CONTENTS

OVERVIEW BY THE DIRECTOR

Dear friends, colleagues and supporters of NCMM,
I am proud to present the 2014 Annual Report from NCMM, which summarizes the activities in the 5th full year of operations at NCMM. Although NCMM is still young, the Centre has grown rapidly in terms of mass and production during these first five years as described below and which holds great promise for the future.

Recent progress

Review of 2014

STAFF AND FUNDING

At the end of 2014, after its fifths full year of operation, NCMM had approx. 100 employees (83 employees excluding Founding partners). NCMM reached its planned size within its fourth year of full operation (2013) and continued to grow in 2014. Furthermore, 5-6 new positions are already being filled on new grants at the first quarter of 2015. The first recruited group (Dr. Nagelhus) and the Founding Partners have now rotated out from NCMM. As a result of these changes, the overall NCMM staff number will be somewhat reduced in 2015 compared to last year.

Extramural funding reached 43 mNOK in 2014 (excluding Founding partners), exceeding the core NCMM budget by almost 2:1. Extramural funding is expected to continue to grow and is estimated to reach 47 mNOK in 2015.

SCIENCE AND PUBLICATION OUTPUT

NCMM PIs reported around 50 NCMM-affiliated papers published in 2014 and the first quarter of 2015, including papers in Nature Rev Cancer, Nature Genetics, Cancer Research, EMBO Journal, Oncogene and other journals. NCMM investigators 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 2015 NCMM PIs (ex. Founding partners) lists some 35 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 5 years is in my view quite impressive.

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 more than 60 national collaborations. The experience after 3–5 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 when 7 outstanding researchers and key research groups working across Norway were appointed Associated Investigators. 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 by the appointment of 5 new members. In addition, Erlend Nagelhus was appointed AI when he rotated out as group leader at NCMM bringing the total number of outstanding senior Norwegian scientists affiliated with NCMM to 13. 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 and in 2014 seven new collaborative projects with AIs received funding from NCMM. Furthermore, in 2015 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 and the first two NCMM YAIs were appointed at the University of Tromsø in 2014.

On the European and international arenas, NCMM investigators 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 NCMM now has completed both evaluations and negotiations of contracts and budgets for the next 5-year operational period it is time to look ahead and review prospects for this period. The Centre is at the moment almost full and NCMM is now probably as stable and established as is possible with this model. The next 2-3 years should bring significant scientific output from PIs harvesting from strategies set out in their first 5-year appointment period. Gradually, I will also expect NCMM groups to rotate, which will involve a second wave of new recruitments and NCMM already plans for recruitment of a group in bioinformatics from 2015/16. The fact that the Faculty of Medicine will host NCMM from 2015 and cooperate closely with the Faculty of Mathematics and Science in this endeavor also offers new opportunities, both strategically with the two Faculties and with more alignment and potential for synergies at all levels.

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 center 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 2015

Kjetil Taskén
Director of NCMM

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.

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. A Danish node (Dandrite) joined the Partnership in 2013. The Partnership is dedicated to the growing field of Life Sciences that investigates the molecular basis of disease and explores molecular and genetically based treatments. It 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 (UiO), as host, the Research Council of Norway (RCN) and Health Region South East (HSE) 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.

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. Funding has now been secured for a second five-year period (2015–2019) and the RCN is currently preparing a revised contract for the second five-year period.

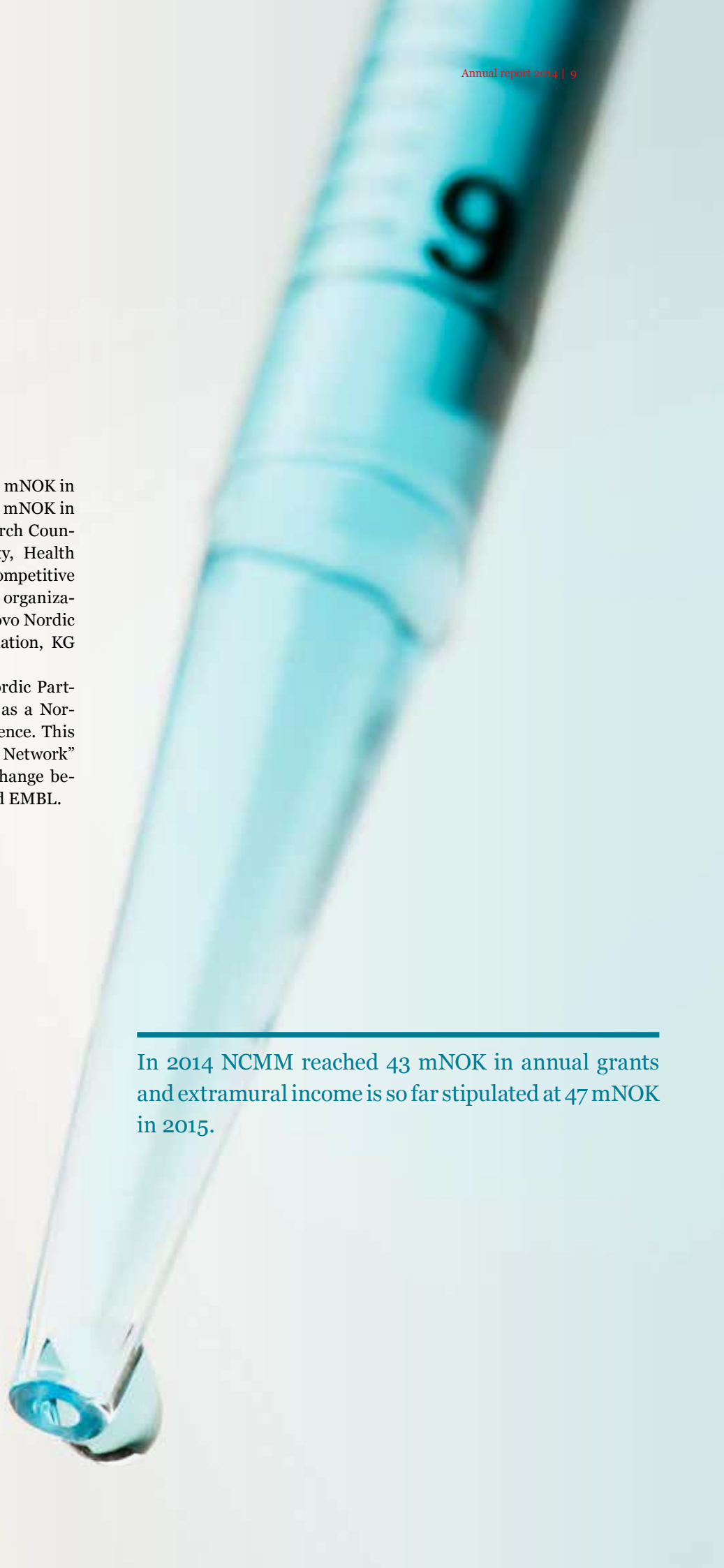
INCOME AND EXPENSES

The NCMM core funding in the first five-year period (2009–2013) was 27 million Norwegian kroner (mNOK) (approximately 3.3 mEUR) per year from the 3 consortia partners UiO, Research Council of Norway and Health SouthEast. Core funding at the same level was also 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) where the core funding will be 31 million Norwegian kroner (approx. 3.8 mEUR). Furthermore, overhead and production-based income comes in addition, which was 4.5 mNOK in 2014 and is budgeted at about the same level for 2015–19. Including transferred funds, NCMM spent 25 mNOK in 2014. For 2015, NCMM has a budget aiming for balance and plans to spend 36 mNOK (see overview of NCMM finances). For the period 2015–2019 we stipulate the NCMM annual core budget expenses to be in the order of 35–36 mNOK (2015-value) with the present level of activity and including transferred funds.

NCMM extramural funding in the form of grants to the group leaders and other competitive funding has increased steadily from 7 mNOK in 2010 to 35

mNOK in 2013. In 2014 NCMM reached 43 mNOK in annual grants and is so far stipulated at 47 mNOK in 2015. 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.



In 2014 NCMM reached 43 mNOK in annual grants and extramural income is so far stipulated at 47 mNOK in 2015.

WELCOME NCMM TO FACULTY OF MEDICINE

Photo: UiO

Dean Frode Vartdal, Faculty of Medicine, UiO.

Faculty of Medicine will like to wish NCMM warmly welcome! The University Board has decided that NCMM from April 1, 2015, will be hosted by Faculty of Medicine instead of being organized under the umbrella of the Molecular Life Science initiative, which was ended by December 31, 2014. NCMM will continue to have its own Board and an earmarked budget from the university, but will otherwise have the same status as the three institutes at the faculty.

The international Evaluation Committee appointed by the Research Council of Norway declared NCMM a clear success already at the evaluation after the first 5-year period. Similar praising was expressed by the NCMM Scientific Advisory Board. The Faculty of Medicine will do its very best to see to it that NCMM can build on its strong scientific basis created since the start in 2008 and help to enhance this excellent milieu's endeavor to translate its strong expertise in basic molecular medicine research into clinical medicine, aiming at better prevention, diagnostics and treatment of diseases.

Being a faculty with a major part tightly integrated with the activity of our two university hospitals and having a close contact with other hospitals in the South-Eastern Health Region, the faculty is in a position to ensure that NCMM research groups can easily team up with and establish research clusters with hospital research groups. Through such clusters scientists at NCMM will get closer to the bedside and thus get better insight into challenges in clinical practice. Importantly in this respect, is that demanding users such as clinicians and their patients are important drivers for innovation. NCMM may on the other hand provide insight and top notch technological skills to scientists and clinicians which will help to enhance the translational process. Moreover, having an excellent staff including world class group leaders NCMM will also be an important arena from which both faculty and hospital departments can recruit highly skilled personnel.

Apart from being an instrument and driver for translational medicine at our university and health region, NCMM has also taken on the task to help to enhance translational medicine nationally, which again is an extension of NCMM function as a node within the EMBL Nordic Partnership. Having a close contact with the three other medical faculties in Norway, our faculty has good possibilities together with our partner faculties to help NCMM fertilize and catalyze translational medicine in Norway.

On behalf of Faculty of Medicine,

Dean Frode Vartdal

GREETINGS FROM SOUTH EASTERN NORWAY REGIONAL HEALTH AUTHORITY

The South Eastern Norway Regional Health Authority (Helse Sør-Øst RHF) values NCMM as an important arena for synergistic collaboration between the University of Oslo and the specialized health care in the field of molecular/translational medicine. The Centre has been successful in recruiting young promising investigators from abroad and has demonstrated an impressive research activity. The ultimate success of the center will hinge on its ability to promote molecular/translational medicine in our health region and also nationally, both in the short and the long-term. The potential benefits for the quality and precision of health care provided to patients will be great. New insights into disease mechanisms will not only potentially spark development of new treatment regimes, but also give opportunities for disease prevention. These are basic arguments for our continued support.

On behalf of HSE

Per Morten Sandset
Director Research and Innovation

Photo: Øystein Horgmo

Per Morten Sandset, Director Research and Innovation, HSE

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.

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. 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 therefore rotated out from NCMM when his first five-year contract ended in November 2014. He has now been appointed NCMM Associate Investigator.

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 was evaluated in 2014 and his position has been renewed for a second five-year period (2015-2020).

Dr. Jens Preben Morth was trained in structural biology at the EMBL Outstation in Hamburg and was recruited from Aarhus University to NCMM in October 2010. 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's appointment as group leader has recently been evaluated and his position is being renewed for a second five-year period (2015-2020).

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. Furthermore, NCMM is in the process of recruiting a new group leader in bioinformatics.

GROUP TASKÉN

SIGNALING NETWORKS IN HEALTH AND DISEASE

Kjetil Taskén

SIGNALING NETWORKS IN HEALTH AND DISEASE

Group leader
Kjetil Taskén

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 main 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. The second main 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 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 signaling complexes (Skånland, Rogne, Dukic, Dinescu). Chemical biology screenings identify small molecular compounds for our research (Lone, Calejo, Østensen, Mylonaku). Furthermore, phospho-flow cytometry using fluorescent cell barcoding allows mapping of complex signal networks, assessing how inhibitory signals feed in and examining how small molecules perturb such signal networks (Lone, Skånland, Lieske, Wehbi). Our recent technology developments now also allow flow-based signalling analyses of adherent cells and high-throughput chemical biology screening by flow cytometry (Landskron, Eroukhmanoff, McClymont).

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 (Aandahl, Landskron, Gunaserkan, Moltu, Bains). 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 (Skånland,

Eroukhmanoff, Stokka, McClymont, Flage-Larsen). 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 (Lone, Gunaserkan, Hagness, Aandahl, Skånland, Lieske).

The improved understanding of signaling networks can be applied to many disease states, including immune-deficiencies (Lorvik, Lieske, Mørk Johnsen, Wehbi), inflammatory disorders (Wehbi, Mørk Johnsen) and cancers (Lone) 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 Ca2+ re-uptake in sarcoplasmic reticulum and thereby heart rate (Calejo, Østensen). 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 (Rogne, Mylonaku, Dinescu).

In terms of clinical investigations, a fourth clinical intervention study with COX-2 inhibitor in HIV patients (Taskén co-PI, Lorvik) is on-going in collaboration with the Department of Infectious Diseases, Oslo University Hospital (OUH). Furthermore, a registry coupling study has been performed (Bains) and a clinical intervention study with use of acetylsalicylic acid 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 with Taskén as partner, The K.G. Jebsen Inflammation Research Centre and K.G. 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.

The group aims to translate our understanding into therapeutic strategies and clinical practice

Group Taskén
Group Mills
Group Morth
Group Hurtado
Group Staerk
Group Nagelhus

Group members
(during 2014 and first quarter of 2015)

Research Scientists:
Einar Martin Aandahl
Johannes Landskron
Sigrid S. Skånland

Postdoctoral fellows:
Ana Isabel Costa Calejo
Lena Eroukhmanoff
Morten Hagness
Guro Mørk Johnsen (until March 2015)
Anna Mari Lone
Kristina Berg Lorvik
Maria-Niki Mylanokou
Marie Rogne (until August 2014)
Vanessa L. Wehbi

PhD Fellows:
Simer Jit Bains
Aleksandra Đukić
Stalin C. Gunasekaran
Nora V. Lieske
Kristine Moltu
Ellen Østensen
Sorina Dinescu (from November 2014 to May 2015)

MSc students:
Lise-Lotte Flage-Larsen (to June 2014)

Administrative Officer:
Berit Barkley

Scientific Officers:
Jorun Solheim
Gladys Tjørhom

Chemical Biology Platform:
Anne Jorunn Stokka
David W. McClymont

Selected Key Publications from PI:

Landskron, J., Helland, Ø., Torgersen, K.M., Aandahl, E.M., Gjertsen, B.T. Bjørge, L., Taskén, K. (2015) Activated regulatory and memory T-cells accumulate in malignant ascites from ovarian carcinoma patients. **Cancer Immunol. Immunother.**, 64: 337-47.

Pidoux, G., Gerbaud, P., Dompierre, J., Lygren B., Solstad, T., Evain-Brion, D., Taskén, K. (2014) The A kinase anchoring protein ezrin interacts with connexin 43 to facilitate protein kinase A control of gap junction communication in cell fusion. **J. Cell Sci.**, 127:4172-4185.

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.

Mosenden R, Singh P, Cornez I, Heglind M, Ruppelt A, Moutschen M, Enerback S, Rahmouni S, and Tasken K. (2011) Mice with disrupted type I protein kinase a anchoring in T cells resist retrovirus-induced immunodeficiency. **J. Immunol.** 186(9): 5119-5130.

Pidoux G, Witczak O, Jarnæss E, Myrvold L, Urlaub H, Stokka AJ, Küntziger T and Taskén K. (2011) Optic Atrophy 1 (OPA1) is an A-Kinase Anchoring Protein that mediates adrenergic control of lipolysis. **EMBO J.**, 30: 4371-4386

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).

Solstad T, Bains SJ, Landskron J, Aandahl EM, Thiede B, Tasken K#, Torgersen KM. (2011) CD147 (Basigin/Emmprin) identifies FoxP3+CD45RO+CTLA4+ activated human regulatory T cells. **Blood**, 118:5141-51. (#Corresponding author).

GROUP MILLS

PROSTATA CANCER

Ian Mills

PROSTATE CANCER GROUP

Group leader
Ian G. Mills

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] and makes the interplay between the AR and other factors a significant theme for further study[3]. 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-ATF[4] arm of the UPR promotes the expression of an autophagy gene, ATG[5], and this is necessary to maximize to transformation phenotype induced by c-Myc overexpression[4]. 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[5]. 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[3].

Autophagy

We have established assays to assess the UPR and autophagy in prostate cancer cells (**Nikolai Engedal**[6]. These assays incorporate functional measures of autophagic activity and using these, we have been able to dissect the functional contribution of autophagic markers such as LC[3] and GABARAPs to the process[7,8]. We are now extending this approach to characterise the response of prostate cancer cells to therapeutic stresses including CAMKK[2] inhibition, thapsigargin derivatives entering pre-clinical trials as prostate cancer therapeutics which have been made available through collaboration with Professor Poul Nissen at the Nordic EMBL Dandrite Centre, and death receptor ligands (**Nikolai Engedal, Morten Luhr, Lisa Gerner, Paula Szalai and Frank Sætre**).

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**)[9-11]. We have recently characterised an enzyme in the hexosamine biosynthesis pathway, UAP[1], as a mediator of resistance to inhibitors of N-linked glycosylation in prostate cancer cells[12]. We have also continued to validate novel glycosylation site-specific antibodies against c-Myc and more recently a pro-inflammatory transcription factor, NF-kB, to further assess feedback relationships between metabolic changes in post-translational modifications to transcriptional regulators (Collaborators: Detroit R&D

Inc). Interrogating transcriptomic and gene expression data we have identified a novel discriminatory signature that identifies localised prostate cancers and is enriched for glycosylating enzymes. Exploring the relationship between AR- and Myc-dependent gene networks in prostate cancer cells we have shown that enzymes in the de novo purine biosynthesis pathway are Myc-dependent in their expression[13]. The rate-limiting enzyme in this pathway required for guanosine monophosphate biosynthesis is overexpressed in aggressive prostate cancer and can be inhibited using a clinically approved therapeutic[13]. This imposes nucleolar stress on prostate cancer cells and can enhance response to anti-androgens in a context-dependent manner (**Stefan Barfeld** and Alfonso **Urbanucci** in conjunction with collaborators at MiMS (Chabes group), Lund (Ceder group), Vancouver (Professor Paul Rennie and Dr. Ladan Fazli) and Tampere (Visakorpi group). In collaboration with Professor Fahri Saatcioglu we have recently identified the IRE[1]-XBP arm of the UPR as AR-dependent as assessed by AR recruitment to regulatory elements controlling expression of genes in this arm of the pathway and activating the IRE1 arm. Furthermore that AR activity can inhibit the PERK-ATF[4] arm[14]. Targeting XBP[1] can affect prostate cancer growth although giving Myc-dependent activation of the PERK-ATF[4] arm in other tumour types it will be important to carefully define dose regimes of drugs targeting arms of the UPR to avoid compensatory acquisition of resistance through activity switching[4,14]. Small molecule inhibitors are now in preclinical trials targeting PERK and IRE[1] in other cancer settings.

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 STHLM[2] 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). An earlier pilot study supported in part by the Anders Jahre Foundation has now led to a provisional patent filing in the U.S.A. (**provisional patent 62099837 - 'prostate cancer markers and uses therof'**) for a blood-based protein biomarker predictive of poor prognosis prostate cancers and therapy response.

The goal of the group is to understand the biology of prostate cancer in order to improve detection and treatment.

We are also continuing to work to validate pleiotropic genetic risk loci associated with prostate cancer and metabolic syndrome n Nordic cohorts for which multi-trait and genetic risk data are available in collaboration with Professor Hans Lilja. More recently we (**Verena Zuber**) have identified a pleiotropic risk locus associated with lung cancer and Gaucher disease based on the same methodology applied in our earlier study in collaboration with Professor Ole Andreassen[15].

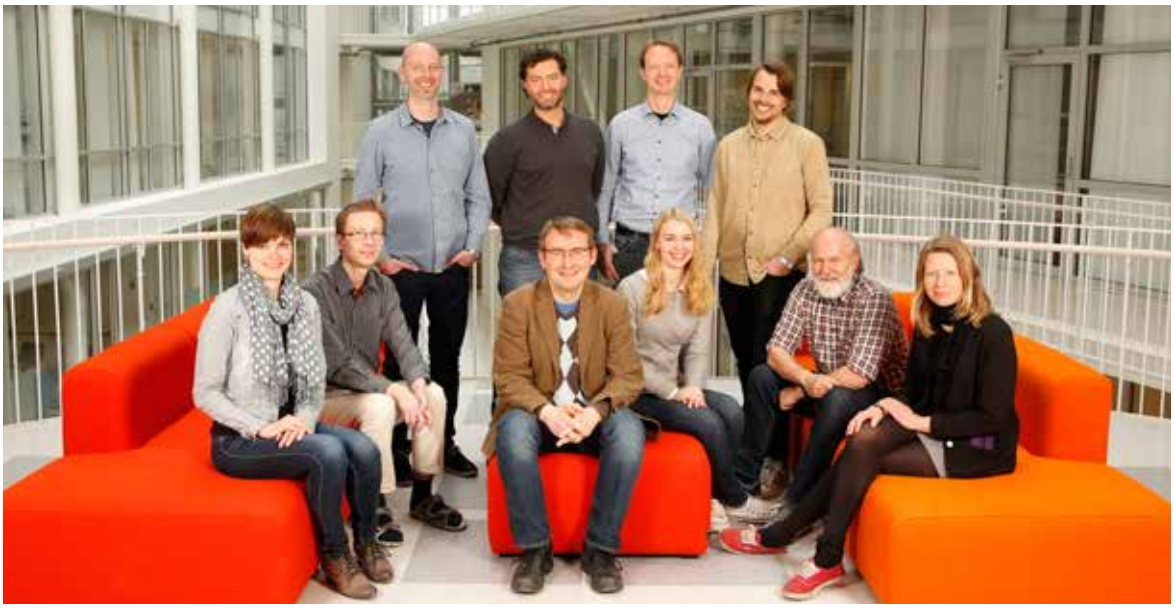
Chromatin biology

We have identified a significant relaxation of chromatin in clinical samples upon progression to castrate-resistant disease. In experimental models this can be driven partly by androgen receptor overexpression and reversed by targeting bromodomain-containing proteins implicating super-enhancers as mediators of transcriptional reprogramming in prostate cancer **(Alfonso Urbanucci).** Furthermore using chromatin marks associated with super-enhancers enriches for prostate cancer risk SNPs further implicating them as key features in the emergence and progression of the disease **(Verena Zuber and Alfonso Urbanucci).**

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.

Group Taskén
Group Mills
Group Morth
Group Hurtado
Group Staerk
Group Nagelhus



Group members and projects

Senior Scientist/ Norwegian Young Talent Awardee
Kim Nikolai Hartlieb Engedal – *fundamental mechanisms of autophagy and applications to treatment responses in prostate cancer.*

Postdoctoral fellows:
Harri Itkonen – *glycosylation and metabolic feedback in prostate cancer*
Alfonso Urbanucci – *coregulators of oncogenic transcription factors and enhancer marks*
Verena Zuber – *pleiotropic and pathway analyses of genome-wide association datasets.*

Head engineers:
Ingrid Jenny Guldvik – *biomarker discovery and validation*
Frank Sætre – *autophagy*

PhD fellows:
Lisa Gerner – *role of CAMKK2 in autophagy*
Stefan Barfeld – *transcriptional regulation by the AR and other transcription factors*
Morten Luhr – *fundamental mechanisms of autophagy and applications to treatment responses in prostate cancer.*

Guest Researcher:
Professor Per Seglen – *Autophagy*

MSc student:
Paula Szalai – *fundamental mechanisms of autophagy and applications to treatment responses in prostate cancer.*

External Funding
In addition to NCMM funding, Mills' group is supported by the Norwegian Cancer Society (Harri Itkonen – postdoctoral researcher). The group also supported by the Movember Foundation (Global Action Plan for biomarker development) and in conjunction with the Norwegian Cancer Society on a Team Science Award , the Research Council of Norway (FRIMEDBIO and Young Talent Award – Dr. Nikolai Engedal) as well as Helse Sør-Øst through an Innovation Grant for biomarker development and a postdoctoral fellowship for Dr. Alfonso Urbanucci.

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GROUP MORTH

MEMBRANE TRANSPORT

J. Preben Morth

MEMBRANE TRANSPORT GROUP

Group leader
J. Preben Morth

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 Ca2+ ATPases and Mg2+ 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).

A 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. We are currently aiming to isolate and characterize proteins that binds to 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 Research Council of Norway, the Norwegian Cancer Society, the Lundbeck Foundation, the Carlsberg Foundation, and the Blix Foundation.

The group investigates proteins involved in acid-base homeostasis and metal ion transport across the cellular membrane

Group Taskén
Group Mills
Group Morth
Group Hurtado
Group Staerk
Group Nagelhus

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Selected Key Publications from PI:

Bjerregaard-Andersen K, Sommer T, Jensen JK, Jochimsen B, Etzerodt M, Morth JP. A proton wire and water channel revealed in the crystal structure of isatin hydrolase. (2014) **J Biol Chem**. 289(31):21351-9.

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GROUP HURTADO

BREAST CANCER

Antoni Hurtado

BREAST CANCER GROUP

Group leader
Antoni Hurtado

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

Understanding Hormone-resistance in HER2 enriched tumors

Previously, we reported that transcription factor FOXA1 mediates ER binding to DNA and its transcriptional activity. Now we have identified FOXA1 as a component of the HER2 signaling pathway in breast cancer. We have determined that diverse receptors of the HER family control the proliferation mediated by FOXA1. Importantly, enhanced signaling of HER2/HER3 confers ER independent growth by reprograming the pioneering function of FOXA1 towards genomic regions of genes associated with poor prognosis and with reduced binding of ER (**Katika and Gilfillan et al, manuscript in preparation for submission**). As mentioned, endocrine resistance is a significant problem in breast cancer treatment. One of the few validated features of hormone resistance is the increased signaling of HER2/HER3 pathway. Our group now provides evidence that FOXA1 activated by the HER2/HER3 pathway induces growth independently of ER and it explains hormone resistance in in vivo patient-derived orthotopic xenograft (PDX) model.

Results from our group have also demonstrated that hormone-resistance is linked with a significant increase of euchromatin status towards genes expressed in patients with poor prognosis. Strikingly, we also noticed that ER binding is not enriched within those specific regions. To validate these observations, we are now analyzing the global chromatin structure in embedded paraffin sections of primary breast tumors and relapsed tumors from patients with poor response to the anti-ER drug Tamoxifen. Primary tumors of patients with good outcome to Tamoxifen will be also included. We will also establish a genomic link between euchromatin regions and the expression of gene associated with poor prognosis (Nanostring) in paired samples of primary and relapsed tumors.

Deciphering how anti-estrogen drugs perform their repressive actions independently of ER

The group works on the hypothesis that anti-ER drugs might also be performing their anti-proliferative actions independently of ER. The hypothesis is based on the idea that a drug may have increased efficacy for this therapeutic application when it targets different proteins. For instance, the anti-ER drugs Tamoxifen and Fulvestrant also target other proteins than ER. It seems that those drugs increase Bcl-2 lev-

The main goal of the group is to understand the mechanism of hormone resistance in breast cancer.

els and inhibit the growth of breast carcinoma cells by modulating PI3K/AKT, ERK and IGF-1R pathways (Long, S et al. JBC, 2006). These results are supported with the fact that a significant number of ER negative patients show an increased survival benefit when adjuvant hormonal therapy is administrated (Li-Heng Yang, J of Breast Cancer, 2012). Hence, one might think that hormone-resistance might also occur via mechanisms independent of ER. However, it is still unknown how these therapies could perform an anti-proliferative effect independently of ER. Now, we propose a multitiered systems-level approach to understand the effect of anti-ER drugs on breast cancer inhibition. We aim to define direct targets of Fulvestrant or Tamoxifen by applying breast cancer cell line protein extracts to Tamoxifen or Fulvestrant affinity matrices and identified binding interactions using LC-MS/MS. This approach has the advantages of examining the entire proteome expressed in the disease-relevant profile (Rix, U. Nat. Chem. Biol. 2009). To validate protein-drug interaction, we will generate a fluorescently labeled analog of the respective compound and determining whether it co-localizes with the proposed protein candidate by using FRET method. In addition to characterizing a physical interaction, it is important to delineate functional implications of drug binding to the target. We will tackle which of these targets contribute to anti-proliferative effects of Tamoxifen and Fulvestrant in breast cancer cells.

Understanding how Tamoxifen represses estrogen-mediated transcription

Estrogen-ER interaction induces conformational changes in ER enabling the binding of co-activators and allowing transcription. Furthermore, Tamoxifen is thought to actively repress transcription by recruiting co-repressors. Yet, the mechanism underlying the ligand specific binding of these co-factors to ER at estrogen-regulated genes is unknown. Preliminary data of my group point at SNAIL and PAX2 functions as critical cooperating regulators of transcriptional repression coordinated by Tamoxifen. These results suggest that several factors might be cooperating with ER for ligand specific ER mediated transcriptional regulation.

This projects aims to understand the role of PAX2 and SNAIL in the repression of ER target genes. This will be important in order to understand how Tamoxifen-ER mediated repression is regulated in breast cancer cells. To achieve these aims, we are now mapping PAX2 and SNAIL chromatin interactions regulated by Tamoxifen. We have already generated inducible cell lines, which conditionally express HA-tagged PAX2 and SNAIL. The data from this experiment will be used to characterize the architecture of the cis-regulatory elements, particularly with regard to highlighting the cooperation between transcription factors. Importantly, Tamoxifen is considered as a partial agonist/antagonist. Hence, this drug does not inhibit completely estrogen-mediated transcription. In part, this effect is due to the ability of Tamoxifen to recruit co-activators and co-repressors simultaneously and the stoichiometric balance of them dictates the antagonist action of Tamoxifen. Hence, we are also evaluating the ability of Tamoxifen to control initiation of transcription in breast cancer cells. We will also explore the agonistic/antagonistic action of Tamoxifen in cells expressing different levels of the repressors PAX2 or SNAIL.

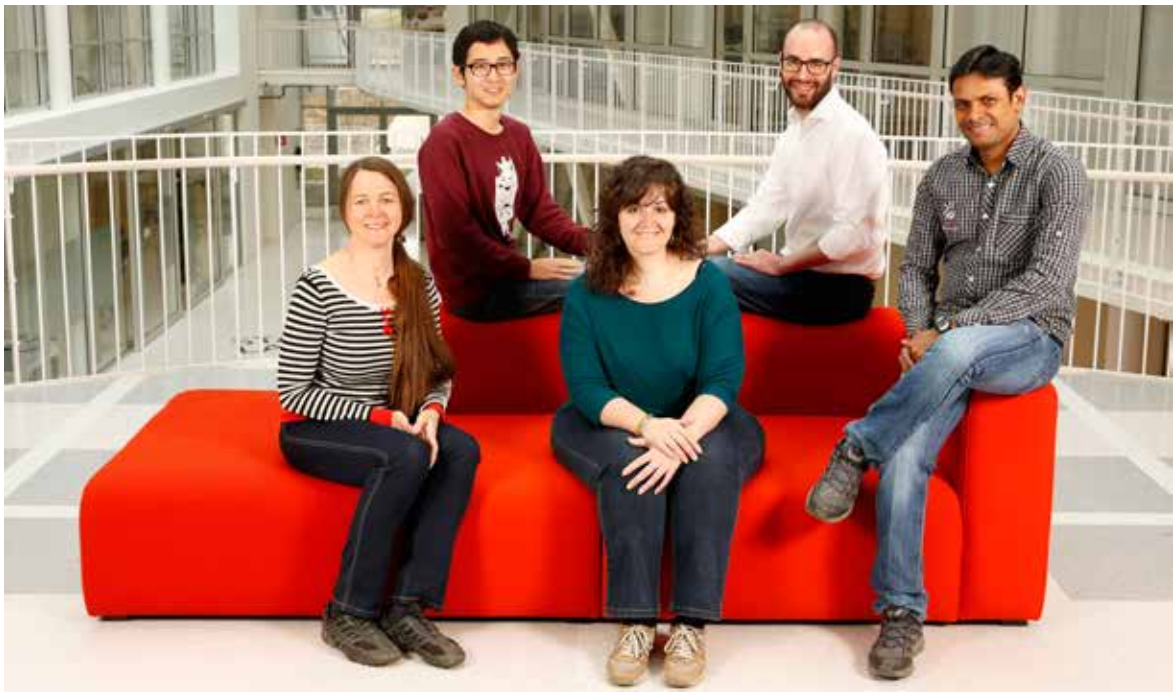
External funding

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 Taskén
Group Mills
Group Morth
Group Hurtado
Group Staerk
Group Nagelhus



Group members

Head Engineer:
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Postdoctoral fellows:
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Sachin Sighn (Starting in June 2015)

PhD fellows:
Elisa Fiorito
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Research assistant:
Helene Zell Thime (50% shared with Sørlie group)

MSc student:
Siri Nordhagen (until June 2014)

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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Tangen IL, Krakstad C, Halle MK, Werner HM, Oyan AM, Kusonmano K, Petersen K, Kalland KH, Akslen LA, Trovik J, Hurtado A, Salvesen HB. Switch in FOXA1 status associates with endometrial cancer progression. **PLoS One**. 2014 May 21;9(5)

GROUP STAERK

STEM CELLS

Judith Staerk

STEM CELL GROUP

Group leader
Judith Staerk

General description of research activity

Hematopoiesis describes the formation of all blood cells throughout life. This is guaranteed by asymmetric cell division of hematopoietic stem cells (HSC) that give rise to HSC and progenitors with limited renewing capacity. These progenitors produce lineage specific daughter cells that in turn form terminally differentiated erythroid/myeloid and lymphoid cells. HSC division and blood cell differentiation is tightly regulated by epigenetics, genetics and activation of specific signaling pathways. The deregulation of one or more of these biological processes can lead to blood disorders such as leukemia. We use primary human samples, patient-derived induced pluripotent stem cells (iPSC) as well as *in vivo* mouse and zebrafish animal models to unravel molecular and epigenetic processes during normal and malignant hematopoiesis.

The broad aims of our research are to:

1. Identify key epigenetic events during human hematopoietic development.
2. Identify underlying mechanisms of impaired blood cell differentiation using transgenic zebrafish and mouse models and iPS cells derived from patients suffering from blood disorders.
3. Understand how the nuclear lamina influences normal and malignant hematopoietic development.

1. Epigenetic dynamics during blood cell differentiation:

We are interested in understanding the dynamics of blood development, in particular the chromatin state and epigenetic signatures during differentiation. Several projects have been started related to this:

i) we performed a genome-wide 450K methylation and 5-hydroxymethylation analysis using genomic DNA isolated from human embryonic stem cells, CD34+ cord blood progenitor cells, cord blood mononuclear cells and myeloid cells (granulocytes) as well as peripheral adult blood cells. One open question in the field is still whether 5hmC serves as a stable epigenetic mark that is important for transcription factor (TF) recruitment, etc. Crossing our 5hmC with publically available ChIP-Seq data sets indicated that 5hmC levels correlate with binding of specific transcription factors known to be important for progenitor renewal. To investigate the

hypothesis that 5hmC is needed to recruit specific TF, we are currently performing sequential ChIP-oxidative bisulfite sequencing in order to define how methylation and 5hmC marks interplay with TF recruitment. To assess the biological relevance, we will use Tet2 deficient mice and primary cells from patients deficient for functional Tet2 in order to assess whether and how reduced 5hmC levels influence the binding of TFs known to be important for normal blood homeostasis.

ii) We are currently analysing FAIRE- and RNA-Seq data sets obtained from umbilical cord blood CD34+, CD34+/CD14+ myeloid progenitors and CD14+ monocytes to determine the chromatin state during monocyte differentiation with the aim to identify novel transcriptional regulators important for monocyte differentiation.

2. MDS related projects

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders characterized by inefficient hematopoiesis and a predisposition to developing acute myeloid leukemia (AML). The underlying cause for MDS is not well understood. Chromosomal abnormalities such as deletion of the long arm of chromosome 5 (5q-) and 7 (7q-) are found in some MDS-patients. The mutation leading to MDS is considered to be an acquired mutation in an HSC or early progenitor and differentiation defects mainly affect erythroid and myeloid lineages. Myeloid progenitors, granulocytes, and at least a sub-fraction of CD34+ cells are thought to harbor the mutation. We are using primary blood samples and iPSC from patient samples that harbor deletions of chromosomes 5 (5q-) as well as iPSC from unclassified MDS (no chromosomal abnormalities) in order to:

1. analyze the potential of MDS-iPSC to differentiate into hematopoietic cells
2. screen miRNA libraries to isolate factors that can reverse the potential block in *in vitro* blood cell differentiation;
3. analyze cytokine receptor trafficking

3. Lamin proteins and hematopoiesis

Another interest of our group is to understand how the nuclear lamina influences normal and malignant hematopoiesis. Lamins are the most abundant proteins in the nucleus and form a filamentous meshwork on the nucleoplasmic side of the nuclear envelope. B-type lamins are ubiquitously expressed and have been shown to be essential for cell survival, while A-type lamins are expressed in differentiated cells and seem to be largely absent from early embryonic tissues. Dysfunction of the nuclear envelope is associated with altered nuclear activity, impaired structural dynamics, aberrant cell signaling and altered gene expression. Importantly, Lamins are involved in chromatin organization and gene regulation with recent reports demonstrating that Lamin A/C bind chromatin regions in a cell lineage specific manner and that this is important to define cell fate. Surprisingly little is known about lamin function and regulation during hematopoiesis and we are currently using ChIP-Seq analysis to determine whether chromatin binding by Lamin A/C and Lamin B1 is blood lineage and differentiation specific. Additionally, we are investigating whether Lamins and the nuclear architecture are deregulated in myelodysplastic syndrome (MDS) and other blood disorders. Related to these studies we have started to generate conditional knockout and transgenic animal models to determine the exact role of Lamin proteins during hematopoietic development.

The group aims to understand molecular processes during normal and malignant hematopoiesis

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Group Mills
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Selected Key Publications from PI:

Staerk J and Constantinescu S.N. The JAK-STAT pathway and hematopoietic stem cells from the JAK2V617F perspective. **JAK-STAT.** 2012 Volume 1:3, 2012

Staerk J, Dawlaty MM, Gao Q, Maetzel D, Hanna J, Sommer CA, Mostolovsky G, Jaenisch R (2010) Reprogramming of human peripheral blood cells to induced pluripotent stem cells. **Cell Stem Cell.** 7(1):20-4.

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GROUP NAGELHUS

GLIO-VASCULAR IMAGING

Erlend Nagelhus

GLIO-VASCULAR IMAGING GROUP

Group leader
Erlend Nagelhus

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.

The group explores roles of glia in neurological disorders by *in vivo* two-photon laser scanning microscopy

Photo: Jarle Nyttingnes

Group Taskén
Group Mills
Group Morth
Group Hurtado
Group Staerk
Group Nagelhus

Selected Key Publications from PI:

Enger R, Tang W, Vindedal GF, Jensen V, Helm PJ, Sprengel R, Looger LL, Nagelhus EA (2015) Dynamics of ionic shifts in cortical spreading depression. **Cereb Cortex**, in press.

Tang W, Szokol K, Jensen V, Enger R, Trivedi C, Hvalby Ø, Helm PJ, Looger LL, Sprengel R, Nagelhus EA (2015) Stimulation-evoked Ca2+ signals in astrocytic processes at hippocampal CA3-CA1 synapses of adult mice are modulated by glutamate and ATP. **J Neurosci** 35:3016-3021.

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Associated members:
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Alexander S. Thrane
Vinita Rangroo Thrane


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NCMM ADMINISTRATION

NCMM Administration

NCMM had at the end of 2014 approx. 100 employees (83 employees excluding Founding Partners). In addition to Centre Director Kjetil Taskén and the 6 research groups, NCMM also has a small administration consisting of Elisa Bjørgo (Administrative Coordinator/CAO), Anita E. Skolem (Financial Officer) and Nina Modahl (Human Resources Officer). The administration is working closely with the administration at the adjacent Biotechnology Centre (BiO) to complement each others expertise and to be able to offer a smooth and effective service to our researchers. Nina Modahl has a joint position at NCMM and BiO and handles personnel matters at both centers. In addition to being NCMM's financial officer, Anita Skolem also handles large purchases for both centers. Elisa Bjørgo has ten years of research experience after her PhD and aims to narrow the gap between scientific and administrative needs by being able to understand both scientific aspects as well as operating the administrative systems.

From the left: Nina Modahl, Anita Skolem and Elisa Bjørgo.

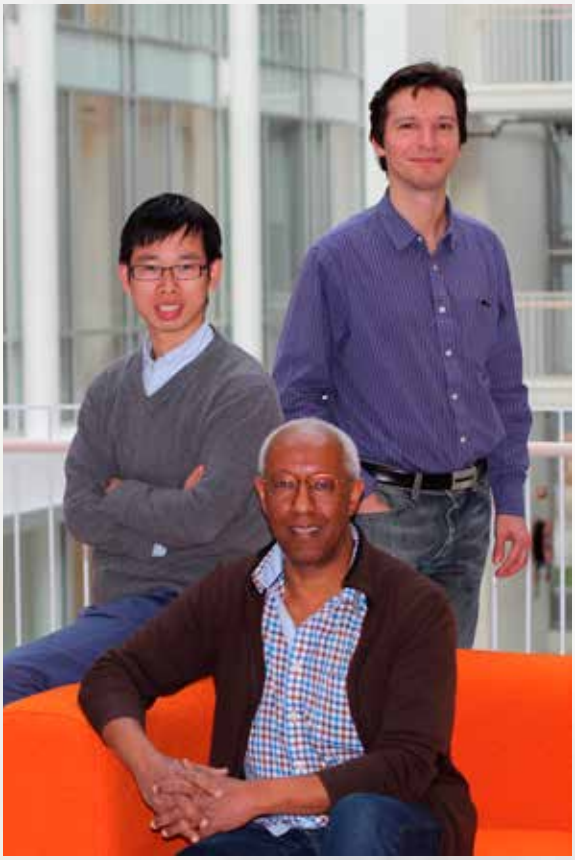


Photo: Ingrid Kjelsvik

From the left: Gang Cheng, Melaku Tadesse and George Magklaras.

IT Team

The IT team provides internal services for employees at both the Biotechnology Centre and NCMM and consists of IT Systems Manager George Magklaras (PhD) and IT Officers Gang Cheng and Melaku Tadesse.

The IT engineers in the team possess a broad range of skills in the areas of personal and scientific (Life Science, Bioinformatics) computing. The IT infrastructure includes:

- 325 desktop and lab instrument computers,
- 110 VoIP telephones
- a number of network laser printers and copy machines -two production data networks with wired (10G, 1G) and wireless (WiFi) capability
- 14 centralized servers for scientific computing, virtualization and file storage services, approximating 65 Tb of backed up disk storage, 128 processing cores, and a total of 488 Gbytes of RAM.

Emphasis is placed in facilitating more than 200 bioinformatics/Life Science Computing applications and environments managing the vital scientific data production for many facilities at the two Centers. The IT Team also assists in provisioning access to the University of Oslo supercomputer (Abel) facilities by interfacing to the Department of Research Computing, at the University Center for Information Technology (USIT).

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.

The network of NCMM Associate Investigators was established in 2010 when 7 outstanding researchers and key research groups working across Norway were appointed Associated Investigators. 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 by the appointment of 5 new members. In addition, Prof. Erlend Nagelhus was appointed Associate Investigator when he rotated out as group leader at NCMM bringing the total number of outstanding senior Norwegian scientists affiliated with NCMM to thirteen:

- **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 Erlend Nagelhus:** Institute of Basic Medical Sciences, University of Oslo (appointed from Jan. 2015)
- **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)

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. In 2014 seven new collaborative projects with AIs received funding from NCMM:

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

In 2015 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.

Furthermore, NCMM has initiated a Young Associate Investigator program 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 first two NCMM YAIs were appointed at the University of Tromsø in 2014 and NCMM is looking forward to collaborating with other institutions as well as to establish a network of NCMM Young Associate Investigators.

NCMM YOUNG ASSOCIATE INVESTIGATORS

Stem Cell Aging and Cancer research Group, Dept. of Medical Biology, The University of Tromsø.

Lorena Arranz

The Arranz group aims at understanding the complex interactions of the leukemic stem cell with its surrounding microenvironment in the bone marrow niche, and their potential contribution to disease development of haematopoietic malignancies. The group's goal is to identify novel therapeutic targets of potential clinical interest using a variety of state-of-the-art techniques in the field, including novel mouse genetic tools, stem cells, omics and advanced imaging. The group has a broad international network and strengthens translational research through established collaborations with the University Hospital of North Norway (UNN).

Acute myeloid leukemia (AML) is the most common form of acute leukemia occurring in adults, its incidence increases with age and the prognosis for the older patient remains bleak. So far, scientific focus has been placed on the search for inflammatory mediators required for development of AML, with no consideration of the anti-inflammatory properties of the bone marrow haematopoietic stem cell niche. The Arranz group aims at understanding the interaction of the leukaemic stem cell with its niche, and its potential contribution to AML development/progression.

Dr. Arranz graduated in biology (biomedicine) and obtained her PhD in physiology at the Universidad Complutense de Madrid (UCM) in 2009. Furthermore, Dr. Arranz has had two postdoc periods at the Fundacion Centro Nacional de Investigaciones Cardiovasculares (CNIC). During her first postdoc she studied the contribution of dysregulated Polycomb proteins in haematopoietic stem cells to both aging and the haematopoietic malignancies. In her second postdoc period she was able to describe for the first time the critical role played by the haematopoietic stem cell niche in the pathogenesis of these disorders. This work was published in Nature and received a Merit Award at the congress of the American Society of Hematology (ASH) in 2013. Dr. Arranz joined the Dept. of Medical Biology at the University of Tromsø in November 2014.

Sören Abel

Sören Abel was recruited from Harvard Medical School where he has been a postdoc in infection biology since 2012. During his postdoc he studied the population dynamics of the enteric pathogen Vibrio cholera during infection. By combining population analysis frameworks with high-throughput DNA sequencing technology and large libraries of tagged pathogens, he generated a new approach for dissection of microbial population dynamics (STAMP), which was recently published in Nature Methods. Furthermore, he holds a PhD in molecular microbiology from the Biozentrum at the University of Basel (2008), where he investigated the molecular mechanisms that regulate the bacterial second messenger c-di-GMP. This regulator of virulence and persistence is highly responsive to the environmental conditions that surround bacteria and enables their adaptation and survival, e.g. in the case of V. cholerae during the transition from host to marine environment. Dr. Abel will join the University of Tromsø in May 2015 and will establish his group at the Dept. of Pharmacy. The Abel group will study how bacterial pathogens adapt to environmental changes during their infection cycle within and between hosts, which molecular factors are of key importance for this adaptation and how these change the pathogens population dynamics.

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).

Oslo University Hospital is a merger of three former university hospitals in Oslo. Biomedical research is one of the hospital's core activities. Research at the hospital is closely interlinked with research undertaken at the University of Oslo.

All NCMM Group Leaders have adjunct appointments in clinical or para-clinical departments in OUH. The experience so far with these affiliations is that they facilitate clinical collaborations, give group leaders better access to patient materials, biobanks and clinical trials and that they are crucial to facilitate translational research. These research collaborations have already resulted in joint publications and NCMM Group Leaders also report on several joint applications for funding of new collaborative projects. Moreover, feed-back from both our Group Leaders as well as from the adjunct departments at OUH reveals an interest to strengthen the interactions further to establish an even more diverse and dynamic research environment in the future.

Adjunct Appointments

Department of Infectious Diseases (OUH)

Group Leader Kjetil Taskén

The department is the largest of its kind in Norway and covers the entire field of 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 and is organized under the Medicine Division at OUH.

Department of Molecular Oncology, Institute for Cancer Research (OUH)

Group leader Ian Mills

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 Cancer Medicine, Surgery and Transplantation at OUH.

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.

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 in clinical departments at the OUH and is interacting with colleagues both nationally and internationally. The institute is organized under the Division of Cardiovascular and Pulmonary Disease at OUH.

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. The department is organized under the Division of Cancer Medicine, Surgery and Transplantation at OUH.

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. The department is organized under the Division of Surgery and Clinical Neuroscience.

FROM DISEASE MECHANISMS TO CLINICAL PRACTICE

NCMM group leaders have so far listed some 35 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-AKAP18d-phospholamban-Serca2 complex for cardio-protective effect in ischemia-reperfusion 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
- Cancer drug sensitivity screening on patient samples with set of 400 cancer drugs to assist clinical decision on individualized therapy choices in chronic lymphatic leukemia, multiple myeloma and ovarian cancer
- Elucidation of the mechanism of action of medroxiprogesterone injection before surgery as a treatment that improves overall and disease-free survival of ER+/HER2- breast cancer patients

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 tumor cells. Evaluation of protein biomarkers in blood samples from patients with prostate cancer undergoing radiotherapy with or without androgen deprivation therapy.

- 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

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)

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).

RESEARCH HIGHLIGHTS

Coping with stress and tipping it over the edge

Secretory cells have high rates of transcription and protein synthesis which place high demands on RNA processing and protein folding machinery. Secretory luminal epithelial cells expressing high levels of the androgen receptor are one possible cell type of origin for prostate cancers. In a recent collaborative study led by Fahri Saatcioglu's group at the Dept. of Biosciences, UiO the Mills group has shown that one arm of the unfolded protein response is highly dependent on AR activity for its expression (Sheng, Arnoldussen et al. 2015). This is then conserved to support oncogenic metabolic stress as the cancer emerges. Targeting AR-dependent genes within the unfolded protein response limited cancer cell growth and tumour development putatively by making the cancer cells more sensitive to the cytotoxic effects of dysregulated metabolism (Barfeld, Itkonen et al. 2014). Examples of similar dependencies exist for other cancer types affecting other arms of the unfolded protein response pathway (Hart, Cunningham et al. 2012).

The nucleolus is a critical subcellular structure for efficient RNA processing and particularly to sustain ribosome biogenesis and support protein biosynthesis. A number of oncogenic transcription factors, particularly MYC, are known to enhance protein synthesis and ribosome biogenesis in cancer cells. In a recent paper NCMM group leader Ian Mills with collaborators (Chabes group (MIMS); Ceder group (Lund University), Visakorpi group (Tampere University) and the Rennie group (University of British Columbia) reported that enzymes required for de novo purine nucleotide biosynthesis are MYC-dependent (Barfeld, Fazli et al. 2015). Drugging one of these enzymes, required for guanine nucleotide biosynthesis, imposed nucleolar stress on prostate cancer cells, leading to a reduction in the levels of nucleolar proteins but also of MYC itself and a concomitant increase in the p53 tumour suppressor in a wild-type cell-line. This stress-associated rebalancing of the levels of an oncogene and a tumour suppressor was accompanied by increased cell-line sensitivity to anti-androgens and androgen synthesis inhibitors that are used clinically to treat prostate cancer(Barfeld, Fazli et al. 2015). The stress-inducing drug used in this study is clinically approved and the pre-clinical repurposing described in this study suggests that stress inducers could be used in combination with other new drugs to enhance therapy response.

In conclusion, targeting pathways to reduce the ability of cancer cells to cope with stress may represent an important general strategy to improve prostate cancer treatment and limit progression. The challenge

will be determining how much stress is too much for the cancer cells whilst preserving a therapeutic index and in which contexts to apply these approaches clinically.

Barfeld, S. J., L. Fazli, M. Persson, L. Marjavaara, A. Urbanucci, K. M. Kaukoniemi, P. S. Rennie, Y. Ceder, A. Chabes, T. Visakorpi and I. G. Mills (2015). "Myc-dependent purine biosynthesis affects nucleolar stress and therapy response in prostate cancer." Oncotarget In Press.

Barfeld, S. J., H. M. Itkonen, A. Urbanucci and I. G. Mills (2014). "Androgen-regulated metabolism and biosynthesis in prostate cancer." Endocr Relat Cancer 21(4): T57-66.

Hart, L. S., J. T. Cunningham, T. Datta, S. Dey, F. Tameire, S. L. Lehman, B. Qiu, H. Zhang, G. Cerniglia, M. Bi, Y. Li, Y. Gao, H. Liu, C. Li, A. Maity, A. Thomas-Tikhonenko, A. E. Perl, A. Koong, S. Y. Fuchs, J. A. Diehl, I. G. Mills, D. Ruggero and C. Koumenis (2012). "ER stress-mediated autophagy promotes Myc-dependent transformation and tumor growth." J Clin Invest 122(12): 4621-4634.

Sheng, X., Y. J. Arnoldussen, M. Storm, M. Tesikova, H. Z. Nenseth, S. Zhao, L. Fazli, P. Rennie, B. Risberg, H. Waehre, H. Danielsen, I. G. Mills, Y. Jin, G. Hotamisligil and F. Saatcioglu (2015). "Divergent androgen regulation of unfolded protein response pathways drives prostate cancer." EMBO Mol Med.

Liver Transplantation as treatment for Colorectal Liver Metastases

Transplantation surgeon and researcher Morten Hagness at the Institute of Clinical Medicine (Oslo University Hospital, OUH) and in NCMM group leader Kjetil Taskén's research group defended his PhD thesis "*Liver Transplantation for Colorectal Liver Metastases - Clinical and Immunological Considerations*" in May 2014. Hagness studied liver transplantation as a treatment against liver metastases in colorectal cancer patients.

Colorectal cancer is a common type of cancer that often spreads to the liver. If the liver metastases are not surgically removed, the patients have poor prognosis. However, in a new study, liver transplants were performed as treatment in patients with this condition. Of the 21 patients that participated in the study, 6 out of 10 were still alive after 5 years and 7 patients were cancer free. Without the liver transplant less than 1 out of 10 would most likely still be alive after 5 years. This study is unique internationally.

The researchers hope to offer this treatment to many new patients. However, donor livers are a limited resource and it is therefore very important that patients that get a liver transplant have good long-term results. In the transplant study material, Hagness and colleagues identified factors that will enable them to identify patients that will benefit most from a liver transplant and they expect that 50-100 patients will be a match for this treatment on a yearly basis. This will improve the long-term outcomes further. The cost of liver transplantation is approximately the same as for chemotherapy but the life quality is significantly improved.

Liver transplant patients must be on lifelong immunosuppressive therapy to prevent rejection of the donor liver. This is a double-edged sword since the immune system is important to fight cancer cells. Many of the transplant patients had recurrence of cancer after transplantation. Secondary cancer in the lung appeared to grow slowly and could often be surgically removed. Furthermore, it also turned out that some of the patients had lung metastases already at the time of transplantation without this affecting survival negatively. Still, the study did not reveal an explosion in cancer growth as a result of immunosuppressive therapy.

Morten Hagness (MD, PhD)

This project has now received funding until 2018 and a new study has been initiated. The researchers are also planning a new study in collaboration with 20 European centers and the researchers are being invited world-wide to give talks about this study. The study has also received attention in Norwegian media:

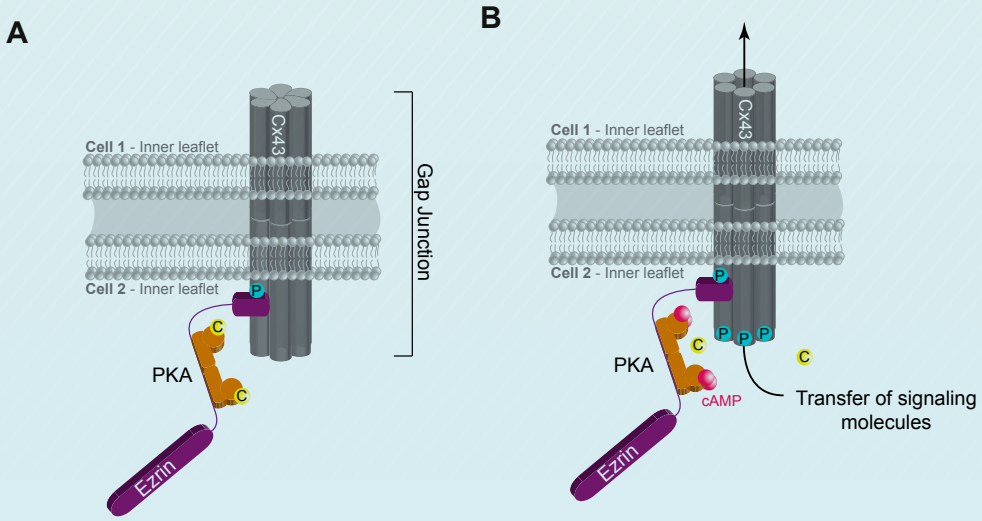
http://www.nrk.no/viten/flere-overlever-kreft-med-ny-lever-1.11740223
http://www.vg.no/nyheter/innenriks/flere-overlever-kreft-med-ny-lever/a/10124054/
http://forskning.no/sykdommer/2014/05/flere-overlever-kreft-med-ny-lever

Identification of a novel signaling complex important for communication and trophoblast cell fusion

NCMM group leader Kjetil Taskén and his colleagues at INSERM (Paris, France) recently identified a signalling complex that controls and regulates the communication between human trophoblasts and that is necessary to obtain cell fusions in the placenta.

Cell fusion processes are complex phenomena that are essential in processes such as placenta formation, fetal development and formation of skeletal muscles. Communication between adjacent cells can occur through gap junctions which are composed of connexin hexamers in the membrane and that align with similar structures on neighboring cells to form gap junction channels that allow for the exchange of ions, metabolites and second messengers. Connexin 43 (Cx43) is a key gap junction protein expressed in fusion competent human cytotrophoblasts. In the present study, the anchoring protein Ezrin is for the first time shown to play a key role in the cell membrane of human trophoblasts where it interacts directly with Cx43 and regulates its phosphorylation status by bringing PKA in close vicinity to Cx43. Thus, Ezrin promotes gap junctional communication by facilitating the spatiotemporal control of Cx43 phos phorylation by PKA, thereby controlling hCG-regulated cell fusion.

The full article *"A PKA-ezrin-Cx43 signaling complex controls gap junction communication and thereby trophoblast cell fusion"* can be found in Journal of Cell Science, Volume 127, 2014, pages 4172-85. doi: 10.1242/jcs.149609



Cx43 gap junction communication is controlled by PKA anchoring through ezrin. (A) Schematic depiction of a resting state gap junction in trophoblast with Cx43 and a compartmentalized pool of PKA anchored to ezrin which again is bound to Cx43. (B) Elevated intracellular cAMP levels lead to activation of PKA and subsequent spatiotemporally controlled phosphorylation of Cx43 which promotes the communication through the gap junction. C, catalytic subunit of PKA; P for phosphorylation; pink dots, molecules of cAMP. Illustration from Pidoux G & Taskén K Commentary.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NCMM PHD DISSERTATIONS

NCMM currently has 18 PhD fellows that have been recruited from nine different countries. This international group of students is working on exciting projects in translational molecular medicine. In 2014 the first two NCMM PhD students defended their thesis.

Harri M. Itkonen

Dr. Harri M. Itkonen

Harri M. Itkonen was recruited from Finland and started as a PhD fellow in Ian Mills' research group in June 2010. In May 2014 he defended the title of his thesis for the PhD degree (philosophiae doctor) at the Department of Biosciences, Faculty of Mathematics and Natural Sciences: "***Glycosylation in prostate cancer***".

Prostate cancer is the most frequently diagnosed cancer in men in the USA and Europe. Cancer cells acquire an ability to proliferate continuously and this is accompanied by alterations in the gene expression program. Cancer cells consume glucose in an energy-inefficient way that enables the build-up of carbon for fast dividing cells. In this work, Itkonen and co-workers used clinical gene expression data and identified the hexosamine biosynthetic pathway (HBP) as a process that is frequently up-regulated in clinical prostate cancer. This pathway supports a single enzyme (O-GlcNAc transferase, OGT) which modifies target proteins via single sugar modification. OGT was shown to be over-expressed in prostate cancer patients with poor prognosis. Inhibition of the OGT activity in cancer cell lines decreased the ability to proliferate, and Itkonen identified a well-described oncogene, MYC, to be lost in cancer cells if OGT activity was inhibited. In addition, Itkonen and co-workers showed that increased expression of the HBP enzymes is accompanied with increased end-product of the pathway, required for the production of secretory proteins. If HBP activity is inhibited, cancer cells are sensitized to the drugs interfering with processing of secretory proteins, which was demonstrated by multiple markers including clinically used prostate cancer biomarker, prostate specific antigen.

In conclusion, Itkonen's Thesis identified a metabolic process that is hyper-activated in cancer cells. This work identified new potential drug targets and serves as a starting point for a more detailed analysis of HBP activity and glycosylation in cancer cells. Dr. Itkonen is currently a postdoc in the Mills group.

Kaare Bjerregaard-Andersen

Kaare Bjerregaard-Andersen was recruited from Denmark and started as a PhD fellow in the research group of Preben Morth in November 2011. In June 2014 he defended the title of his thesis for the PhD degree (philosophiae doctor) at the Department of Biosciences, Faculty of Mathematics and Natural Sciences: "***Structural and biophysical studies of the mammalian Na+ dependent Cl--HCO3- exchanger NCBE and the bacterial enzyme isatin hydrolase***". The degree is a joint degree between the University of Oslo and Aarhus University in Denmark.

Dr. Kaare Bjerregaard-Andersen

During his studies, Kaare Bjerregaard-Andersen used X-ray crystallography supplemented by biophysical techniques to study the molecular structure of the sodium-coupled chloride-bicarbonate exchanger (NCBE). In addition, he elucidated the protein structural basis of catalysis of the enzyme isatin hydrolase.

A stable and controlled pH is essential to cellular function. The pH can be controlled by maintaining a buffering system for minimizing the effect of sudden pH challenges to the organism. In the human body, 2/3 of the buffering capacity is based on bicarbonate. The solute carrier 4 family (SLC4) comprises the major group of membrane proteins responsible for facilitating bicarbonate transport across the plasma membrane. However, little is known about the molecular structure of this important family of proteins. During his studies, Kaare Bjerregaard-Andersen characterized the sodium-coupled chloride-bicarbonate exchanger (NCBE), a SLC4 member predominantly found in the choroid plexus of the brain and highly involved in pH homeostasis of the cerebrospinal fluid. He determined the atomic structure of the N-terminal cytoplasmic region of the protein and identified potential novel ligands. Furthermore, he characterized regions of intrinsically disordered protein structure in the cytoplasmic domain and recognized these regions in the super family of SLC4 bicarbonate transporters. In addition to his work on NCBE, Bjerregaard-Andersen also determined the atomic structure of the metalloenzyme isatin hydrolase. Here he identified a proton wire and water channel which he showed to be catalytically involved. The structural work was supported by enzyme kinetic and biophysical studies. The structure represents the first characterized member of its class of metal-dependent hydrolases. Based on the enzymatic characterization he contributed to the development of a quantification assay for isatin in human blood.

These new findings contribute to our understanding of the molecular structure and function of sodium-coupled bicarbonate transporters being composed of ordered as well as disordered structure. Bjerregaard-Andersen's work provides detailed understanding of the structural basis of catalysis by the isatin hydrolase. Dr. Bjerregaard-Andersen is currently a postdoc in the Morth group at NCMM.

NCMM EVENTS 2014

Photo: MIMS, Umeå

Participants at the 5th NMMN Meeting in Umeå. Sweden.

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.

The 5th NMMN Meeting was hosted by MIMS in Umeå, Sweden on 26-28 August 2014 where more than 120 participants from all the four Nordic EMBL nodes as well as from EMBL enjoyed two days of scientific interaction. Altogether 38 talks including a keynote lecture by Dr. Emmanuelle Charpentier on her discoveries on CRISPR-Cas9 discovery and its applications as well as some 50 posters were presented during the meeting. Harri Itkonen from NCMM was one of 4 poster award winners. Furthermore, the annual Nordic EMBL Partnership Steering Committee meeting also took place during the NMMN conference.

Photo: Elisa Fiorito, NCMM

NCMM Scientific Retreat

In November 2014, NCMM and the Biotechnology Centre organized a joint scientific retreat that took place at the Quality Spa & Resort Son, just outside Oslo. This two-day event included both scientific talks and discussions, a social dinner and outdoor activities. The purpose of such an annual retreat is to provide both researchers and administrative staff an opportunity to interact both professionally and socially, hopefully contributing to both a pleasant but also a more effective and collaborative working atmosphere.

NCMM PhD training courses

NCMM has established an annual two-week national PhD courses in Molecular Medicine (MF9120BTS) that is organized every autumn. The aim of this course is to provide a good overview of selected topics in molecular medicine that are relevant for understanding disease mechanisms and development, aspects of translational medicine and the future of diagnostics and targeted therapies integrated to stratified, tailored and personalized medicine. In 2014, 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. The course aims to give its participants insights into the translational and clinical aspects of science. Furthermore, students in clinical medicine get the opportunity to gain new insights into molecular mechanisms, disease models and preclinical work.

Photo: Johannes Landskron

Forsker Grand Prix

Forsker Grand Prix is a popular science event where scientists from various disciplines get the opportunity to present their research in just a few minutes. NCMM PhD fellow Stefan Barfeld was one of 10 chosen candidates to compete in the Oslo regional final in September 2014 and the title of his presentation was “The invisible enemy”.

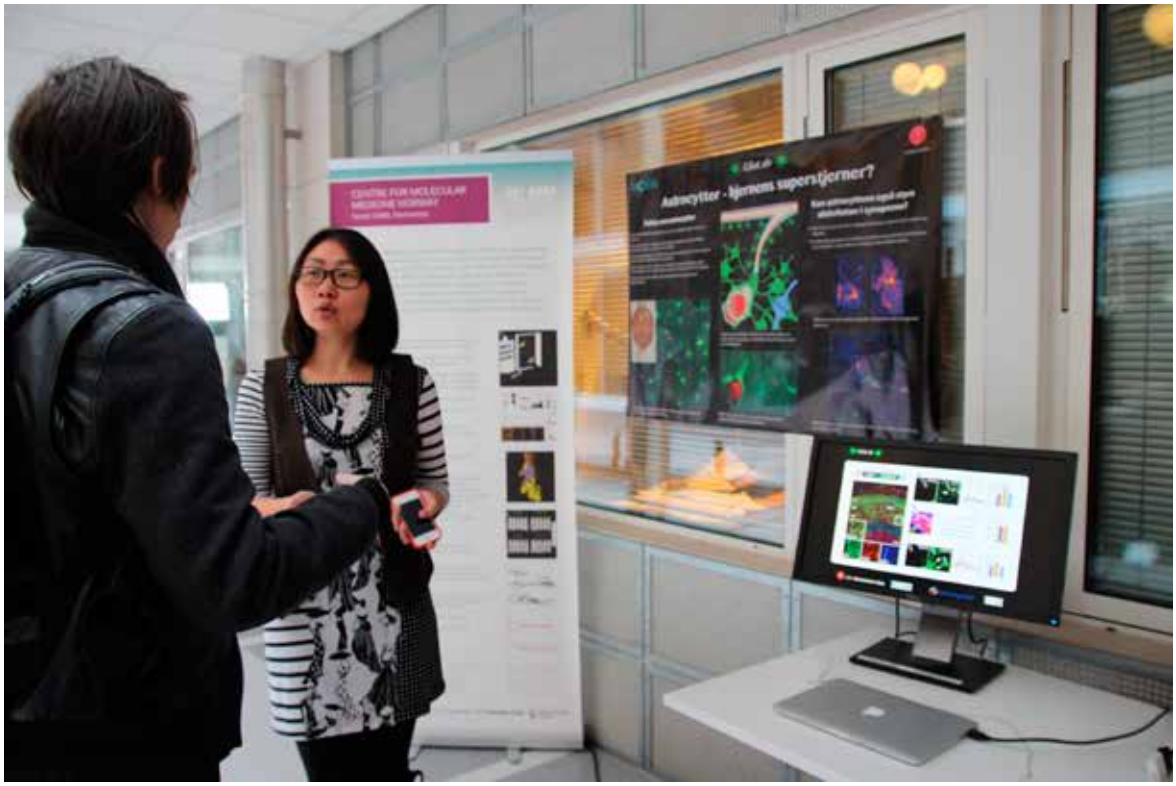
Photo: Benjamin A. Ward, Høyskolen i Oslo og Akershus.

PhD fellow Stefan Barfeld presenting «The invisible enemy» at Forsker Grand Prix 2014.

Social Committee

The Biotechnology Centre (BiO) and NCMM have a joint social committee organizing regular events to strengthen the social interactions between the centres. Both BiO and NCMM have an international staff and building up social networks in Norway is important for the employees to thrive and thus perform well also professionally. Among the social activities organized by the committee are annual summer and Christmas parties and coaching for and participation in the traditional running relay Holmenkollstafetten. The race is open to everyone and every year, approximately 2500 teams and 40 000 participants from all of Norway meet compete here in Oslo.

Photo: Astrid Lund, Oslo Science Park



Cutting Edge 2014: GliaLab stand.

NCMM Stand at Cutting Edge 2014

In October 2014, the Oslo Innovation Week was organized with more than 40 different events all over Oslo. One of the events was Cutting Edge aiming to highlight new technology and research important for the future. NCMM and the GliaLab had a stand at this event that attracted many visitors. The GliaLab is studying functions of astrocytes, the predominant glial cell type of the central nervous system. NCMM Group Leader Erlend Nagelhus is heading the GliaLab that aims to resolve roles of astrocytes in the healthy and diseased brain. Their principal technology is in vivo two-photon laser scanning microscopy that allows real-time imaging of physiological and pathophysiological processes in the brain of living animals.

NCMM – STRUCTURE

NCMM is organized with non-tenured positions for outstanding young investigators and is hosted by the University of Oslo (UiO). The Centre is considered strategically important to spear head development and recruitment across UiO and OUH as well as to other national institutions. Until the end of 2014 both NCMM and the adjacent Biotechnology Centre (BiO) were placed under Molecular Life Science (MLSUiO), a strategic inter-facultary steering group reporting directly to the Rector. However, MLSUiO was replaced by a new and broader Life Science initiative from January 2015 and the Faculty of Medicine is therefore now hosting both NCMM and BiO following a formal decision by the University Board in March 2015. In addition, 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 governing body is the NCMM Board whereas the RCN operates the NCMM National Reference Group (see separate sections).


2
PARKEN BAKERI

From left to right: Ingvild Mikkola, Jan G. Bjålie , Øystein Krüger, Finn Eirik Johansen, Ragnhild A. Lothe and NCMM Director Kjetil Taskén.

Photo: Johannes Landskron

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. The Board consists of the Chair and five members representing NCMM's host the University of Oslo as well as the consortium partners Health South-East Regional Health Authority (HSE) and the Research Council of Norway (RCN) that co-finances and co-directs NCMM. 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 2014 the Board has had a special focus on securing long-term funding for the second five-year period (2015–2019). Furthermore, the Board has been involved in the evaluation processes of NCMM group leaders Ian Mills and J. Preben Morth and in the recruitment process for a new group leader in bioinformatics.

Current Board members are:

Chair:
Professor Ragnhild A. Lothe, Oslo University Hospital (OUH) – Radiumhospitalet and University of Oslo (UiO)

Members:
Professor Jan G. Bjålie, Faculty of Medicine, UiO
Professor Finn Eirik Johansen, Faculty of Mathematics and Natural Sciences, UiO
Professor Magnar Bjørås, OUH – Rikshospitalet
Professor Ole Sejersted, OUH – Ullevål
Professor Terje Espevik, Norwegian University of Science and Technology, Trondheim (representing the National Reference Group)

Deputy Members:
Professor Jens Petter Berg, Faculty of Medicine, UiO
Associate Professor Ingvild Mikkola, University of Tromsø (representing the National Reference Group)
Head of Research Øystein Krüger, Dept. of Research and Innovation, South-Eastern Norway Regional Health Authority (HSE)

After recruitment of international young and talented group leaders in the first period of NCMM, the Centre continues to publish excellent science and succeeds in receiving an increasing amount of extramural funding. Entering the second period we are pleased to report to the Faculty of Medicine, University of Oslo. The success of the translational projects of NCMM we believe can be ascribed to the united academic and clinical knowledge among the project participants, affiliated with the University of Oslo and the Oslo University Hospital

Chair R A Lothe

Photo: Johannes Landskron (NCMM/BIO)

From left to right: Alvis Brazma, Erich Nigg, Margaret Frame, SAB Chair Leif Groop, Annika Lindblom and Richard Treisman.

SCIENTIFIC ADVISORY BOARD (SAB)

The NCMM Scientific Advisory Board (SAB) was appointed by the Board in June 2011 and was in 2014 re-appointed as a joint SAB for NCMM and the Biotechnology Centre of Oslo from 2015. The main mission of the SAB 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 fourth site-visit took place in March 2015. This year the SAB was also involved in the evaluation process of NCMM group leader J. Preben Morth regarding the renewal of his position as group leader.

After the fourth visit, the SAB was pleased to see that "researchers at NCMM now have established themselves in the new environment and created research groups with translational application of biomedical research as a common denominator". Moreover, the SAB stated that NCMM researchers have "been able to build real bridges to the hospital, not at least in the field of cancer and haematological malignancies". Furthermore, regarding renewal of group leader J. Preben Morth the overall view of the SAB as well as the external reviewers was that "Dr Morth is a committed and effective structural biologist" and that he "has overcome major challenges in setting up an effective structural biology pipeline at the institute, and provides a rigorous biochemical/biophysical perspective which complements the more cell based and organismal approaches of the other research groups". The SAB thus recommended that he should be reappointed for a second five-year period.

The Scientific Advisory Board consists of six internationally renowned scientists:

Professor Leif Groop (Chair), 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
Professor Margaret Frame, Science Director and Chair of Cancer Biology, Edinburgh Cancer Research Centre. Edinburgh, UK

NATIONAL REFERENCE GROUP

The National Reference Group has been established by the Research Council of Norway (RCN) 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)

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

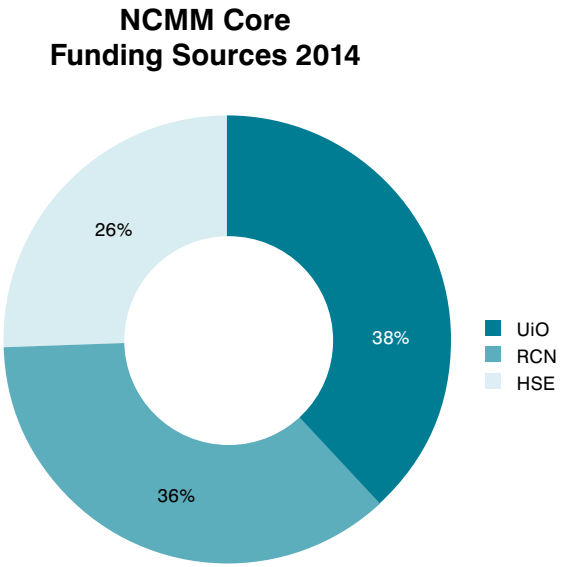
Professor Anne-Brit Kolstø
University of Oslo

Professor Vidar M. Steen
University of Bergen

NCMM FUNDING

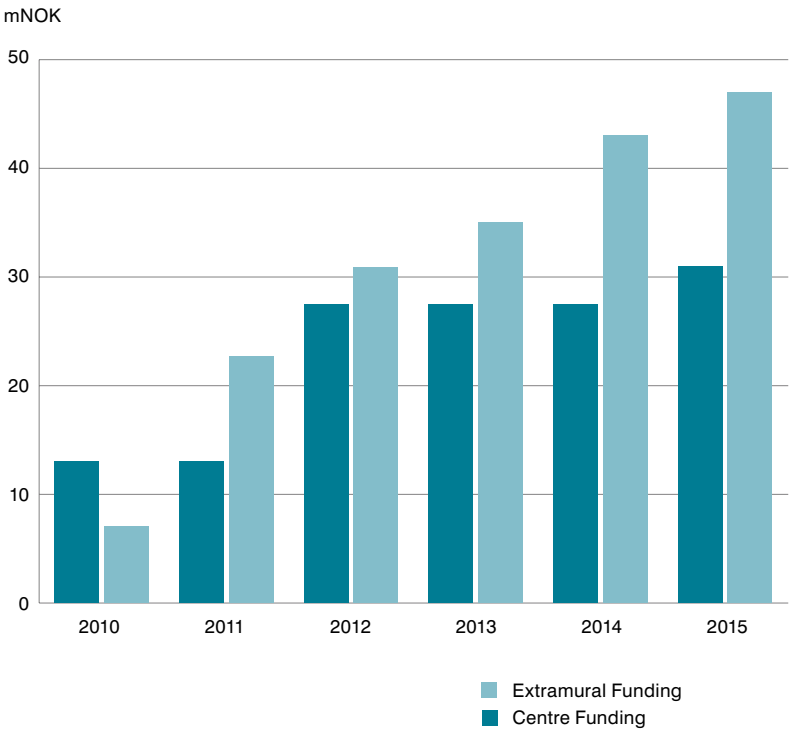
The **NCMM core funding** in the first five-year period (2009–2013) was 27 million Norwegian kroner (mNOK) (approximately 3.3 mEUR) per year from the 3 consortia partners UiO, Research Council of Norway and Health SouthEast. Core funding at the same level was also secured for the interim year 2014 and NCMM's partners have committed to fund the Centre for a second five-year period (2015-2019) where the core funding will be 31 million Norwegian kroner (approx. 3.8 mEUR) per year. Furthermore, overhead and production-based income comes in addition, which was 4.5 mNOK in 2014 and is budgeted at about the same level for 2015-19. Including transferred funds, NCMM spent 25 mNOK in 2014. For 2015, NCMM has a budget aiming for balance and plans to spend 36 mNOK. For the period 2015-2019 we stipulate the NCMM annual core budget expenses to be in the order of 35-36 mNOK (2015-value) with the present level of activity and including transferred funds.

NCMM extramural funding in the form of grants to the group leaders and other competitive funding has increased steadily from 7 mNOK in 2010 to 35 mNOK in 2013. In 2014 NCMM reached 43 mNOK in annual grants and is so far stipulated at 47 mNOK in 2015. 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.

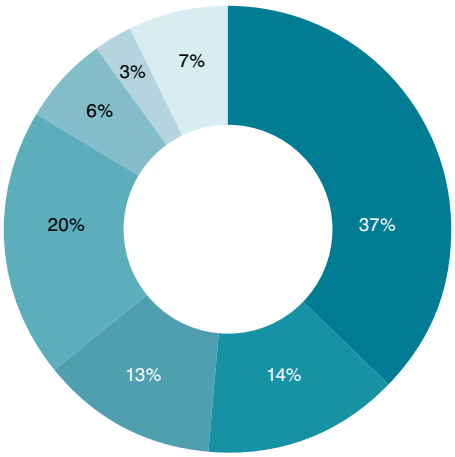


FUNDING STATISTICS

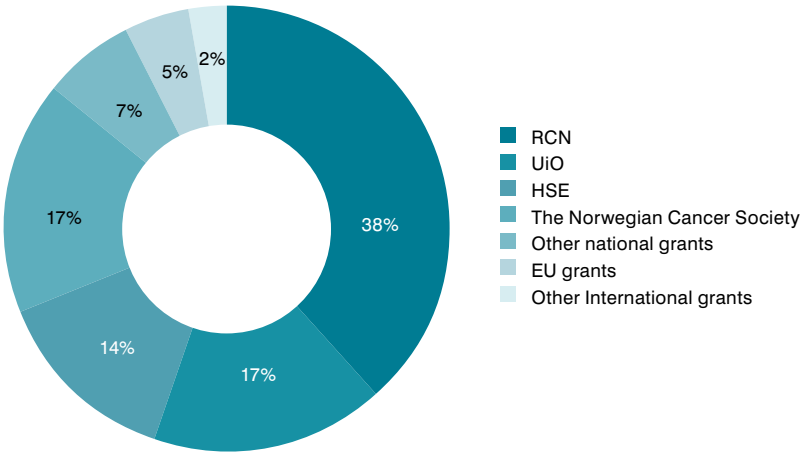
The illustrated funding overview includes only NCMM groups, including that of the Director from 2011. The 2015 data are based on accounts for the first quarter as well as on budget numbers for the rest of 2015.



Extramural Funding Sources 2014



Estimated Extramural Funding Sources 2015



The 2015 overview is an estimate of extramural funding sources based on budget and on secured grants.

NCMM – AFFILIATED PUBLICATIONS

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Brain region specific modulation of ethanol-induced depression of GABAergic neurons in the brain reward system by the nicotine receptor antagonist mecamylamine. Adermark L, Söderpalm B, Burkhardt JM (2014). **Alcohol**. 48, 5: 455-461. doi: 10.1016/j.alcohol.2014.06.004

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Shared common variants in prostate cancer and blood lipids. Andreassen OA, Zuber V, Thompson WK, Schork AJ, Bettella F, PRACTICAL Consortium, CRUK GWAS, Djurovic S, Desikan RS, Mills IG, Dale A (2014). **Int J Epidemiol.** 43: 1205-14. doi: 10.1093/ije/dyu090

Meta-analysis of prostate cancer gene expression data identifies a novel discriminatory signature enriched for glycosylating enzymes. Barfeld S, East P, Zuber V, Mills IG (2014). **BMC Med Genomics** 7: 513. DOI 10.1186/s12920-014-0074-9

Androgen-regulated metabolism and biosynthesis in prostate cancer. Barfeld S, Itkonen H, Urbanucci A, Mills IG (2014). **Endocr Relat Cancer** 21: T57-66. doi: 10.1530/ERC-13-0515

A proton wire and water channel revealed in the crystal structure of isatin hydrolase. Bjerregaard-Andersen K, Sommer T, Jensen JK, Jochimsen B, Etzerodt M, Morth JP (2014). **J Biol Chem**. 289: 21351-9. doi: 10.1074/jbc.M114.568824

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Endosomal signalling and oncogenesis. Engedal KN, Mills IG (2014). **Methods Enzymol**. 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 A, Skjelland M, Bjerkeli V, Sagen EL, Taskén K, Bendz B, Gullestad L, Holm S, Biessen EA, Aukrust P (2014). **Atherosclerosis** 234: 352-59. doi: 10.1016/j.atherosclerosis.2014.03.021

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A PKA-ezrin-Cx43 signaling complex controls gap junction communication and thereby trophoblast cell fusion. Pidoux G, Gerbaud P, Dompierre J, Lygren B, Saunders TS, Evain-Brion D, Taskén K (2014). **J Cell Sci.** 127: 4172-85. doi: 10.1242/jcs.149609

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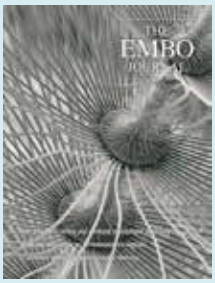

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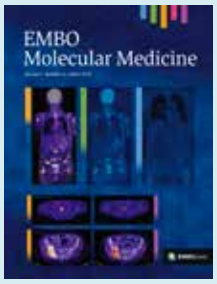

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Patents filed in 2014

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Cyclic Amino Compounds for Use in the Treatment of Cardiac Disorders. Inventors: Klaveness J, Taskén K, et al. US Patent Application No. 14/549,414 . Filed: 20-November-2014.

Prostate cancer markers and uses thereof. Inventors: Ian Mills and Ingrid J. Guldvik. US Patent Application No. 62099837. Filed: 5-January-2015.

Press Items

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.

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Norwegian Cancer Society: brochure on personalized medicine, Interview with Kjetil Taskén sent to 600 000 households in Norway.

Nasjonal Kreftsatsning: Klinisk kreftgenomikk – hva skal til? Panel discussions with NCMM group leader Ian Mills: https://www.youtube.com/watch?v=4xMeXIoAJ_U&feature=youtu.be

Nasjonal Kreftsatsning: Klinisk kreftgenomikk – hva skal til? Panel discussions with NCMM Director Kjetil Taskén: https://www.youtube.com/watch?v=hN34wFMOG_M

PERSONNEL

DIRECTOR AND ADMINISTRATION

Director
Professor Kjetil Taskén

Chief Administrative Officer
Dr. Elisa Bjørgo

Financial Officer
Anita Skolem

Human Resources Officer
Nina Modahl

RESEARCH GROUPS

Glio-vascular Imaging Group

NCMM Group Leader
Professor Erlend A. Nagelhus

Senior Engineer
P. Johannes Helm

Engineer
Iren Seflandt

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Dr. Anna Thoren
Dr. Klas H. Pettersen

Postdoctoral Fellows
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Dr. Wannan Tang

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Rune Enger
Gry F. Vindedal

Students enrolled in the Medical Student Research Program:
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Brana Rosic
Jarand Berg Hjukse

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Vinita Rangroo Thrane

Prostate Cancer Group

NCMM Group Leader
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Head Engineers
Ingrid Jenny Guldvik
Frank Sætre

Guest Researcher
Per O. Seglen

Researcher
Dr. Kim Nikolai Hartlieb Engedal

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Dr. Verena Zuber
Dr. Harri Itkonen

PhD Fellows
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Stefan Barfeld
Morten Luhr

MSc Student
Paula Szalai

Membrane Transport Group

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Steffi Munack (from September 2014)

Postdoctoral Fellows
Dr. Harmonie Perdreau Dahl
Dr. Kim Langmach Hein
Dr. Kaare Bjerregaard-Andersen
Dr. Johannes Bauer (from February 2015)

PhD Fellows
Theis Sommer
Saranya Subramani

MSc Students
Carolina Alvadia
Nina Fagernes (until June 2014)
Michele Montrasio (from September 2014)

Breast Cancer Group

NCMM Group Leader
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Dr. Venkata S. Somisetty (from November 2014)
Dr. Yogita Sharma (until February 2014)
Dr. Sachin Sighn (from June 2015)

PhD Fellow
Elisa Fiorito
Shixiong Wang (from October 2014)

Research assistant
Helene Zell Thime

MSc student
Siri Nordhagen (until June 2014)

Signaling Networks in Health and Disease

NCMM Group Leader
Professor Kjetil Taskén

Senior Researchers
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Dr. Johannes Landskron
Dr. Sigrid Skånland

Postdoctoral Fellows
Dr. Ana Isabel Costa Calejo
Dr. Lena Eroukhmanoff
Dr. Morten Hagness
Dr. Guro Mørk Johnsen
Dr. Anna Mari Lone
Dr. Kristina Berg Lorvik
Dr. Maria-Niki Mylanokou
Dr. Marie Rogne (until August 2014)
Dr. Vannessa L. Wehbi

PhD Fellows
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Aleksandra Dukić
Stalin C. Gunasekaran
Nora Lieske
Kristine Moltu
Ellen Østensen
Sorina Dinescu (from November 2014)

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Gladys Tjørhom

Administrative Officer
Berit Barkley

Chemical Biology Platform
Dr. Anne Jorunn Stokka
David McClymont

Stem Cell Group

NCMM Group Leader
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Principial Engineer
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Kirsti E. Præsteng (from March 2015)

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Dr. Xavier Tekpli
Dr. Ida Jonson
Dr. Marie Rogne (from August 2014)
Dr. Safak Caglayan (from September 2014)
Dr. Adnan Hashim (from February 2015)

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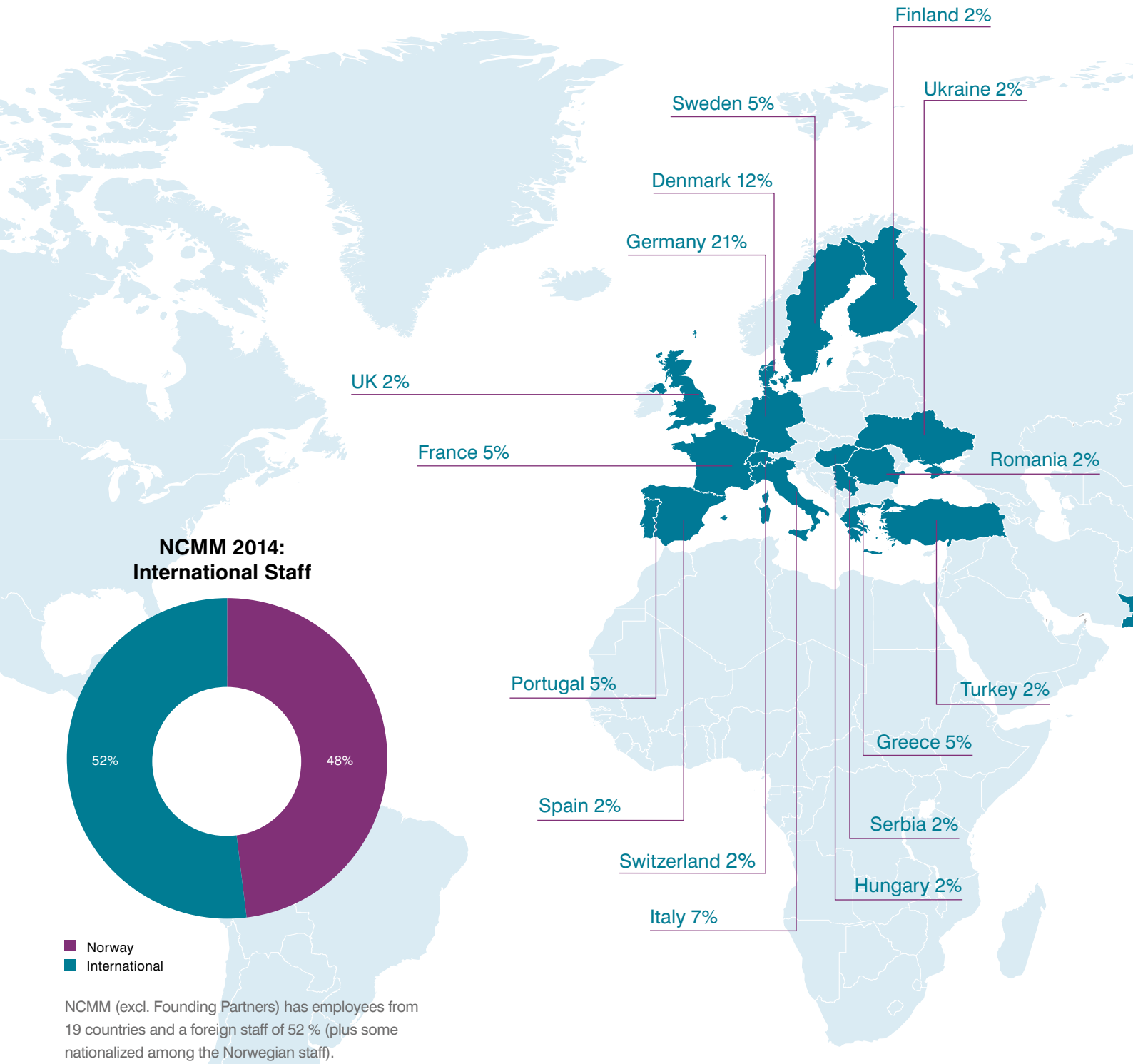
Julia-Kristina Jensen Madsen-Østerbye
Oksana Svärd

IT Team

Dr. George Magklaras
Gang Cheng
Melaku Tadesse

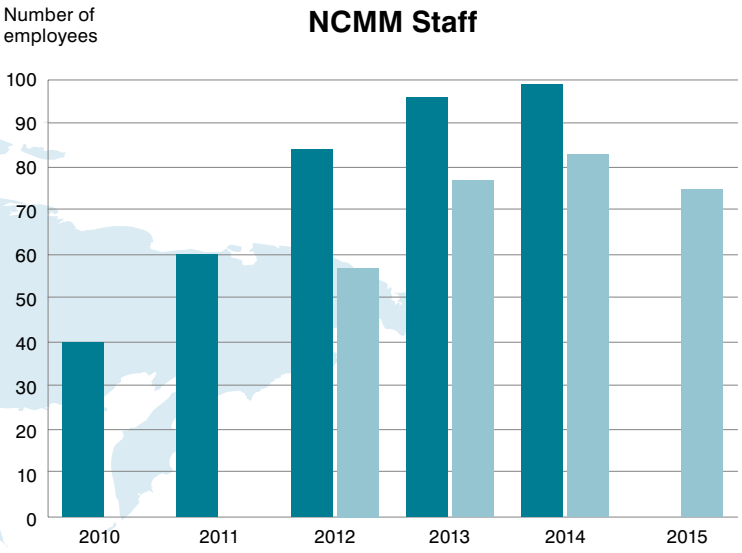
NCMM INTERNATIONAL STAFF DISTRIBUTION



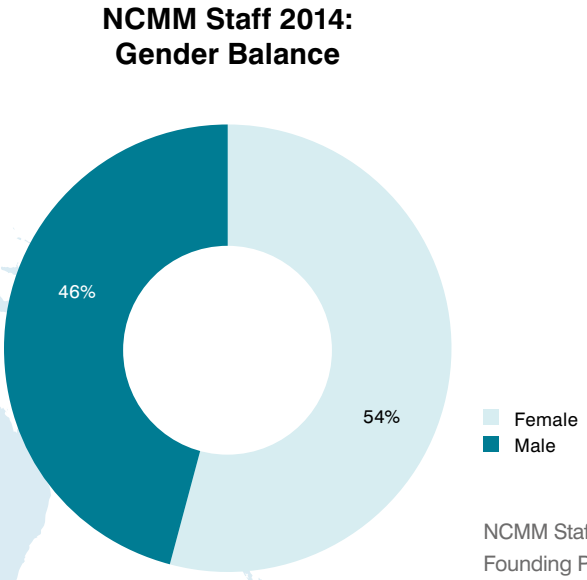
NCMM 2014: International Staff

NCMM (excl. Founding Partners) has employees from 19 countries and a foreign staff of 52 % (plus some nationalized among the Norwegian staff).

PERSONNEL STATISTICS



* Numbers for 2015 are estimated. The staff will be reduced in 2015 due to rotation of one research group out of the center. In addition, the Founding Partners (FP) arrangement has been terminated from 2015.



NCMM Staff excl. Founding Partners

Form og ombrekking: Millimeterpress
Merete Dagsgard/Lise Myhre
Trykk: Rolf Ottesen
Foto: Millimeterpress, Terje Heiestad
der ikke noe annet er skrevet