NCMM

Centre for Molecular Medicine Norway

Nordic EMBL Partnership for Molecular Medicine

ANNUAL REPORT 2013

FROM DISEASE MECHANISMS TO CLINICAL PRACTICE

Photo: Jarle Nyttingnes

CONTENTS

OVERVIEW BY THE DIRECTOR

Dear friends, colleagues and supporters of NCMM,
I am proud to present the 2013 Annual Report from NCMM, which summarizes the activities in the 4th full year of operations at NCMM. Although NCMM is still very young, the Centre has grown rapidly in terms of mass and production during these first four years as described below and which holds great promise for the future.

NCMM Director Kjetil Taskén.
Photo: Jarle Nyttingnes

RECENT PROGRESS - Review of 2013

STAFF AND FUNDING

At the end of 2013, after its fourth full year of operation, NCMM had **96 employees** (77 employees excluding Founding partners). NCMM has within its fourth year of full operation reached its planned size. **Extramural funding** reached 45 mNOK in 2013 (including Founding partners), exceeding the core NCMM budget by almost 2:1 (including founding partner grants). Extramural funding is expected to continue to grow and is estimated to reach 47 mNOK (excluding Founding partners) in 2014.

SCIENCE AND PUBLICATION OUTPUT

NCMM PIs reported around 60 NCMM-affiliated papers (44 papers ex. Founding Partners) published in 2013 and the first quarter of 2014, including papers in Nature Rev Cancer, Nature Genetics, Nature Medicine, EMBO J., Physio. Rev., Cancer Res., Autophagy, Blood and other journals. NCMM investigators (ex. Founding partners) have also filed patents, have started new commercialization projects and report a number of appearances in popular media. The breadth and depth of the research that now goes on in NCMM is very exciting and spans from molecular mechanisms regulating normal physiology and contributing to disease to prognostic studies, looking at association of disease markers and clinical outcome as well as involvement in clinical intervention trials.

TRANSLATIONAL RESEARCH

As of Q1 2014 NCMM PIs (ex. Founding partners) lists **30 observational or interventional clinical studies** in the areas of therapy and disease mechanisms as well as in the molecular markers, diagnostics and monitoring areas. The extent of clinical collaborations and translational and clinical studies after only 4 years is, in my view as well as in that of the external evaluation committee and the Scientific Advisory Board, quite impressive.

NCMM MIDTERM EVALUATION

The NCMM midterm evaluation took place in Oslo with a site-visit on May 6 and a hearing on May 7 2013. The Committee's report was released from the Research Council of Norway (RCN) in September 2013. The evaluation was carried out by an external, international committee. In addition, EMBL General Director Iain Mattaj was present as an observer.

The Committee's report included a summary, presentation of the committee and evaluation of NCMM and its activities in accordance with the mandate and the template given by the Research Council of Norway (RCN). The Committee based their report on submitted material as well as the site-visit and hearing on May 6-7. Submitted material included self-evaluations of the Centre as well as each research group in accordance to the template provided by the RCN. Furthermore, additional information was submitted on the request of the Committee.

The NCMM Board perceived the evaluation report as a thorough and balanced review of the activities taking place at NCMM and was very satisfied with the fact that the Centre is declared a clear success already after the first 5-year period. Furthermore, NCMM was very pleased with the stated support in the report to the Centre's management, recruitment of group leaders, scientific production in the first five-year period as well as establishment of infrastructure and translational research activities (for more information see separate section).

In summary, the Committee unanimously recommended that NCMM is allowed to run for a second five-year period and that funding should be strengthened to consolidate the success already achieved, to ensure further growth and to build up strategic areas in order to come above critical mass. The Committee believes that this is crucial for the Centre to obtain an increased reputation and visibility internationally. All NCMM's owners have now decided to fund the Centre for a second five-year period (2015-2019) and final negotiations are currently taking place to determine the budget for this period.

COLLABORATION AND NETWORKS

As a part of the focus on translational research, NCMM Group Leaders are all established with **adjunct appointments** in clinical or para-clinical departments at Oslo University Hospital (OUH). This involves increasing interactions and collaborations with Departments of Neurology, Urology, Infectious Diseases, Hematology and Institutes of Experimental Medicine and Cancer Research (Departments of Cancer Prevention and Genetics), illustrating the breadth of application and extension of the molecular medicine research going on in NCMM. Furthermore, NCMM has close links with the Biotechnology Centre as well as additional collaborations across Norway. In fact, NCMM group leaders report some **60 national collaborations**. The experience after 2-4 years with these affiliations is that they facilitate clinical collaborations, give group leaders better access to patient materials, biobanks and clinical trials and are crucial to facilitate translational research.

A network of **NCMM Associate Investigators** was established in 2010 and these appointments, subject to application and evaluation by a Selection Committee, are based on scientific excellence and translational merit as well as added value and compatibility with the NCMM mission. The network was extended in 2011, bringing the total number of outstanding senior Norwegian scientists affiliated with NCMM to 12. Collaborations with this group have been boosted by joint meetings and by a seed money program initiated by the NCMM Board to foster collaborative projects. A call for funding from the NCMM Program for networking with Associate Investigators was published in the end of 2013, resulting in funding of 7 new collaborative projects between NCMM PIs and AIs from March 2014. Furthermore, in 2014 there will also be a call for selection of new Associate Investigators where already appointed AIs can apply for renewal and where the Founding partners and new, outstanding researchers are welcome to apply. NCMM has also initiated a Young Associate Investigator program.

On the **European and international arenas**, NCMM investigators now enjoy numerous collaborations across the world (more than **60 international collaborations** reported). Research interactions with the three other nodes in the Nordic EMBL Partnership and the EMBL are also increasing rapidly. Implementation at NCMM of the practices of the parent EMBL in recruitment and rotation of staff at all levels also offers the opportunity of recruiting top talent at all levels on an international arena.

FUTURE PROMISE

As evident from the present report, NCMM is still in the building-up phase as a new centre with a focus on young investigators. However, with the excellent set of brilliant young Group Leaders recruited at an international arena, I am sure NCMM is at the start of a very interesting endeavor with great potential for future excellence originating from its own research and there are clear signs of that coming through. A first milestone was reached when NCMM in 2013 completed its midterm evaluation with a positive outcome and the Centre is now looking forward to the next five-year period from 2015.

In summary, the Nordic EMBL Partnership in Molecular Medicine holds great promise for collaboration and joining forces by drawing on each other's strengths. Lastly, as a national centre for molecular medicine with responsibility to build networks and facilitate translational research, NCMM with its National Reference Group and Network of NCMM Associate Investigators is a tool that can be used to foster collaboration and excellence in research which partners across Norway are invited to take ownership to and utilize.

April 2014

Kjetil Taskén
Director of NCMM

NCMM HISTORY IN BRIEF

The Centre for Molecular Medicine Norway (NCMM) is part of the Nordic EMBL Partnership for Molecular Medicine which was established in 2007 as a joint venture (2008-2012) between the European Molecular Biology Laboratory (EMBL) and the Universities of Helsinki, Oslo and Umeå and involved the creation of national sister centres in the three countries. The Partnership between EMBL, the Institute for Molecular Medicine Finland (FIMM, www.fimm.fi), the Centre for Molecular Medicine Norway (NCMM, www.ncmm.uio.no) and the Laboratory for Molecular Infection Medicine Sweden (MIMS, www.mims.se) is dedicated to the growing field of Life Sciences that investigates the molecular basis of disease and explores molecular and genetically based treatments. The Danish Research Institute of Translational Neuroscience (DANDRITE, www.dandrite.au.dk) joined the partnership as the Danish node in 2013 when a new Partnership Agreement was signed for 2013-2022.

The Partnership is a coordinated Nordic research infrastructure network that capitalizes on regional, complementary strengths in the Nordic countries and each of the four partner nodes brings in a unique set of expertise, skills and facilities encompassing EMBL's recognized research strengths in the areas of molecular, cellular and developmental biology, bioinformatics and structural biology. Altogether, the Nordic EMBL Partnership constitutes a coordinated Nordic infrastructure for enhancing molecular medicine scientific findings through a translational research pipeline, putting scientific discoveries into clinical use in an efficient way and equipping the partners to tackle some of the most challenging problems of biomedicine.

NCMM was formally inaugurated as a joint venture between the University of Oslo, as host, the Research Council of Norway and Health Region South East upon signing of the contract and consortium agreement at the end of 2008. The overall objective of NCMM is to conduct cutting edge research in molecular medicine and facilitate translation of discoveries in basic medical research into clinical practice. NCMM focusses particularly on disease mechanisms where Norway has clear strengths and investigates mechanisms of non-communicable diseases such as cancer, cardiovascular and CNS-related disease and immune disorders. NCMM develops and adapts technologies for personalized medical applications and has unravelled new diagnostic methods and drug targets. Furthermore, NCMM is a national partner in both the EU-ESFRI project European Advanced Translational Infrastructure (http://www.eatris.eu) planning the future of translational research in Europe and the EU-ESFRI project EU-OPENSCREEN (Chemical Biology, http://www.eu-openscreen.eu).

NCMM had its first full operational year in 2010 and a midterm evaluation carried out by an external, international committee took place in 2013. The committee recommended that NCMM should be continued for a second five-year period and that funding should be strengthened to consolidate the success already achieved, to ensure further growth and to build up strategic areas in order to come above critical mass. The committee further stated that continued focus and resources to consolidate and strengthen NCMM is crucial for the Centre to continue to build reputation and visibility internationally.

INCOME AND EXPENSES

The NCMM core funding in the first five-year period (2009-2013) was 27 million Norwegian kroner (mNOK) (approximately 3.7 mEUR) per year from the 3 consortia partners UiO, Research Council of Norway and Health SouthEast, the regional health authority for Southern and Eastern Norway. Core funding at the same level has also been secured for the interim year 2014 and NCMM's partners have also committed to fund the centre for a second five-year period (2015-2019). Final budget negotiations are currently taking place. Furthermore, overhead and production-based income comes in addition, which was 1.7 mNOK in 2013. Including transferred funds, NCMM spent 31.5 mNOK in 2013. For 2014, NCMM has a budget aiming for balance and plans to spend 31 mNOK. For the period 2015-2019 we stipulate the NCMM annual core budget expenses to be in the order of 35 mNOK (2015-value) with the present level of activity.

NCMM extramural funding in the form of grants to the group leaders and other competitive funding (excluding Founding Partners) was approx. 7 mNOK in 2010, 23 mNOK in 2011, 31 mNOK in 2012 and reached 35 mNOK in annual grants in 2013. This includes grants from the Research Council of Norway, Norwegian Cancer Society, Health SouthEast, European Commission, NIH, competitive grants at UiO and private foundations and organizations such as the Lundbeck Foundation, Novo Nordic Foundation, Novo Seed, Carlsberg Foundation, KG Jebsen Centres, Movember and others.

The Nordic nodes within the EMBL Nordic Partnership are also supported by Nordforsk as a Nordic Network of National Centres of Excellence. This network, *Nordic Molecular Medicine Network* (NMMN), promotes collaboration and exchange between FIMM, NCMM, MIMS, Dandrite and EMBL.

Photo: Ola Sæther, UiO

The Evaluation of NCMM was organized by the Research Council of Norway. Special Advisor Marianne Grønsleth was present at both the site-visit and the hearing in May 2013.

NCMM EVALUATION

- Declared a clear success already after the first 5-year period

The NCMM midterm evaluation took place in Oslo in May 2013 with both a site-visit and a hearing. The Committee's report was released from the Research Council of Norway in September 2013. A strong support to management, recruitment and scientific production as well as translational research activities is expressed throughout this report.

The evaluation was carried out by an international, external committee consisting of Prof. Matthew Albert (Institute Pasteur, Paris, France), Prof. Margaret Frame (University of Edinburgh, UK) and Prof. Thomas Perlmann (Karolinska Institute, Sweden). In addition, EMBL General Director Iain Mattaj was present as an observer.

The Committee's evaluation report includes a summary, presentation of the committee and evaluation of NCMM and its activities in accordance with the mandate and the template given by the Research Council of Norway (RCN). The report is based on submitted material as well as the site-visit and hearing on May 6-7. Submitted material included self-evaluations of the Centre as well as each research group in accordance to the template provided by the RCN. Furthermore, additional information was submitted on the request of the Committee.

NCMM perceives the report as a thorough and balanced review of the activities taking place at NCMM and are very satisfied with the fact that the Centre is declared a clear success already after the first 5-year period. Furthermore, we are pleased with the stated support in the report to the Centre's management, recruitment of group leaders, scientific production in the first five-year period as well as establishment of infrastructure and translational research activities.

The Committee points out the need for mentoring of group leaders by increasing the presence of more senior scientists at the Centre. Furthermore, the Committee addresses the need to build up expertise and capacity in statistics, bioinformatics and systems biology. It is also pointed out that rotation of group leaders must be planned carefully. These recommendations are all in line with needs also identified previously by the NCMM Scientific Advisory Board. The Committee also points out that additional funding will be required in order to follow up these needs. NCMM believes that this could strengthen the Centre significantly if done in close collaboration with the Centre's owners and board.

The Evaluation Committee highlights NCMM's strong potential. Furthermore, it is pointed out that in order to continue recruitment and renewal processes also in the next five-year period, funding predictability is required also beyond the second five-year period. In summary, the Committee unanimously recommended that NCMM is allowed to run for a second five-year period and that funding should be strengthened to consolidate the success already achieved, to ensure further growth and to build up strategic areas in order to come above critical mass. The Committee believes that this is crucial for the Centre to obtain an increased reputation and visibility internationally.

MLS UiO
Molecular Life Science
- an multifaculty priority research area at UiO

GREETINGS FROM MOLECULAR LIFE SCIENCE (MLS^{UIO})

We have behind us an important year for NCMM. The conclusions of the NCMM midterm evaluation were very positive and reassuring, confirming that the Centre is on an upward track. The international committee congratulated both the Centre and its management for their achievements in a short period of time. Similar appraisal is heard from the NCMM Scientific Advisory Board. Furthermore, in 2013 the Research Council announced a call dedicated to young research talents. In this competition, NCMM group leaders scored very high compared to the limited size of the Centre. For the University of Oslo (UiO) and the interfaculty initiative MLS^{UiO}, under which NCMM is organized, these achievements provide a very clear message: establishing NCMM as a joint effort between UiO and the Health South East authorities (HSE) was a correct initiative. The management of the Centre, and in particular its Director Kjetil Tasken, deserves full credit for having succeeded in transforming a brave idea into real practise, shaping a new centre of international visibility from the scratch.

This year is also a year where many decisions affecting the future of NCMM will be taken. UiO is about to adopt a new strategy for the Life Sciences. Several of the key ambitions of this strategy are clearly in line with how NCMM operates. International recruitment of young research talents is an important ambition for a university having as its objective to be a leading European research university. So are building of networks with prestigious research institutions. We are pleased to see that NCMM has attracted researchers from very prominent institutions, such as Cambridge and MIT. The link that NCMM provides to the prestigious EMBL is in accordance with the ambitions of UiO. Furthermore, novel networks are also being established regionally, nationally as well as at the Nordic level. Being part of the Nordic EMBL Partnership for Molecular Medicine, with close links to EMBL-affiliated centres in Finland, Sweden and Denmark, allows for access to both infrastructure and collaborations with excellent researchers.

On the university side, NCMM has been organized under MLS^{UiO}, a multifaculty priority research area at UiO. This umbrella initiative will be reorganized in 2014 and it remains to be decided precisely how NCMM and the Biotechnology Centre of Oslo will be placed in a new organizational structure. However, regardless of this, the successful concept on which NCMM is built, will be continued and developed further.

NCMM is a highly appreciated instrument for the strategy of the University of Oslo. NCMM has shown through its activities that it is able to meet UiO's great expectations and ambitions and we wish the Centre a continued success in the years to come.

On behalf of MLS^{UiO}

Professor
Odd Stokke Gabrielsen
MLS^{UiO} Chair

2013 EVENTS

SAB Visit
(February)

The SAB visited NCMM in February 2013 as well as in March 2014. In addition to scientific presentations and discussions with group leaders, the director and NCMM Board, the SAB also enjoyed a scientific lunch with NCMM PhD fellows and postdocs.

Evaluation
(May)

The NCMM midterm evaluation took place in May and included a site-visit as well as a hearing at the Research Council of Norway. The Centre was declared a success already after its first 5-year period (see separate section).

Visits to EMBL
(June/Feb 14)

A group of 20 PhD fellows and postdocs representing all the Nordic EMBL Partnership nodes visited the EMBL in June. In addition, administrative staff from all the Nordic nodes enjoyed a two-day visit in February 2014.

Photos: J. Landskron / J. Lorentzen (NCMM, UiO) and M. Kainisto

National PhD Course
(November)

The annual two-week national PhD course in Molecular Medicine (MF9120BTS) was organized in November. In 2013, topics of the course included disease mechanisms and development, animal models of disease, biobanks, health registries and biomarker discovery, drug targeting and pharmacology, structure-based understanding of disease and drug targeting, tailored and personalized medicine as well as advanced cell-based therapies.

Scientific Retreat
(December)

In December NCMM and the Biotechnology Center in Oslo organized a joint scientific retreat that took place at Sundvolden Hotel, just outside Oslo. During this two-day event both internal and invited speakers presented both visions and scientific data. The event also offered many opportunities for social activities at dinner and into the small hours.

NMMN Meeting
(September)

In September NCMM hosted the 4th Nordic Molecular Medicine Network Meeting in Oslo. More than 150 participants from all the four Nordic EMBL Partnership nodes as well as from EMBL enjoyed two days of scientific interaction (see separate section).

NCMM GROUP LEADERS

In the period 2009-11 NCMM hired five new young group leaders. In addition, appointed NCMM Director Kjetil Taskén is leading a research group at NCMM.

Dr. **Erlend A. Nagelhus** returned to NCMM in November 2009 from a Research Assistant Professor position at Rochester University, NY. He was formerly affiliated with Centre for Molecular Biology and Neuroscience, a Norwegian CoE embedded in the Institute for Basic Medical Sciences and has also received training as a neurologist. Nagelhus does molecular and functional analysis of glial cells with focus on aquaporins and associated molecules at the brain-blood and brain-liquor interfaces using in vivo imaging techniques. In 2013 Nagelhus was appointed Professor of Medicine (Physiology) at the University of Oslo and he will therefore rotate out from NCMM when his first five-year contract ends in November 2014.

Dr. **Ian G. Mills** was recruited from Cambridge Research Institute, Cancer Research UK, University of Cambridge and started in February 2010. Mills is interested in transcriptional and regulatory networks in prostate cancer and aims to better define the interplay between membrane trafficking, metabolism and transcription in prostate cancer as proteins in regulatory hubs for these processes have potential value as cancer biomarkers and therapeutic targets. Mill's appointment as group leader has recently been evaluated and his position has been renewed for a second five-year period (2015-2019).

Dr. **Jens Preben Morth** was trained in structural biology at the EMBL Outstation in Hamburg and was recruited from Aarhus University to NCMM. His research is in the area of structure and function of membrane transporters. Morth has also started a new program on pH regulation and structure function studies on bicarbonate transporters. His research has relevance to cardiology, neurobiology and kidney diseases. Morth started in October 2010 and will be evaluated for renewal of his appointment as group leader in 2015.

Professor **Kjetil Taskén**, identified by the Research Council as one the founding members of NCMM, served as Interim Director 2008-10 and was appointed Director from January 2011. His research is in the area of cell signaling and immunomodulation with application in immune diseases, inflammation and tumor immunology.

Dr. **Toni Hurtado** did his PhD at the Vall Hebron Hospital in Barcelona and his postdoc at Cambridge Research Institute, University of Cambridge. Hurtado started as a Group Leader at NCMM in August 2011. His research is focused on breast cancer, estrogen sensitivity and the role of co-factors in transcriptional networks.

Dr. **Judith Staerk** trained at the Ludwig Institute for Cancer Research and Catholic University in Brussels, did her postdoc at Whitehead Institute, MIT working with stem cells and started in her NCMM Group Leader appointment in January 2012. Her research is focused on stem cell biology, hematopoetic stem cells and myeodysplastic and myeloproliferative syndromes.

The research groups at NCMM are presented in more detail in the following pages.

Photo: Jarle Nyttingnes

Group leader:
Erlend Nagelhus

Erlend Nagelhus

GLIO-VASCULAR IMAGING GROUP

The Nagelhus group explores roles of glia in neurological disorders by *in vivo* two-photon laser scanning microscopy. This minimally invasive technique offers real-time imaging of physiological and pathophysiological processes in the brains of living animals. Through a cranial window of the thinned skull, the group studies brain-fluid dynamics, calcium signaling in cellular microdomains, cell morphology and motility as well as cerebral blood flow. The overall aim is to gain insight into mechanisms by which glial cells interact with neurons and the vasculature. Understanding neuronal-glial-vascular interactions may provide new treatment strategies for brain disorders involving perturbed circulation and water homeostasis. The group has a longstanding interest in the physiological roles of aquaporin-4 and associated molecules in glial endfeet.

Nagelhus joined NCMM in 2009. His group runs the neuroimaging activity in the Letten Centre at the Institute of Basic Medical Sciences (IMB), Domus Medica. The group has also established a new laboratory, GliaLab, in the Annex of Domus Medica. GliaLab accommodates a two-photon microscope for imaging in awake behaving animals. This microscope is funded by the Research Council of Norway through NORBRAIN: A Large-scale Infrastructure for 21st century Neuroscience. Nagelhus is since 2013 Professor in Physiology at the Faculty of Medicine, and also holds a position as Adjunct Professor at the Department of Neurosurgery, University of Rochester Medical Center, Rochester, New York.

Photo: Jarle Nyttingnes

Group members

Senior engineer:
P. Johannes Helm
Iren Sefland

Researchers:
Vidar Jensen
Anna Thoren
Klas H. Pettersen

Postdoctoral fellows:
John Burkhardt
Wannan Tang

PhD fellows:
Rune Enger
Gry F. Vindedal

Students enrolled in the Medical Student Research Program:
Cecilie E. Bugge
Didrik Bakke Dukefoss
Brana Rosic

Associated members:
Alexander S. Thrane
Vinita Rangroo Thrane
Vigdis Andersen Eidsvaag (PhD student)

SELECTED KEY PUBLICATIONS FROM PI:

Nagelhus EA, Ottersen OP (2013) *Physiological roles of aquaporin-4 in brain*. **Physiol Rev**, 93(4):1543-62.

Rangroo Thrane V, Thrane AS, Wang F, Cotrina ML, Smith NA, Chen M, Xu Q, Kang N, Fujita T, Nagelhus EA, Nedergaard M (2013) *Ammonia triggers neuronal disinhibition and seizures by impairing astrocyte potassium buffering*. **Nat Med**. 19(12):1643-8.

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Group leader:
Ian G. Mills

Ian Mills
PROSTATE CANCER GROUP

Prostate cancer accounts for one third of all male cancer cases in Norway and is the second most signifcant cause of cancer mortality in men in Europe. The goal of the group is to understand the biology of prostate cancer in order to improve detection and treatment. Prostate cancer is driven by the androgen receptor and also characterized by genomic mutations and rearrangements. We have previously reported that the androgen receptor drives the expression of a metabolic gene network[1] and that a subgroup of androgen receptor binding sites associated with aggressive metastatic prostate cancers are tissue-specific. Motif co-enrichment at tissue-specific androgen receptor binding in metastatic disease also suggests that the androgen receptor (AR) may be co-recruited along with pro-inflammatory (NF-kB and STATs) and stem cell-associated (c-Myc and GATA) transcription factors[2]. Genes associated with these sites provide a prognostic signature for progression and include genes regulated by unfolded protein response (UPR) pathways. In lymphoma the PERK-ATF4 arm of the UPR promotes the expression of an autophagy gene, ATG5, and this is necessary to maximize to transformation phenotype induced by c-Myc overexpression[3]. Therapeutically drugs that target not only the AR but also metabolic processes that are regulated by the AR and other oncogenic factors are increasingly being central to the disease[4]. Beyond metabolism, the prostate cancer field is increasingly interested in the interplay between the AR and other transcription factors/co-regulators with the aim of enhancing the efficacy of therapeutics particularly in castrate-resistant disease and enhancing pro-apoptotic stress responses in cancer cells[5].

AUTOPHAGY AND STRESS RESPONSES

We have established assays to assess the UPR and autophagy in prostate cancer cells (Nikolai Engedal)[6]. Autophagy assays now include functional measures of autophagic activity and using these, we are able to show that there is a significant distinction between the induction of expression of autophagic and ER stress markers when cells are challenged versus autophagic flux, which can be simultaneously inhibited6. These assays form an important basis for drug screening to dissect the contribution of autophagy and ER stress responses to castrate resistance, CAMKK2 inhibition and resistance to chemo- and radiotherapy (Nikolai Engedal, Morten Luhr, Lisa Gerner). We have been joined by Professor Per Seglen as a Guest Researcher who has pioneered the autophagy field and the assays and inhibitors used to assess it[7-10].

C-MYC GLYCOSYLATION AND STRESS RESPONSES

Stress responses significantly affect protein stability and are also modulated by glycosylation. In the last year we have identified AR target genes in the hexosamine biosynthesis pathway (HBP) which generates an aminosugar conjugate, UDP-GlcNAc, to support N-linked glycosylation in the ER and OGlcNAcylation of intracellular proteins which can occur in the cytoplasm and nucleus (Harri Itkonen, Ingrid Guldvik)[11,12]. Changes in the expression of HBP enzymes change the intensity of the ER stress response and the expression of activity of OGlcNAc transferase (OGT), which utilizes UDP-GlcNAc as a substrate and impacts significantly on the protein turnover of important oncogenes, including c-Myc. Future work will focus on a more systematic characterization of glycome response to drug treatments and the generation and characterization of glycosylation site-specific antibodies both as biomarkers and laboratory research tools (Collaborators: Detroit R&D Inc, Professor Gerald Hart, Johns Hopkins and Professor Bernd Thiede, UiO). A key question is whether sugar-modified oncogenes interact with the same protein complexes and DNA sequences as the total oncogenic pool in cells. As reported c-Myc stability is affected by OGT inhibition and in other studies we are utilizing a range of metabolic and epigenetic inhibitors to reduce c-Myc expression and activity in prostate cancer cells either by silencing enhancers using epigenetic inhibitors or by imposing metabolic stress by drugging c-Myc target genes (Alfonso Urbanucci, Stefan Barfeld).

BIOMARKERS

We continue to work on biomarker discovery supported by the Movember Foundation and the Norwegian Cancer Society (Ingrid Guldvik). Collaborating with the Janus Serum Bank/Norwegian Cancer Registry and Professors Fredrik Wiklund and Henrik Grönberg at the Karolinska Institute (CAPS and STHLM3 cohorts), we are validating protein biomarkers in serum and plasma samples. The discovery phase is supported by Professor Fahri Saatcioglu (UiO/IBV) and the proteomics expertise of Professor Bernd Thiede (UiO/Biotechnology Centre). We are also working to identify pleiotropic genetic risk loci associated with prostate cancer and metabolic syndrome in collaboration with Professor Ole Andreassen (OUS), and have identified significant overlapping risk loci enrichment for prostate cancer and blood lipid traits (Verena Zuber). These will be further validated in Nordic cohorts for which multi-trait and genetic risk data are available.

FOR THE FUTURE:

As we build up a more comprehensive picture of the metabolic and genomic changes underpinning the development of prostate cancer can we generate new disease models that capture the evolution of the disease and allow us to effectively test and incorporate ageing as well as dietary and other environmental factors? Reprogramming primary cells will be critically important to achieve this goal.

Photos: Jarle Nyttingnes

Group members and projects

Postdoctoral fellows:
Kim Nikolai Hartlieb Engedal
– calcium regulation of autophagy
Alfonso Urbanucci
– coregulators of oncogenic transcription factors
Verena Zuber
– pleiotropic and pathway analyses of genome-wide association datasets.

Head engineer:
Ingrid Jenny Guldvik
– biomarker validation

PhD fellows:
Lisa Gerner
– role of CAMKK2 in autophagy
Harri Itkonen
– glycosylating enzymes and pathways in prostate cancer
Stefan Barfeld
– transcriptional regulation by the AR and other transcription factors

Guest Researcher:
Professor Per Seglen - Autophagy

MSc student:
Morten Luhr

External Funding
In addition to NCMM funding, Mills' group is supported by the Norwegian Cancer Society, Molecular Life Sciences (University of Oslo) and two EU FP7 programs: P-CUBE (Infrastructure for Protein Production Platforms) and PRO-NEST (Prostate Research Organizations-Network of Early Stage Training), an EU/Marie Curie Training Network grant. The group also supported by the National Institutes of Health (USA), the Movember Foundation, the Research Council of Norway (FRIMEDBIO and Young Talent Award – Dr. Nikolai Engedal) as well as Helse Sør-Øst (Dr. Alfonso Urbanucci)

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The Mills Lab

Photos: John Hughes

Group Leader:
J. Preben Morth

J. Preben Morth

MEMBRANE TRANSPORT GROUP

The Morth group employs a structural systems biology approach to investigate the proteins involved in acid-base homeostasis and metal ion transport across the cellular membrane.

A variety of techniques are used in order to identify and characterize both soluble and membrane bound proteins involved in pH regulation. A bioinformatics approach is used to target new proteins and interaction partners of interest. X-ray crystallography and several biophysical methods to obtain structural information as well as biochemical techniques are also used, including activity assays and fluorescence spectroscopic measurements.

To study the 3D atomic structure of membrane proteins, the group is currently developing purification and lipid vesicle reconstitution protocols. The aim is to purify and characterize these membrane proteins.

Acid-base homeostasis is fundamental to our understanding of human physiology and is essential to cellular function. The main buffering system found in the human body is based on bicarbonate. The SLC4 proteins are the main facilitators of bicarbonate transport across the plasma membrane, however, not much is known about the structural basis of function and regulation of these. The N-terminal cytoplasmic domain (NTD) of the sodium-coupled chloride bicarbonate exchanger (NCBE), found predominantly in the choroid plexus of the brain, has been cloned, expressed and purified. The core domain found centrally in the NTD has been crystallized and the structure determined at 4.0 Å resolution. The NTD of NCBE is found to contain regions of intrinsic protein disorder and these disordered regions are conserved among all bicarbonate transporters of the SLC4 family. The disordered regions coincide with regions of sequence variation, indicating that although sequence is not conserved, the disorder is.

The system is strongly dependent on the ion gradients maintained by the P-type ATPases. The group therefore aims to develop a complete structural model for anion transport and recognition. Structural analysis of P-type ATPases will continue with focus on the prokaryotic Ca^{2+} ATPases and Mg^{2+} ATPases. In particular, we are focusing on their function as participants in virulence systems. The systems in question originate from *Listeria monocytogenes and Salmonella typhimurium*, and our work on translation in infectious diseases like Salmonella will bridge the gap between lab bench and clinic. Our strong focus on developing in vitro assays to study these particular membrane transporters will allow direct inclusion into the exciting drug screening platforms available both at the Biotechnology Centre (BiO) and elsewhere. Furthermore, these projects benefit from the broad scientific community located in Oslo, focusing on infectious diseases (headed by Anne-Brit Kolstø, School of Pharmacy, UiO and Tone Tønjum, OUH-Rikshospitalet).

Recently, a new translational project focusing on identification of large supramolecular complexes implicated in the Wnt pathway was initiated by the Morth group. We are performing structural studies of a human ADP-ribosyltransferase tankyrase (TNKS), trying to identify novel direct interaction partners by using a proteomics approach in collaboration with Bernd Thiede (BiO). Tankyrases belong to the poly (ADP-ribose) polymerase (PARP) superfamily and are involved in various cellular functions such as telomere maintenance, centrosome maturation, Wnt signaling, embryonic development and the pathogenesis of Cherubism. Our project was initiated by the structure determination of the TNKS PARP domain in complex with of a novel cancer drug candidate developed by Stefan Krauss (NCMM Founding Partner and OUH). We are currently aiming to isolate and characterize the full length tankyrase enzyme, a protein of more than 1200 residues and with several potential and verified interaction partners. We are therefore combining our structural and biochemical studies with cellular assays, using the strong imaging platforms build up by Oddmund Bakke (UiO) and Harald Stenmark (OUH-Radiumhospitalet).

EXTERNAL FUNDING

In addition to NCMM funding, the group is supported by the Lundbeck Foundation, the Carlsberg Foundation, the Norwegian Research Council and the Blix Foundation.

Group members

Postdoctoral fellows:
Harmonie Perdreau Dahl
Kim Langmach Hein

PhD fellows:
Kaare Bjerregaard-Andersen
Saranya Subramani
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Master Students:
Carolina Alvadia
Nina Fagernes

Principal engineer:
Hanne Guldsten

SELECTED KEY PUBLICATIONS FROM PI:
Bjerregaard-Andersen K, Perdreau-Dahl H, Guldsten H, Praetorius J, Jensen JK, Morth JK, "The N-terminal cytoplasmic region of NCBE display features of an intrinsic disordered structure and represents a novel target for specific drug screening" (2013), **Front. Physiol**. - Membrane Physiology and Membrane Biophysics, 4, pp. 320.

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The Morth Lab

Photos: Jarle Nyttingnes, John Hughes

Group Leader: Antoni Hurtado

Antoni Hurtado

BREAST CANCER GROUP

The main interest of my research is to understand the mechanism of hormone resistance in breast cancer. Breast cancer is a heterogeneous disease and tumors are generally classified into ER positive, HER2 positive and the triple negative (TN) subtype, which lacks hormone receptors and HER2. Considering the expression of these two markers, 70-75% of the tumors are ER positive, 20% fall in the group of HER2 positive and the remaining are the TN. Furthermore, half of the HER2 positive tumors are also ER positive. Patients can be treated with therapies that target these factors, which are known to induce proliferation. However, patients can also become resistant to these therapies and this is the main cause of metastasis and death in breast cancer.

We have previously demonstrated that cooperative transcription factors are crucial for regulating ER function. Importantly, it provides a unique opportunity for modulation of their function in hormone-resistant breast cancers. Therefore, the interest of my group is focused in identifying and characterizing the action of these factors.

RESEARCH OF THE GROUP

HER2 and PI3K kinases control FOXA1 induced proliferation in breast cancer: Implications in hormone resistance

The FOXA1 transcription factor is expressed in all ER and HER2 tumors and its expression is associated with proliferation, metastasis and differentiation. Recently, we have identified the HER2 signaling pathway as a direct regulator of FOXA1 function both in HER2+/ER+ as well as in HER2+/ER- breast cancers subtypes (Katika et al, manuscript in preparation). By means of specific inhibitors targeting the kinase activities of MEK and PI3K/mTOR we have identified the HER2 signaling pathway as a key regulator of FOXA1 function in the HER2+ breast cancer subtype. Furthermore, we have revealed that FOXA1 executes a transcriptional program that controls proliferation, apoptosis and metastasis in breast cancer. Importantly, the treatment of cells with specific ligands for HER3/HER2 dimers (Heregulin) induces ER-independent growth. However, this growth is still FOXA1-dependent. As mentioned, endocrine resistance is a significant problem in breast cancer treatment. One of the few validated features of hormone resistance is the hyper-activation of the HER2/HER3 pathway. We now provide evidence that FOXA1 activated by the HER2/HER3 pathway induces growth independently of ER and this might explain hormone resistance. Altogether, these results suggest a new role of FOXA1 inducing transcription of genes crucial for proliferation and under the control of the HER2 signaling pathway. The role of FOXA1 as a direct transcriptional activator in breast cancer is unexpected as FOXA1 is generally associated with pioneering functions of ER. Further studies in human samples are needed to validate this hypothesis.

Identification and characterization of tumor-specific cell signaling pathways regulating FOXA1 functions

Our results have also elucidated that FOXA1 controls apoptosis and metastasis in breast cancer, suggesting that this transcription factor can play different roles in breast cancer and that other cell-signaling pathways, besides HER2 signaling, might be required to control FOXA1 functions. Therefore, we hypothesize that FOXA1 integrates input signals originating from multiple cell-signaling pathways to generate output responses that culminate in control of proliferation, differentiation or metastasis in HER2 as well as in ER breast cancer subtypes. By identifying the entire cell-signaling pathways required for FOXA1 activation and the consequences of its activation, we will be able to elucidate how FOXA1 integrates cellular signals to control tumorigenic processes.

Characterization of the role of CTCF in ER-dependent gene regulation

The estrogen receptor (ER) is a transcription factor playing a major role in ER positive breast cancer. After binding estrogen, it interacts with DNA to activate or repress the transcription of specific genes. Recent research has shown that other factors have an essential role in the regulation of ER transcriptional activity. These proteins include chromatin modifying complexes and proteins involved in the formation of chromatin loops. The interplay between these factors and ER activates a specific transcriptional program which induces breast cancer cell proliferation. CTCF is a transcription factor necessary for long-range intra- and inter-chromosomal interactions. It is able to interact with the nuclear matrix to bring specific genomic regions into the "transcription factories", it can bind insulator/boundary elements to define transcription blocks and it plays a role in the "communication" between gene enhancer and promoter. To understand how estrogen influences CTCF binding at a genome wide level, we performed CTCF ChIP-seq in cell lines after estrogen treatment and observed a redistribution of CTCF chromatin interactions upon estrogen stimulation. Interestingly, we could confirm that our CTCF ChIP experiment represent actively transcribing regions, suggesting an important role for CTCF in the interaction between ER enhancers and active promoters. Currently, we are validating putative chromatin interactions by performing 3C experiments. We also aim to confirm the importance of these enhancers on ER-mediated transcriptional regulation. For that, we will use artificial zinc fingers to tether CTCF with active enhancers. Moreover, this analysis is also helpful in identifying the enhancers and repressors regions playing a crucial role in ER transcriptional regulation.

Identification and characterization of ER cooperating transcription factors

Estrogen may activate or repress transcription of ER target genes potentially by recruiting distinct classes of co-regulators that have chromatin remodeling properties. The estrogen-ER interaction induces conformational changes in ER, enabling binding of co-activators and allowing transcription. Furthermore, the drug tamoxifen is thought to actively repress transcription by recruiting co-repressors. However, the mechanism underlying the ligand specific binding of these co-factors to ER at estrogen-regulated genes is still unknown. Preliminary data of my group point at SNAIL and PAX2 functions as critical cooperating regulators of transcriptional repression induced by tamoxifen. These results suggest that several factors might be cooperating with ER for ligand-specific ER-mediated transcriptional regulation. This project aims to understand the role of PAX2 and SNAIL in the repression of ER target genes. This will be important to understand how tamoxifen- and ER-mediated repression is regulated in breast cancer cells.

EXTERNAL FUNDING

In addition to NCMM funding, the breast cancer group is supported by the Norwegian Cancer Society (post-doctoral position), the University of Oslo (PhD position) and by the NCMM Program for Networking with Associate Investigators and Founding Partners.

Research collaboration:

- Prof. Anne-Lise Børresen-Dale and Dr. Therese Sørlie (Oslo University Hospital) – Crosstalk between FOXA1 and HER2 breast tumors.
- Dr. Anne Jorunn Stokka (Biotechnology Center of Oslo) – Identification and characterization of tumor-specific cell signaling pathways regulating FOXA1 binding to the chromatin.
- Prof. Helga Salvessen (Haukeland University Hospital, Bergen) – Role of FoxA1 in endometrial cancers and response to anti-ER therapies.
- Dr. Meritxell Bellet (Vall-Hebron Research Institute, Barcelona, Spain) – Quantitative methods to predict endocrine response.
- Dr. Julio Saez-Rodriguez (EBI-EMBL, Cambridge, UK) – Computational modeling of transcription factor activity by cell signaling pathways.
- Prof. Vessela Kristensen (Oslo University Hospital) – Breast Cancer susceptibility loci and gene expression.

Group members

Head Engineer:
Siv Gilfillan

Postdoctoral fellows:
Baoyan Bai (from August 2013)
Madhu Katika (until February 2014)

PhD fellow:
Elisa Fiorito

Researchers:
Elena Gonzalez Sanchez (from August 2013)
Yogita Sharma (from July 2013)

MSc student:
Siri Nordhagen (from June 2013)

SELECTED KEY PUBLICATIONS FROM PI AND GROUP:
Hurtado A, Holmes KA, Ross-Innes CS, Schmidt D and Carroll JS. FoxA1 is a key determinant of estrogen receptor function and endocrine response, Nature Genetics, 2011, January.

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The Hurtado Lab

Photos: Jarle Nyttingnes, John Hughes, F. Saggio

Group Leader: Judith Staerk

Judith Staerk

STEM CELL GROUP

The generation of induced pluripotent stem cells from patient and healthy donor cells can be achieved by ectopic expression of four transcription factors: Oct4, Klf4, c-Myc and Sox2. This process resets the somatic genome into a pluripotent epigenetic state that is equivalent to embryonic stem (ES) cells. Our lab uses mouse models, somatic cell reprogramming and genetically modified ES cells combined with proteomics and biochemical assays to understand processes during hematopoietic development. Hematopoiesis describes the sustained production of blood cells, which is guaranteed by the presence of hematopoietic-specific stem cells (HSC) that have the capacity to self-renew and to produce daughter cells that give rise to mature blood cells throughout life.

THE BROAD AIMS OF OUR RESEARCH ARE TO:

1. Identify the transcriptional networks of early human hematopoietic specification.
2. Identify key epigenetic events during hematopoietic development.
3. Identify underlying mechanisms of impaired blood cell differentiation using transgenic mouse models and iPS cells derived from patients suffering from blood disorders.

Photo: John Hughes

Group members

Postodoctoral fellows:
Xavier Tekpli
Ida Jonson

PhD fellows:
Julia-Kristina Madsen-Østerbye
Oksana Svärd

Engineer:
Hasina Hossain

SELECTED KEY PUBLICATIONS FROM PI:

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Lyssiotis CA*, Foreman RK*, Staerk J*, Garcia M, Mathur D, Markoulaki S, Hanna J, Lairson LL, Charette BD, Bouchez LC, Bollong M, Kunick C, Brinker A, Cho CY, Schultz PG, Jaenisch R (2009) *Reprogramming of murine fibroblasts to induced pluripotent stem cells with chemical complementation of Klf4*. **Proc Natl Acad Sci USA.** 106(22):8912-7 (*equal contribution)

Staerk J, Lacout C, Sato T, Smith SO, Vainchenker W, Constantinescu SN (2006) An amphipathic motif at the transmembrane-cytoplasmic junction prevents autonomous activation of the thrombopoietin receptor. **Blood** 107(5):1864-71.

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Group leader: Kjetil Taskén

Kjetil Taskén

– SIGNALING NETWORKS IN HEALTH AND DISEASE

A major goal of the Taskén group is to understand the role of the cAMP second messenger system and other signal networks in the regulation of cellular function and its involvement in disease mechanisms. Furthermore, the group aims to translate this understanding into therapeutic strategies and clinical practice.

One focus is to understand complex intracellular signaling networks and how such networks require anchoring and localization through A kinase anchoring proteins (AKAPs) or other scaffold proteins. The group investigates how these signaling networks mediate hormonally regulated physiological and pathophysiological processes. A second focus is cAMP- and regulatory T cell-mediated immune-modulation with application in immune diseases, inflammation and tumor immunology. In pursuit of this understanding, the group maps signaling pathways, identifies targets, develops tools to perturb signaling (peptidomimetics, small molecular compounds) and provides "proof-of-principle" experiments using specific disease models.

The Taskén group employs a variety of techniques in bioinformatics, proteomics, phospho-flow analysis, chemical biology high-throughput screening assays and genetic tools in order to screen new targets for in vitro and in vivo function. In order to isolate signaling complexes from a variety of targets, including T cells, cardiomyocytes, adipocytes, placenta cells and organelles such as lipid droplets and mitochondria, a chemical genomics approach is used in combination with phospho-proteomics to understand spatiotemporal dynamics of phosphorylation in anchored cAMP signaling complexes organized by AKAPs. Chemical biology screenings identify small molecular compounds for our research. Furthermore, phospho-flow cytometry using fluorescent cell barcoding allows processing of up to 64 samples with different stimulations and perturbations in the same run. Setups and antibody panels are established for mapping T cell signaling pathways, signaling by prostaglandins, cytokines and other inflammatory mediators as well as regulatory T cell pathways that allow mapping of complex signal networks, assessing how inhibitory signals feed in and examining how small molecules perturb such signal networks. Our recent technology developments now also allow flow-based signalling analyses of adherent cells and high-throughput chemical biology screening by flow cytometry.

The group studies cAMP immunomodulation and involvement of regulatory T cells in HIV, mouse AIDS and various cancers where tumor immunology is of significance. Projects include studies of regulatory T cells and anti-tumor immune responses in colorectal cancer and ovarian carcinoma. In addition, cancer and immune cell signaling analyses are being performed by phospho-flow cytometry to find biosignatures and a recent interest is now to rig drug sensitivity screens to explore the possibility to assist treatment choices in individualized cancer therapy. Furthermore, systems biology analyses are applied on the phospho-flow data from single cell signaling as well as from mixed cell populations with Treg immunosuppression.

The improved understanding of signaling networks can be applied to many disease states, including immune-deficiencies, inflammatory disorders and cancers and will promote the development of highly specific pharmaceuticals that maximize their therapeutic value, while minimizing unwanted side-effects.

Current research also includes examination of cAMP and beta-adrenergic signaling in the heart and in adipocytes with relevance to cardiovascular and metabolic diseases, including studies of an AKAP18 signal complex regulating Ca^{2+} re-uptake in sarcoplasmic reticulum and thereby heart rate. Ongoing work includes chemical biology high-throughput screening, subsequent characterization of hits as well as proof-of-concept studies in vivo. Another ongoing project investigates the function of Opa1 in regulating cAMP signaling in liposomes and mitochondria.

In terms of clinical investigations, a fourth clinical intervention study with COX-2 inhibitor in HIV patients (Taskén co-PI) is on-going in collaboration with the Department of Infectious Diseases, Oslo University Hospital (OUH). Furthermore, a clinical intervention study with use of NSAID to block the observed effects of PGE2 in metastatic colorectal cancer is currently under development to assess the secondary prophylactic effect (collaboration with the Dept. of Gastrosurgery, OUS).

EXTERNAL FUNDING:

In addition to support from NCMM and the Biotechnology Centre of Oslo, the Taskén group has funding from a variety of sources including the Research Council of Norway, the Norwegian Cancer Society, Health South-East Regional Health Authority, the EU 7th Framework and ESFRI programmes, Nordforsk, MLSUiO, Novo Nordic Foundation as well as from the K.G. Jebsen Foundation that is funding two new translational research centres starting with Taskén as partner, Jebsen Inflammation Research Centre and Jebsen Centre for Immunotherapy.

COLLABORATORS:

The Taskén group enjoys collaboration with a wide network of more than 20 international collaborators as well as some 20 national collaborators and clinical partners on different projects.

Group members (during 2013 and first quarter of 2014):

Research Scientists:
Einar Martin Aandahl
Johannes Landskron

Postdoctoral fellows:
Aba Isabel Costa Calejo (from Nov. 2013)
Lena Eroukhmanoff
Morten Hagness (from Sept. 2013)
Guro Mørk Johnsen
Anna Mari Lone
Kristina Berg Lorvik (from Oct. 2013)
Maria-Niki Mylanokou
Marie Rogne
Sigrid Skånland
Susanne Weedon-Fekjær
Vanessa L. Wehbi (started Jan. 2014)

PhD Fellows:
Simer Jit Bains (started March 2014)
Aleksandra Đukić (started May 2013)
Stalin C. Gunasekaran
Morten Hagness (Thesis submitted fall 2013)
Nora Lieske
Kristine Moltu
Ellen Østensen

MSc students:
Lise-Lotte Flage-Larsen (started April 2013)

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Chemical Biology Platform:
Anne Jorunn Stokka
David McClymont

SELECTED KEY PUBLICATIONS FROM PI:

Scott, J.D., Dessauer, C.W., Taskén, K. (2013) *Creating order from chaos: Cellular regulation by kinase anchoring.* **Annu. Rev. Pharmacol. Toxicol.**, 53:187-210.

Brudvik, K.W., Henjum, K., Aandahl, E.M., Bjørnbeth, B.A., Taskén, K. (2012) *Anti-tumor Immune Responses Associate with Clinical Outcome in Patients with Liver Metastasis from Colorectal Cancer.* **Cancer Immunol Immunother.**, 61:1045-1053.

Vang, T., Liu, W.H., Delacroix, L., Wu, S., Vasile, S., Dahl, R., Yang, L., Francis, D., Landskron, J., Taskén, K., Tremblay, M.L., Lie, B.A., Page, R., Mustelin, T., Rahmouni,S. Rickert, R.C., Tautz, L. (2012) *Dynamic interaction between lymphoid tyrosine phosphatase and C-terminal Src kinase controls T cell activation*. **Nature Chem. Biol.**, 8:437-46.

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Kalland ME, Oberprieler NG, Vang T, Taskén K#, Torgersen KM. (2011) *T cell signaling network analysis reveals distinct differences between CD28 and CD2 co-stimulation responses in various subsets and in the MAPK pathway between resting and activated regulatory T cells.* **J. Immunol.**, 87:5233-45. (#Corresponding author).

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Oberprieler NG, Lemeer S, Kalland ME, Torgersen KM, Heck AJ, and Tasken K. (2010) *High-resolution mapping of prostaglandin E2-dependent networks identifies a constitutively active PKA node in CD8+CD45RO+ T cells.* **Blood**. 116(13): 2253-2265.

The Taskén Lab

Photos: Jarle Nyttingnes

NCMM ASSOCIATE INVESTIGATORS

NCMM has established strong collaborative links to key scientists and research groups working across Norway to further develop its scientific and technological capabilities and to facilitate translational networking. The Associate Investigator category is meant for outstanding scientists who are currently based in Norway, whose expertise is compatible with the NCMM research areas and who are interested in collaborating with NCMM and in contributing to the building of an NCMM Molecular Medicine and Translational Research Network. Associated Investigators continue to work at their host institutions but are credited an affiliation to NCMM and the Nordic EMBL Partnership.

These appointments, subject to application and evaluation by a Selection Committee, are based on scientific excellence and translational merit. In the first two calls (2009 and 2011), a total of 12 Associate Investigators have been appointed. Nominations are being made for a time period of three years but are renewable. In December 2013 the NCMM Board decided that a third call can be published when the final negotiations for the second long-term budget (2015-2019) have been finalized, given that the budget includes allocations for a national role and networking activities.

We refer to the 2012 annual report for a detailed presentation of NCMM's Associate Investigators:

- **Professor Lars Akslen:** The Gade Institute, Section of Pathology, University of Bergen and Centre for Cancer Biomarkers (CCBIO, Centre of Excellence 2013)
- **Professor Ole A. Andreassen:** KG Jebsen Centre for Psychosis Research (Centre of Excellence 2013), Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo
- **Professor Rolf Bjerkvig:** NorLux Neuro-Oncology, Department of Biomedicine, University of Bergen and Centre de Recherche Public de la Santé, Luxembourg
- **Professor Bjarne Bogen:** Centre for Immune Regulation (CIR, Centre of Excellence since 2007) and Cellular and Molecular Immunology Research Group, Institute of Clinical Medicine, University of Oslo
- **Professor Anne-Lise Børresen-Dale:** KG Jebsen Centre for Breast Cancer Research and Department of Genetics, Institute for Cancer Research, Oslo University Hospital
- **Professor Geir Christensen:** Cellular and Molecular Biology of Myocardial Hypertrophy and Heart Failure, Institute for Experimental Research, Oslo University Hospital and University of Oslo
- **Professor Arne Klungland:** Laboratory for Genome Repair and Regulation, Department of Microbiology, Oslo University Hospital and Institute for Basic Medical Sciences, University of Oslo
- **Professor Per E. Lønning:** Section of Medicine, University of Bergen and Department of Oncology, Haukeland University Hospital
- **Professor Pål R. Njølstad:** KG Jebsen Centre for Diabetes Research, University of Bergen and Haukeland University Hospital
- **Professor Ole P. Rekvig:** Department of Medical Biology, University of Tromsø
- **Professor Helga B. Salvesen:** Department of Clinical Medicine, University of Bergen, Department of Obstetrics and Gynaecology, Haukeland University Hospital and Centre for Cancer Biomarkers (CCBIO, Centre of Excellence 2013)
- **Professor Vidar M. Steen:** Center for Medical Genetics and Molecular Medicine, University of Bergen and KG Jebsen Centre for Psychosis Research (Centre of Excellence 2013)

Photo: Ola Sæther, UiO

NCMM has through the NCMM Program for Networking with Associate Investigators and Founding Partners allocated funding for collaborative projects between NCMM groups and Associate Investigators and Founding Partners. These grants are meant as seed money for new collaborative projects and three calls have been announced in the period 2011-2014. The following collaborative projects have been supported:

GRANT ALLOCATIONS FROM NCMM PROGRAMME FOR NETWORKING WITH ASSOCIATE INVESTIGATORS AND FOUNDING PARTNERS

ASSOCIATE INVESTIGATOR/ FOUNDING PARTNER	COLLABORATING NCMM GROUP	FUNDING YEAR	PROJECT TITLE
Amiry-Moghaddam	Morth	2014	Identification of novel markers of astrocyte heterogeneity
Børresen-Dale	Hurtado	2014	In vivo study of the intratumoral heterogeneity in breast cancer and its impact on therapy response
Christensen	Morth	2014	Structural basis and physiological role of PDE3A1 coupling to SERCA2 in cardiomyocytes
Klungland	Staerk	2014	CRISPR/Cas9 to generate one step knockout and transgenic mouse models
Klungland	Nagelhus	2014	Optogenetic control of brain fluid dynamics and waste clearance
Rekvig	Mills	2014	Prostate cancer: The impact of the anti-apoptotic Trap 1 and pro-apoptotic DNaseI genes on prognosis and therapy resistance
Salvesen	Hurtado	2014	Identification of transcriptional regulatory elements regulated by HDAC inhibitors in advanced endometrial tumors
Andreassen/Steen	Mills	2012	Enrichment methods to improve gene discovery in prostate cancer for functional follow up
Akslen	Mills	2012	Wholegenome sequencing to identify DNA mutations and differential transcription expression in prostate cancers
Bogen	Mills	2012	ER stress responses – underlying mediators and treatment resistance and progression in multiple myeloma and prostate cancer
Klungland	Staerk	2012	The role of 5-hydroxymethylcytosine in hematopoietic stem cell homeostasis and myelodysplastic syndrome pathogenesis
Krauss	Morth	2012	Tankyrase inhibitor –biotarget validation and fine tuning of lead compound
Salvesen	Hurtado	2012	The role of FoxA1 in hormone-resistant endometrial cancers
Akslen	Mills	2011	Detection of biological markers for prostate cancer in urine samples and tumor tissues
Børresen-Dale	Hurtado	2011	Signaling pathways in HER2 positive breast cancers and its crosstalk with Estrogen Receptor
Christensen	Morth	2011	Stress-induced myocardial signaling; indentification of interacting signaling molecules
Krauss	Mills/Morth	2011	The druggable Wnt/ b-catenin proteome: functional implications on stemcellness and cancer.
Steen/Andreassen	Nagelhus	2011	Phenotypic characterization of complement-control deficient mice modelinig the risk of psychotic disorder

NCMM is also in the process of establishing an NCMM Young Associate Investigator category for young talented researchers that are recruited as group leaders/ PIs at another institute and where the conditions are similar to the NCMM model. These Young Associate Investigators will be affiliated with NCMM and NCMM is therefore involved in the recruitment process. The University of Tromsø is in the process of hiring 1-2 Young Associate Investigators and NCMM is looking forward to collaborating with other institutions as well to establish a network of NCMM Young Associate Investigators.

NCMM FOUNDING PARTNERS

Group Leader:
Prof. Mahmood Amiry-Moghaddam

Laboratory for molecular neuroscience

Laboratory of Molecular Neuroscience (LMN) is one of three founding members of NCMM. The research at LMN is focusing on molecular mechanisms involved in the development of acute and chronic neurodegenerative diseases. We aim to unravel the molecular basis for cell death and edema development in stroke and other neurological conditions and to explore the pathophysiology of Alzheimer's disease, Parkinson's disease and temporal lobe epilepsy. Long time goals include to identify new molecular targets for neuroprotective strategies in stroke, epilepsy, Parkinson's disease and Alzheimer's disease and to develop novel approaches for the treatment of brain edema. A special focus of the research in our group is on brain extracellular matrix, astrocyte polarity and the role of aquaporin water channels in the pathophysiology of disease and as possible drug targets in the disease.

Group Leader:
Stefan Krauss

Unit for Cell Signaling

The Unit for Cell Signaling works on druggable interference points in Hh and Wnt/ß-catenin signaling. Hh and Wnt signaling is central in development, in adult stem cell niches and in a broad number of malignant tumors. We have studied aspects of these pathways in different models and are now using developmental signaling pathways to develop selective pathway inhibitors, in particular directed towards canonical Wnt signaling/beta-catenin. In recent years we have developed a series of highly specific Tankyrase inhibitors. To understand the central implication of tankyrase on stemcellness, differentiation and growth, the inhibitors are currently being tested on cancer and stem cell models in vitro and in vivo. One of our drugs (OD270), a highly specific Tankyrase antagonist, has reached lead status and serves at current as industry benchmark. Furthermore, we analyse the role of ß-catenin, p120 and other armadillo proteins in specific cancer cells using zinc finger nuclease (ZFN)-based knockout models. We are also using Chemical Biology as well as ZFNs to study links between Hh and Wnt signaling.

Photo: John Hughes

RESEARCH COLLABORATION WITH OSLO UNIVERSITY HOSPITAL

*NCMM's overall objectives are to conduct research in molecular medicine and facilitate **translation of basic medical research into clinical practice**. In order to enable translational research, NCMM has developed strong links to South-Eastern Norway Regional Health Authority and its subsidiary Oslo University Hospital (OUH).*

Adjunct Appointments

DEPARTMENT OF NEUROLOGY (OUH)
- Group Leader Erlend Nagelhus

The Department of Neurology examines and treats patients with diseases of the brain, spine and peripheral nerves as well as certain muscular diseases. The department has outpatient clinics, hospital wards and laboratories located both at Ullevål Hospital and Rikshospitalet. Research areas within the department include movement disorders, epilepsy, stroke and diseases of the brain's blood supply, MS and other inflammatory diseases of the central nervous system, disorders of the neck and back as well as painful disorders of the peripheral nerves.

DEPARTMENT OF INFECTIOUS DISEASES (OUH)
- Group Leader Kjetil Taskén

The department is the largest of its kind in Norway and covers the entire field in infectious medical conditions, such as tropical medicine, HIV, tuberculosis as well as severe and life threatening bacterial and viral infections. The Department of Infectious Diseases runs an extensive research programme, especially related to the diseases HIV/AIDS and hepatitis. The department is also responsible for a variety of advanced educational courses in infectious diseases.

DEPARTMENT OF CANCER PREVENTION, INSTITUTE FOR CANCER RESEARCH (OUH)
- Group leader Ian Mills (10%)

The Institute for Cancer Research has strong international research groups within biochemistry, cell and tumor biology, genetics, radiation biology, immunology and cancer prevention. For more than 30 years there has been a close interaction between researchers at this institute and cancer surgeons, oncologists and pathologists. The emphasis on translational science has resulted in numerous clinical protocols based on in-house research and the institute is a key partner in the Comprehensive Cancer Center, organizationally under the Division of Surgery and Cancer Treatment at OUH.

DEPARTMENT OF UROLOGY (OUH)
- Group Leader Ian Mills (10%)

The Department of Urology studies and treats surgical disorders of the urinary tract and male genitals. Urology is a comprehensive discipline that requires a high degree of specialized knowledge and high-tech surgical techniques. The development of new treatments in this field is rapid and research and education are therefore a very high priority at the department.

INSTITUTE FOR EXPERIMENTAL MEDICAL RESEARCH (OUH)
- Group leader Preben Morth

The Institute for Experimental Medical Research is primarily focusing on heart disease research as well as teaching. In particular, the institute is performing research on congestive heart failure with a special interest in heart electrophysiology and membrane pumps. The institute is involved in extensive collaborations with other laboratories an clinical departments at the OUH and are interacting with colleagues both nationally and internationally.

DEPARTMENT OF GENETICS, INSTITUTE FOR CANCER RESEARCH (OUH)
- Group Leader Toni Hurtado

The main goal of the department is to follow the linear time course of predisposition, initiation, early stages and advanced disease and to dissect the molecular mechanisms triggered at each stage. Furthermore, the department is focusing on how to follow the multi-dimensional interactions at various levels in a systems biology approach to better perform risk estimation, prognostication and prediction.

DEPARTMENT OF HAEMATOLOGY (OUH)
- Group Leader Judith Staerk

Patients with all types of blood diseases are treated at the Department of Haematolgy. The department's goal is to deliver excellent patient care, provide advanced teaching in the field of blood diseases and perform research of high international standard. Furthermore, the department conducts research in most of the areas in which treatment is provided.

Photo: John Hughes

FROM DISEASE MECHANISMS TO CLINICAL PRACTICE

NCMM group leaders have so far listed 30 on-going operational and interventional clinical studies in the fields of therapy and disease mechanisms as well as in the molecular markers, diagnostic and monitoring areas. An overview of these translational and clinical studies is presented here.

On-going development in the area of therapy

- Immunomodulating cAMP antagonists and PKA anchoring disruptors (immunodeficiency and anti-tumor immune responses)
- Small molecular inhibitors of tankyrase for colorectal and other cancers with an activated Hh-Wnt-b-catenin signaling pathway
- Aquaporin 4 (AQP4) antagonists for brain edema and AQP4 involvement in brain swelling
- Disruption of the PKA-AKAP18-phospholamban-Serca2 complex for cardio-protective effect in ischemia-rep-erfusion damage
- Small molecule inhibitors of OGlcNAc tranferase and de novo purine biosynthesis enzymes to destabilize oncogenic signaling in prostate cancer
- Bromodomain inhibition to enhance responses to androgen deprivation/anti-androgens in prostate cancer.
- Targeting of Na+/K+-ATPase and Serca2 in neurobiology and heart disease
- Suppression mechanisms by regulatory T cells with application in immune diseases, autoimmunity and cancer
- iPSC disease-modeling of blood disorders
- Assay development and structural analysis of the membrane proteins in virulence operon mgtCBR specific to pathogenic bacteria
- Structural analysis of bicarbonate transporters and investigation of pH homeostasis
- Method and pipeline for cancer drug sensitivity screening in chronic lymphatic leukemia, multiple myeloma and ovarian cancer (to start) and glioblastoma (reported)

PROOF-OF-CONCEPT IN HUMANS

- Effect of anti-inflammatory drug (COX-2 inhibitor Phase IIA) on immune function (CD38 o.a.) and vaccine responses in HIV-infected patients.
- Vaccine and radiation in prostate cancer – Ultimovacs Trial.
- Secondary preventive effect of acetyl salicylic acid in metastatic colorectal cancer (to start)

On-going development in the area of diagnostics and monitoring

- Prostate cancer markers – serum/plasma protein biomarkers, overlapping genetic risk factors for prostate cancer and blood lipid traits, transcript-based biomarkers in urine and circulating tumour cells
- New biochemical markers for MAO diseases & early screen Parkinson
- Single cell analysis of inflammatory signaling events by fluorescent cell bar-coded phospho-flow cytometry for diagnostics and monitoring
- Regulatory T cell markers in HIV and other immune diseases
- Flow cytometry-based biomarkers in mitogenic signaling pathways for drug sensitivity screens

Furthermore, NCMM is involved in three translational KG Jebsen Research Centres that were established in 2013. The KG Jebsen Foundation has stated that translational research is of high priority to them and the Norwegian Ministry of Health and Care Services has also highlighted this type of research as an important priority area for strengthening clinical research. NCMM is connected to the KG Jebsen Centres for Breast Cancer Research (led by Prof. Anne-Lise Børresen-Dale), Inflammation Research (led by Prof. Guttorm Haraldsen) and Cancer Immunotherapy (led by Prof. Johanna Olweus).

Photo: Jarle Nyttingnes

RESEARCH HIGHLIGHTS

New knowledge about ammonia's effects on glia cells can change the future treatment of hepatic coma

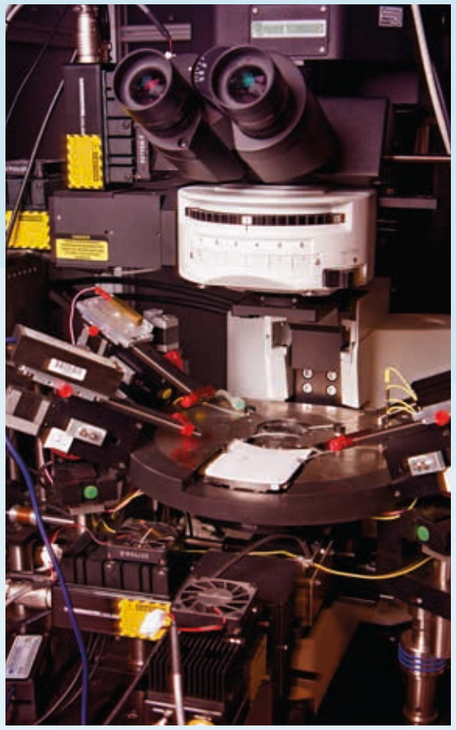


Photo: John Hughes

Ammonia is very toxic to the brain and NCMM group leader Erlend Nagelhus and his colleagues at the University of Rochester Medical Center, New York, recently revealed why: the glia cells' ability to remove potassium ions is disturbed. This finding may result in new treatment of patients with hepatic coma.

Ammonia is an essential building block in amino acids but is also a toxic waste product and in the brain, only glia cells can remove ammonia. High ammonia levels due to e.g. liver failure can result in seizures, coma and death. Nagelhus and colleagues have recently revealed that ammonia exerts its toxic effect by inhibiting potassium transport in glia cells. This leads to an accumulation of potassium in the extracellular fluids and an increased uptake of potassium chloride in nerve cells. Furthermore, this changes the nerve cells' equilibrium potential and thus inhibitory impulses fail. The researchers also demonstrated that ammonia damages can be reduced by using a diuretic drug that blocks potassium chloride transporters.

Previous examinations of the effects of ammonia on brain cells have mostly used single cells or histological preparations and these studies have shown that glia cells that are exposed to ammonia swell rapidly. Here, in vivo two-photon imaging was used to study the effect of ammonia on nerve and glia cells in the cerebral cortex of living mice. Nagelhus and colleagues revealed that swelling of glia cells is not necessary for ammonia to exert its toxic effects on the brain. On the contrary, three-dimensional imaging as well as volume analysis of single cells revealed that glia cells in the cerebral cortex shrink slightly upon acute ammonia accumulation.

Ammonia toxicity does not only affect patients with alcoholic liver disease but also children with congenital enzyme defects in the liver. Since ammonia is also a major waste product when the neurotransmitter glutamate is being degraded, ammonia might also play a role for some children suffering from epilepsy. An approved diuretic drug, burinex, already used in the clinic can improve both symptoms and survival for patients with increased ammonia levels in their blood. Further animal experiments as well as clinical trials are required to determine whether burinex and other chloride transporter inhibitors may be used to counteract ammonia damage.

The full article *"Ammonia triggers neuronal disinhibition and seizures by impairing astrocyte potassium buffering"* can be found in Nature Medicine, Volume 19, 2013, Pages 1643-8. doi: 10.1038/nm.3400

Boosting understanding of prostate cancer risk

SHARED GENETIC RISK FACTORS FOR PROSTATE CANCER AND BLOOD LIPID TRAITS

The NCMM Associate Investigator programme has funded collaboration between the Mills Group and Professor Ole Andreassen/NORMENT to identify multi-trait/disease genetic risk factors. This funding enabled them to recruit Dr. Verena Zuber and with access to genome-wide association studies data for prostate cancer (Mills/PRACTICAL Consortium; http://ccge.medschl.cam.ac.uk/consortia/practical/) and blood lipid traits (Andreassen/Global Lipids Consortium; http://www.sph.umich.edu/csg/abecasis/public/lipids2013) they were able to perform the first global comparison of genetic risk loci across these datasets. Numerous clinical epidemiology studies have reported associations between blood cholesterol levels and prostate cancer risk. This collaborative study is the first to look at a genetic level and has uncovered significant genetic risk enrichment between prostate cancer and hypercholesterolemia and also between prostate cancer and triglyceridemia.

FUTURE STUDIES ON ADDITIONAL COHORTS

Future work will focus on confirming these findings in single multi-trait cohorts for which genotyping data is available, including the Malmö Diet & Cancer Cohort (http://www.med.lu.se/klinvetmalmo/befolkningsstudier/malmoe_kost_cancer). If validated it may open the way to incorporating these risk loci and blood lipid measurements into a risk stratification model for prostate cancer or to inform prevention studies. In a separate project the Mills Group is collaborating with Professors Henrik Grönberg and Fredrik Wiklund at the Karolinska Institute in Stockholm to build biomarkers into a prospective population-based risk stratification study, STHLM3 (http://sthlm3.se/). This is one example of a study in which these genetic risk factors could in future be tested. Nordic clinical studies and collections can provide a clear path to improve prostate cancer risk stratification and we are excited to contribute to this.

BEYOND PROSTATE CANCER

This is the first time our new statistical tools have successfully been applied to cancer phenotypes. These findings support the utility of the approach in cancer and we are now involved in follow-up studies to evaluate the common polygenic risk factors in several cancer types as well as determining their overlap with other human diseases. Cancer datasets to support this future work are provided by the NIH GAME-ON Consortium (http://epi.grants.cancer.gov/gameon/), a genetic risk and function consortium exploring ovarian, colorectal, breast, prostate and lung cancer within which the Mills Group participates.

The article *"Shared common variants in prostate cancer and blood lipids"* has recently been accepted for publication in the **International Journal of Epidemiology** and is currently in press.

Sugar feedback – a post-translational enhancer of oncogenic activity

SHARED GENETIC RISK FACTORS FOR PROSTATE CANCER AND BLOOD LIPID TRAITS

Prostate cancer is the most common cancer in men in Norway and metabolic reprogramming is a critical factor in localised disease and progression1. By utilizing prostate cancer gene expression data and chromatin immunoprecipitation data, we discovered that the hexosamine biosynthetic pathway (HBP) is over-expressed in localized prostate cancer and regulated by the androgen receptor2. This pathway produces UDP-N-acetylglucosamine (UDP-GlcNAc) and cell lines with high levels of the HBP enzymes have significantly elevated levels of this metabolite. UDP-GlcNAc is utilized by O-GlcNAc transferase (OGT) to modify target proteins via single sugar conjugation. Inhibition of OGT resulted in decrease in cancer cell proliferation and a reduction in the protein levels of c-Myc without impacting transcription of the genes. OGT inhibition therefore represents an important feedback between metabolic flux and oncogenic signaling, operating post-translationally2. Future studies will systematically define the spectrum of OGT-mediated changes in cancer cells upon drug treatment and at multiple stages in the disease. OGlcNAc site-specific antibodies for important oncogenes will be generated with the goal of better stratifying prostate cancer by generating protein level data to complement the extensive transcriptomic and genomic datasets already available for the disease.

1 Barfeld, S. J., Itkonen, H. M., Urbanucci, A. & Mills, I. G. *Androgen-regulated metabolism and biosynthesis in prostate cancer*. **Endocr Relat Cancer**, doi:10.1530/ERC-13-0515 (2014).

2 Itkonen, H. M. *et al. O-GlcNAc transferase integrates metabolic pathways to regulate the stability of c-MYC in human prostate cancer cells*. **Cancer Res** 73, 5277-5287, doi:10.1158/0008-5472.CAN-13-0549 (2013).

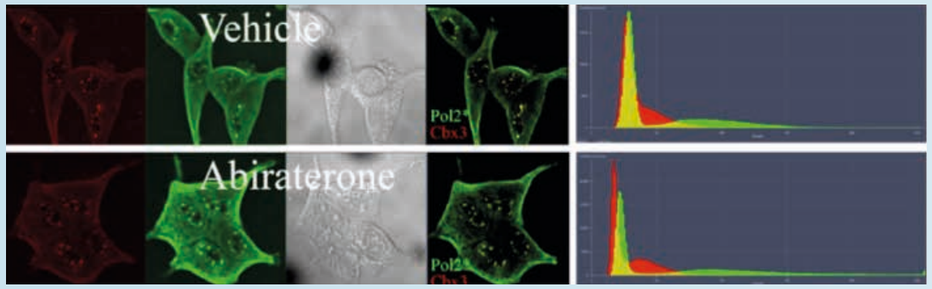


Image: Harri Itkonen, NCMM. Treatment of prostate cancer cells with a clinically approved adrogen synthesis inhibitor, Abiraterone, leads to the dissociation of RNA polymerase II from CBX3, resulting in disruption of transcriptional activity.

Bicarbonate transporter proteins as novel targets for specific drug screening

Acid-base homeostasis is fundamental to our understanding of human physiology and is essential to cellular function. The main buffering system found in the human body is based on bicarbonate and selective transport of bicarbonate across the plasma membrane is facilitated by specific integral membrane proteins belonging to the SoLute Carrier 4 (SLC4) protein family. However, not much is known about the structural basis of function and regulation of these proteins. The sodium-dependent bicarbonate transporter NCBE is predominantly expressed in the central nervous system (CNS) and its main function is to regulate intracellular neuronal pH as well as to maintain the pH homeostasis across the blood-cerebrospinal fluid barrier. The cytoplasmic N-terminal of NCBE is likely to be involved in bicarbonate recognition and transport and contains key areas of regulation involving pH sensing and protein-protein interactions.

Protein function is traditionally thought to depend primarily on the chemical environment created by the 3D structure of the macromolecule and it is believed that the composition of the primary structure supports certain secondary and tertiary structures of the macromolecule. In recent years, attention has turned to proteins containing non-structured regions. In particular, focus has been on the function of these regions. Intrinsic disordered protein regions (IDPRs) are defined as protein regions having no rigid three-dimensional structure under physiological conditions. They are believed to be involved in signaling networks in which specific, low affinity, protein-protein interactions play an important role. NCMM group leader Preben Morth and his colleagues have recently succeeded in crystallizing the core region of the N-terminal domain of NCBE and demonstrated that it contains regions of intrinsic disorder and that these disordered regions are conserved among all bicarbonate transporters of SLC4.

IDPRs are especially common as mediators of protein-protein interactions. Many are found in proteins related to signaling and are therefore important in understanding diseases such as neurodegenerative diseases and cardiovascular disease. For these reasons they represent a class of high value pharmaceutical targets but due to their poorly characterized properties they have not yet been investigated to any great extent. NCBE has recently been reported as a potential neuronal drug target. The development of specific inhibitors against NCBE, or of any SLC4 members in general, would benefit our understanding of the sodium and bicarbonate transport mechanism and perhaps lead to novel drugs that selectively target specific SLC4 family members. Morth and colleagues therefore aim to elucidate the biophysical properties of this group of proteins in future studies to target individual members selectively with novel inhibitors.

The full article *"The N-terminal cytoplasmic region of NCBE displays features of an intrinsic disordered structure and represents a novel target for specific drug screening"* can be found in **Frontiers in Physiology**, Volume 4, 2013, doi: 10.3389/fphys.2013.00320.

Phospho-specific flow cytometry – an important tool for understanding signaling pathways activated in cancer patients.

Recent advances in molecular profiling technologies, such as genetic and metabolic screening, have opened for disease treatment strategies based on a more individualized approach by providing molecular assays to aid targeting of individual patient disease profiles. Such tailored therapies or 'personalized medicine' have already been successfully applied for immune-related diseases and certain cancers, improving both diagnosis and risk stratification. Development of novel patient stratification tools for cancer is a challenge that requires advanced molecular screening and a detailed understanding of tumor signaling networks.

Whereas several parameters utilized to phenotype tumor samples have a static nature, evaluation of dynamic events is key for monitoring the regulation of intracellular signaling in cancer cells and evaluating specificity and efficacy of drugs directed against particular targets in patient samples. NCMM group leader Kjetil Taskén and colleagues have introduced phospho-specific flow cytometry (phosphoflow) as a new molecular tool for evaluation of intracellular signaling in tumor samples from patients suffering from e.g. colorectal cancer, ovarian carcinoma and glioblastoma to find biosignatures. Furthermore, a recent interest is now to rig drug sensitivity screens to explore the possibility to assist treatment choices in individualized cancer therapy.

In a recent study published in Journal of Neurooncology, phosphoflow was used on glioblastoma patient samples to identify activated mitogenic signaling pathways in each patient. Glioblastoma is a highly invasive malignant tumor of the central nervous system associated with a particularly poor prognosis (median survival 9–15 months) due to the aggressive nature of the cancer and a lack of efficient treatment options. The high degree of molecular and cellular heterogeneity within these tumors makes them difficult to treat and the current treatment options consisting of surgery followed by radiation and chemotherapy are only palliative. Primary glioblastoma commonly presents genetic alterations such as amplification of the epidermal growth factor receptor gene, EGFR, mutations or loss of the phosphatase and tensin homolog gene, PTEN, as well as mutations of the phosphatidylinositol 3-kinase PIK3CA gene. In this study, phosphoflow was used to visualize changes in phospho-epitopes following growth factor-induced stimulation before and after treatment with the mTOR inhibitor rapamycin. Correlating these signaling profiles with functional analyses, clinical parameters and biochemical differences may provide sufficient conditions as companion diagnostics to assist in defining a treatment strategy that will improve the current outcome for this cancer.

Addressing the heterogeneity of cancer signaling more effectively by identifying signal mediators and subpopulations of tumor cells that may be targeted by specific drugs should be a critical element in tailoring future patient-specific therapies for cancer patients.

The full article "*EGF signalling and rapamycin-mediated mTOR inhibition in glioblastoma multiforme evaluated by phospho-specific flow cytometry*" can be found in **Journal of Neurooncology**, Volume 112, 2013, pages 49–57. DOI 10.1007/s11060-012-1035-9. Authors: I. Cornez, M. Joel, K. Taskén, I.A. Langmoen, J.C. Glover and T. Berge.

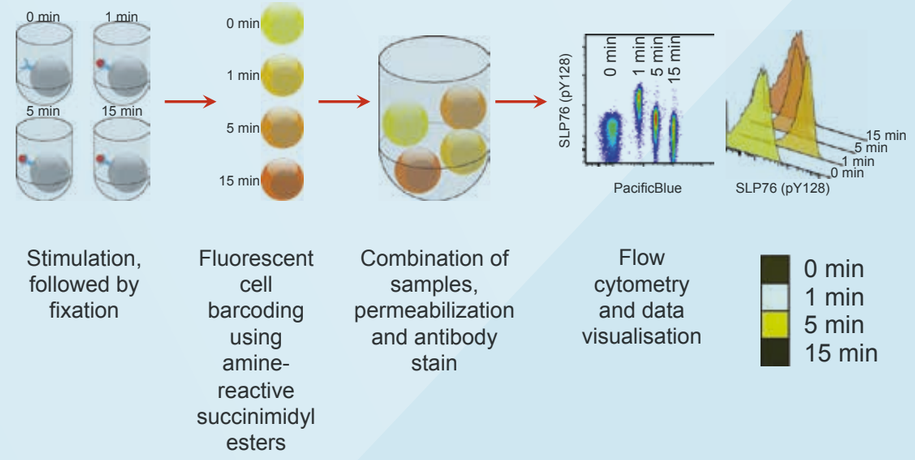


Figure: Workflow in phosphoflow cytometric analysis of immune cell or cancer cell signalling including multiplexing using fluorescent cell barcoding (FCB) (Ill. Johannes Landskron, Taskén Lab)

NORDIC MOLECULAR MEDICINE NETWORK MEETING

The Nordic Molecular Medicine Network (NMMN) is a Nordic Network of National Centres of Excellence and is supported by NordForsk (http://www.nordforsk.org/en), an organization under the Nordic Council of Ministers that provides funding for Nordic research cooperation as well as advice and input on Nordic research policy.

The NMMN aims to promote collaboration and exchange between EMBL and the Nordic EMBL Partnership nodes FIMM, MIMS, NCMM and from 2013 also DANDRITE. To achieve this, EMBL and NMMN organize annual networking meetings where the Nordic nodes alternate as hosts. The network also provides support to PhD students and postdocs for travels to the other partners and EMBL for collaborations, workshops and courses.

NCMM hosted the 4th NMMN Meeting at the Oslo Science Park in September 2013 where more than 150 participants from all the four Nordic EMBL nodes as well as from EMBL enjoyed two days of scientific interaction. PhD fellows and postdocs opened the meeting with a student organized scientific speed dating followed by a lecture on career opportunities within the research field. The official NMMN program was opened with a keynote lecture by Dr. Jan Korbel from the EMBL and altogether, 35 talks including 5 keynote lectures as well as 65 posters were presented during the meeting. NordForsk was represented by Leif Eriksson who also gave a talk. Furthermore, the annual Nordic EMBL Partnership Steering Committee meeting also took place during the NMMN conference.

The 5th NMMN Meeting will be hosted by MIMS and will take place in Umeå, Sweden, in August 2014.

Enthusiastic PhD fellows and postdocs met for scientific speed dating and group discussions.

Photos: j. Lorentzen and J. Landskron (NCMM/BiO, UiO)

Excellent science was communicated by 35 speakers, including the keynote speakers Jan Korbel (EMBL), Erlend Nagelhus (NCMM), Jonathan Knowles (FIMM), Stephen Cusack (EMBL-Grenoble) and Anders Nykjær (Dandrite)

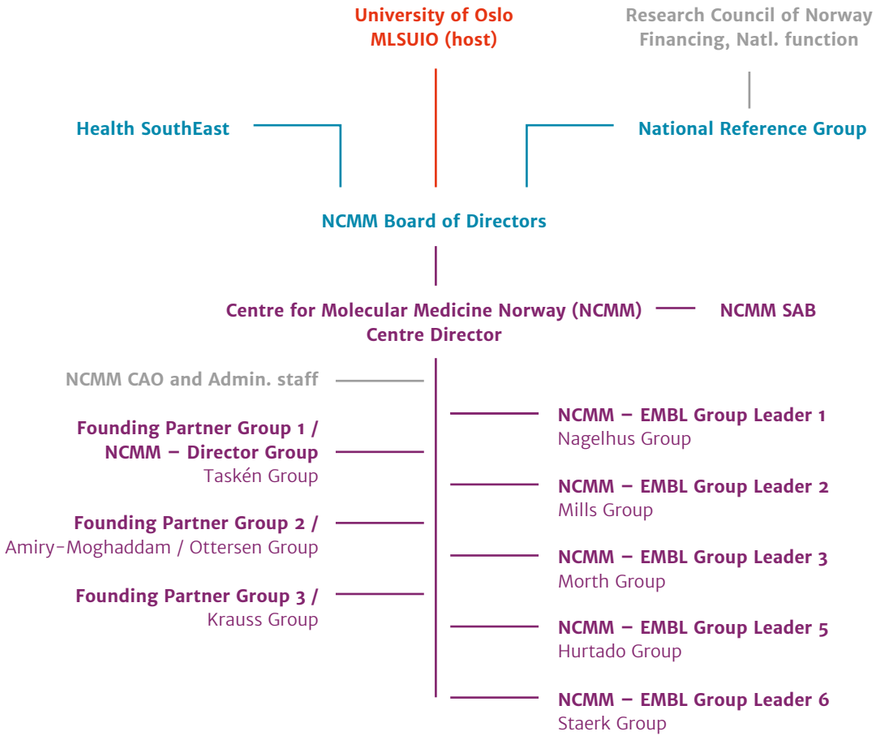
65 posters were presented during the poster sessions where many enthusiastic discussions took place. A poster award committee consisting of Preben Morth (NCMM), Fredric Login (MIMS), Tiia Luukkonen (FIMM) and Mads Kjølby selected 3 poster award winners; from the left: Saranya Subramani (NCMM), Vilja Pietiäinien (FIMM) and Joseph Lyons (Dandrite).

Photos: J. Lorentzen and J. Landskron (NCMM/BiO, UiO)

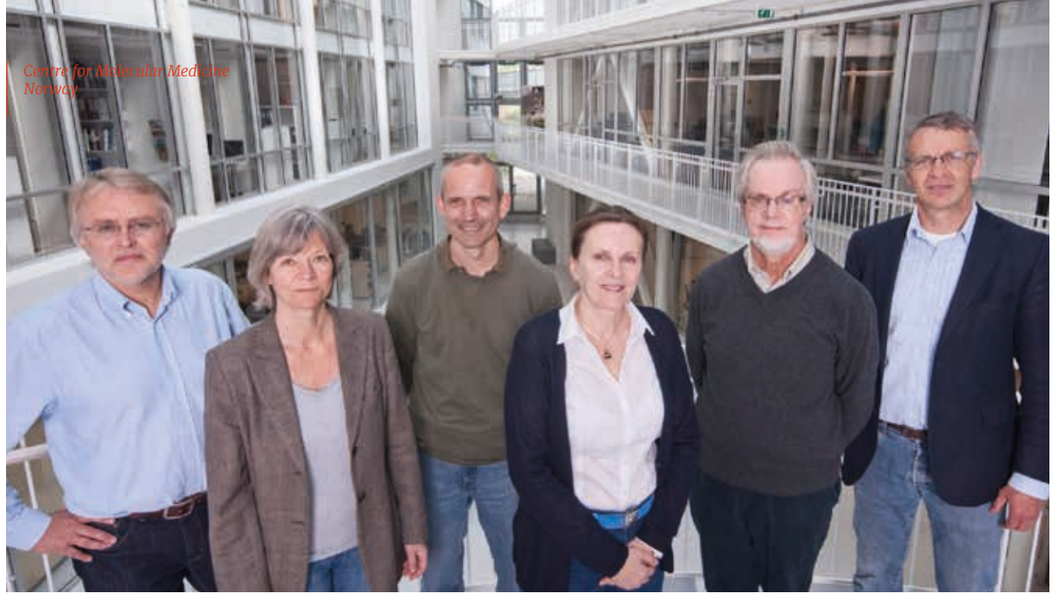
Photo: John Hughes

NCMM STRUCTURE

NCMM is hosted by the University of Oslo (UiO) and placed under Molecular Life Science (MLSUiO), a strategic inter-facultary steering group reporting directly to the Rector. Two consortium partners, Health South East Regional Health Authority (HSE) and the Research Council of Norway (RCN), co-finances and co-directs NCMM.



Organizational chart for NCMM: The NCMM governing body is the Board of the NCMM whereas the RCN operates the NCMM National Reference Group (see separate sections).



From left to right: Terje Espevik, Guro Valen, Finn-Eirik Johansen, Ragnhild A. Lothe, Ole Sejersted and Øystein Krüger. Photo: John Hughes

NCMM BOARD

The NCMM Board is responsible for initiating NCMM activities and, in collaboration with the Director, for ensuring the Centre's overall coordination and progress. The Board's decisions are invaluable for promoting excellence in the Centre's recruitments, research, collaborations, translational value as well as economy.

MEMBERS OF THE BOARD

The Board consists of the Chair and five members representing NCMM's host the University of Oslo and the two consortium partners Health South-East Regional Health Authority (HSE) and the Research Council of Norway (RCN) that co-finances and co-directs NCMM. In addition, one member is appointed from the National Reference Group. The Board steers and supervises NCMM's activities and finances and does also approve the center's strategic plans, objectives and budget.

In 2013 the Board has had a special focus on the mid-term evaluation of NCMM and on securing long-term funding for the second five-year period (2015-2019). Furthermore, the Board has been involved in the evaluation process of NCMM group leader Ian Mills. The Board also had a separate meeting with the SAB during their visit in March 2014.

The current Board members are:

Chair:
Professor Ragnhild A. Lothe, OUH-Radiumhospitalet/UiO

Members:
Professor Jan B. Bjåli, Factulty of Medicine, UiO
Professor Finn-Eirik Johansen, Faculty of Science and Mathematics, UiO
Director of Research/Professor Magnar Bjørås, Dept. of Microbiology, Oslo University Hospital (OUH)
Head of Institute for Experimental Research/Professor Ole Sejersted, OUH (representing the National Reference Group)
Special Advicer Marianne Grønsleth, RCN (Observer)

Deputy Members:
Professor Guro Valen, Faculty of Medicine, UiO
Assistant Professor Ingvild Mikkola, University of Tromsø (representing the National Reference Group)
Head of Research Øystein Krüger, Dept. of Research and Innovation, HSØ

GREETINGS FROM THE CHAIR OF THE BOARD

In September 2013 the midterm evaluation report presented by the committee members Matthew L. Albert, Director Dept. Immunology, Pasteur Institute, Margaret Frame, Director Edinburgh Cancer Research Centre and Thomas Perlmann, Director of the Ludwig Institute for Cancer Research, Karolinska Institute, concluded with "its resounding support for continuation" of NCMM. The committee was "impressed by the early success in establishing NCMM" and they emphasized the effort and high quality management by the NCMM director, Kjetil Taskén. Although pointing out that "changing patient care does not happen overnight and is the responsibility of an intricate patchwork" of many stakeholders, they were impressed by the ongoing translational activities and stated that further support to NCMM will aid "to nurture Norwegian excellence and translational output for patients".

In view of this report and its recommendations the NCMM Board is confident of the continued success of NCMM and satisfied with the continued support of the South East Regional Health Authorities, the University of Oslo as well as the Research Council of Norway.

The Board reports to the interfaculty initiative at UiO, Molecular Life Science (MLSUiO) under which NCMM is organized, and we would like to acknowledge the very best collaboration with MSLUiO and its leader, Odd Stokke Gabrielsen. Finally, we compliment the director, Kjetil Tasken, for the achievements and brilliant management of the Centre.

On behalf of the board,
RALothe

From left to right: NCMM Director Kjetil Taskén, Richard Treisman, Erich Nigg, Annika Lindblom, SAB Chair Leif Groop and Alvis Brazma. Photo: Johnannes Landskron (NCMM/BiO)

SCIENTIFIC ADVISORY BOARD (SAB)

The NCMM Scientific Advisory Board (SAB) was appointed by the Board in June 2011 and their main mission is to offer academic and strategic advice as well as benchmark the performance of the groups and Centre internationally. To access recent progress and future strategies, the SAB has therefore decided to meet with NCMM core members annually and the third site-visit took place in March 2014. This year the SAB were also involved in the evaluation process of NCMM group leader Ian Mills regarding the renewal of his position as group leader.

After the third visit, the view of the SAB was that "NCMM has built up a portfolio of promising young investigators committed to translational application of biomedical research". Moreover, the SAB stated that "the number of clinical studies already in progress for such a small unit indicates that NCMM has made an impressive start at translational work". Furthermore, regarding renewal of group leader Ian Mills the overall view of the SAB as well as the external reviewers was that "his first period has been very successful, despite a lot of newcomer's challenges" and the SAB thus recommended that he should be reappointed for a second five-year period.

MEMBERS OF THE SCIENTIFIC ADVISORY BOARD

The Scientific Advisory Board consists of five internationally renowned scientists:

Chair:
Professor Leif Groop
Head of Lund University Diabetes Centre
Department of Endocrinology
Clinical Sciences Malmø
Lund University, Sweden

Professor Erich Nigg
Director of Biozentrum
Basel, Switzerland

Professor Richard Treisman
Director of CRUK London Research Institute
Lincoln's Inn Fields Laboratories
London, UK

Dr. Alvis Brazma
EMBL Senior Scientist & Senior Team Leader
EMBL-EBI Hinxton
Cambridge, UK

Professor Annika Lindblom
Chair of Department of
Molecular Medicine and Surgery
Karolinska Institutet
Stockholm, Sweden

NATIONAL REFERENCE GROUP

The National Reference Group has been established to facilitate national coordination and to ensure that other regions of Norway benefit from the academic and recruitment opportunities represented by the EMBL node. Members of the group are appointed by the RCN for a two-year period and represent the universities as well as the regional health authorities. The reference group is represented in the NCMM Board by one member. The National Reference group currently consists of:

Professor Terje Espevik
Norwegian University of Science and Technology, NTNU
(Member of the NCMM Board)

Assistant Professor Ingvild Mikkola
University of Tromsø
(Deputy member of the NCMM Board)

Professor Anne-Brit Kolstø
University of Oslo

Professor Vidar M. Steen
University of Bergen

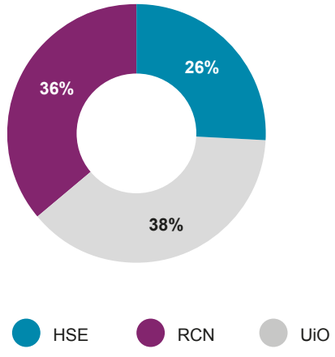
NCMM FUNDING

The **NCMM core funding** in the first five-year period (2009-2013) was 27 million Norwegian kroner (mNOK) (approximately 3.7 mEUR) per year from the 3 consortia partners UiO, Research Council of Norway and Health SouthEast. Core funding at the same level has also been secured for the interim year 2014 and NCMM's partners have also committed to fund the centre for a second five-year period (2015-2019). Final budget negotiations for the next five-year period are currently taking place. In addition to the core funding, the centre receives some overhead and production-based income from UiO (1.7 mNOK in 2013). Including transferred funds, NCMM spent 31.5 mNOK in 2013 on its core budget. For 2014, NCMM has a budget aiming for balance and plans to spend 31 mNOK.

For the period 2015-2019 we stipulate the NCMM annual core budget expenses to be in the order of 35 mNOK (2015-value) with the present level of activity, when adjusting for price and salary increases from when NCMM was planned and including the national function which was not budgeted for in the first 5-year period.

NCMM extramural funding in the form of grants to the group leaders and other competitive funding (ex. Founding Partners) reached approx. 7 mNOK in 2010, 23 mNOK in 2011, 30 mNOK in 2012, 35 mNOK in 2013 and is stipulated to exceed 45 mNOK in 2014. This includes grants from the Research Council of Norway, the Norwegian Cancer Society, Health SouthEast, European Commission, NHI, competitive grants at UiO and private foundations and organizations such as the Lundbeck Foundation, Novo Nordic Foundation, Carlsberg Foundation, KG Jebsen Centres, Movember and others. Furthermore, the Nordic nodes within the EMBL Nordic Partnership in Molecular Medicine are also supported by NordForsk as a Nordic Network of National Centres of Excellence. This network "Nordic Molecular Medicine Network" (NMMN) has promoted collaboration and exchange between FIMM, NCMM, MIMS, DANDRITE and EMBL.

NCMM CORE FUNDING SOURCES 2013

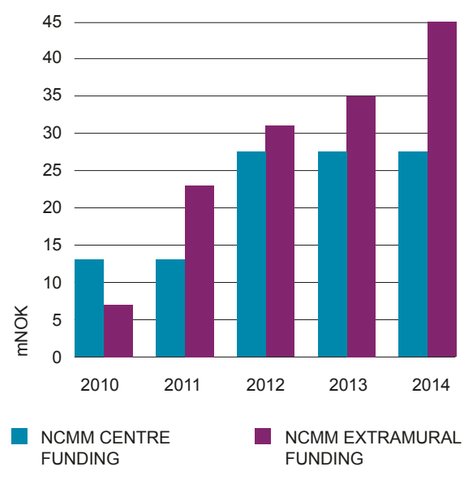


FUNDING STATISTICS

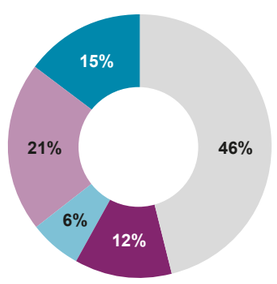
The illustrated funding overview includes only NCMM groups, including that of the Director from 2011. Finances of the Founding Partners not accounted at NCMM have not been included. The 2014 data are based on accounts for the first quarter as well as on budget numbers for the rest of 2014.

The overview of extramural funding sources includes NCMM groups but not finances of the Founding Partner groups accounted elsewhere. The 2014 overview is an estimate of extramural funding sources based on budget and on secured grants.

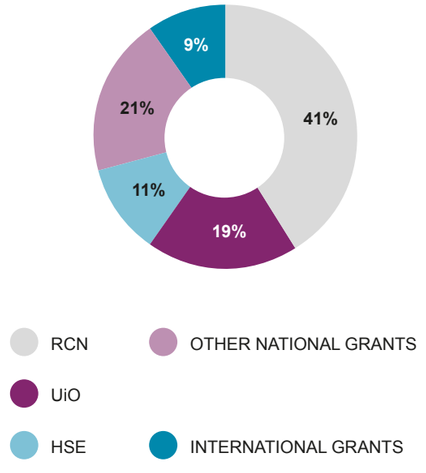
CORE FUNDING VS EXTRAMURAL FUNDING



EXTRAMURAL FUNDING SOURCES 2013



ESTIMATED EXTRAMURAL FUNDING SOURCES 2014



NCMM-AFFILIATED PUBLICATIONS

NCMM PUBLICATIONS FROM 2013

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Ion pathways in the sarcoplasmic reticulum Ca2+-ATPase. Bublitz M, Musgaard M, Poulsen H, Thøgersen L, Olesen C, Schiøtt B, Morth JP, Møller JV, Nissen P (2013). **J Biol Chem.** 288, 10759-10765. doi: 10.1074/jbc.R112.436550

EGF signalling and rapamycin-mediated mTOR inhibition in glioblastoma multiforme evaluated by phospho-specific flow cytometry. Cornez I, Joel M, Taskén K, Langmoen IA, Glover JC, Berge T (2013). **J Neurooncol** 112, 49-57. doi: 10.1007/s11060-012-1035-9

Modulation of intracellular calcium homeostasis blocks autophagosome formation. Engedal N, Torgersen ML, Guldvik IJ, Barfeld SJ, Bakula D, Sætre F, Hagen LK, Patterson JB, Proikas-Cezanne T, Seglen PO, Simonsen A, Mills IG (2013). **Autophagy** 9, 475-1490. doi: 10.4161/auto.25900

Cooperating transcription factors mediate the function of estrogen receptor. Fiorito E, Katika MR, Hurtado A (2013). **Chromosoma** 2, 1-12. doi: 10.1007/s00412-012-0392-7

The protein phosphatase 2A regulatory subunit Ppp2r2a is required for Connexin-43 dephosphorlyation during epidermal barrier acquisition. Gerner L, Youssef G, O'Shaughnessy RF (2013). **Exp Dermatol** 22, 754-756. doi: 10.1111/exd.12234

Identifying ligand-binding hot spots in proteins using brominated fragments. Grøftehauge MK, Therkelsen MØ, Taaning R, Skrydstrup T, Morth JP, Nissen P (2013). **Acta Crystallogr Sect F Struct Biol Cryst Commun.** 69(Pt 9):1060-5. doi: 10.1107/S1744309113018551

Evidence that pericytes regulate aquaporin-4 polarization in mouse cortical astrocytes. Gundersen GA, Vindedal GF, Skare O, Nagelhus EA (2013). **Brain Struct Funct**. DOI 10.1007/s00429-013-0629-0

Strontium, Calcium Analogue in Membrane Transport Systems. Hein KL, Morth JP (2013). **Encyclopedia of Metalloproteins**10.1007/978-1-4614-1533-6_176© Springer Science, Business Media New York 2013

N-linked glycosylation supports cross-talk between receptor tyrosine kinases and androgen receptor. Itkonen HM, Mills IG (2013). **PLoS One** 8, e65016. doi:10.1371/journal.pone.0065016

O-GlcNAc transferase integrates metabolic pathways to regulate the stability of c-MYC in human prostate cancer cells. Itkonen HM, Minner S, Guldvik IJ, Sandmann MJ, Tsourlakis MC, Berge V, Svindland A, Schlomm T, Mills IG (2013). **Cancer Res** 15, 5277-5287. doi:10.1158/0008-5472.CAN-13-0549

A functional link between FOXA1 and breast cancer SNPs. Katika MR, Hurtado A (2013). **Breast Cancer Res.** 15, 303 [Epub ahead of print]

Probing determinants of cyclopiazonic acid sensitivity of bacterial Ca2+-ATPases. Kotšubei A, Gorgel M, Morth JP, Nissen P, Andersen JL (2013). **FEBS J** 280, 5441-5449. doi: 10.1111/febs.12310

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Cell signaling analyses in the functional genomics era. Rogne M, Taskén K (2013). **N Biotechnol** 30, 333-338. doi: 10.1016/j.nbt.2013.01.003

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The androgen receptor induces a distinct transcriptional program in castration-resistant prostate cancer in man. Sharma NL, Massie CE, Ramos-Montoya A, Zecchini V, Scott HE, Lamb AD, MacArthur S, Staerk R, Warren AY, Mills IG, Neal DE (2013). **Cancer Cell** 23, 35-47. doi:10.1016/j.ccr.2012.11.010 (2013)

The RIAD peptidomimetic inhibits HIV-1 replication in humanized NSG mice. Singh M, Singh P, Vaira D, Torheim EA, Rahmouni S, Taskén K, Moutschen M (2013). **Eur J Clin Invest** doi: 10.1111/eci.12200. [Epub ahead of print]

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The autoimmune-predisposing variant of lymphoid tyrosine phosphatase favors T helper 1 responses. Vang T, Landskron J, Viken MK, Oberprieler N, Torgersen KM, Mustelin T, Tasken K, Tautz L, Rickert RC, Lie BA (2013). **Hum Immunol.** 74, 574-585. doi: 10.1016/j.humimm.2012.12.017

Structural basis and SAR for G007-LK, a lead stage 1,2,4-triazole based specific tankyrase 1/2 inhibitor. Voronkov A, Holsworth DD, Waaler J, Wilson SR, Ekblad B, Perdreau-Dahl H, Dinh H, Drewes G, Hopf C, Morth JP, Krauss S (2013). **J Med Chem.** 56, 3012-3023. doi: 10.1021/jm4000566

Rab3Gap1 mediates exocytosis of Claudin-1 and tight junction formation during epidermal barrier acquisition. Youssef G, Gerner L, Naeem AS, Ralph O, Ono M, O'Neill CA, O'Shaughnessy RF (2013). **Dev Biol.** 380, 274-285. doi:10.1016/j.ydbio.2013.04.034

Photo: John Hughes

NCMM EMERGING PUBLICATIONS 2014

Shared common variants in prostate cancer and blood lipids. Andreassen OA, Zuber V, Thompson WK, Schork AJ, Bettella F, Djurovic S, Desikan RS, Consortium TP, Gwas TC, Mills IG et al. (2014). **International Journal of Epidemiology** (In Press).

Androgen-regulated metabolism and biosynthesis in prostate cancer. Barfeld S, Itkonen HM, Urbanucci A, Mills IG (2014). **Endocr Relat Cancer** 2014 Feb 4. [Epub ahead of print]

A phenotypic screening approach to identify anticancer compounds derived from marine fungi. Ellinger B, Silber J, Prashar A, Landskron J, Weber J, Rehermann S, Müller FJ, Smith S, Wrigley S, Taskén K, Gribbon P, Labes A, Imhoff JF (2014). **Assay Drug Dev. Technol.** 2014 Apr;12(3):162-75. doi: 10.1089/adt.2013.564 (In Press)

Endosomal signaling and oncogenesis. Engedal N, Mills IG (2014). **Methods in enzymology** 535, 179-200. doi: 10.1016/B978-0-12-397925-4.00012-2

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Activated platelets promote increased monocyte expression of CXCR5 through prostaglandin E2-related mechanisms and enhance the anti-inflammatory effects of CXCL13. Halvorsen B, Smedbakken LM, Michelsen AE, Skjelland M, Bjerkeli V, Sagen EL, Taskén K, Bendz B, Gullestad L, Holm S, Biessen EA, Aukrust P (2013). **Atherosclerosis** 234, 352-359. doi: 10.1016/j.atherosclerosis.2014.03.021

Role of Hes6 in castration-resistant prostate cancer. Lamb AD, Ramos-Montoya A, Russel R, Carroll T, Massie CE, Shaw GL, Sharma NL, Warren AY, Mills IG, Neal DE (2014). **The Lancet** 383:S67

Maintaining and reprogramming genomic androgen receptor activity in prostate cancer. Mills IG (2014). **Nat Rev Cancer** 14, 187-198. doi: 10.1038/nrc3678

HOXB13, RFX6 and prostate cancer risk. Mills IG (2014). **Nature Genet.** 2014 Feb;46(2):94-5. doi: 10.1038/ng.2881.

HES6 drives a critical AR transcriptional programme to induce castration-resistant prostate cancer through activation of an E2F1-mediated cell cycle network. Ramos-Montoya A, Lamb AD, Russel R, Carroll T, Jurmeister S, Galeano-Dalmau N, Massie CE, Boren J, Bon H, Theodorou V et al. (2014). **EMBO Molecular Medicine** 2014 Apr 14. pii: emmm.201303581v1. doi: 10.1002/emmm.201303581

The ETS family member GABP modulates androgen receptor signalling and mediates an aggressive phenotype in prostate cancer. Sharma NL, Massie CE, Butter F, Mann M, Bon H, Ramos-Montoya A, Menon S, Stark R, Lamb AD, Scott HE et al. (2014). **Nucleic Acids Research Accepted** (In Press).

T-cell co-stimulation through the CD2 and CD28 co-receptors induces distinct signaling responses. Skånland SS, Moltu K, Berge T, Aandahl EM, Taskén K (2014). **Biochem J** 2014 Mar 25. [Epub ahead of print]

Nuclear ARRB1 induces pseudohypoxia and cellular metabolism reprogramming in prostate cancer. Zecchini V, Madhu B, Russel R, Pértega-Gomes N, Warren AY, Gaude E, Borlido J, Stark R, Ireland-Zecchini H, Rao R, et al. (2014) **EMBO J** (In Press)

PATENTS FILED IN 2013

Compounds that Regulate Phospholamban Phosphorylation. Inventors: Taskén, K., Lygren, B. Østensen, E., Klaveness, J. U.K. Patent Application Serial No. GB1208775.5, Filed: 18-May-2012. PCT/EP2013/060263 filed May 17, 2013

Cyclic Amino Compounds for use in the Treatment of Cardiac Disorders. Inventors: Klaveness, J., Taskén, K., et al. U.K. Patent Application Serial No. GB1320506.7. Filed: 20-November-2013.

PRESS ITEMS

UiO, Institutt for Klinisk Medisin, Ferbruary 26, 2013: Nye KG Jebsen sentre (http://www.med.uio.no/klinmed/om/aktuelt/aktuelle-saker/2013/nye-k-g-jebsen-sentre.html)

Stiftelsen Kristian Gerhard Jebsen, 2013: Satsing på betennelsesforskning (http://www.stiftkgj.no/?page_id=328)

UiO, March 22, 2013: Kan immunsystemet kurere kreft slik det kurerer influensa? (http://www.uio.no/om/aktuelt/arrangementer/uio-festivalen/arrangementer/livsvitenskap/kan-immunsystemet-kurere-kreft.html)

VG, April 5, 2013, pp 10-11: 6 nye våpen mot kreft (kilde: skreddersydd medisin, Taskén)

Dagens Medisin, April 11, 2013: Skreddersydd kreftbehandling utfordrer diagnosesystemene

(Taskén, http://www.dagensmedisin.no/nyheter/skreddersydd-kreftbehandling-utfordrer-diagnosesystemene/)

Forskningsrådet, June 19, 2013: Kaster lys over gliacellenes hemmeligheter (Interview with Erlend Nagelhus on Glia cells and two-photon laser scanning microscopy): http://www.forskningsradet.no/prognett-nevronor/Nyheter/Kaster_lys_over_gliacellenes_hemmeligheter/1253987447311/p1224698072633

Prostate Cancer Team Science Award, Movember Report Card, September 2013: http://uk.movember.com/report-cards/view/id/1209/prostate-cancer-team-science-award

Collaborative prostate cancer project led by Kristin A. Taskén supported by the Movember Foundation, OUH, October 2013: http://ous-research.no/home/institute/news/13855

Norsk Farmaceutisk Tidsskrift, 11/2013, pp 2-3. Article (Kronikk) by Jo Klaveness, Ellen Østensen Kjetil Taskén. "Felleskatologen 2020"

Nature Medicine, News & Views, December 5, 2013: Reassessing the role of astrocytes in ammonia neurotoxicity. (Comment on Rangroo Thrane et al. Nature Medcine Paper: http://www.nature.com/nm/journal/v19/n12/full/nm.3420.html

Kjetil Taskén profiled in Norwegian Cancer Society Donor Campaign, 9 national newspapers and magazines on January 17, 18, 24 and 25, 2014.

Bedre Helse no. 3, 2014 pp30-31. "Dette visste du ikke om betennelser", Interview with Kjetil Taskén on inflammation research.

Public release, April 30, 2014: Prostate cancer and blood lipids share genetic links: http://www.eurekalert.org/pub_releases/2014-04/uoc--pca043014.php

Photo: John Hughes

PERSONNEL

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Director
Professor Kjetil Taskén

Chief Administrative Officer
Dr. Elisa Bjørgo

Financial Officer
Anita Skolem

Personnel Officer
Nina Modahl

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NCMM Group Leader
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Senior Engineer
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Iren Sefland

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Dr. Anna Thoren
Dr. Klas H. Pettersen (from January 2014)

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Dr. Karolina Szokol
Dr. Wannan Tang

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Rune Enger
Alexander S. Thrane (until June 2013)
Vinita Rangroo Thrane (until June 2013)
Gry F. Vindedal

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Didrik Bakke Dukefoss
Brana Rosic

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Head Engineer
Ingrid Jenny Guldvik

Guest Researcher
Per O. Seglen

Postdoctoral Fellows
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Dr. Alfonso Urbanucci
Dr. Verena Zuber

PhD Fellows
Harri Itkonen
Lisa Gerner
Stefan Barfeld

MSc Student
Morten Luhr

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Principial Engineer
Hanne Guldsten

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Dr. Kim Langmach Hein

PhD Fellows
Kaare Bjerregaard-Andersen
Theis Sommer
Saranya Subramani

MSc Students
Carolina Alvadia
Nina Fagernes

SIGNALING NETWORKS IN HEALTH AND DISEASE

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Dr. Johannes Landskron

Postdoctoral Fellows
Dr. Ana Isabel Costa Calejo (from November 2013)
Dr. Lena Eroukhmanoff
Dr. Morten Hagness (from September 2013)
Dr. Guro Mørk Johnsen
Dr. Anna Mari Lone
Dr. Kristina Berg Lorvik (from October 2013)
Dr. Maria-Niki Mylanokou
Dr. Marie Rogne
Dr. Sigrid Skånland
Dr. Susanne Weedon-Fekjær (until August 2013)
Dr. Vannessa L. Wehbi (from January 2014)

PhD Fellows
Simer J. Bains (from March 2014)
Aleksandra Duki
Stalin C. Gunasekaran
Nora Lieske
Kristine Moltu
Ellen Østensen

MSc students
Lise-Lotte Flage-Larsen

Scientific Officers
Jorun Solheim
Gladys Tjørhom

Administrative Officer
Berit Barkley

Chemical Biology Platform
Dr. Anne Jorunn Stokka
David McClymont

BREAST CANCER GROUP

NCMM Group Leader
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Head Engineer
Dr. Siv Gilfillan

Postdoctoral Fellow
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Dr. Madhu Katika
Dr. Yogita Sharma (from July 2013)

PhD Fellow
Elisa Fiorito

Researcher
Elena Gonzales Sanchez (from August 2013)

STEM CELL GROUP

NCMM Group Leader
Dr. Judith Staerk

Principial Engineer
Hasina Hossain

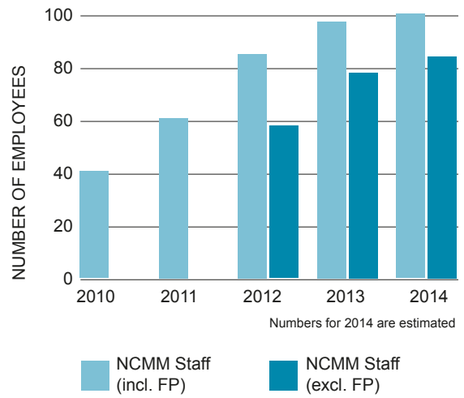
Postdoctoral Fellow
Dr. Xavier Tekpli
Dr. Ida Jonson (from April 2014)

PhD Fellows
Julia-Kristina Madsen-Østerbye
Oksana Svärd

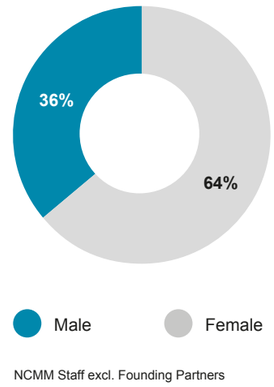
Photo: Jarle Nyttingnes

PERSONNEL STATISTICS

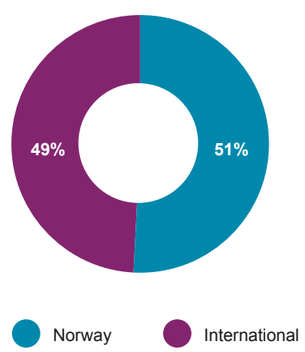
NCMM STAFF



NCMM STAFF 2013: GENDER BALANCE



NCMM 2013: INTERNATIONAL STAFF



NCMM (excl. Founding Partners) has employees from 18 countries and a foreign staff of 49% (plus some nationalized among the Norwegian staff).

NCMM INTERNATIONAL STAFF DISTRIBUTION

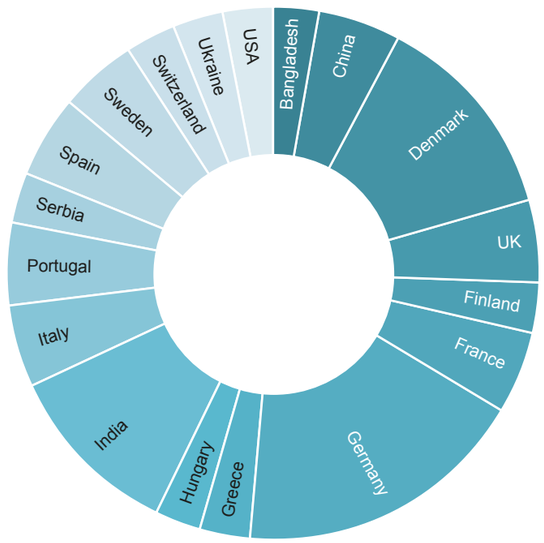


Photo: Jarle Nyttingnes

Photo: John Hughes

NCMM PARTNERSHIPS, COLLABORATIONS & AFFILIATIONS

NCMM Partners:

UiO : University of Oslo

The Research Council of Norway

HELSE SØR-ØST

Nordic EMBL Partnership for molecular medicine:

FIMM Institute for Molecular Medicine Finland

MIMS Molecular Infection Medicine Sweden

NCMM Centre for Molecular Medicine Norway

DANDRITE Danish Research Institute of Translational Neuroscience

EMBL

National & international collaborations:

BIO The Biotechnology Centre of Oslo

Centre for Molecular Biology and Neuroscience

ESFRI

EU-OPENSCREEN Chemical keys for life's locks

EATRIS

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