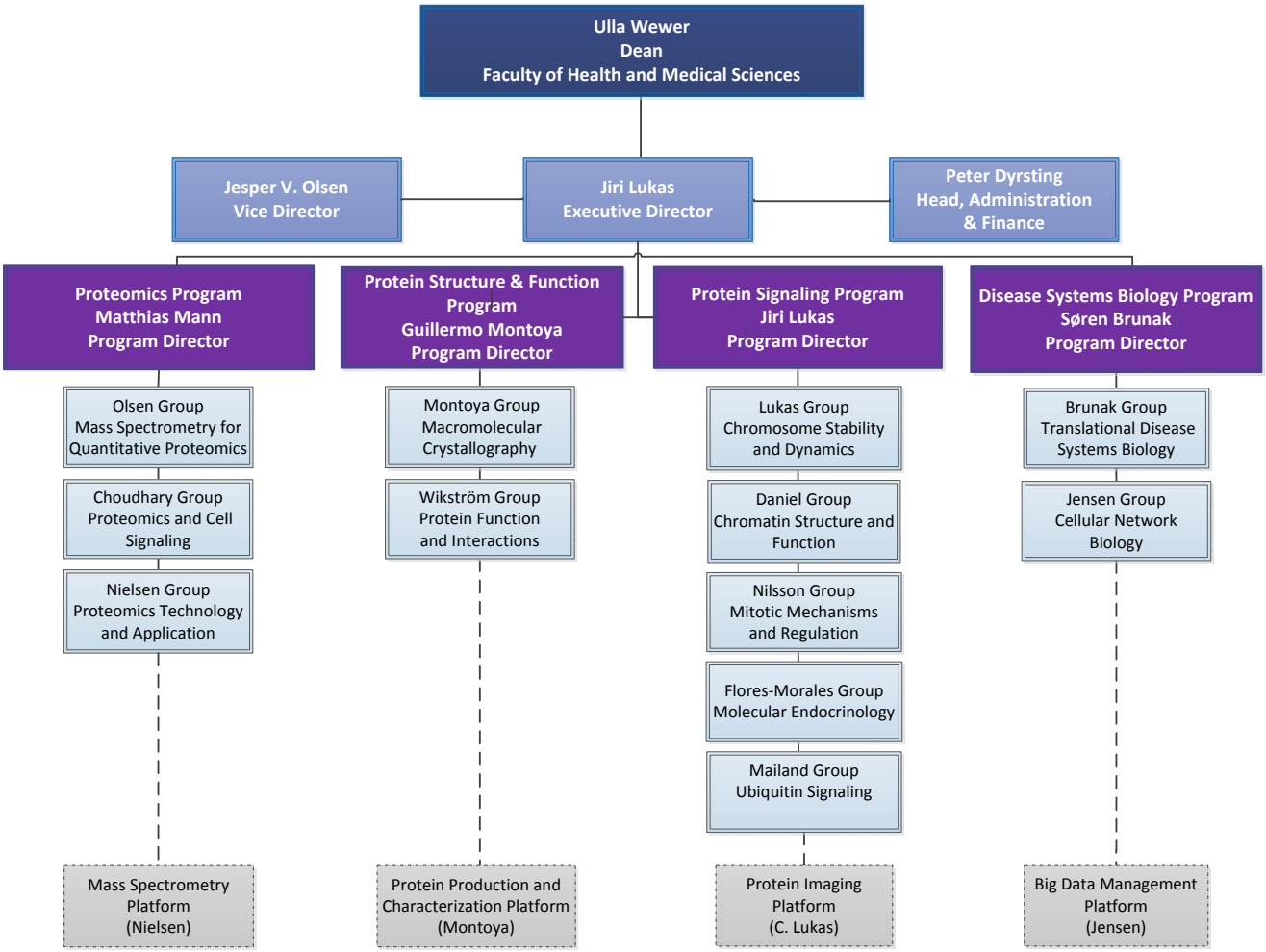

Stephanie Munk


Kai Neelsen


Louise von Stechow


Luis Toledo

NNF Center for Protein Research Organizational Chart



CPR management, research programs, research groups, and technological platforms

Center Management

CPR is a research center established at the Faculty of Health and Medical Sciences at the University of Copenhagen. CPR is managed by an executive management team consisting of:

- Ulla Wewer, Dean of the Faculty of Health and Medical Sciences
- Jiri Lukas, Executive Director, Program Director, CPR
- Jesper Velgaard Olsen, Vice Director, CPR
- Matthias Mann, Program Director, CPR
- Søren Brunak, Program Director, CPR
- Guillermo Montoya, Program Director, CPR
- Peter Dyrsting, Head of Administration & Finance, CPR

The work of the management team is based on frequent interactions at three levels: (1) the dean, the executive director and the vice director who typically meet twice a month to discuss strategic matters, (2) the program directors meet every 3 months to discuss and depict scientific development for CPR, and (3) the executive director, the vice director and the head of administration meet every week to streamline day-to-day management of CPR.

In addition, group leader meetings take place 6-8 times a year to ensure information- and knowledge sharing and to create a forum for discussion of CPR issues.

The administration team at CPR provides support to CPR's employees and management. The team currently consists of 10 members covering the areas of laboratory support, human resources, purchasing, research coordination, finance, IT and communication.

CPR Group leaders

Protein Signaling Program

- Professor Jiri Lukas (Chromosome Stability and Dynamics)
- Associate Professor Jeremy A. Daniel (Chromatin Structure and Function)
- Associate Professor Jakob Nilsson (Mitotic Mechanisms and Regulation)
- Professor Amilcar Flores-Morales (Molecular Endocrinology)
- Professor Niels Mailand (Ubiquitin Signaling)

Disease Systems Biology Program

- Professor Søren Brunak (Translational Disease Systems Biology)
- Professor Lars Juhl Jensen (Cellular Network Biology)

Proteomics Program

- Professor Jesper Velgaard Olsen (Mass Spectrometry for Quantitative Proteomics)
- Professor Chunaram Choudhary (Proteomics and Cell Signaling)
- Professor Michael Lund Nielsen (Proteomics Technology Development and Application)

Protein Structure Program

- Professor Guillermo Montoya (Macromolecular Chrystallography)
- Associate Professor Mats Wikström (Protein Function and Interactions)

Scientific Advisory Board

CPR is privileged to have a scientific advisory board consisting of highly prominent and well-known scientists, all of them renowned scientific authorities in their scientific fields.

The board provides advice on the strategic direction of the center as well as on the progress and development of the scientific program. The board also assists in the establishment of external collaborations.

Board members are invited by the center's executive management, each member providing expertise and experience within one or more of the center's scientific fields. In 2014, the board consisted of the following 7 members:

Anthony Hyman (chair), Group Leader and Director of the Max-Planck Institute of Molecular Cell Biology and Genetics, Dresden (Germany): Cell cycle control, high-throughput screens.

Pernille Rørth (stepped down from the SAB in 2014), Deputy Director, Institute of Molecular and Cell Biology, A-STAR (Singapore): Cell motility, developmental biology.

Torben Falck Ørntoft, Head of Department of Molecular Medicine, Aarhus University Hospital, Skejby (DK): Translational cancer research.

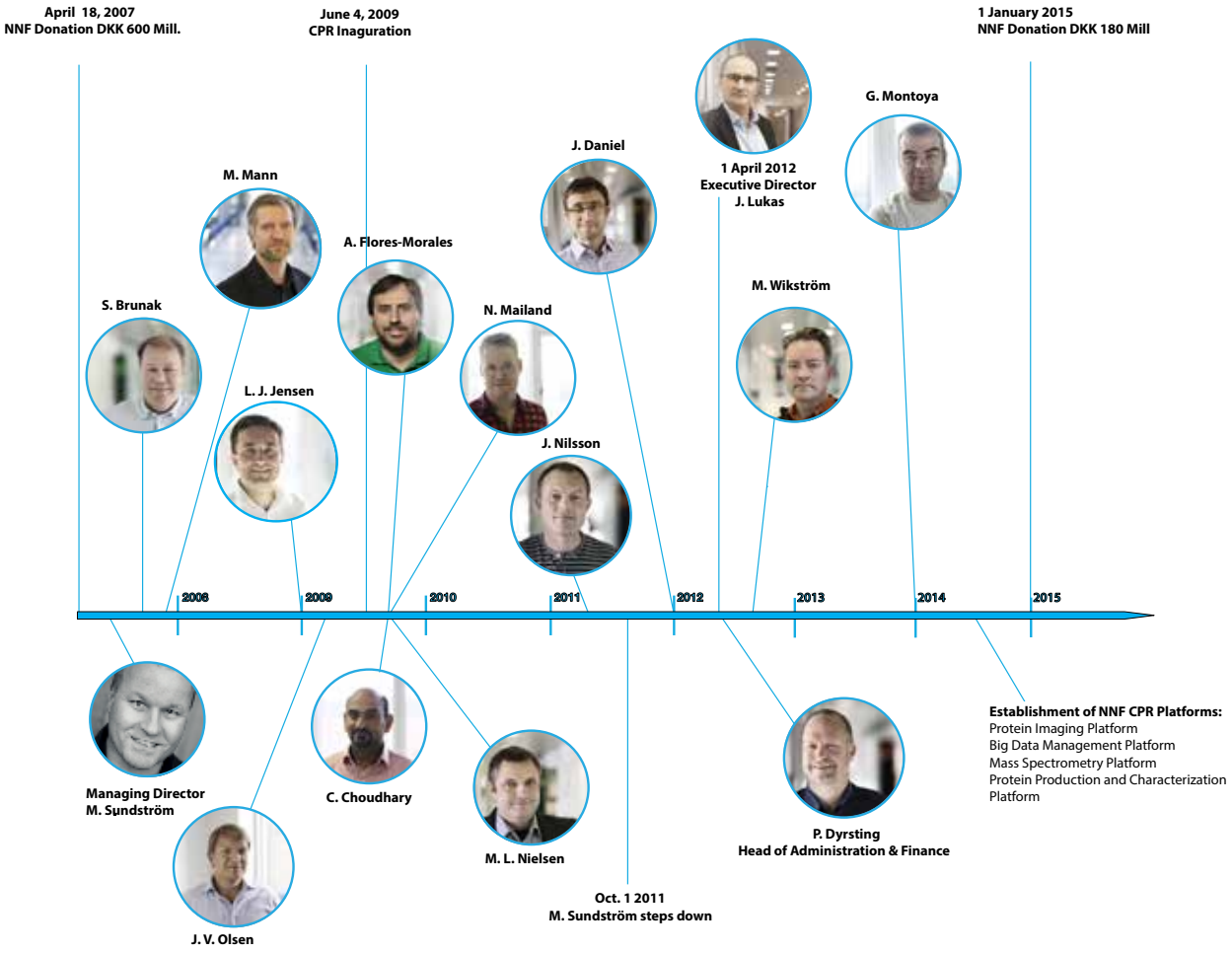
Ivan Dikic, Director of the Institute of Biochemistry, Goethe University, Frankfurt and Scientific Director of the FMLS/A Institute for Molecular Life Sciences, Frankfurt (Germany): Ubiquitin signaling.

André Nussenzweig, Chief of Laboratory of Genome Integrity, NCI/NIH, Center for Cancer Research, Bethesda (US): DNA damage response, mouse models of genome instability disorders.

Poul Nissen, Principal Investigator at Department of Molecular Biology, Centre for Structural Biology, University of Aarhus (DK): Structural biology.

Angus Lamond, Professor of Biochemistry, Wellcome Trust Centre for Gene Regulation and Expression, College of Life Sciences, University of Dundee (UK): Proteomics, advanced imaging.

CPR Timeline
Major events in CPR history since 2007



Protein Signaling Program

As a result of the CPR mid-term transition, the former Disease Mechanisms Program has been renamed the Protein Signaling Program to better reflect the focus on basic mechanistic dissection of protein signaling pathways.

Program Director, Jiri Lukas

The program consists of five research groups that span ubiquitin signaling (Niels Mailand), chromosome segregation (Jakob Nilsson), mouse models for DNA damage responses (Jeremy A. Daniel), pathogenesis of endocrine tumors (Amilcar Flores-Morales), and chromosome dynamics during the cell cycle and after environmental and endogenous stress assaults (Jiri Lukas).

The research of all five groups is focused on protein pathways involved in genome integrity maintenance. This strong biomedical focus spreads far beyond the program by providing exciting and medically relevant 'endpoints' of protein research carried out across CPR. The benefit of the program's contribution to the CPR mission is best illustrated by a number of high-profile collaborative publications with other CPR groups, which not only increases the global visibility of CPR but also strengthens the intrinsic synergy and collaborative spirit. The latter clearly constitutes one of CPR's strongest competitive assets.

The program continues to provide strong support to protein imaging. We are delighted to see that this technology has expanded and become autonomous to such extent that we have been able to upgrade it to a fully independent Protein Imaging Platform.

Under the leadership of Professor Claudia Lukas, this platform supports the entire center with state-of-the-art microscopy as described in the following section.

Protein Imaging Platform
Platform Leader: Professor Claudia Lukas

Advanced light microscopy is a key technology at CPR that enables researchers to visualize and measure protein dynamics, function, and localization in their cellular environment.

Microscopy is also the method of choice for cell-based screening assays such as small molecule compound screens for drug discovery and genetic screens for diverse cellular functions using siRNA or gene editing tools.

The Protein Imaging Platform is coordinated by Professor Claudia Lukas and operated by Jutta Bulkescher (microscopy support) and Gopal Karemore (image analysis support). Together, this team supports all CPR scientists with top-level instrumentation for confocal-, widefield-, and high-content protein imaging as well as in-house support and training for microscopy and quantitative image analysis.

Our aim is to provide personal hands-on training and advice for the entire workflow of all microscopy-based experiments carried out across CPR and we encourage every user to develop a high level of independence.

We also enable and mediate interaction of microscopy users within the NNF Center Cluster thanks to sharing the imaging staff and facilities with the DanStem Center located in the same building as CPR.

In addition to the hands-on technical support, the platform organizes regular seminars and user meetings on microscopy and actively networks with Core Facility for Integrated Microscopy at the Faculty of Health and Medical Sciences at the University of Copenhagen and other microscope users in the Copenhagen area and beyond, including EMBL, the hub of technological innovation in protein imaging worldwide.

Protein Imaging Platform

Claudia Lukas, Platform leader, professor

Jutta Bulkescher, Technical Assistant

Gopal Karemore, Senior Consultant


Nikon
Type 120

Chromosome Stability & Dynamics/Lukas Group
Group Leader: Professor Jiri Lukas

The Chromosome Stability and Dynamics group was established at CPR in April 2012 when Professor Jiri Lukas and his group were recruited to CPR from The Danish Cancer Society.

2014 witnessed a major transition in the Chromosome Stability and Dynamics group. After a very successful postdoctoral time in the lab, Matthias Altmeyer and Dorthe Helena Larsen moved on to establish their independent careers. In addition, PhD students Ronni Sølvhøj Pedersen and Thorkell Gudjónsson successfully defended their theses before top international experts from the genome integrity field.

We are very proud of all our young colleagues and wish them the best in their future careers. A natural problem faced by a group leader after four outstanding scientists leave the lab is: 'What am I going to do the next day?' Fortunately, we have recruited two exceptional talents: Fena Ochs has started as a new PhD student in June 2014 after very successful master's studies at the Rockefeller University in New York. We are equally happy to welcome Kumar Somyajit, who will join the lab in early 2015 as a postdoc after exceptionally productive PhD studies at the University of Bengalore.

Research aim
The main research focus of the group remains on development and application of advanced protein imaging technologies and high-content screens to study the workings and dynamics of repair and signaling protein pathways induced by various forms of genotoxic stress. We capitalize on our long-standing experience in real-time imaging of proteins in single cells as well as on introducing to the field a new analytical approach dubbed Quantitative Image Based Cytometry (QIBC), which allows us to quantitatively measure protein dynamics at the cell population level. We are using these approaches to address fundamental conceptual questions such as: What are the limiting components of protein signaling networks that guard the integrity of replicating genomes? Which proteins dictate the choice of DNA repair pathway and how do these decisions reflect the type and magnitude of chromosomal damage? Which forms of genotoxic stress can be passed from one cell generation to the next and what are the proteins that ensure that events like these do not transform to lasting genetic or epigenetic alterations?

Key achievements
The key achievement in 2014 was the successful conclusion of a long-term project carried out by Dorthe Helena Larsen and aiming at understanding nuclear dynamics of the NBS1 protein, one of the key essential eukaryotic genome caretakers involved in cellular responses to DNA breakage *(54)*.

In this work, conceived and carried out in close collaboration with Manuel Stucki (University of Zürich), we uncovered an unexpected role of NBS1 in controlling ribosomal RNA transcription in response to DNA damage. In a nutshell, we were able to show that after DNA damage, NBS1 interacts with a highly mobile nucleolar factor, TCOF1/Treacle, and that this interaction is required to transiently translocate NBS1 to nucleoli where it participates in rRNA silencing.

Lukas group

Emilie Baron, master's student

Maj-Britt Druedahl Rask, technician

Kai Neelsen, postdoc

Fena Ochs, PhD student

Ronni S. Pedersen, postdoc

Andreas WIllems, lab assistant

Luis Toledo, postdoc

Claudia Lukas, professor

Merete Grøfte, technician

Jiri Lukas, group leader

We are very excited about these findings because they extend in a mechanistic way the original concept, launched in our lab more than a decade ago, of molecular messengers connecting the sites of DNA damage with vital metabolic factories throughout the cell nucleus.

In 2014, Jiri Lukas won the 42nd Foundation ARC Leopold Griffuel Prize. This prize is considered among the highest international cancer research awards and comes with €125.000 (DKK 930.000) to support research in the Lukas group.

Luis Toledo was awarded DKK 2.5 M from the Danish Council for Independent Research, section for Medical Sciences and an additional DKK 0.5 M Sapere Aude award for a project entitled 'Exploring replication catastrophe and Replication Protein A as novel players in cancer diagnosis and treatment'. Kai Neelsen obtained a Marie Curie Intra-European Fellowship of DKK 1.7 M for the project 'The role of ubiquitin and ubiquitin-like modifiers in replication stress'. In addition, The Danish Cancer Society granted Jiri Lukas DKK 3.5 M for the project 'Opdagelse af nye cancer gener i den beskrevne del af det humane genom'.

Last but not least, postdoc Matthias Altmeyer moved on in early 2014 to establish an independent career and is already well advanced in building up his own group at the University of Zürich thanks to a prestigious grant from the Swiss National Foundation.

Dissemination
On behalf of CPR, Jiri Lukas coordinated the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' (Favrholm). He was also one of the main organizers of the 60th Benzon Symposium on 'Nuclear Regulation by Ubiquitin' (Copenhagen) as well as plenary speaker. He was also one of the main organizers of the conference.

Jiri Lukas was keynote speaker at the London Cell Cycle Club (University College London) and the annual conference of ARC Foundation for Cancer Research (Paris, October 2014).

Members of the Lukas group spoke at several conferences, including the Abcam Conference on 'Maintenance of Genome Stability', St. Kitts (Jiri Lukas), the 60th Benzon Symposium on 'Nuclear Regulation by Ubiquitin', Copenhagen (Jiri Lukas), the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling', Favrholm (Matthias Altmeyer), the Fusion Conference on 'DNA Replication as a Source of DNA Damage: From Molecules to Human Health', Casablanca (Jiri Lukas and Luis Toledo). In addition, Claudia Lukas, Luis Toledo, Matthias Altmeyer and Kai Nielsen presented posters at several of these occasions.

Internal collaborators

Michael Lund Nielsen (Proteomics Program) on the role of protein modification by Poly(ADP-ribosyl)ation in genotoxic stress responses.
Werner Streicher, Irina Pozdnyakova (Protein Production & Characterization Platform) on the mechanism of Poly(ADP-ribose)-mediated protein accumulation at damaged chromosomes.
Jesper V. Olsen (Proteomics Program) on ATR phosphoproteome and its function during replicative stress.
Jeremy A. Daniel (Protein Signaling Program) on mouse models for the role of RPA in DNA replication stress responses.
Guillermo Montoya, Stefano Stella (Protein Structure and Function Program) and **Jakob Nilsson** (Protein Signaling Program) on tagging DNA repair proteins by advanced gene editing.

External collaborators

Jan Ellenberg, Rainer Pepperkok, Beate Neumann, Jean-Karim Heriche (Advanced Light Microscopy Facility, EMBL, Germany) on high-content protein imaging and siRNA screens.
Jiri Bartek (Danish Cancer Society) on protein pathways subverted in cancer.
Andre Nussenzweig (NCI/NIH, US) on the function of RNF168 ubiquitin ligase.
Oskar Fernandez-Capetillo (CNIO, Spain) on functional characterization of the ATR/CHK1 signaling pathway.
Kirsten Grønbæk (Department of Hematology, Rigshospitalet) on improving stratification of patients with hematological malignancies based on RPA imaging assays developed in our group.

Chromatin Structure & Function/Daniel Group
Group Leader: Associate Professor Jeremy Austin Daniel

The Chromatin Structure and Function group was established in January 2012 and is headed by Associate Professor Jeremy A. Daniel. In 2014, the group recruited two postdocs. Ewa Ohlsson joined us after her PhD studies at the Finsen Laboratory and Valentyn Oksenych joined us from Boston Children's Hospital's Program in Cellular and Molecular Medicine.

The mission of the Daniel group is to identify therapeutic targets for cancer by investigating basic mechanisms for how dynamic chromatin environments impact the stability of our genomes. DNA double-strand breaks (DSBs) are caused by exogenous damage, collapsed replication forks, and also transiently occur during physiological conditions as part of programmed DNA rearrangements in lymphocytes called V(D)J recombination and class-switch recombination. Once damaged, a DNA lesion such as a DSB must first be made accessible by changes in chromatin structure to allow for subsequent DNA repair to occur. A better physiological understanding of how cells repair their DNA within the context of chromatin holds the potential to promote or suppress the efficiency of DNA repair, with implications for healthy aging, cancer prevention, and for sensitizing cancer cells to therapeutic agents.

The approach of the Daniel group is to utilize mouse genetics together with a combination of biochemistry, flow cytometry, genomics, and proteomics for investigating how protein complexes that modify or associate with chromatin regulate genome stability and prevent lymphoid malignancy. Proteomic screens for chromatin-interacting factors and chromatin modifying complexes are being carried out in combination with targeted gene inactivation in mice.

Research aim
The aim of the research in the Daniel group during 2014 was to continue developing the research projects initiated in its first two years and initiate additional projects with newly hired personnel.
Specifically, the group developed a project investigating the mechanism and specificity for how the PTIP-associated histone H3K4 methyltransferase complex functions in B lymphocytes. The group also developed a project investigating the role of a novel DNA damage response protein called Scai in the homologous recombination and non-homologous end-joining DSB repair pathways using a Scai-deficient mouse model. In addition, the group initiated research projects that include investigating the role of acetyltransferases in B lymphocytes and identifying functional proteins at DNA breaks with quantitative proteomics. By devoting our energy to these research aims, we were able to synergize with other groups at CPR and stay biologically focused using the mouse as a physiological model organism.

Internal collaborators

Michael Lund Nielsen (Proteomics Program) on identifying functional proteins at DNA breaks with quantitative proteomics in primary lymphocytes.
Chunaram Choudhary (Proteomics Program) on the mechanism and specificity of PTIP complex function in B lymphocytes.
Niels Mailand (Protein Signaling Program) on the biological function of novel DNA damage response factors with murine gene inactivation.
Jiri Lukas (Protein Signaling Program) on the role of replicative stress in cancer and the hematopoietic system.
Guillermo Montoya (Protein Structure & Characterization Program) on the mechanism and specificity of PTIP complex function in B lymphocytes.

External collaborators

Andres Contreras-Lopez (Center for Healthy Aging, University of Copenhagen) on the role of replicative stress in the hematopoietic system.
Sharon Y. Dent (University of Texas, MD Anderson Cancer Center, US) on the role of acetyltransferases in B lymphocytes.
Andre Nussenzweig (NCI/NIH, US) on the mechanism of PTIP function.
Kai Ge (NIDDK/NIH, US) on the mechanism and specificity of PTIP complex function in B lymphocytes.
Joan Yuan (Stem Cell Center/Lund University, Sweden) on the role of chromatin regulators in fetal and adult lymphopoiesis.
Tanya Paull (HHMI/University of Texas, US) on the mechanism of ATM activation using mouse models.
Fred Alt (HHMI/Harvard Medical School, US) on the role of the non-homologous end-joining DNA repair pathway in development.

Key achievements
The group has recruited additional personnel, was awarded an International Master grant from Lundbeck Foundation (a five year PhD with integrated MSc), and has made significant progress on multiple projects in the lab.

To investigate the mechanism and specificity of PTIP complex function in B lymphocytes, the group has obtained evidence for a critical protein interaction that is responsible for the function of PTIP in IgH class-switch recombination; identified the region of PTIP that interacts with the MLL-like histone H3K4 methyltransferase complex and the significance of this interaction for IgH class-switch recombination; and has generated a novel GFP tagged knock-in mouse model to study the localization and associated proteins of endogenous PTIP in primary tissues.

The group has obtained evidence for an important role for the Scai protein, a novel DNA damage response factor, in maintaining genome stability and in germ cell development.

To investigate the role of acetyltransferases in B lymphocytes, the group has obtained preliminary evidence for an acetyltransferase that promotes IgH class-switching and is currently developing unique genetic tools to explore this further in vivo. To identify functional proteins at DNA breaks with quantitative proteomics, the group has developed an experimental workflow using primary murine lymphocytes, which they will build upon in the coming years.

Andreas Mund was granted a prestigious Marie Curie Intra-European Fellowship of DKK 1.7 M for the project 'Identifying Functional Proteins at DNA Breaks with Quantitative Proteomics in Primary Lymphocytes'. Members of the group served as peer-reviewers for multiple manuscripts.

Dissemination
In 2014, the group leader co-organized the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' (Favrholm).

Members of the group participated in international conferences including a Cold Spring Harbor Laboratory meeting on gene expression and signaling in the immune system in New York and a Fusion conference on DNA replication as a source of DNA Damage in Casablanca, Morocco. Postdoc Andreas Mund won 'Best Poster' prize at the meeting in Casablanca. A member of the group also presented our work locally at a meeting in the Copenhagen Chromosome Biology Club, a research interest group that we see as an important opportunity to discuss our research with CPR's neighboring institutions.

Daniel Group: Andreas Mund, postdoc, **Ewa Ohlsson**, postdoc, **Linda Starnes**, postdoc, **Rebeca Soria**, technician, **Valentyn Oksenych**, postdoc, **Christian Dirk Buch**, laboratory assistant, **Dan Su**, postdoc, **Jeremy A. Daniel**, group leader, **Laura Pikkupeura**, PhD student.

Mitotic Mechanisms & Regulation/Nilsson Group
Group Leader: Associate Professor Jakob Nilsson

The Mitotic Mechanisms and Regulation group was established at CPR in 2011 and is headed by Associate Professor Jakob Nilsson. In 2014, the group was joined by PhD student Emil Peter Thrane Hertz who did his master's studies at the Finsen Laboratory.

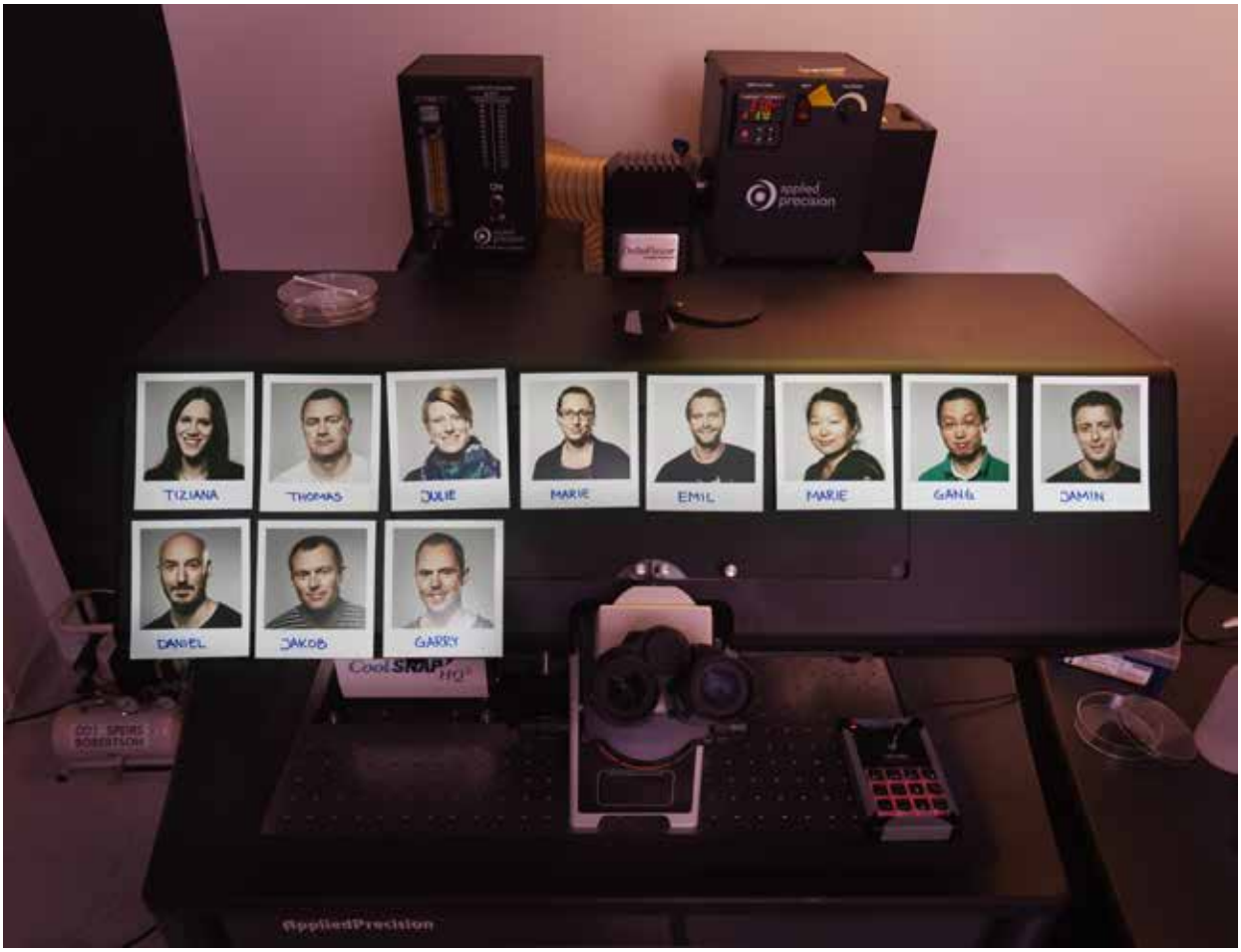
The group focuses on understanding how the genetic material is equally segregated into the two new daughter cells during cell division. In particular, we focus on how a large ubiquitin ligase called the Anaphase Promoting Complex is regulated by the spindle assembly checkpoint and how protein phosphatases coordinate cell division events.

We take an interdisciplinary approach and combine biochemistry, cell biology and live cell microscopy to carefully dissect the mechanisms underlying chromosome segregation.

Research aim
In 2014, we focused on understanding how the spindle assembly checkpoint proteins interact with and get activated at a large protein structure called the kinetochore. This is important to understand, as it is the main mechanism ensuring equal chromosome segregation. We also focused our efforts on establishing novel methods to look at protein-protein interactions in vivo by implementing a proximity dependent ligation method and site-specific photo-crosslinking approaches.

Key achievements
In 2014, the Nilsson group has focused on understanding regulation of the Spindle Assembly Checkpoint (SAC) and how checkpoint proteins are recruited to kinetochores. We identified a novel role of the Mad1 checkpoint protein and in particular how a globular C-terminal domain contributes to checkpoint signaling *(43)*.

In addition we elucidated how the target of the checkpoint, the protein Cdc20, is localized to kinetochores *(46)*. This work revealed an unexpected function of the BubR1 checkpoint protein in localizing Cdc20. The outcome of these two studies is a better understanding of how Cdc20 is specifically assembled into inhibitory complexes at kinetochores.



We also analyzed how the inhibitory complexes generated by the checkpoint act in the cytoplasm to delay mitotic progression. We found that stable binding of the inhibitory complexes to a large ubiquitin ligase, the APC/C, is essential for a functional checkpoint *(27)*. Furthermore we elucidated how stable binding to the APC/C is achieved which provided insight into how pre-clinical APC/C inhibitors might work.

The Danish Council for Independent Research (Medical Sciences) granted Garry Sedgwick DKK 2.2 M for the project 'Novel Mechanisms Guarding against aneuploidy in human cells'. The Danish Cancer Society granted Jakob Nilsson DKK 1.5 M for the project 'How a tumor suppressor protects against aneuploidy and chromosome instability'.

Dissemination
The group organized the 4th Annual Meeting of the Nordic Mitosis Network at CPR where several of the projects were presented. Furthermore, upon publication of our work, the stories were highlighted on the University of Copenhagen webpage and through press releases.

Our work has been presented in the form of invited seminars, posters and talks at international and local meetings. The list includes the Cold Spring Harbor cell cycle meeting (US) with oral presentation by Jakob Nilsson and posters by Jamin Hein and Tiziana Lischetti, the CNRS conference on 'Cell Cycle: Bridging scales in cell division' (France) with posters by Marie Sofie Yoo Larsen and Jakob Nilsson, and the Nordforsk Mitotic Network annual meeting (Norway) with talks by Marie Sofie Yoo Larsen, Tiziana Lischetti, Jamin Hein, Gang Zhang, Julie Schou and Garry Sedgwick.

Internal collaborators

Michael Lund Nielsen, Jesper V. Olsen and Chunaram Choudhary (Proteomics Program) on mass spectrometry of mitotic regulators and genetic analysis of these.
Guillermo Montoya (Protein Structure & Characterization Program) on structural aspects of protein phosphatases and mitotic regulators.

External Collaborations

Kristian Helin (BRIC, University of Copenhagen) on epigenetic regulators and their influence on cell division.
Michael Lisby (Department of Biology, University of Copenhagen) on regulation of replication proteins during cell division.
Silke Hauf (Department of Biological Sciences, Virginia Tech, US) on the mitotic checkpoint.
Viji Draviam (Department of Genetics, University of Cambridge, UK) on microtubule regulators.
Victor Bolanos Garcia (Department of Biological and Medical Sciences, Oxford Brookes University, UK) on structural aspects of the spindle assembly checkpoint.

Nilsson Group

Tiziana Lischetti, postdoc, **Thomas Kruse**, postdoc**, Julie Schou**, postdoc, **Marie Winther Sørensen**, laboratory assistant, **Emil Hertz**, PhD student, **Marie Sofie Yoo Larsen**, PhD student, **Gang Zhang**, postdoc, **Jamin Hein**, PhD student, **Daniel Hayward**, postdoc, **Jakob Nilsson**, group leader, **Garry Sedgwick**, postdoc.

Molecular Endocrinology/Flores-Morales Group
Group Leader: Professor Amilcar Flores-Morales

The Molecular Endocrinology group was established in 2009 and is headed by Professor Amilcar Flores-Morales.

2014 saw the beginning of a new era for the Molecular Endocrinology group. From 1 September, Amilcar Flores-Morales has obtained a professorship in clinical prostate cancer research at the Department of Veterinary Disease Biology, Section for Molecular Disease Biology (Faculty of Health and Medical Sciences). After a transition phase where the group continues to be based at CPR, it will move to Section for Molecular Disease Biology, which is located in facilities at the Danish Cancer Society.

With this change, the group will move their research into a more clinical setting where it will benefit from interacting with groups working directly in the field of translational oncology. Amilcar Flores-Morales will stay associated to CPR through his coordination of the elective undergraduate course 'Advanced methods for the analysis of protein disease mechanisms' and will contribute to other educational and talent development activities at CPR.

The Molecular Endocrinology group applies quantitative molecular profiling methodologies to the study of clinical samples and pre-clinical model systems in order to identify pathogenic mechanisms responsible for prostate cancer progression with a translational focus. To this end, we combine integrative analysis of quantitative proteomic and genomic data with experimental approaches in cellular and rodent models in order to identify and validate new biomarkers of disease progression and novel pharmaceutical targets for the treatment of advanced metastatic prostate cancer.

Research aim
Prostate cancer is the most diagnosed cancer among men in Western societies and a leading cause of death. The advent of genomic technologies has boosted our understanding of the somatic genetic changes occurring in localized prostate tumors, with several studies describing global transcriptome changes as well as genetic and epigenetic alterations. Unfortunately, these genetic events are generally poor predictors of changes at the proteome level. Consequently, our knowledge of the protein-driven mechanisms responsible for the initiation and progression of prostate cancer remains limited.

The implementation of methodologies for proteome-wide quantitative profiling has the potential to provide a molecular link between genotype and phenotype and facilitate the identification of biomarkers or actionable targets for individualized treatment of prostate cancer. The overall aim of the Flores-Morales group is to identify novel strategies for the prevention and treatment of advanced prostate cancer. To this end, we make extensive use of high-throughput quantitative analyses, including gene expression and proteomics profiling to analyze human tissue biopsies as well as animal and cell models in order to outline clinically relevant signaling pathways involved in prostate cancer progression.

Flores-Morales group:

Idranil Paul, postdoc
Charlotte Lavallee, PhD student
Kim Hjorth-Jensen, postdoc
Amilcar Flores-Morales, group leader
Diego Iglesias, postdoc
Cecilie Berglund Ove, laboratory assistant

Key achievements
In 2014, we aimed at completing the quantitative proteomic analysis of prostate cancer clinical samples representing all stages of tumor progression, including benign, prostate localized and metastatic prostate cancer tissue. We have also characterized the proteome changes associated with androgen ablation therapy and neuroendocrine trans-differentiation of castration resistant tumors *(34)*. We also aimed at using these data resources to unveil novel mechanisms involved in prostate cancer initiation, metastatic progression and resistance to castration therapy.

We expect that the clinical proteomic profiles we have generated can serve to identify new biomarkers of disease progression and possible pharmaceutical targets for the treatment of castration resistant prostate cancer *(34* and *Iglesias-Gato et al., in press, Molecular Cancer)*. Indeed, the University of Copenhagen has filed a patent application for a novel biomarker of disease progression discovered by Flores-Morales and collaborators through proteomic analysis of prostate cancer clinical samples. This new biomarker can be used to select patients that will benefit from active therapy and thereby avoid the very high levels of excessive treatment that characterize the clinical management of prostate cancer patients today (Neuropeptide Y as a prognostic marker of prostate cancer /Danish Patent and Trademark Office/ PA 2015 70077).

Amilcar Flores-Morales was the main coordinator and organizer of the elective undergraduate course that CPR hosted in 2014 in 'Advanced methods for the analysis of protein disease mechanisms'. The objective of this practical course is to raise interest in modern protein research among undergraduate students. In coming years, Amilcar Flores-Morales will continue to organize and coordinate CPR's teaching activities at the Faculty of Health and Medical Sciences.

In 2014, the group attracted two grants, which they will bring with them to the new location at Department of Veterinary Disease Biology, Section for Molecular Disease Biology: DKK 1.4 M from the Danish Cancer Society for the project 'Molecular and functional characterization of SPOP, a new tumor suppressor in prostate cancer' and DKK 2.4 M from the Danish Council for Independent Research (Medical Sciences) for the project 'Characterization of a novel AR regulator and tumor suppressor in prostate cancer'.

Dissemination
The group leader co-organized the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' (Favrholm). Diego Iglesias-Gato was invited speaker at Prostate Cancer Meeting 2014 (Sweden) and 9th International Conference of Anticancer Research (Greece).

Members of the group presented their research in poster sessions at several conferences including the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' (Diego Iglesias-Gato), Max Quant Summer School, NIH, US (Diego Iglesias-Gato, Kim Hjorth Jensen), Advances in Prostate Cancer Research - AACR-Prostate Cancer Foundation Conference, US (Diego Iglesias-Gato, Amilcar Flores-Morales), and the 60th Benzon Symposium on Nuclear Regulation by Ubiquitin, Denmark (Amilcar Flores-Morales).

Internal collaborators

Michael Lund Nielsen, Jesper V. Olsen (Proteomics Program) on quantitative analysis of protein-protein interactions and post-translational modification in preclinical models of prostate cancer disease progression.
Jakob Nilsson (Protein Signaling Program) on the effects of prostate cancer mutated genes on mitotic progression.

External Collaborations

Matthias Mann (Max-Planck Institute of Biochemistry, Germany) on proteomic profiling of clinical samples.
Yuanjie Niu (Tianjin Institute of Urology, China) and Leandro Fernande-Perez (University of Las Palmas GC, Spain) on animal models of prostate cancer.
Colin Collins (University of British Columbia, Canada) on characterizating the mechanisms of tumor neuroendocrine trans-differentiation using xenografted primary tumor models.
Gunnar Norstedt (Karolinska Institute, Sweden) on characterizating physiological functions of SOCS ubiquitin ligases.
Clinician scientists from the Scandinavian Prostate Cancer Group where we have access to unique clinical material from clinical trials:

Anders Bergh, Pernilla Wikstrom, University of Umeå, Sweden
Anders Bjartell, University of Lund, Sweden
Peter Iversen, Ben Vainer, Rigshospitalet, Copenhagen

Ubiquitin Signaling/Mailand Group
Group Leader: Professor Niels Mailand

The Ubiquitin Signaling group was established in 2009 and is headed by Professor Niels Mailand. The key focus of the group is to understand how signaling processes, primarily those mediated by ubiquitin and ubiquitin-like modifier proteins, underpin and regulate cellular responses to DNA damage to promote genome stability maintenance in mammalian cells.

To this end, our overarching strategy is to combine unbiased proteome- and genome-wide approaches (through collaboration, see below) with cell biology-, biochemistry-, and imaging-based methods in which the group has strong expertise, for discovery and detailed functional characterization of new factors and signaling processes that protect the integrity of the genome following DNA damage and other stresses.

Research aim
Most of our current research efforts fit broadly into the following themes:

- Proteome-wide mapping and characterization of ubiquitin-dependent signaling processes in the DNA damage response.
- Systematic identification of proteins recruited to damaged DNA and in-depth functional studies of selected new factors.
- Regulation of DNA damage responses by the ubiquitin-like modifier protein SUMO.
- Signaling responses to cell stress.

These activities, all of which combine systems-wide and more focused studies, represent a logical continuation of our main research efforts and achievements during the past few years. A series of powerful mass spectrometry-based screens has given us unique new insights into the organization and dynamics of the DNA damage response on a systems-wide level and we are now characterizing a range of new factors and signaling processes in genome stability control mechanisms first identified in these screens. We anticipate that this undertaking will continue to be a major focus for the group in the coming years and that the results from these studies will yield important new insights into the mechanisms underlying genome stability protection at the molecular level.

Key achievements
The group published six papers in 2014, including publications in Molecular Cell and EMBO Reports *(9, 17, 23, 24, 52, 69)*. By the end of 2014, a number of additional papers from the group, mainly describing new regulators of the DNA damage response identified in the screens described above, were at advanced stages of revision in high-impact journals.

We also have a continuous focus on expanding the range of methodologies available in the lab. For instance, during the past year, we implemented CRISPR-Cas9 genome editing technology, lentivirus technology, and DNA combing analysis in the lab.

The group successfully passed its first 5-year evaluation in 2014. The evaluation took place during a site visit May 30 by a committee of international experts consisting of Professors Lene Juel Rasmussen (UCPH), Yosef Shiloh (Tel Aviv University, Israel), Ronald Hay (University of Dundee, UK) and Penny Jeggo (University of Sussex, UK). Niels Mailand presented the group's accomplishments and future research plans and mem-

bers of the group presented their research in more detail during a poster session allowing for informal discussion with the expert committee.

The group continued to successfully secure competitive grants in 2014. Niels Mailand was awarded a 5-year Consolidator Grant from the European Research Council (ERC) as well as a project grant from the Danish Council for Independent Research. He is also a co-principal investigator in Center for Chromosome Stability (CCS), a new Danish National Research Foundation Center of Excellence headed by Professor Ian Hickson (University of Copenhagen).

Simon Bekker-Jensen received a prestigious Sapere Aude DFF-Starting Grant of DKK 7.1 M and Petra Schwertman was awarded a 2-year DFF-MOBILEX mobility grant of DKK 2.1 M, both from Danish Council for Independent Research. Finally, Godelieve Smeenk was granted a Marie Curie Intra-European Fellowship of DKK 1.6 M. Niels Mailand served as a frequent reviewer of manuscripts for Nature, Cell and Science and their sister journals, and was elected a panel member for evaluation of European Research Council (ERC) Consolidator Grants 2014.

Dissemination
Maintaining an active presence at scientific conferences is a strong priority for the lab and in 2014, many group members participated in local and international meetings to disseminate our research findings.

Niels Mailand was invited speaker at several conferences, including the EMBO Conference: Ubiquitin and 'ubiquitin-like proteins' (Argentina), the 60th Benzon Symposium: Nuclear Regulation by Ubiquitin (Copenhagen), the 5th Genome Dynamics in Neuroscience Meeting (Denmark), EMBO Young Investigator Meeting (Germany) and the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' (Favrholm). Ian Gibbs-Seymour presented a talk at the Abcam Conference 'Maintenance of Genome Stability' (St. Kitts).

Internal collaborators

Chunaram Choudhary (Proteomics Program) on proteomics-based exploration of the ubiquitin system.
Jeremy A. Daniel (Protein Signaling Program) on mouse knockout models of new DNA damage response factors.
Guillermo Montoya (Protein Structure & Characterization Program) on biophysical characterization of proteins and protein domains.

External collaborators

Anja Groth (BRIC, University of Copenhagen,) on discovery and characterization of new factors in cellular responses to replication stress.
Matthias Mann (Max-Planck Institute of Biochemistry, Germany) on proteomics-based discovery of new components of the DNA damage response.
Wim Vermeulen, Jurgen Marteijn (Erasmus MC, The Netherlands) on ubiquitylation and SUMOylation in nucleotide excision repair.
Titia Sixma (Netherlands Cancer Institute, Netherlands) on biochemical and structural analysis of ubiquitylation processes.

Mailand Group

Bine Hare Villumsen, PhD student, **Niels Mailand**, group leader, **Sara Lund Poulsen**, postdoc, **Louise Aagaard Nilausen**, master's student, **Maxim Tollenaere**, PhD student, **Anita Ripplinger**, PhD student, **Wenjing Zheng**, postdoc, **Tina Thorslund**, associate professor, **Yasuyoshi Oka**, postdoc, **Godelieve Smeenk**, postdoc, **Saskia Hoffmann**, PhD student, **Simon Bekker-Jensen**, associate professor, **Petra Schwertman**, postdoc, **Julie Nielsen**, laboratory assistant, **Peter Haahr**, PhD student, **Rebecca Kring Hansen**, PhD student, **Stine Smedegaard**, PhD student.

Disease Systems Biology Program
Program Director: Søren Brunak

Program Director Søren Brunak

The program is led by Professor Søren Brunak and consists of two groups: Cellular Network Biology (Lars Juhl Jensen) and Translational Disease Systems Biology (Søren Brunak).

The Disease Systems Biology Program uses and develops computational techniques for the joint analysis of molecular, clinical and literature data.

The Disease Systems Program is responsible for CPR's Big Data Management Platform that provides supercomputer resources and advanced storage schemes to research projects across the center and its collaborative stakeholders.

The Big Data Management Platform uses its own computing facilities as well as the new Danish National Life Science Supercomputer, which is a joint project between the University of Copenhagen, the Technical University of Denmark, and the Danish e-infrastructure collaboration.

The program has a strong focus on the role of proteins in terms of molecular level network biology operating at the cellular, organ or organismal levels, and integration of clinical data from individuals, which can point at proteins that may become drugs or drug targets, explain disease comorbidities, or rationalize adverse drug reactions by taking human proteome variation into account.

Within network biology, the eukaryotic cell cycle is a major theme of the program, as is systems level analysis of data generated at CPR, for example data on post-translational modifications.

Big Data Management Platform
Platform leader: Professor Lars Juhl Jensen

The purpose of the Big Data Management Platform is to provide 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.

The primary users are therefore the other platforms that need stable data management solutions, rather than individual researchers at CPR.

The platform is coordinated by Professor Lars Juhl Jensen who works closely with Computer Specialist Rebeca Quinones.

The platform currently provides large-scale storage and backup solutions to safely capture and archive data. In the future, the platform will also be able to provide the computational power required for the often very compute-intensive initial data analysis. To this end, the platform has access to the new National Life Science Supercomputer, named Computerome, which is a joint project between the University of Copenhagen, the Technical University of Denmark and the Danish e-infrastructure collaboration.

In addition to Computerome, which ranks as the 121st fastest supercomputer in the world (November 2014), the platform has access to other computational infrastructure shared with Center for Biological Sequence Analysis at the Technical University of Denmark.

Big Data Management Platform: Rebeca Quinones, computer specialist, **Lars Juhl Jensen**, platform leader

Cellular Network Biology/Jensen Group
Group Leader: Professor Lars Juhl Jensen

The group was established in January 2009 and is headed by Professor Lars Juhl Jensen. The group is purely computational and uses data- and text-mining techniques to analyze a wide variety of data types from public sources and collaborators. The overarching theme of the group's research is to study cellular regulation from a protein network perspective.

A core activity within the group is the development and maintenance of web-based community resources, which integrate heterogeneous evidence on aspects of protein function, e.g. their interactions, regulation, localization and disease associations. We use these resources in network-based studies of cellular regulation and phenotypes and they are the basis for in-house collaborations with the Proteomics program on analysis of mass-spectrometry data.

The group also has many external collaborations, many of which center around applying our highly flexible text-mining technology to a variety of biological problems.

External collaborators

Enrico Cappellini (University of Copenhagen) on paleoproteomics.
Thomas Frimurer (University of Copenhagen) on cheminformatics.
Jan Gorodkin (University of Copenhagen) on RNA bioinformatics.
Ebba Holme Hansen (University of Copenhagen) on medical data mining.
Eske Willerslev (University of Copenhagen) on paleoproteomics.
Rune Linding (Technical University of Denmark) on bioinformatics.
Lise Aagaard (University of Southern Denmark) on medical data mining.
Peer Bork (Structural and Computational Biology Unit, European Molecular Biology Laboratory (EMBL), Germany) on network biology.
Yesid Cuesta (Universidad Federal de Minas Gerais, Columbia) on network biology.
Niall Haslam (University College Dublin, Ireland) on bioinformatics.
Michael Kuhn (Technische Universität Dresden, Germany) network biology.
Christian von Mering (University of Zurich, Switzerland) on network biology.
Sean I. O'Donoghue (CSIRO Computational Informatics, Australia) on data visualization.
Tudor I. Oprea (University of New Mexico, US) on data and text mining.
Evanglos Pafilis (Hellenic Centre for Marine Research, Greece) on text mining.
Burkhard Rost (Technische Universitität München, Germany) on text mining.
Reinhard Schneider (University of Luxembourg, Luxembourg) on data and text mining.

Research aim
The main aim was to finalize a number of interrelated resources that have been under development for the past several years. Together, they use data- and text-mining methodologies to associate proteins with each other, their localization within the cell and the body, diseases and other phenotypes, as well as their transcriptional and post-translational regulation.

We expect these resources to have impact in several ways. Firstly, they make available the results of our research in a way that actively encourages reuse. Secondly, we already have projects within the group that make use of them to study, for example, host-pathogen interactions and the link between cell-cycle regulation and phenotypes.

Key achievements
Over the past year, the group has managed to meet the aim of launching and publishing a number of resources. The three closely tied protein databases COMPARTMENTS, DISEASES and TISSUES are now all publicly available, the two former have been published *(5, 54)* and a manuscript on the latter has been submitted. Similarly, the KinomeXplorer web resource for analysis of phosphoproteomics data has been published in Nature Methods within the past year *(29)*.

Internal collaborators

Søren Brunak (Disease Systems Biology Program) on medical data mining.
Chunaram Choudhary, Michael Lund Nielsen, Jesper V. Olsen (Proteomics Program) on proteomics.

Cellular Network Biology: Xiaoyong Pan, PhD student, **Alberto Santos Delgado**, PhD student, **Lars Juhl Jensen**, group leader, **Jan Refsgaard Nielsen**, PhD student, **Helen Cook**, PhD student, **Enric Mosella**, master's student, **Kalliopi Tsafou**, PhD student

Maintaining existing community resources is at least as important as developing new ones. In 2014, the group has worked major updates of two heavily used existing databases, namely STRING v10 and Cyclebase v3, and two publications describing the work have been accepted *(63, 68)*.

In 2014, the group has continued the long string of productive collaborations with other groups at the center. This has resulted in six joint publications in 2014 *(10, 19, 20, 33, 62, 67)*, one of which was published in Nature Communications and was covered extensively in mainstream media *(33)*.

Dissemination

A key activity of the group is the development of web resources, which are used by more than 10,000 researchers around the world in a typical week. This brings the results of the research performed within the group to a much larger audience than most scientific publications, and arguably in a more useful manner.

In addition to this and to publications in scientific journals, Lars Juhl Jensen has taught the methodologies on international PhD- and postdoc-level courses and works on ensuring that the methodologies are applied in industry through his role as scientific advisor of Intomics A/S.

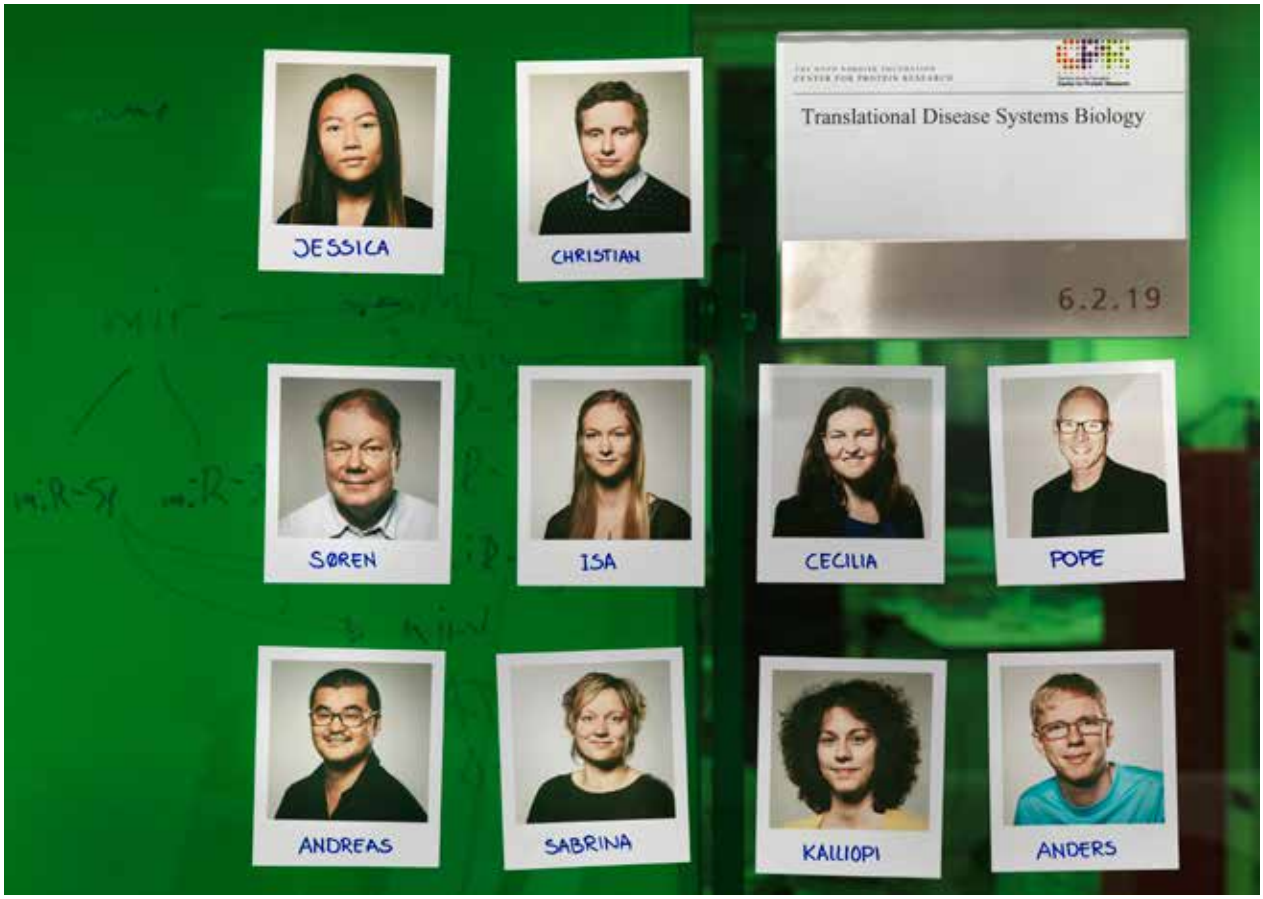
Lars Juhl Jensen co-organized the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' (Favrholm) and presented the group's results at numerous scientific conferences, symposia, and seminars for both academia and industry.

He also runs a scientific blog, is active on social media including Twitter, was interviewed on the radio news, and participated in a Science Slam for the general public at the Euroscience Open Forum (ESOF) with members of the Translational Disease Systems Biology group.

Lars Juhl Jensen was invited to give keynote lectures and talks at several occasions, including the European Student Council Symposium (France), Symposium at University of Cape Town (South Africa), 'Computational Biology Symposium' (Chile), Gene Forum Conference (Estonia), ALPSP International Conference (UK), Applications of Bioinformatics in Molecular Biology (Greece) and Biological Data Visualization (Belgium).

Translational Disease Systems Biology/Brunak Group

The Translational Disease Systems Biology Group was established in 2008 and is headed by Professor Søren Brunak. The group is highly interdisciplinary as it includes several MD-PhDs and others with backgrounds within genetics, biochemistry, pharmacology, bioinformatics and computer science.



Brunak Group: Jessica Xin Hu, research assistant, **Christian Simon**, PhD student, **Søren Brunak**, group leader, **Isa Kirk**, PhD student, **Cecilia Engel Thomas**, research assistant, **Pope Mosely**, Professor, **Andreas Bok Andersen**, research assistant, **Sabrina Gade Ellesøe**, PhD student, **Kalliopi Tsafou**, PhD student, **Anders Boeck Jensen**, postdoc..

The group works on computational data integration approaches across data domains spanning the molecular clinical levels, where the latter address clinical data from the healthcare sector. It also engages in its own data generation efforts, for example disease-cohort specific exome and whole genome sequencing, revealing information on proteome variation in terms of sequence and in terms of copy number affecting protein complex formation via stoichiometry.

We have a specific emphasis on broadening an already cross-disciplinary field to include what traditionally has been the domain of 'medical informatics'. Clinical and phenotypic data from the healthcare sector is combined with molecular level data, predominantly genome and proteome information. We use data on comorbidities obtained from electronic patient records and registries in order to understand better the network biology of individuals, in particular rewired protein interaction networks. The aim is to integrate the comorbidity data in the context of patient stratification and group patients by their side-effect profiles and further link these to the variation in protein drug targets and off-target effects involving proteins. Another focus is to characterize disease trajectories based on temporal analysis of disease terminology data from patient records across millions of patients. We now use these methods to define cohorts which may be subjected to screening, for example by clinical proteomics approaches.

Research aim

In 2014, we have worked towards further developing frameworks that relate to temporal analysis of patient data and to provide approaches for disease trajectory construction from Danish and foreign healthcare sector data. While the original methodology, published in Nature Communications in 2014 *(33)*, mainly focused on diagnoses trajectories, we now have a much broader aim of including procedures, drug treatments and other data affecting the health-status of individuals.

Key achievements
In the area of clinical data mining, we have produced new patient stratification methods based on data in electronic patient records focusing on data from Steno Diabetes Center.

Our adverse drug reaction approach was published in Drug Safety in 2014 *(20)*. We have had special attention on ADR-ADR correlations, which also leads to new patient stratification schemes. ADR-ADR correlations can be both positive and inverse in the sense that one ADR can protect against another, leading to knowledge on the underlying molecular etiology.

In the network biology area we have shown that lineage-specific interface proteins match up the cell cycle and differentiation in embryo stem cells *(58)*. These proteins are mainly regulated at the post-transcriptional level. We have also improved our mapping of the human protein interactome onto the human genome. A major discovery has been that syntenic regions in the human genome contain proteins with a higher tendency to form protein complexes. This is the first time the full protein interactome has been shown to be related to the structure of the genome and presumably in this manner exert a selection pressure on how the genome controls the distribution of the 20,000 proteins it encodes (Kirk et al., The protein interactome correlates with the syntenic LEGO block structure of mammalian genomes, submitted data).

Dissemination
Group leader Søren Brunak co-organized the 19th Pacific Symposium of Biocomputing (US) 'Cancer Panomics: Computational Methods and Infrastructure for Integrative Analysis of Cancer High-Throughput 'Omics' Data'. In addition, Søren Brunak has presented the group's work at numerous scientific conferences, symposia, and discussion panels for both academia and industry.

One of the 2014 highlights was the press conference organized by Nature at the Euroscience Open Forum (ESOF) meeting, where Søren Brunak was invited to present the disease trajectory publication published the same day in Nature Communications. The press conference generated world-wide attention in news media on the work. At the ESOF meeting, Søren Brunak also hosted a science slam session in front of a general public audience with Anders Boeck Jensen, Isa Kirk and Lars Juhl Jensen.

Internal collaborators

Matthias Mann (Proteomics Program) on clinical proteomics and patient stratification.

Lars Juhl Jensen (Disease Systems Program) on medical data mining.

Chunaram Choudhary (Proteomics Program) on proteomics.

Jesper V. Olsen (Proteomics Program) on proteomics and disease systems biology.

Alicia Lundby (Proteomics Program) on proteomics and disease systems biology.

External collaborators

Torben Hansen (University of Copenhagen) on personalized type 2 diabetes treatment.

Oluf Pedersen (University of Copenhagen) on personalized type 2 diabetes treatment.

Karsten Kristiansen (University of Copenhagen) on genome analysis.

Anders Krogh (University of Copenhagen) on genome analysis.

Ebba Holme Hansen (University of Copenhagen) on medical data mining.

Eske Willerslev (University of Copenhagen) on human variation.

Thorkild I.A. Sørensen (University of Copenhagen) on gene-diet interactions, colectomy disease trajectories.

Mikkel H. Schierup (Aarhus University) on bioinformatics.

Thomas Werge (Mental Centre Sct. Hans, Roskilde) on network biology and human variation.

Lise Aagaard (University of Southern Denmark) on medical data mining.

Pierre Baldi (UC Irvine, US) on machine learning in bioinformatics.

Ewan Pearson (University of Dundee, UK) on personalized type 2 diabetes treatment.

Paul Franks (Lund University, Sweden) on personalized type 2 diabetes treatment.

Tudor I. Oprea (University of New Mexico, US) on the druggable proteome.

Pope Moseley (University of New Mexico, US) on disease trajectories.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Proteomics Program

Program Director, Matthias Mann

Proteomics is the large-scale and unbiased analysis of the proteins present in a biological system.

Just like genomics, proteomics is making dramatic, technology-driven advances. At CPR, we continuously develop and apply a world-leading proteomics platform – a technological foundation for asking biological questions that could never be answered before. Within the broad area of proteomics, the program is especially active in the analysis of post-translational modifications (PTMs) of proteins by mass spectrometry. PTMs are of key importance in biology and medicine because they govern the activity, binding partners, localization and half-lives of proteins. In addition to studying fundamental biological processes, our interest is now turning towards the use of proteomics to elucidate clinical questions such as disease diagnosis and mechanisms. Like all 'omics' disciplines, proteomics requires big data analysis and this is pursued in the group and through collaboration with the Disease Systems Biology Program.

The program is headed by Professor Matthias Mann, who is also a Max-Planck director in Münich, and is comprised of three independent groups. Professor Jesper V. Olsen is a world-leader in the analysis of protein phosphorylation and mass spectrometry, Professor Chunaram Choudhary studies cell signaling mediated by acetylation and ubiquitylation and Professor Michael Lund Nielsen concentrates on less studied modifications, such as poly(ADP-ribos)ylation and novel mass spectrometry-based measurement technologies.

The program is responsible for CPR's Proteomics Platform, which is headed by Professor Michael Lund Nielsen and provides analytical proteomics support for CPR research groups and collaborators.

Mass Spectrometry Platform

Platform leader: Michael Lund Nielsen

Mass spectrometry is a powerful technology for the characterization of proteins and their modifications and it has been instrumental in establishing CPR as a forefront center in protein research.

Our success is based on the cutting-edge proteomics platform that we have established and continuously developed during the past five years.

With the formal introduction in 2014 of one technological platform under each of the CPR research programs, the Mass Spectrometry Platform has been established as a separate unit headed by Professor Michael Lund Nielsen and operated by mass spectrometry specialist Dorte Breinholdt Bekker-Jensen.

The aim of the CPR Mass Spectrometry Platform is to ensure that CPR retains world-leading mass spectrometry technology, to provide technical support and maintenance for the Proteomics Program and to provide analytical proteomics support for CPR research groups and CPR's collaborative stakeholders.

We work closely with leading proteomics instrument manufacturers to develop new software and hardware for the mass spectrometry field. With this co-development of next-generation mass spectrometry instrumentation, we ensure our ability to perform state-of-the art proteomics research both now and in the future, allowing us to tackle the most interesting and complex biological applications.

The platform has access to the latest generation Orbitrap mass analyzers, the Q Exactive HF mass spectrometers, which provide unprecedented accuracy, speed and sensitivity. This cutting-edge equipment enables us to measure complete human proteomes to a depth of more than 10,000 different proteins in hours or less.

Proteomics platform: Dorte Breinholdt Bekker-Jensen, Mass Spectrometry Specialist, **Michael Lund Nielsen** Platform Leader

Mass Spectrometry for Quantitative Proteomics/Olsen Group
Group Leader: Professor Jesper Velgaard Olsen

The Mass Spectrometry (MS) for Quantitative Proteomics group was established in 2008 and is headed by Professor Jesper V. Olsen.

Our major scientific focus is quantitative high-resolution MS-based proteomics with emphasis on MS technology development and biological applications. We have a strong interest in applying the technology that we develop to systems-wide analyses of dynamic post-translational modifications that regulate cell signal transduction pathways, e.g. phosphorylation and SUMOylation.

We are continuously developing the phosphoproteomics technology to be more robust, reproducible and rapid. We collaborate with MS vendors to beta-test and develop new MS instrumentation for large-scale proteomics and PTM analyses. We are also actively developing and applying large-scale quantitative interaction proteomics screens using high-resolution MS as the read-out.

Research aim
The overall research aim of the Olsen Group is development of quantitative proteomics technology and its application to biological questions. We focus on developing our technology for quantitative interaction proteomics and PTMs screens to analyze tissue samples from rodent models as well as patient material.

Key achievements
A key achievement in 2014 was the publication in Nature Methods and Nature Genetics of our proteomics strategy for functional annotation of large-scale genomics data. We developed an integrated tissue-specific affinity-based interaction proteomics technology to identify causal genes in loci from genome-wide association studies *(47)*. We applied our technology to identify genes crucial for repolarization of human hearts by analyzing protein interaction networks in the heritable disease called Long-QT-Syndrome *(3)*.

We also focused on technology development in MS instrumentation, acquisition methods and offline peptide fractionation strategies for deep proteome and phosphoproteome profiling and applied it to different types of mammalian cells, which we published in two technology papers in Journal of Proteome Research *(4, 39)*.

The Olsen group is involved in a number of collaborative research projects and in 2014, 17 papers were published with strong local or international partners, e.g. Eske Willerslev (Nature Genetics, *72*) and Alfred Vertegaal (Molecular Cell, *64*).

In 2014, the Olsen group successfully passed its first 5-year evaluation. It took place during a site visit Februay 28 by a committee of experts: Professors Kristian Strømgaard (UCPH) and Yasushi Ishihama (Kyoto University), and Associate Professors Forrest White (MIT) and Jarrod Marto (Dana-Farber Cancer Institute). Jesper V. Olsen presented the group's accomplishments and future research plans and members of the group presented their research in more detail during a poster session allowing for informal discussion with the expert committee.

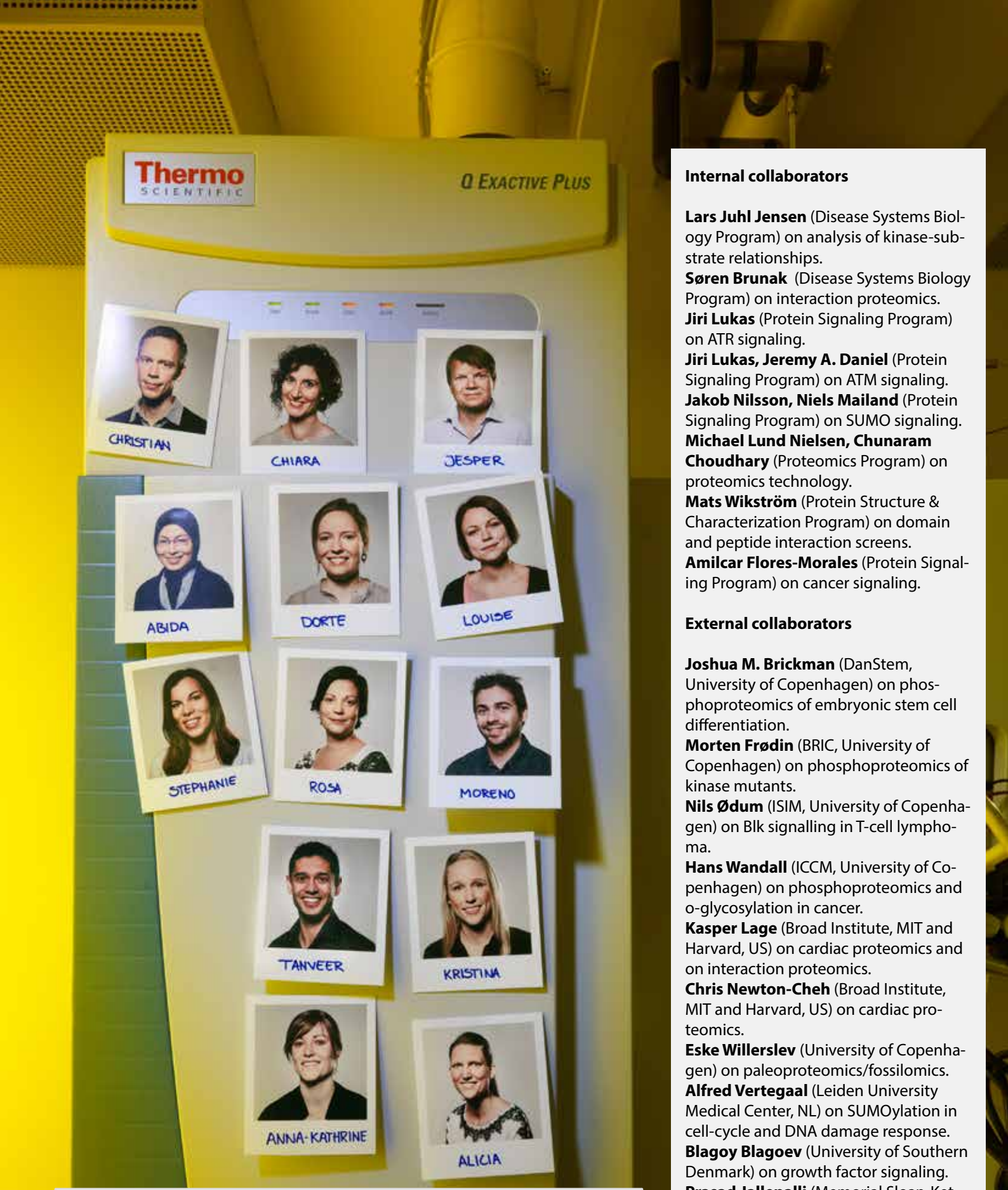
Jesper V. Olsen received grants from Danish Cancer Society (DKK 1.5 M) and Fabrikant Vilhelm Pedersen og Hustrus Mindelegat (DKK 1.0 M). Louise von Stechow received DKK 2.2 M from Danish Council for Independent Research.

Dissemination
Group leader Jesper V. Olsen chaired and organized the Phosphoproteomics session at the International MS Conference in Geneva and was invited speaker at the 3rd Nordic Proteomics Conference (Finland), the US-HUPO Conference (Seattle), the Thermo Fisher User's meeting at ASMS (Baltimore), the 'PTMs control of protein function' at the Max-Planck Institute in Cologne and the first Danish-Israel Science Meeting at the Weizmann Institute.

Jesper V. Olsen was also interviewed about the human proteome for the radio program 'Videnskabens Verden' on Danish Radio and our papers in Nature Methods and Nature Genetics were highlighted by Videnskab.dk and several Danish newspapers.

Group members presented their research at conferences world-wide: Chiara Francavilla and Alicia Lundby were invited speakers at the Gordon Research Conference on Fibroblast growth factors in Development and Diseases (California) and Copenhagen Meeting on Cardiac Arrhythmia, respectively.

Christian Kelstrup and Kristina Bennet Emdal spoke at the 13th HUPO World Congress (Spain) and Rosa Jersie-Christensen at the 6th International Symposium on Biomolecular Archeology (Switzerland). Group members also participated in meetings for the EU FP7 projects UPStream and PRIME-XS, and presented posters at numerous conferences.



Olsen Group

Christian Kelstrup, postdoc, **Chiara Francavilla**, postdoc, **Jesper V. Olsen**, group leader, **Abida Sultan**, academic employee, **Dorte Breinholdt Bekker-Jensen**, mass spectrometry specialist, **Louise von Stechow**, postdoc, **Stephanie Munk**, postdoc, **Rosa Jersie-Christensen**, PhD student, **Moreno Papetti**, PhD student, **Tanveer Singh Batth**, PhD student, **Kristina Emdal**, PhD student, **Anna-Kathrine Pedersen**, PhD student, **Alicia Lundby**, postdoc.

Internal collaborators

Lars Juhl Jensen (Disease Systems Biology Program) on analysis of kinase-substrate relationships.
Søren Brunak (Disease Systems Biology Program) on interaction proteomics.
Jiri Lukas (Protein Signaling Program) on ATR signaling.
Jiri Lukas, Jeremy A. Daniel (Protein Signaling Program) on ATM signaling.
Jakob Nilsson, Niels Mailand (Protein Signaling Program) on SUMO signaling.
Michael Lund Nielsen, Chunaram Choudhary (Proteomics Program) on proteomics technology.
Mats Wikström (Protein Structure & Characterization Program) on domain and peptide interaction screens.
Amilcar Flores-Morales (Protein Signaling Program) on cancer signaling.

External collaborators

Joshua M. Brickman (DanStem, University of Copenhagen) on phosphoproteomics of embryonic stem cell differentiation.
Morten Frødin (BRIC, University of Copenhagen) on phosphoproteomics of kinase mutants.
Nils Ødum (ISIM, University of Copenhagen) on Blk signalling in T-cell lymphoma.
Hans Wandall (ICCM, University of Copenhagen) on phosphoproteomics and o-glycosylation in cancer.
Kasper Lage (Broad Institute, MIT and Harvard, US) on cardiac proteomics and on interaction proteomics.
Chris Newton-Cheh (Broad Institute, MIT and Harvard, US) on cardiac proteomics.
Eske Willerslev (University of Copenhagen) on paleoproteomics/fossilomics.
Alfred Vertegaal (Leiden University Medical Center, NL) on SUMOylation in cell-cycle and DNA damage response.
Blagoy Blagoev (University of Southern Denmark) on growth factor signaling.
Prasad Jallepalli (Memorial Sloan-Kettering, US) on kinase-substrate target identification of cell-cycle regulated kinases.
Ugo Cavallaro (European Institute of Oncology, Italy) on cancer signaling and tumor analysis.

Proteomics Technology Development & Application/Nielsen Group
Group Leader: Associate Professor Michael Lund Nielsen

The Proteomics Technology Development and Application group was established in 2009 and is headed by Professor Michael Lund Nielsen.

The focus of the Nielsen group is to develop new proteomic technologies and implement these in relevant biological areas. To this end, the group employs high-resolution quantitative mass spectrometry based upon the proprietary Q Exactive HF platform.

The group has most recently established proteomics methodologies for characterization of post-translational modifications (PTMs), such as ubiquitylation, arginine methylation, citrullination, ADP-ribosylation and other cellular signaling molecules like phosphoinositides.Moreover, the group is engaged in a number of collaborative research projects with internal, local and international scientific groups.

Research aim
The group aims to further improve current methodologies for comprehensive characterization of less studied PTMs. In particular, a strong research focus is on comprehensive characterization of poly-ADP-ribosylation and arginine methylation by quantitative proteomics.

We expect that the methods developed for targeting less studied PTMs, such as poly-ADP-ribosylation, will shed light on novel aspects related to the given PTM. With the development of so-called PARP inhibitors that specifically target the enzymes responsible for catalysing poly-ADP-ribosylation, our methodology will allow us, for the first time, to characterize the cellular response of such inhibitors. Such knowledge has remained elusive due to the lack of unbiased methodologies for characterizing poly-ADP-ribosylated protein substrates.

Key achievements
In 2014, the Nielsen group published six research articles in international peer-reviewed journals, including one in Nature, one in Cell Reports, one in Nature Cell Biology, and two in Molecular and Cellular Proteomics *(14, 36, 38, 41, 45, 67)*.

Nielsen Group

Elisabeth Jakobsen, technician

Maria Vistrup Madsen, laboratory assistant, master's student

Kathrine Beck Sylvestersen, postdoc

Michael Lund Nielsen, group leader

Sara Charlotte Larsen, postdoc

Rita Martello, postdoc

Meeli Mullari, PhD student

Clifford Young, postdoc

Group leader Michael Lund Nielsen was awarded the prestigious Sapere Aude research grant from The Danish Council for Independent Research. Additionally, postdoc Kathrine B. Sylvestersen received a research grant from the Lundbeck Foundation for her continued studies of arginine methylation in human cells.

In 2014, the Nielsen group successfully passed its first 5-year evaluation. It took place during a site visit Februay 28 by a committee of international experts consisting of Professors Kristian Strømgaard (UCPH) and Yasushi Ishihama (Kyoto University, Japan) and Associate Professors Forrest White (MIT, US) and Jarrod Marto (Dana-Farber Cancer Institute, US). Michael Lund Nielsen presented the group's accomplishments and future research plans and members of the group presented their research in more detail during a poster session allowing for informal discussion with the expert committee.

Dissemination
Group leader Michael Lund Nielsen co-organized the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' (Favrholm).

Members of the Nielsen group participated in a number of conferences in 2014, including the Cold Spring Harbor meeting on PARP (talk by Rita Martello), the 62nd Conference of the American Society for Mass Spectrometry, Baltimore US (posters by Sara C. Larsen and Kathrine B. Sylvestersen), the 60th Benzon Symposium on 'Nuclear Regulation by Ubiquitin', Copenhagen (poster by Michael Lund Nielsen) and the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' (posters by Rita Martello, Sara C. Larsen and Kathrine B. Sylvestersen).

The group also participated in the annual meetings of EU FP7 projects Euratrans and PRIME-XS.

Internal collaborators

Jeremy A. Daniels (Protein Signaling Program) on DNA damage.
Jakob Nilsson (Protein Signaling Program) on mitosis.
Amilcar Flores-Morales (Protein Signaling Program) on arginine methylation.
Niels Mailand (Protein Signaling Program) on ubiquitylation.
Lars Juhl-Jensen (Disease Systems Biology Program) on bioinformatics and proteomics.
Jiri Lukas (Protein Signaling Program) on PARylation.

In 2014, the Nielsen group established an Instagram account depicting the everyday life and scientific accomplishment of the group. (https://instagram.com/nielsengroup/).

The Nielsen group organized a successful PhD course entitled 'Mass Spectrometry-based proteomics and its applications in biology'. Group leader Michael Lund Nielsen organized a one day introduction to mass spectrometry-based proteomics for master's students attending the course 'Advanced Protein Science I'. Additionally, Michael L. Nielsen gave a keynote lecture on proteomics as part of the PhD mass spectrometry course 'Mass spectrometry coupled to separation techniques in bioanalytical chemistry', organized by Department of Pharmacy, University of Copenhagen.

External collaborators

Michael Lisby (Department of Biology, University of Copenhagen) on biotinylation.
Olaf Nielsen (Department of Biology, University of Copenhagen) on lysine acetylation.
Anja Groth (BRIC, University of Copenhagen) on DNA damage.
Jonas Thue Treebak (NNF Center for Metabolic Research, University of Copenhagen) on biotinylation.
Javier Pena-Diaz (Center for Healthy Aging, University of Copenhagen) on DNA damage.
Tony Kouzarides (University of Cambridge, UK) on histone PTMs.
Michael O. Hottiger (University of Zürich, Switzerland) on PARylation.
Andre Nussenzweig (NIH, US) on PARylation
Manuel Stuecki (University of Zürich, Switzerland) on DNA damage.
Philip M. Iannaccone (Northwestern University, Chicago, US) on transcription.
Norbert Hübner (MDC, Germany), **Michal Pravenec** (Czech Academy of Sciences, CZ) on EURAtrans.
Bernhard Lüscher (Aachen University, Germany) on MARylation.
Albert Heck (University of Utrecht, NL) on proteomics technology.
Gonçalo Castelo-Branco (Karolinska Institute, Sweden) on citrullination.
Olle Sangfelt (Karolinska Institute, Sweden) on ubiquitylation.

Proteomics & Cell Signaling/Choudhary Group

Group Leader: Professor Chunaram Choudhary

The Proteomics and Cell Signaling group was established in 2009 and is headed by Professor Chunaram Choudhary.

A major focus of the group is to investigate the dynamics of post-translational modification-based cell signaling networks.

The group uses high resolution mass spectrometry to investigate protein ubiquitylation and acetylation. We combine these proteomic approaches with cell and molecular biology techniques to understand the functional roles of acetylation and ubiquitylation.

Research aim
To better understand the functional importance of acetylation, the group has developed a new method to investigate the stoichiometry of individual acetylation sites. This powerful approach allows us to distinguish low abundant acetylation sites from acetylation sites that occur at high stoichiometry and aids in the prioritization of acetylation sites for investigating their functional roles.

Key achievements
Using our novel stoichiometry estimation approach, we showed that most acetylation sites in yeast occur at very low stoichiometry *(74)*. Importantly, we showed that most high stoichiometry acetylation sites are present on nuclear proteins many of which have known important functions such as gene transcription. Combining quantitative proteomics and genetic manipulation, we showed that most acetylation in mitochondria is present at a low level and occurs through a non-enzymatic mechanism. Strikingly, we found that acetylation in yeast is regulated in a sub-cellular compartment specific manner, suggesting that compartmentalization of eukaryotic cells played an important role in the evolution of the specificity in acetylation signaling. Our results revealed important connections between metabolism and acetylation, which will help in understanding the functional roles of acetylation in metabolic regulation.

In 2014, group leader Chunaram Choudhary received a prestigious Hallas-Møller Investigator Award of DKK 11.0 M from The Novo Nordisk Foundation for the project 'Unraveling the regulatory landscape of lysine acetylation modifying enzymes'. Postdoc Rajat Gupta was granted DKK 0.3 M from European Molecular Biology Organization (EMBO) for a Long-Term Fellowship.

In December 2014, the Choudhary group successfully passed its first 5-year evaluation. It took place during a site visit by a committee of international experts consisting of Professors Anne Grapin-Botton (Danstem, UCPH), Angus Lamond (University of Dundee, UK), Kathryn Lilley (Cambridge University, UK) and Scott Hiebert (Vanderbilt University, US). Chunaram Choudhary presented the group's accomplishments and future research plans and members of the group presented their research in more detail during a poster session allowing for informal discussion with the expert committee.

Internal collaborators

Niels Mailand (Protein Signaling Program) on ubiquitylation and DNA damage signaling.
Jeremy A. Daniel (Protein Signaling Program) on DNA damage signaling in mouse models.
Jakob Nielsen (Protein Signaling Program) on mitosis.
Michael Lund Nielsen and Jesper V. Olsen (Proteomics Program) on quantitative proteomics.

External collaborators

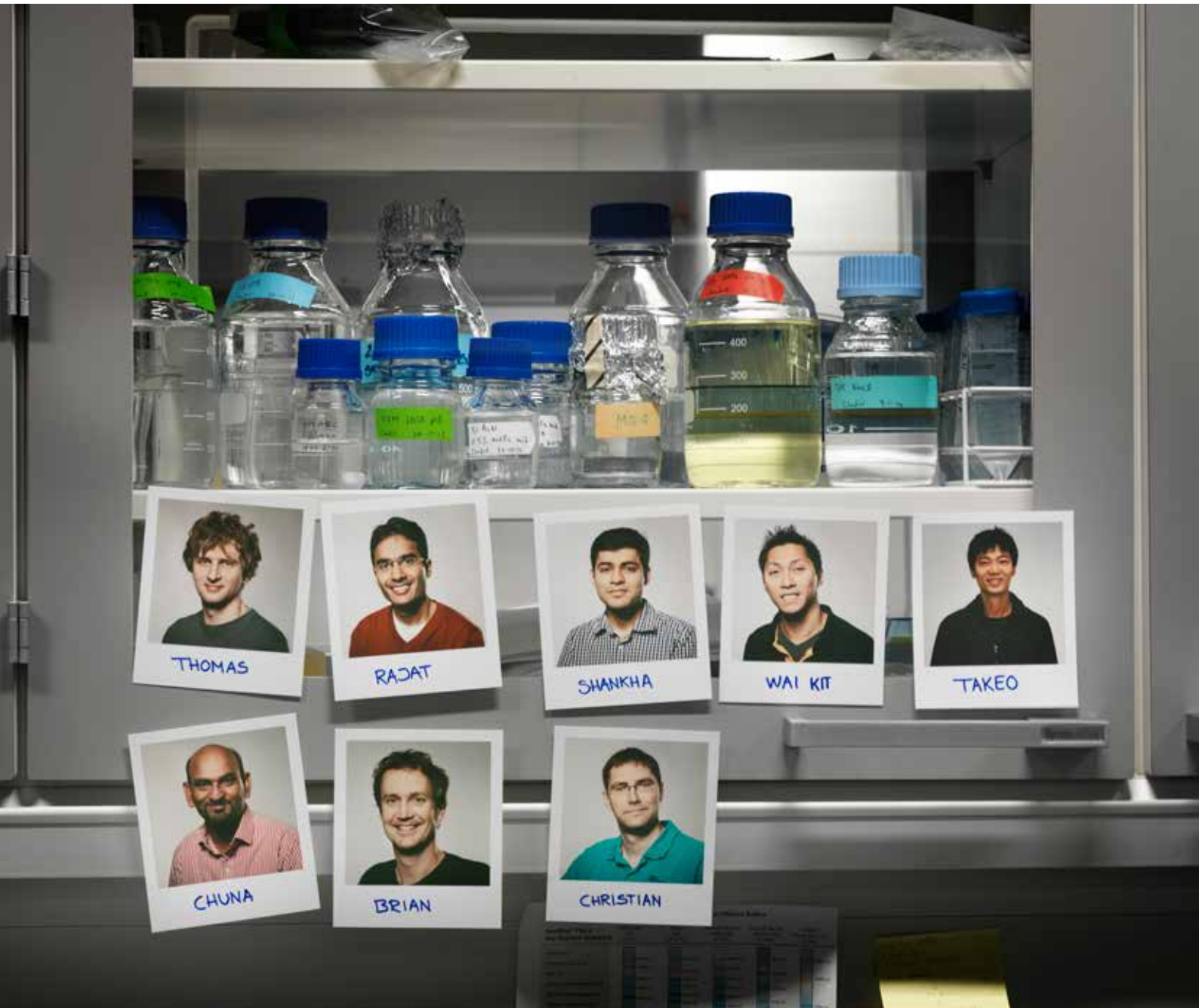
Steve P. Jackson (University of Cambridge, UK) on DNA damage signaling.
Matthias Mann (Max-Planck Institute for Biochemistry, Germany) on quantitative mass spectrometry.
Rudolf Zechner (University of Graz, Austria) on metabolism and acetylation.

Dissemination
In 2014, Chunaram Choudhary was invited to speak at two high-level conferences: Post-translational protein modifications in epigenetics and metabolism, Copenhagen, and 7th Garvan Signaling Symposium, Sydney, Australia. He was also selected for an oral presentation at the 60th Benzon Symposium: Nuclear Regulation by Ubiquitin, Copenhagen.

Vytautas Iesmantavicius, a PhD student in the group, was selected for an oral presentation at the 13th Annual World Congress of Human Proteome Organization (HUPO) in Madrid, Spain.

Group members presented posters at the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' (Brian T Weinert, Christian Schölz, Vytautas Iesmantavicius, Shankha Satpathy) as well as the 60th Benzon Symposium, Copenhagen (Shankha Satpathy).

Choudhary group: Thomas Wild, postdoc, **Rajat Gupta**, postdoc, **Shankha Satpathy**, PhD student, **Wai Kit Chu**, postdoc, **Takeo Narita**, postdoc, **Chunaram Choudhary**, group leader, **Brian Weinert**, postdoc, **Christian Schölz**, postdoc.



Protein Structure & Characterization Program
Program Director: Guillermo Montoya

Program Director,
Guillermo Montoya

The main objective of the Protein Structure and Function Program is to expand the mechanistic understanding of key cellular processes in cell cycle progression and genome integrity.

Macromolecules underlie all biological processes and play either dynamic roles in catalysis or signaling or static roles in scaffolding or information storage. Nearly every major process in a cell is carried out by assemblies of ten or more protein molecules.

The assemblies of these macromolecules, the molecular machines of the cell, and their timely interactions, perform the majority of cellular functions. Malfunctions of protein pathways that orchestrate cell proliferation and guard the integrity of the genome are involved in the development of many diseases. However, the functions of proteins cannot be understood if we consider them individually and separate from their molecular and cellular contexts. Our current comprehension of cellular processes at the molecular level contains limited knowledge of the cellular organization, localization and action mechanisms of these molecular machines.

The goal of the Protein Structure and Function Program is to fill the gap of information between our current knowledge and the understanding of the molecular mechanisms that control the function of the molecular machines of the cell. Our research area lies at the interface of physics, chemistry, and biology, thus we combine biochemical, biophysical, structural, cellular and computational approaches. To achieve this aim, our program strongly synergizes with other research groups at CPR, at the University of Copenhagen and at international level.

The program is headed by Professor Guillermo Montoya and is comprised by two independent research groups. Guillermo Montoya is leader of the Macromolecular Crystallography group and Mats Wikström leads the Protein Function and Interactions group. In addition, the program is responsible for the Protein Production and Characterization Platform, which supports CPR scientists with research projects requiring protein production and structural-functional protein analysis.

Protein Production and Characterization Platform
Platform leader: Guillermo Montoya

The identification of novel and/or transient multiprotein cellular complexes has accelerated considerably as a consequence of proteome-wide analysis of protein-protein interactions, powerful multiple-affinity protein purification methods and ultrasensitive MS. The concept of the cell as a collection of multicomponent protein machines, one for every major biological process, has thereby emerged and this poses formidable challenges for protein production technologies.

To stay on the cutting edge of this area of protein science, the Protein Structure and Function Program was established in January 2014 under the leadership of Guillermo Montoya and the former Protein Production Facility was embedded in this program and transformed in to the new Protein Production and Characterization Platform. The transformation process exceeds that of the changed name. The new platform will build on the achievements and expertise of the former Protein Production Facility, which was previously supervised by Bjørn Voldborg and Mats Wikström, respectively, and which had developed robust protocols to express and purify single domains and small proteins. The new platform will expand these methods to produce proteins and protein complexes that are involved in key cellular processes, but extremely challenging to produce for structural and mechanistic studies. Examples include molecular machines with multiple subunits such as CCT, MCM2-7 and CMG complexes, or giant kinases such as MASTL, ATM or PLK4.

We will integrate and focus the platform even more closely with research projects at CPR. In addition to protein production, this will include in-depth biochemical and biophysical characterization for structure-function studies. We will develop a state-of-the-art advanced platform by implementing new methods and innovative approaches that will allow us to tackle protein complexes and transient protein interactions involved in normal cellular function and disease.

The new platform is coordinated by Professor Guillermo Montoya and is organized in three teams: Prokaryotic Protein Expression (team leader Andrea Lages Lino Vala), Eukaryotic Protein Expression (team leader Giuseppe Cazzamali), and Biophysical Protein Characterization (team leader to be recruited to CPR early 2015).

Platform team members:

Motiejus Melynis, technician

Alison Lilley, technician

Andrea Lages Lino Vala, academic coordinator

Tasja Ebersole, technician

Giuseppe Cazzamali, academic coordinator

Ganesha Pandian Pitchai, PhD student

Mille Egeberg Ottosen, laboratory assistant

Irina Pozdnyakova, academic research technician

Khalid Pardes, technician

Havva Koc, technician

Mia Funk Nielsen, technician

Michael Ross WIlliamson, technician

Guillermo Montoya, platform leader

Protein Function and Interactions/Wikström Group
Group Leader: Associate Professor Mats Wikström

The Protein Function and Interactions group was established in August 2012 and is headed by Associate Professor Mats Wikström.

The Protein Function and Interactions group is focused on understanding the molecular details in macromolecular recognition with particular emphasis on protein-protein interactions. This group has established strong research projects within the areas of biophysics and structural biology including both high-resolution NMR spectroscopy and X-ray crystallography. The current projects are within the following areas:

- Structure and dynamics of a novel SUMO Interacting Motif.
- Structure and function for virulence determinants of the pathogen Streptococcus pyogenes.
- Biophysical and structural studies of the interaction matrix of insulin-like growth factor binding proteins (IGFBPs).

Research aim
The aim of the research during 2014 has been to further advance our structural studies in relation to the previously identified new SUMO-binding motif and the novel virulence factor from group A streptococci. In addition, we have during this year developed an efficient expression system for all human insulin-like growth factor binding protein to provide the means for further studies of the IGFBP interaction matrix.

Key achievements
In 2014, research in the Wikström group has focused on the following three areas:

The Novel virulence factor sHIP: We have performed additional studies of the novel virulence factor sHIP from group A streptococci identified in a collaborative effort with Lund University, Sweden *(75)*. Our studies have shown that sHIP binds and inhibits the antibacterial activity of histidine rich glycoprotein (HRG), and

that sHIP primarily interacts with the histidine-rich region of HRG. Using heteronuclear NMR techniques, we were able to determine the complex between sHIP and the HRG peptide that has provided further understanding of the function of this new virulence factor (Wisniewska et al, manuscript in preparation).

Structural analysis of a complex between SUMO1 and the ZZ domain of CBP/p300 reveals a new interaction surface on SUMO: We have previously, in collaboration with the Mailand group, discovered a novel SUMO-binding motif recognized as a ZZ zinc finger domain. In this study we have identified the binding epitopes in the ZZ domain from CBP and SUMO1 using NMR spectroscopy. The binding site on SUMO1 represents a completely novel epitope for SUMO interacting motifs (SIMs) adjacently to that for canonical SIMs. ITC experiments supports the model by showing that the mutation of key residues in the binding site abolishes binding and that SUMO1 can simultaneously and non-cooperatively bind both the ZZ domain and a canonical SIM-motif.

Development for eukaryotic expression system for all human insulin-like growth factor binding proteins (IGFBPs): Insulin-like growth factor binding proteins (IGFBPs) display many functions in humans including the regulation of the insulin-like growth factor (IGF) signaling pathway. In order to conduct structural and functional investigations, large quantities of recombinant proteins are needed. We have therefore developed a mammalian HEK293 expression system suitable for over-expression of secretory full-length human IGFBP-1 to -7. We could show that the recombinant IGFBPs contained PTMs and exhibited high-affinity interactions with their natural ligands IGF-1 and IGF-2 *(71)*.

Dissemination
Mats Wikström was invited speaker at the meeting 'Host-parasite Interactions – Innate immunity therapy' (Sweden) and postdoc Carl Diehl was invited speaker at the 4th Annual User group Meeting, BioNMR (Poland). In May 2014, group leader Mats Wikström co-organized the PhD course 'Practical Aspects of Protein Purification' with Jakob Nilsson, head of the Mitotic Mechanisms and Regulation Group.

Wikström group:

Sofia Møller, master's student, **Magdalena Wisniewska**, postdoc, **Jesper Langholm Jensen**, postdoc, **Mats Wikström**, group leader, **Carl Diehl**, postdoc, **Anne Sofie Wanscher**, PhD student

Internal collaborators

Niels Mailand (Protein Signaling Program) on structure and dynamics of novel SUMO-binding motifs.

External collaborators

Lars Björck (Lund University and Lund University Hospital, Sweden) on mechanistic studies of virulence factors from group A streptococci.

Johan Malmström (Lund University, Sweden) on proteomic mass spectrometric analyses of secreted proteins from group A streptococci.

Michael Gerstenberg (Novo Nordisk A/S, Denmark) on the interaction matrix for insulin-like growth factor binding proteins.

Macromolecular Chrystalogy/Montoya Group
Group Leader: Professor Guillermo Montoya

The Macromolecular Crystallography group was established at CPR in 2014 and is headed by Professor Guillermo Montoya who joined CPR from a position as Senior Group Leader at the Spanish National Cancer Research Centre (CNIO) in Madrid. Several team members from the Macromolecular Crystallography group in Madrid have joined Guillermo Montoya at CPR.
The human genome is a sophisticated and complex coding system capable of producing thousands of different proteins in a tightly controlled way. These macromolecules and their interactions underlie all biological processes and the focus of our group is on the molecular understanding of the role played by macromolecules involved in key cellular processes and to understand the molecular mechanisms that govern the function of different cellular machines.

Structural determination reveals an unparalleled view into the design principles of living systems at levels that span from basic mechanistic questions regarding protein function, to the evolutionary relationships between cellular components. Our work focuses on the structural and dynamic interactions of these biomolecules and their complexes. For this aim, we combine biophysical and biochemical assays with structure approaches such as X-ray crystallography and electron microscopy.

Research aim
Our research efforts are focused in the following themes:

- Understanding the molecular mechanism of CCT/TRiC control of cell cycle progression
- Deciphering the mechanism of DNA unwinding during genome replication
- Regulation of the kinase loop involved in cell division
- Design of specific protein-DNA interactions for genome editing
- Structural mechanisms of telomere protection

All these research lines represent a continuation of our main research efforts during the past few years. The detailed understanding of these key mechanisms will be the major focus for the group in the coming years and we expect that our results will shed light on crucial molecular processes for the cell.

Key achievements
A major task in 2014 was to move our lab from Madrid and establish the Macromolecular Crystallography group at CPR. This included the introduction of a state of the art crystallization facility at CPR with the equipment we need to characterize and crystallize proteins in order to perform our research objectives. We have also completed the integration and development of those of our projects that need the production of protein complexes in the Protein Production and Characterization Platform at CPR.

The group published eight research articles in 2014, of which three were affiliated with CPR, including one publication in Nature Structural & Molecular Biology and two in Nature Communications *(35, 49, 50)*. Two of these papers received attention on international social media.

In the first paper, published in Nature Structural & Molecular Biology *(49)*, we demonstrated a method for producing biological crystals that has allowed us to

Internal collaborators

Jeremy A. Daniel (Protein Signaling Program) on new DNA damage response factors.
Niels Mailand (Protein Signaling Program) on biophysical characterization of proteins and protein domains.

External collaborators

Carol Robinson (University of Oxford, UK) on mass spectrometry of protein complexes.
Imre Berger (EMBL-Grenoble, France) on production of protein complexes.
Christiane Schafitzel (EMBL-Grenoble, France) on electron microscopy of protein complexes.
F. Blanco (cicBiogune, Spain) on discovery and characterization of new factors in cellular responses to replication stress.
J.M. Valpuesta (CNB-CSIC, Spain) on electron microscopy studies of chaperonins.
Marcos Malumbres (CNIO, Spain) on structure-function studies of mitotic kinases.
Travis Stracker (IRBB, Spain) on structure function studies of kinases involved in the DNA damage response.

observe - for the first time - DNA double strand breaks. We also developed a computer simulation that makes this process, which lasts in the order of millionths of a second, visible to the human eye.

In the second paper, published in Nature Communications *(50)*, we uncovered the molecular interaction between TACC3 and chTOG, and demonstrated how TACC3 recruits chTOG to the microtubules during cell division. Our results indicate that TACC3's function depends completely on this interaction, so that mutations in TACC3 prevent chTOG from correctly incorporating into the microtubules. The study will allow for a better understanding of microtubule dynamics and we anticipate that it could help optimize current oncological therapies that are specifically designed to target microtubules.

Group leader Guillermo Montoya was elected panel member for evaluation of BiostructX EU granting time in structural biology facilities. He was also invited to participate as associated editor of 'Inside the Cell', a new cell biology journal of the Wiley group.

Dissemination

Guillermo Montoya was keynote speaker at Proteine2014 (University of Padua, Italy), Synthetic Biology Congress (London) and the 2nd Copenhagen Bioscience Conference on 'PTMs in Cell Signaling' (Favrholm). In addition, he was invited speaker at MAX-IV Users meetings, University of Lund (Sweden) and Distinguished Seminar CIC-CSIC, University of Salamanca (Spain).

Upon publication, three of our articles in 2014 have received attention on international social media. We have also edited a video in you tube describing our research into BuD and its future applications (www.youtube.com/watch?v=YFutF3Cqk3U).

Montoya group:

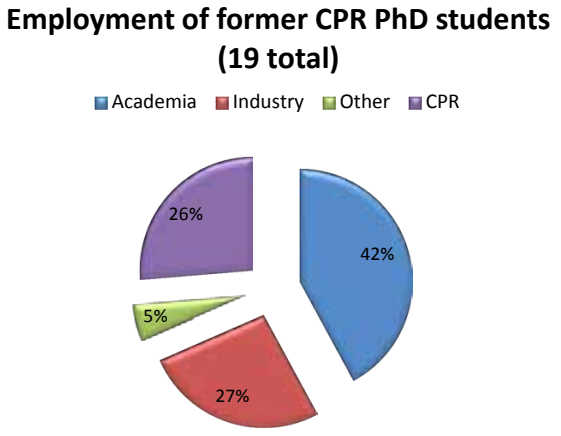
Stefano Stella, associate professor, **Pablo Mesa,** associate professor, **Elisabeth Bragado Nilsson,** academic research technician, **Gulnahar Mortuza,** associate professor, **Guillermo Montoya**, group leader, **Dario Hermida Aponte,** PhD student, **Pablo Alcón Hernandez,** PhD student.

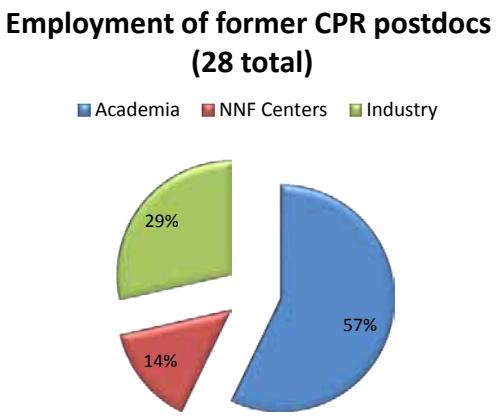
Training and Education

Training and education of scientists comprises the foundation that CPR builds upon. Approximately 55% of the CPR's current employees are junior researchers, including postdocs, PhD students, and undergraduate students. We aim to create an unmatched career development portfolio to attract the best talents, allow them to reach top international level early in their careers, and provide them with unique skills to compete for leadership positions both in academia and industry. Our vision of a complete protein scientist is best described as a person equipped with skills in a broad range of complementary protein technologies and capable of applying them to address fundamental challenges in academic research, the biotech/pharma industry or the healthcare sector. Additional hallmarks of a complete scientist include good scientific practice, intellectual understanding, entrepreneurship and ambition for continuous innovation.

In 2014, we continued an initiative launched in 2013 to prepare our young scientists for conferences and giving presentations, in the form of CPR Research in Progress (CPR-IP) meetings. Two PhD students or postdocs present unpublished results to their peers at these meetings, where the chair is instructed to call primarily on junior researchers in the following discussion. On the initiative of CPR's Student and Postdoc Association, the frequency of the CPR-IP meetings was recently increased to 3-4 times per month.

In 2014, 9 graduate students finalized their education and defended their dissertations and 10 postdocs left CPR. A top research center is based on a continuous flow of young scientists in short-term positions and it is our aim that talented scientists perceive CPR as an excellent career move. We are pleased to see that the number of CPR researchers securing influential positions outside CPR is growing. Our policy to create complete protein scientists who are sought after by academia and industry also secures rotation of scientific staff, avoids scientific 'inbreeding', and develops CPR's image as a hub for attracting new talent and developing them into highly qualified protein experts. The figure below shows the distribution of first jobs taken by postdocs and PhD students after they leave CPR.



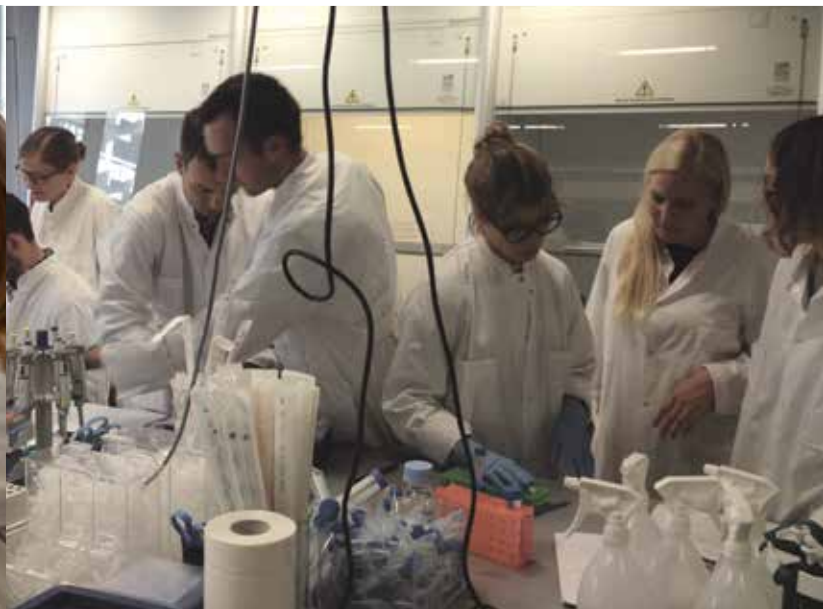


The scientific accomplishments outlined in the group sections of this report would not have been possible without the enthusiasm and strong support from the Dean of the Faculty of Health and Medical Sciences. CPR is aware of the privilege of being part of the Faculty and we are strongly determined to play a leading role in impacting on its scientific and, importantly, also its educational landscape. In 2014, CPR organized for the first time what is to become an annual undergraduate course in 'Advanced methods for the analysis of protein disease mechanisms' with the objective of offering undergraduate students theoretical grounding in and practical experience of modern protein research. This elective course, coordinated by Professor Amilcar Flores-Morales, is not restricted to CPR but open to the entire University. In practical terms, this course will provide approximately 35 hours of classroom courses and 25 hours of hands-on exercises in recombinant protein production, biophysical characterization of proteins, protein crystallization, protein imaging in living cells, enzymology, and MS-based proteomics. Each course will accommodate up to 20 students.

Because advanced proteins technologies generate vast amounts of data, the practical education in protein methods is appropriately complemented by the 'Introduction to Bioinformatics' course for undergraduates provided annually to the Faculty by experts from CPR's Disease Systems Biology Program as part of 'Advanced Cell Biology' course for Human Biologists. In addition, Professor Lars Juhl Jensen from the program taught in the PhD course 'Statistical Methods in Bioinformatics' offered by the Graduate Program in Bioinformatics and Biostatistics at University of Copenhagen.

The CPR Proteomics Program offered the PhD course 'Mass Spectrometry-based proteomics and its applications in biology' organized by Professor Michael Lund Nielsen and his group. Michael Lund Nielsen also organized a one day introduction to mass spectrometry-based proteomics as part of the master's student course 'Advanced Protein Science I'.

Finally, Associate Professors Mats Wikström and Jakob Nilsson organized the PhD course 'Practical Aspects of Protein Purification'.



CPR Seminar Series and CPR Conferences

The CPR seminar series

During the year, CPR has arranged a number of research seminars with invited speakers in our CPR Seminar Series.

5 February, hosted by Michael Lund Nielsen:
Tony Kouzarides, University of Cambridge and Deputy Director of the Gurdon Institute, UK.

4 March, hosted by Jakob Nilsson:
Daniel Gerlich, Institute of Molecular Biotechnology, Austrian Academy of Science, Vienna.

29 April, hosted by Jesper V. Olsen and Jiri Lukas:
Kristian Strømgaard, Department of Drug Design and Pharmacology, Medicinal Chemistry, University of Copenhagen.

7 May, hosted by Mats Wikström and Jakob Nilsson:
Imre Berger, EMBL Grenoble, France.

20 May, hosted by Jeremy A. Daniel:
Andre Nussenzweig, Laboratory of Genome Integrity, NCI/NIH, US.

3 June, hosted by Jeremy A. Daniel:
Barry Sleckman, Washington University, US.

25 June, hosted by Claudia Lukas:
Zuzana Storchova, Max-Planck Institute of Biochemistry, Germany.

22 August, hosted by Chunaram Choudhary:
Kazuhiro Iwai, Department of Molecular and Cellular Physiology, Graduate School of Medicine at Kyoto University

12 September, hosted by Søren Brunak:
Chris Sander, Computational Biology Program, Memorial Sloan-Kettering Cancer Center, US.

14-18 September, hosted by CPR and NNF:
Copenhagen Biosciences Conference on PTMs in Cell Signalling, Favrholm, Denmark.

7 October, hosted by Jakob Nilsson:
Hiro Yamano, UCL Cancer Institute, London.

24 October, hosted by Faculty of Health and Medical Sciences: **Guillermo Montoya** inaugural lecture.

11 November, hosted by Jeremy A. Daniel:
Kai Ge, NIDDK/NIH US.

25 November, hosted by Claudia Lukas:
Lothar Schermelleh, Department of Biochemistry/Micron Advanced Bioimaging Unit, University of Oxford.

15 December, hosted by Matthias Mann:
Kathryn Lilley, Cambridge Centre for Proteomics, UK,
Scott Hiebert, Vanderbilt University School of Medicine, US.

The Copenhagen Biosciences Conference on 'PTMs in Cell Signaling'

In 2012, CPR achieved international impact by introducing 'Protein posttranslational modifications (PTMs) in cell signaling' as a regular meeting in a new series of high profile NNF-sponsored Copenhagen Bioscience Conferences. Encouraged by the great success of the first meeting, we decided to establish this topic at the highest international level in Copenhagen, with the aim of matching for instance the Gordon Research Conferences or Keystone meetings that cover other aspects of contemporary biomedical science.

Thus in 2014, CPR and NNF jointly organized the second bi-annual Copenhagen Bioscience Conference on PTMs in Cell Signaling. The organizing committee included four CPR group leaders from different programs: Jeremy A. Daniel, Amilcar Flores-Morales, Lars Juhl Jensen and Michael Lund Nielsen.

A string of the world's top scientists in the field of protein research were headlining a program that included lectures on clinical proteomics, chromatin biology, DNA damage signaling, cell cycle, disease pathways, and signaling systems and networks.

The purpose of the Copenhagen Bioscience Conferences is to enable participants to build an international network and relationships and to exchange knowledge and ideas. To achieve this, the conferences aim to promote a relaxed, trusting and open atmosphere for scientific debate.

In addition, CPR makes an effort to keep the topic of the conference as broad as possible, which has been endorsed by the speakers and journal editors as an important means to integrate fields of science and to promote the much needed interdisiplinary encounters, which otherwise might not have happened.

To start the conference off, a group of renowned researchers made themselves available for an informal question session with the younger conference participants, including Professor Michael Yaffe (MIT), Professor Yang Shi (Harvard Medical School) and Professor Margaret A. Goodell (Beylor College of Medicine).

PhD Student Kristina B. Emdal from CPR was excited about this format.

It was one of the best things I have ever experienced career-wise. I talked to Michael Yaffe, and just to sit in a relaxed setting asking questions was really rewarding. He gave some personal and honest answers, and I had

some excellent guidance on career issues, says Kristina B. Emdal.

During the conference, a total of 22 renowned researchers gave 25-minute talks while half as many talented researchers were invited to give 10-minute short talks.

One of those given this opportunity was Debbie Marks, Assistant Professor at Havard Medical School:

'It is a fantastic opportunity, even if it is only 10 minutes, because people get to hear what you do. People do look at posters, but it is not the same. Having people see you on stage improves the opportunity for networking and establishing collaborations. Also, having to talk about your research forces you to communicate more clearly, says Debbie Marks, before commenting on the research presented at the conference.
The scientific level is very high. It is up to the standard of the Gordon and Keystone conferences. It is world class', she says.

The social part of the program included a harbour tour of Copenhagen and a visit to the Royal Danish Opera. The social arrangements and excursions were designed to help the participants establish new contacts – as were the two poster sessions conducted during the conference. As all participants, including speakers, had accepted to be present at the conference venue for the entire conference, the poster sessions were humming with activity.

The conference once again was a great success, as evidenced by the feedback from a selection of the participants:

Maxim A. X. Tollenaere, PhD student (CPR)

What has been your best experience?
To meet the experts is definitely a highlight for me. Normally you hear about someone famous within the field, someone you only know from a paper. It has been exciting to meet them – they are human too, and they all have a lot of interesting stories about their careers. The organizers arranged mixed seating at the dinner tables, which means that every night I have shared a table with a PI or somebody who gave a talk. Furthermore, the PI Pub was great. I mean – I met Michael Yaffe there – and I really like his work.

What do you take home from the conference?
This is my first large international conference – so the experience is important to me. Furthermore, I take home a new collaboration possibility and new ideas for my own project on how I can lift it to a higher level.

Inês Chen, Editor (Nature Structural & Molecular Biology, US)

Why are you participating in the conference?
For an editor it is an ideal setting. The program is very broad, which means I can cover a lot of ground and learn about new approaches within the different fields.

Cristina C. Santini, Postdoc (Technical University of Denmark)

You also participated in the first "PTMs in Cell Signaling" conference two years ago - why did you come back?
I am participating because it was really interesting the first time. The organizers make it easy for us participants to get to know each other both personally and scientificly. If you talk to someone you admire scientifically and

Tony Hunter, Inês Chen, Cristina C. Santini & Maxim A. X. Tollenaere

Maxim A. X. Tollenaere receives the prize for best PhD poster

At the Opera

at the same time make a personal connection with the person, this connection is much deeper and longer lasting.

What do you take home from the conference?
I take home a lot of excitement for the topic and about my own work – on my iPod I have a list of things I want to do with my research.

Would you like to come back for another PTM conference?
I will probably not be working in Denmark in two years, but I would definitely fly in from the US to participate. It is the conference of the year.

Professor Michael Yaffe, PI (MIT, US)
This is a really great meeting. Certainly one of the best I have gone to in a year: Fantastic speakers, great organizers, important topics. You couldn't handpick a better group of scientists who are open and sharing and willing to really get engaged in science.

I hope to be back in another two years, said Michael Yaffe.

Needless to say, we at CPR are already looking forward to co-organizing the next Copenhagen Bioscience Conference on PTMs in Cell Signaling in 2016.

Visit the conference homepage: http://www.cph-bioscience.com/conferences/ptms-cell-signaling-2014

Invited speakers at the CBC on PTMs in Cell Signaling, 2014

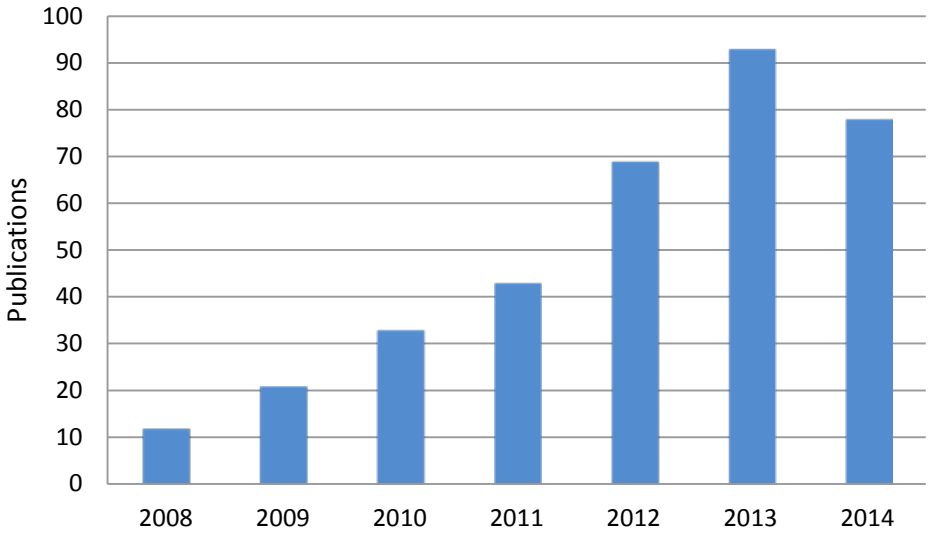
Alfonso Valencia, Spanish National Cancer Research Centre (CNIO), Spain.
Chris Sander, Memorial Sloan-Kettering Cancer Center, US.
Eric J. Brown, Perelman School of Medicine, University of Pennsylvania, US.
Guillermo Montoya, CPR, University of Copenhagen, Denmark.
Hanno Steen, Boston Children's Hospital and Harvard Medical School, US.
Henrik Daub, Evotec, Munich, Germany.
Jo R. Morris, University of Birmingham, UK.
John Blenis, Harvard Medical School, Department of Cell Biology, US.
John Diffley, Clare Hall Laboratories, London Research Institute, UK.
Karolin Luger, Howard Huges Medical Institute, Colorado State University, US.
Marcus Bantscheff, Cellzome, Heidelberg, Germany.
Margaret Goodell, Baylor College of Medicine, US.
Matthias Mann, CPR, University of Copenhagen, Denmark.
Michael Yaffe, Massachusetts Institute of Technology (MIT), US.
Natalie Ahn, University of Colorado, US.
Pedro Beltrao, The European Bioinformatics Institute (EMBL), UK.
Stephen Elledge, Harvard Medical School, Department of Genetics, US.
Tanya Paull, Howard Hughes Medical Institute, University of Texas, US.
Tony Hunter, The Salk Institute for Biological Studies, US.
Yang Shi, Harvard Medical School, Department of Cell Biology, US.

Alfonso Valencia & Chris Sander

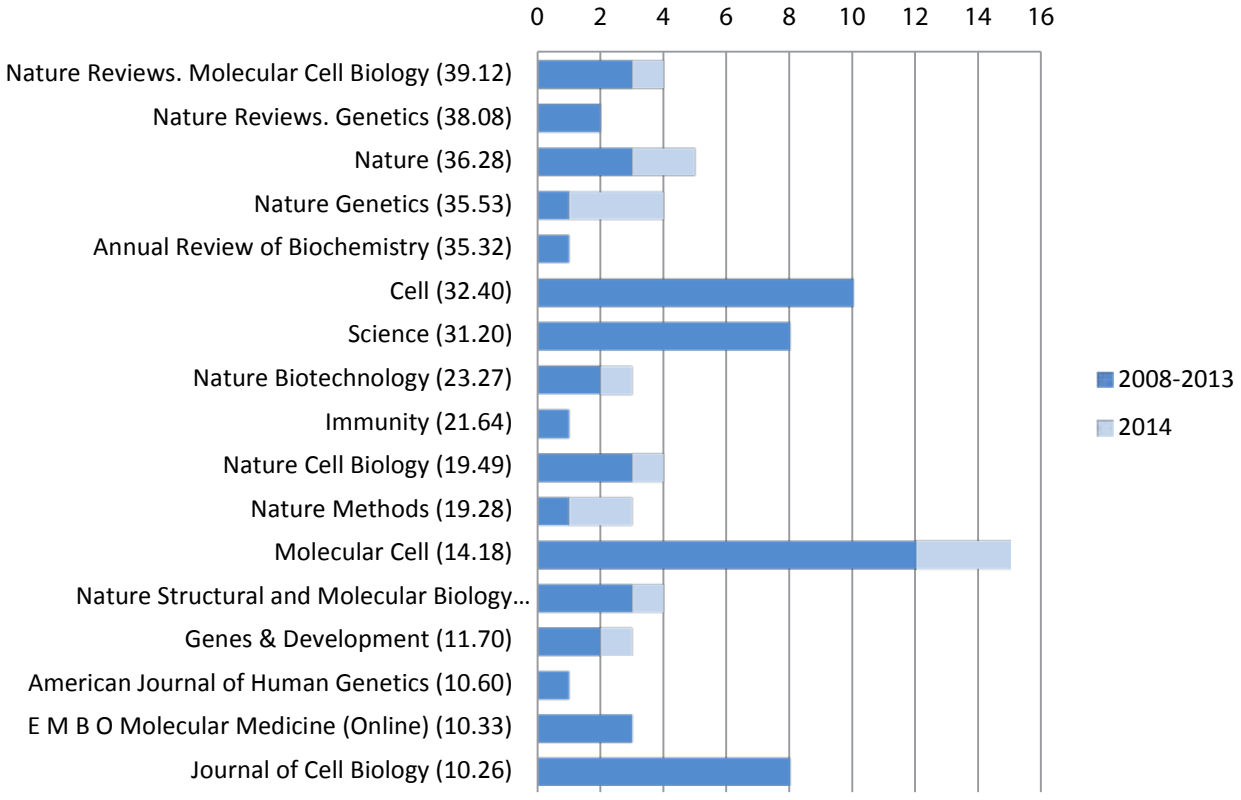
Kristina B. Emdal and her collegues at the conference

Scientific Output

In 2014, CPR has once again been very productive with regard to publishing papers in peer-reviewed journals. More than 75 research papers were accepted in scientific journals, including 22 papers in prestigious publishing houses such as Nature, Science, Cell and their sister journals.



Number of papers authored or co-authored by CPR scientists.

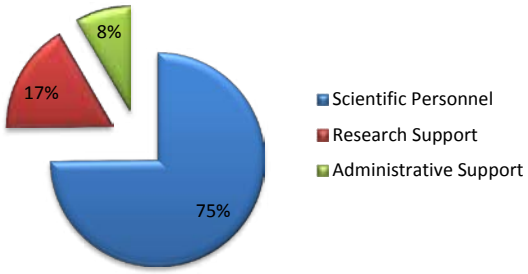


CPR papers published in journals with impact factor ≥10 (impact factors are given in brackets).

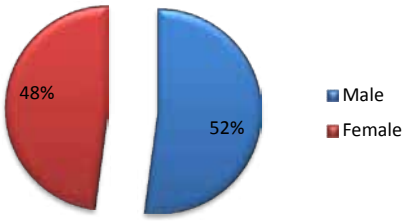
CPR Key Facts

The diagrams represent key data about CPR from 2014.

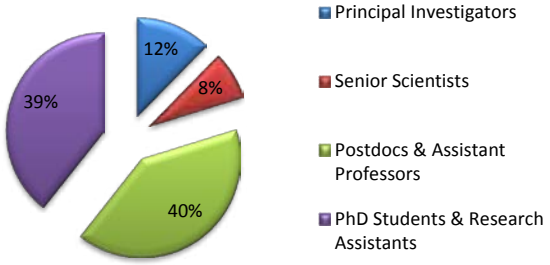
Staff



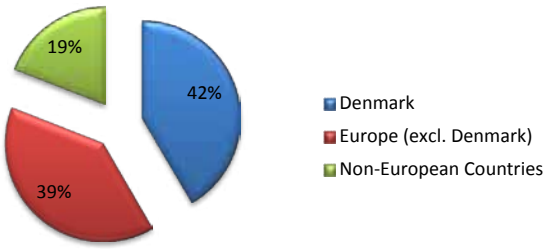
Gender distribution



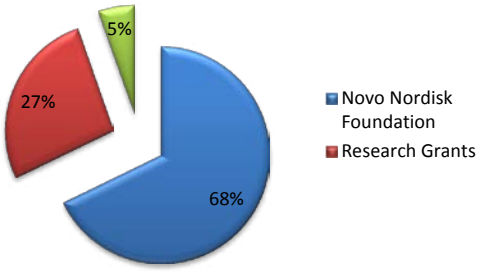
Scientific Staff - Functions



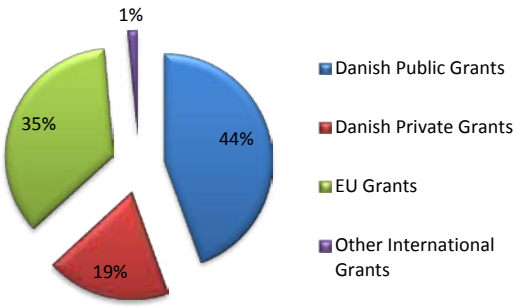
Scientific Staff - Nationalities



Funding 2014



Research Grants 2014



Research Grants and Awards

The following list, summarizes awards and grants that were awarded in 2014.

Awards
Professor Jiri Lukas received the 42nd Léopold Griffuel Award of DKK 0.9 M (€ 0.13 M) from Fondation ARC pour la recherche sur le cancer for 'Lukas' astonishing achievements in the field of DNA damage response and cell cycle'.

Professor Chunaram Choudhary recieved the Danish Cancer Society' Junior Researcher Award DKK 75,000 (€ 10,000)

EU Grants
Professor Niels Mailand received a 5-year Consolidator Grant of DKK 14.9 M (€ 2.0 M) for the project 'Regulation of DNA damage responses at the replication fork'.

Postdoc Godelieve Smeenk received a Marie Curie Intra-European Fellowship of DKK 1.6 M (€ 0.22 M) for the project 'Identification of Novel Regulators of Translesion DNA synthesis in human cells'.

Postdoc Andreas Mund received a Marie Curie Intra-European Fellowship of DKK 1.7 M (€ 0.23 M) for the project 'Identifying Functional Proteins at DNA Breaks with Quantitative Proteomics in Primary Lymphocytes'.

Postdoc Kai Neelsen received a Marie Curie Intra-European Fellowship of DKK 1.7 M (€ 0.23) for the project 'The role of ubiquitin and ubiquitin-like modifiers in replication stress'.

Danish Public Grants
Postdoc Petra Schwertman received a Mobilex grant of DKK 2.1 M (€ 0.28 M) from The Danish Council for Independent Research (Medical Sciences) for the project 'Molecular mechanisms of DNA-protein crosslink repair in genome stability maintenance'.

Postdoc Garry Sedgwick was granted DKK 2.2 M (€ 0.29) from The Danish Council for Independent Research (Medical Sciences) for the project 'Novel Mechanisms Guarding against aneuploidy in human cells'.

Postdoc Louise von Stechow received a Sapere Aude DFF-Research Talent Grant of DKK 2.2 M (€ 0.29 M) from The Danish Council for Independent Research (Medical Sciences) for the project 'Systems biology analysis of DNA damage induced phosphorylation responses in cancer cells'.

Postdoc Luis Toledo received a Sapere Aude DFF-Research Talent Grant of DKK 2.6 M (€ 0.34 M) from The Danish Council for Independent Research (Medical Sciences) for the project 'Exploring replication catastrophe and Replication Protein A as novel players in cancer diagnosis and treatment'.
Associate Professor Simon Bekker-Jensen received a Sapere Aude DFF-Starting Grant of DKK 7.1 M (€ 0.95 M) from The Danish Council for Independent Research (Medical Sciences) for the project 'Writers and readers of ubiquitylated histones in the DNA Damage Response'.

Professor Michael Lund Nielsen received a Sapere Aude DFF-Advanced Grant of DKK 7.0 M (€ 0.94 M) from The Danish Council for Independent Research (Natural Sciences) for the project 'Deciphering the signaling networks of PARP inhibitors by quantitative mass spectrometry'.

Professor Niels Mailand was granted DKK 2.6 M (€ 0.34 M) from The Danish Council for Independent Research (Medical Sciences) for the project 'Genome Stability Maintenance at the Replication Fork'.

Professor Lars Juhl Jensen was granted DKK 0.3 M (€ 0.04 M) from The Danish Agency for Science, Technology and Innovation for his project 'Text-mining to identify fusions and classify them according to diseases'.

Danish Private Grants
Professor Chunaram Choudhary received a Hallas-Møller Investigator Award of DKK 11.0 M (€ 1.48 M) from The Novo Nordisk Foundation for the project 'Unraveling the regulatory landscape of lysine acetylation modifying enzymes'.

Professor Jiri Lukas was granted DKK 3.5 M (€ 0.47 M) from The Danish Cancer Society for the project 'Opdagelse af nye cancer gener i den beskrevne del af det humane genom'.

Associate Professor Jakob Nilsson was granted DKK 1.5 M (€ 0.20 M) from The Danish Cancer Society for the project 'How a tumor suppressor protects against aneuploidy and chromosome instability'.

Professor Jesper Velgaard Olsen was granted DKK 1.5 M (€ 0.24 M) from The Danish Cancer Society for the project 'Proteomics analysis of chemotherapy responses of breast cancer cells'.

Postdoc Kathrine Beck Sylvestersen was granted DKK 1.4 M (€ 0.19 M) from The Lundbeck Foundation for the project 'Deciphering the signaling networks of arginine methylation in the DNA damage response by quantitative mass spectrometry'.

Professor Michael Lund Nielsen was granted DKK 1.2 M (€ 0.16 M) from The Novo Nordisk Foundation for the project 'Site-specific and functional characterization of arginine mono-methylation in human cells by quantitative proteomics'.
Professor Jesper Velgaard Olsen was granted DKK 1.0 M (€ 0.13 M) from Fabrikant Vilhelm Pedersen og Hustrus Mindelegat for the project 'Epidermal growth factor receptor (EGFR) signaling in lung tissue: In-depth analysis of the regulated tyrosine phosphorylation network and its biological implications'.

Professor Matthias Mann was granted DKK 2.5 M (€ 0.34 M) from Center for Inflammation and Metabolism, Rigshospitalet, for the project 'The BAT secretome project'.

International Grants
Postdoc Rajat Gupta was granted DKK 0.3 M (€ 0.05 M) from European Molecular Biology Organization (EMBO) for a Long-Term Fellowship.

Staff

A comprehensive list of employees (106) and affiliated personnel; guest researchers, laboratory assistants, bachelor- and master's students (18) organized by research program and group. The list also includes employees that left or joined CPR in 2014.

Protein Signaling Program
Program Director: Jiri Lukas

Chromosome Stability and Dynamics
Jiri Lukas
Group Leader, Professor

Claudia Lukas
Professor

Luis Toledo Lazaro
Postdoc

Kai Neelsen
Postdoc

Matthias Altmeyer
Postdoc

Fena Ochs
PhD Student

Thorkell Gudjónsson
PhD Student

Ronni Sølvhøj Pedersen
PhD Student

Merete Grøfte
Technician

Maj-Britt Druedahl Rask
Technician

Andreas Willems
Laboratory Assistant

Emilie Baron
Master Student

Protein Imaging Platform
Claudia Lukas, Professor,
Professor, Platform Leader

Jutta Bulkescher
Technical Assistant

Gopal Karemore
Image Analysis Expert

Chromatin Structure and Function
Jeremy A. Daniel,
Group Leader, Associate Professor

Linda Starnes
Postdoc

Su Dan
Postdoc

Andreas Mund
Postdoc

Ewa Ohlsson
Postdoc

Valentyn Oksenych
Postdoc

Cody Colon-Berezin
Research Assistant

Rebeca Soria
Technician

Christian Dirk Buch
Laboratory Assistant

Laura Pikkupeura
Master student

Mitotic Mechanisms and Regulation
Jakob Nilsson
Group Leader, Associate Professor

Daniel Hayward
Postdoc

Thomas Kruse
Postdoc

Garry Sedgwick
Postdoc

Gang Zhang
Postdoc

Tiziana Lischetti
Postdoc

Julie Schou
Postdoc

Marie Sofie Yoo Larsen
PhD Student

Jamin Hein
PhD Student

Emil Hertz
PhD Student

Marie Winther Sørensen
Laboratory Assistant

Dimitriya Hristoforova Garvanska
Master Student

Molecular Endocrinology
Amilcar Flores-Morales
Group Leader, Professor

Diego Iglesias
Postdoc

Kim Hjorth-Jensen
Postdoc

Indranil Paul
Postdoc

Charlotte Lavallee
PhD Student

Cecilie Berglund Ove
Laboratory Assistant

Ubiquitin Signaling
Niels Mailand
Group Leader, Professor

Simon Bekker-Jensen
Associate Professor

Tina Thorslund
Associate Professor

Yasuyoshi Oka
Postdoc

Godelieve Smeenk
Postdoc

Petra Schwertman
Postdoc

Sara Lund Poulsen
Postdoc

Wenjing Zheng
Postdoc

Ian Gibbs-Seymour
Postdoc

Jannie Rendtlew-Danielsen
Postdoc

Bine Hare Villumsen
PhD Student

Stine Smedegaard
PhD Student

Saskia Hoffmann
PhD Student

Anita Ripplinger
PhD Student

Maxim Tollenaere
PhD Student

Rebecca Kring Hansen
PhD Student

Peter Haahr
PhD Student

Louise Nilausen
Master student

Julie Nielsen
Laboratory Assistant

Disease Systems Biology Program
Program Director, Søren Brunak

Big Data Management Platform
Lars Juhl Jensen
Professor, Platform leader

Rebeca Quinones
Computer Specialist

Cellular Network Biology
Lars Juhl Jensen
Group Leader, Professor

Jan Refsgaard Nielsen
PhD Student

Alberto Santos Delgado
PhD Student

Helen Cook
PhD Student

Xiaoyong Pan
PhD Student

Christina Kjær
PhD Student

Sandra Walsh
Master Student

Enric Mosella
Bachelor Student

Translational Disease Systems Biology
Søren Brunak
Group Leader, Professor

Thomas Blicher
Associate Professor

Anders Boeck Jensen
Postdoc

Sabrina Gade Ellesøe
PhD Student

Kalliopi Tsafou
PhD Student

Christian Simon
PhD Student

Isa Kirk
PhD Student

Karl Robert Gunnar Eriksson
PhD Student

Freja Karuna Hemmingsen Sørup
PhD Student

Andreas Bok Andersen
Research Assistant

Jessica Xin Hu
Research Assistant

Cecilia Engel Thomas
Research Assistant

Rafal Wolanin
IT Programmer

Proteomics Program
Program Director: Matthias Mann

Mass Spetrometry Platform
Michael Lund Nielsen
Professor, Platform Leader

Dorte Breinholdt Bekker-Jensen
Mass Spectrometry Specialist

Aske Wulff Helge
Laboratory Assistant

Sofie Føns
Laboratory Assistant

Clinical Proteomics
Matthias Mann
Group Leader, Professor

Atul Deshmukh
Postdoc

Mass Spectrometry for Quantitative Proteomics
Jesper Velgaard Olsen
Group Leader, Professor

Chiara Francavilla
Postdoc

Alicia Lundby
Postdoc

Christian Kelstrup
Postdoc

Louise von Stechow
Postdoc

Stephanie Munk
Postdoc

Tanveer Singh Batth
PhD Student

Kristina Bennet Emdal
PhD Student

Jón Otti Sigurðsson
PhD Student

Rosa Rakownikow Jersie-Christensen, PhD Student

Moreno Papetti
PhD Student

Anna-Kathrine Pedersen
PhD Student
Anna Fontaki
Research Asssistant

Abida Sultan
Academic Employee

Proteomics Technology Development and Application
Michael Lund Nielsen
Group Leader, Professor

Clifford Young
Postdoc

Rita Martello
Postdoc

Kathrine Beck Sylvestersen
Postdoc

Stephanie Jungmichel
Postdoc

Sara Charlotte Larsen
PhD Student

Meeli Mullari
Research Assistant

Elisabeth Jakobsen
Technician

Maria Vistrup Madsen
Laboratory Assistant and Master's Student

Proteomics and Cell Signaling
Chunaram Choudhary
Group Leader, Professor

Wai Kit Chu
Postdoc

Christian Schölz
Postdoc

Brian Weinert
Post doc

Thomas Wild
Post doc

Rajat Gupta
Postdoc

Takeo Narita
Postdoc

Vytautas Iesmantavicius
PhD Student

Shankha Satpathy
PhD Student

Protein Structure Program
Program Director:
Guillermo Montoya

Protein Production and Characterization Platform
Guillermo Montoya
Professor, Platform leader

Andrea Lages Lino Vala
Academic Coordinator

Giuseppe Cazzamali
Academic Coordinator

Werner Streicher
Academic Coordinator

Irina Pozdnyakova
Academic Research Technician

Alison Lilley
Technician

Tasja Ebersole
Technician

Michael Ross Williamson
Technician

Havva Koc
Technician

Khalid Pardes
Technician

Motiejus Melynis
Technician

Christina Lenhard
Technician

Mia Funk Nielsen
Technician

Mille Egeberg Ottosen
Laboratory Assistant

Protein Function and Interactions
Mats Wikström
Group Leader, Associate Professor

Jesper Langholm Jensen
Postdoc

Carl Diehl
Postdoc

Magdalena Wisniewska
Postdoc
Anne Sofie Wanscher
PhD Student

Sofia Møller
Master Student

Macromolecular Crystallography
Guillermo Montoya,
Group Leader, Professor

Gulnahar Mortuza
Associate Professor

Pablo Mesa
Associate Professor

Stefano Stella
Associate Professor

Pablo Alcón Hernandez
PhD Student

Dario Hermida Aponte
PhD Student

Ganesha Pandian Pitchai
PhD Student

Elisabeth Bragado Nilsson
Academic Research Technician

Kamila Kamuda
Laboratory Assistant

Center Administration
Head of Administration, & Finance
Peter Dyrsting

Nanna Christoffersen
Research Coordinator

Camilla Johansson
HR Consultant

Mette Efland
Personnel Administration Assistant

Lotte Skipper
Information Officer

Bente Larsen Jensen
Purchase Coordinator

Johannes Ali Klint
Laboratory Support

Ivan Jensen
Laboratory Attendee

Sorin Daescu Andersen
Academic Officer

Tracy Davis
Service Assistant

Carina Rask
Service Assistant

Publications

A comprehensive list of papers published in 2014, including papers published online ahead of print in 2014. Papers published online ahead of print in 2013 were included in the annual report for 2013.

1. **Genome-wide association study identifies three novel genetic markers associated with elite endurance performance**
   Ahmetov, .I, Kulemin, N., Popov, D., Naumov, V., Akimov, E., Bravy, Y., Egorova, E., Galeeva, A., Generozov, E., Kostryukova, E., Larin, A., Mustafina, L., Ospanova, E., Pavlenko, A., Starnes, L., Żmijewski, P., Alexeev, D., Vinogradova, O., Govorun, V. (21 Oct 2014) Biology of Sport. 32, 1, p. 3-9

2. **Renal-Retinal Ciliopathy Gene Sdccag8 Regulates DNA Damage Response Signaling**
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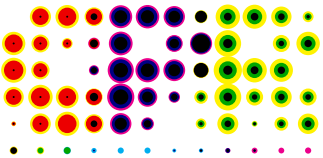

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