NCMM

Centre for Molecular Medicine Norway
Nordic EMBL Partnership for Molecular Medicine

Annual Report 2012

FROM DISEASE MECHANISMS
TO CLINICAL PRACTICE


Photo: Ola Sæther, UiO

Contents

NCMM Director Kjetil Taskén. Photo: John Hughes

Overview by the Director

Dear friends, colleagues and supporters of NCMM, I am proud to present the 2012 Annual Report from NCMM, which summarizes the activities in the 3rd full year of operations at NCMM. Although NCMM is still very young, the centre has grown rapidly in terms of mass and production during these 3 first years as described below and which holds great promise for the future.

NCMM HISTORY

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. The Partnership between EMBL, the Institute for Molecular Medicine Finland (FIMM, www.fimm.fi), the Centre for Molecular Medicine Norway (NCMM, www.ncmm.uio.no) and the Laboratory for Molecular Infection Medicine Sweden (MIMS, www.mims.se) is dedicated to the growing field of Life Sciences that investigates the molecular basis of disease and explores molecular and genetically based treatments. In 2012, a donation from the Lundbeck foundation allowed the establishment of a Danish Institute for Translational Neuroscience, Dandrite, at Aarhus University (www.dandrite.au.dk). Its formal opening and inauguration as member of the Nordic EMBL Partnership on March 5 2013 coincided with the signing of a new Partnership Agreement for the next ten years (2013-2022, see separate item).

Aiming to combine complementary strengths in the Nordic EMBL Partnership, each partner brings in a unique set of expertise, skills and facilities encompassing EMBL's recognized research strengths. This equips the partners to tackle some of the most challenging problems of biomedicine. The Partnership provides access to scientific infrastructure, including databases, facilities and instrumentation as well as to clinical materials and networks. Furthermore, training activities are provided by the partners, and the Partnership adopts the EMBL model for international recruitment, staff turnover and scientific reviews.

NCMM was formally inaugurated as a joint venture between the University of Oslo, as host, the Research Council of Norway and Health Region South East upon signing of the contract and consortium agreement at the end of 2008. NCMM had its first full operational year in 2010. 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 will investigate mechanisms of non-communicable diseases such as cancer, cardiovascular and CNS-related disease and immune disorders. NCMM will develop and adapt technologies for personalized medical applications and will be expected to unravel new diagnostic methods and drug targets. NCMM is also a partner in the EU-ESFRI project European Advanced Translational Infrastructure (www.eatris.eu) planning the future of translational research in Europe.

NCMM Structure

NCMM has a **Board** with representatives from the **University of Oslo** and Health **SouthEast Regional Health Authority** that co-funds and co-hosts NCMM (see separate section on the Board of Representatives), a non-voting member from the **Research Council of Norway** that co-funds NCMM together with the host institutions and a Board member that represents the **National Reference Group** (see separation section) that represents all universities and health regions in Norway and oversees and assists with the function as a national centre for molecular medicine.

FOUNDING PARTNERS

NCMM has three founding partners (Ole Petter Ottersen, Kjetil Taskén, Stefan Krauss) that were identified by the Research Council of Norway based on an excellence evaluation in molecular medicine. The founding partners together with their groups, were linked to NCMM for the first-five year period to provide scientific mass from the start, but have their main affiliation elsewhere at the University/University Hospital. **Dr. Ottersen** currently serves at the Rector of UiO and acting Group Leader Dr. Mahmood **Amiry-Moghaddam** now represents his group. **Dr. Taskén** has functioned as the Acting Director of NCMM from the start in 2008 and is, from 2011, appointed as the joint Director of NCMM and the Biotechnology Centre of Oslo (term 2011-14). At the same time the involvement of his group in NCMM was strengthened so that it now constitutes one of the 6 groups in NCMM, see below. **Dr. Krauss** heads a Centre for Research Based Innovation focused on tumor stem cells, CAST. In addition, NCMM during 2009-11 hired five new group leaders, Dr. Ian G. Mills, Dr. Erlend A. Nagelhus, Dr. J. Preben Morth, Dr. Toni Hurtado and Dr. Judith Staerk which has brought NCMM to the planned number of groups.

NCMM GROUP LEADERS

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.

Dr. **Ian G. Mills** was recruited from Cambridge Research Institute, Cancer Research UK, University of Cambridge, UK and started in February 2010. Dr. 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.

Dr. **Jens Preben Morth** trained in structural biology at the EMBL Outstation in Hamburg and was recruited from Aarhus University to NCMM. His research is in the area of structure and function of membrane transporters, in particular membrane pumps or P-type ATPases such as the sodium and calcium ATPases. Morth also starts a new program on pH regulation and structure function studies on bicarbonate transporters. His research has relevance to cardiology, neurobiology and kidney diseases. Morth started in October 2010.

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

Dr. **Toni Hurtado** did his PhD at the Vall Hebron Hospital in Barcelona and his postdoc at Cambridge Research Institute, University of Cambridge. Hurtado started as a Group Leader at NCMM in August 2010. His research is focused on breast cancer, estrogen sensitivity and the role of co-factors in transcriptional networks.

Dr. **Judith Staerk** trained at the 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.

INCOME AND EXPENSES

The annual **NCMM core funding** is 27 million Norwegian kroner (mNOK) (approximately 3.7 mEUR) per year from the 3 consortia partners UiO, Research Council of Norway and Health SouthEast, the regional health authority for Southern and Eastern Norway. In addition comes overhead and production-based income, which was 1.8 mNOK in 2012. Including transferred funds, NCMM spent 31 mNOK in 2012 on its core budget and plans to spend 32.5 mNOK in 2013, drawing on a transferred reserve in the first 5-year period (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 mNOK (2015-value) with the present level of activity.

NCMM extramural funding in the form of grants to the group leaders and other competitive funding (ex. Founding partners) was approx. 7 mNOK in 2010, 23 mNOK in 2011, 30 mNOK in 2012 and seems to reach 40 mNOK in annual grants in 2013. This includes grants from the Research Council of Norway (7), Norwegian Cancer Society (6), Health SouthEast (2), European Commission (5), NIH (1), competitive grants at UiO (4) and private foundations and organizations such as the Lundbeck Foundation, Novo Nordic Foundation, Novo Seed, Carlsberg Foundation, KG Jebsen Centres (3), 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 and EMBL.

Recent Progress – Review of 2012

STAFF AND FUNDING

At the end of 2012, after its third full year of operation, NCMM had **84 employees** as the eight groups headed by newly recruited group leaders and founding partners are fully operative (versus 60 end 2011). We anticipate that NCMM will **continue to grow in 2013** as some 12 new positions are being filled on new grants at the first half of 2013 and expect NCMM to reach its planned size well inside the first 5-year funding period. **Extramural funding** reached 47 mNOK in 2012, exceeding the core NCMM budget by almost 2:1 (including founding partner grants), which is expected to continue to grow in 2013 (42 mNOK external grants as of Q1 2013).

SCIENCE AND PUBLICATION OUTPUT

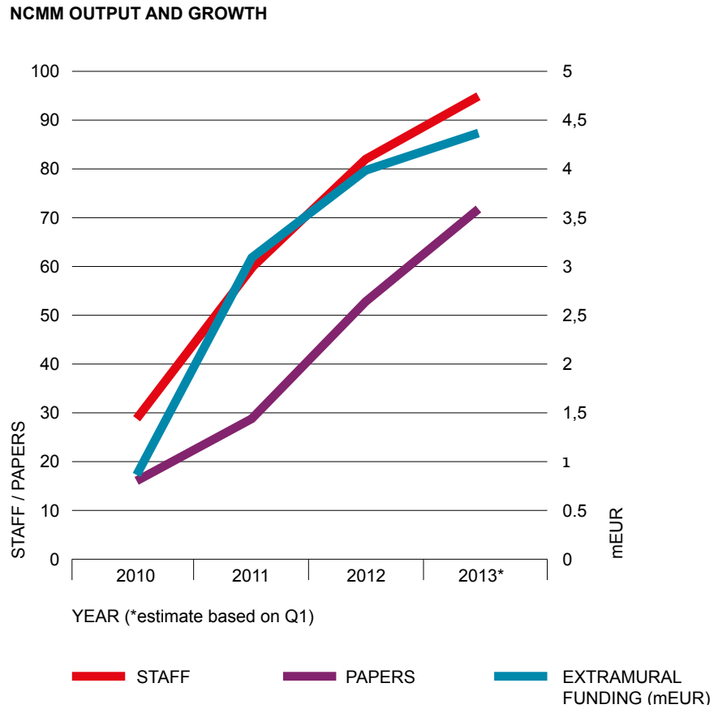
NCMM PIs report over 50 NCMM-affiliated papers published in 2012 (versus 29 in 2011), including papers in Cancer Cell, Nat Chem Biol., PNAS (3), EMBO J., Blood, J Clin Invest., Science Transl Med., Cancer Res., Oncogene and other journals. Furthermore, several papers are already emering in the first quarter of 2013, bringing the total to **more than 100 papers** so far. NCMM investigators have also filed patents (altogether **15 patents** during the first 3-years), have started some 10 new commercialization projects and report a number of appearances in popular media. Scientific highlights from the research are presented throughout this report in the individual group sections. 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 2013 NCMM PIs lists some **24 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 3 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. 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) in Oslo University Hospital which also illustrates the breadth of application and extension of the molecular medicine research going on in NCMM as well as collaborations with the Biotechnology Centre



and across Norway. In fact, NCMM group leaders report some 60 national collaborations.

The network of **NCMM Associate Investigators** was further extended in 2011 by the appointment of 5 new members of this group bringing the total number of outstanding senior Norwegian scientists affiliated with NCMM to 12. Collaborations with this group have been boosted by joint meetings and by a seed money programme initiated by the NCMM Board to foster collaborative projects and these activities were continued in 2012. NCMM PIs report around 10 current projects with AIs.

On the **European and international arenas**, NCMM investigators now enjoy numerous collaborations across the world (more than **50 international collaborations reported**). Research interactions with the Finish and Swedish centres in the Nordic EMBL Partnership and the EMBL are also increasing rapidly and NCMM welcomes the addition of a new Danish centre to enter the Partnership from 2013. Implementation at NCMM of the practices of the parent EMBL in recruitment and rotation of staff at all levels also offers the opportunity of recruiting top talent at all levels on an international arena.

FUTURE PROMISE

As evident from the present report, NCMM is still, after 3 years of its first 5-year funding period, in the building-up phase as a new centre with a focus on young investigators. However, with the excellent set of brilliant young Group Leaders recruited at an international arena, I am sure NCMM is at the start of a very interesting endeavor with great potential for future excellence originating from its own research and there are clear signs of that coming through. The NCMM Scientific Advisory Board appears to be in agreement with this assessment as they state in their conclusions from the SAB visit in February 2013 that "*NCMM is on very successful upward trajectory, and that recruitment of the 5 group leaders has been a very successful endeavor*". NCMM also completed its mid-term evaluation this month and now awaits funding decisions for the next five-year period from 2015.

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

May 2013

Kjetil Taskén
Director of NCMM

Photo: John Hughes

Nordic EMBL Partnership for molecular medicine

Agreement renewal and inclusion of a Danish node

With the recent opening of the Danish Research Institute of Translational Neuroscience (DANDRITE) at Aarhus University and its inclusion as the Danish node in the Nordic Partnership with the European Molecular Biology Laboratory (EMBL), the Nordic EMBL Partnership now provides a coordinated infrastructure and a platform for new initiatives across the Nordic countries in major areas of molecular medicine. During the inauguration ceremony at Aarhus University in March 2013, the partnership agreement between the Nordic universities and EMBL was extended for ten more years.

The Nordic EMBL Partnership for Molecular Medicine was established in 2007 as a joint venture (2008-2012) between the EMBL and the Universities of Helsinki (Finland), Umeå (Sweden) and Oslo (Norway) and involved building of national sister institutions in the three countries. The Partnership is based on complementing research expertise and a common aim to rise to challenges in biomedicine as well as to foster industry collaborations. In the five years since the launch of the partnership, the network has indeed emerged as a strategic player in Europe in the molecular understanding of disease mechanisms. The impact and success has now been recognized with the signing of a renewed partnership agreement for an extended period of 10 years (2013-2023) upon the inclusion of a new Danish Node. Rector Ole Petter Ottersen and NCMM Director Kjetil Taskén both signed the new agreement together with EMBL Director General Iain Mattaj and the university rectors and directors of the other Nordic EMBL nodes.

DANDRITE (Aarhus University) joins the Institute for Molecular Medicine Finland (FIMM, University of Helsinki), Centre for Molecular Medicine Norway (NCMM, University of Oslo), the Laboratory for Molecular Infection Medicine Sweden (MIMS, Umeå University) and EMBL. All nodes benefit from scientific, infrastructural and administrative support from EMBL as well as from the know-how of operational procedures in international recruitment, staff-turnover and external review. The majority of the group leaders at the nodes are young scientists recruited through international calls on the basis of scientific excellence and the EMBL model for recruitments.

From left to right: Thomas Wilhelmsson (Rector, University of Helsinki), Lena Gustafsson (Vice-Chancellor, Umeå University), Lauritz B. Holm-Nielsen (Rector, Aarhus University) and Ole Petter Ottersen (Rector, University of Oslo)

From left to right: Poul Nissen (Director, DANDRITE), Olli Kallioniemi (Director, FIMM), Bernt Eric Uhlin (Director, MIMS) and Kjetil Taskén (Director, NCMM)

Photos: Lars Kruse/ AU Kommunikation

The signed agreement summarizes each partner's contribution to the Partnership. **NCMM** facilitates the translation of basic medical research into clinical practice. The centre addresses disease mechanisms and exploits available biobanks and health registries. **FIMM** has a mission to solve grand challenges in human health through the application of personalized medicine. The centre investigates molecular mechanisms of disease, using genomics and medical systems biology. Research at **MIMS** is focused on microbial pathogenicity and molecular infection medicine. Finally, **DANDRITE** pursues translational research in neuroscience drawing on infrastructures for advanced brain imaging in patients and animal models and for structural and functional studies of membrane proteins as well as computer-assisted drug discovery.

The joint Nordic EMBL Partnership will include aproximately 50 research groups and a staff of 500 employees in the 4 national nodes with a combined, core budget exceeding 15 mio€ annually from the host universities, national funding bodies in Norway, Sweden and Finland,

and the private Lundbeck Foundation in Denmark. The Partnership provides a joint, Nordic powerhouse for molecular medicine and translational research with shared access to scientific infrastructure, including databases, facilities and instrumentation as well as to clinical materials and networks across the Nordic countries.

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

Greetings from Molecular Life Science (MLS^{UiO})

We have behind us a year where the visibility of NCMM has been further enhanced. The recent mid-term evaluation of the centre had several spin-off benefits beyond the evaluation per se. The management of the centre had put together an impressive self-evaluation and many people at different levels at several institutions have been engaged in looking into the centres activities. The University of Oslo (UiO) and the interfaculty initiative MLSUiO gave a very supportive comment to the process.

International recruitment of young research talents is an important ambition for a university having as its objective to be a leading European research university. So are building of networks with prestigious research institutions. We are pleased to see that NCMM has attracted researchers from very prominent institutions, such as Cambridge and MIT. The link that NCMM provides to the prestigious EMBL is in accordance with the ambitions of UiO. Novel networks are being developed, both regionally, nationally and at the Nordic level. Group leaders at NCMM are offered adjunct appointments at the Oslo University Hospital (OUH) in addition to their positions at NCMM, which contributes to the extensive collaboration between UiO and OUH. Developing the interaction between UiO and OUH is a strategic priority at UiO and NCMM is a significant initiative in this strategy. The Nordic perspective is also very important in these matters. Being part of the Nordic EMBL Partnership for Molecular Medicine, with close links to EMBL-affiliated centres in Finland, Sweden and Denmark, allows for access to both infrastructure and collaborations with excellent researchers. It may often be faster and easier to mobilize shared infrastructures and resources on a Nordic level than on the larger EU level.

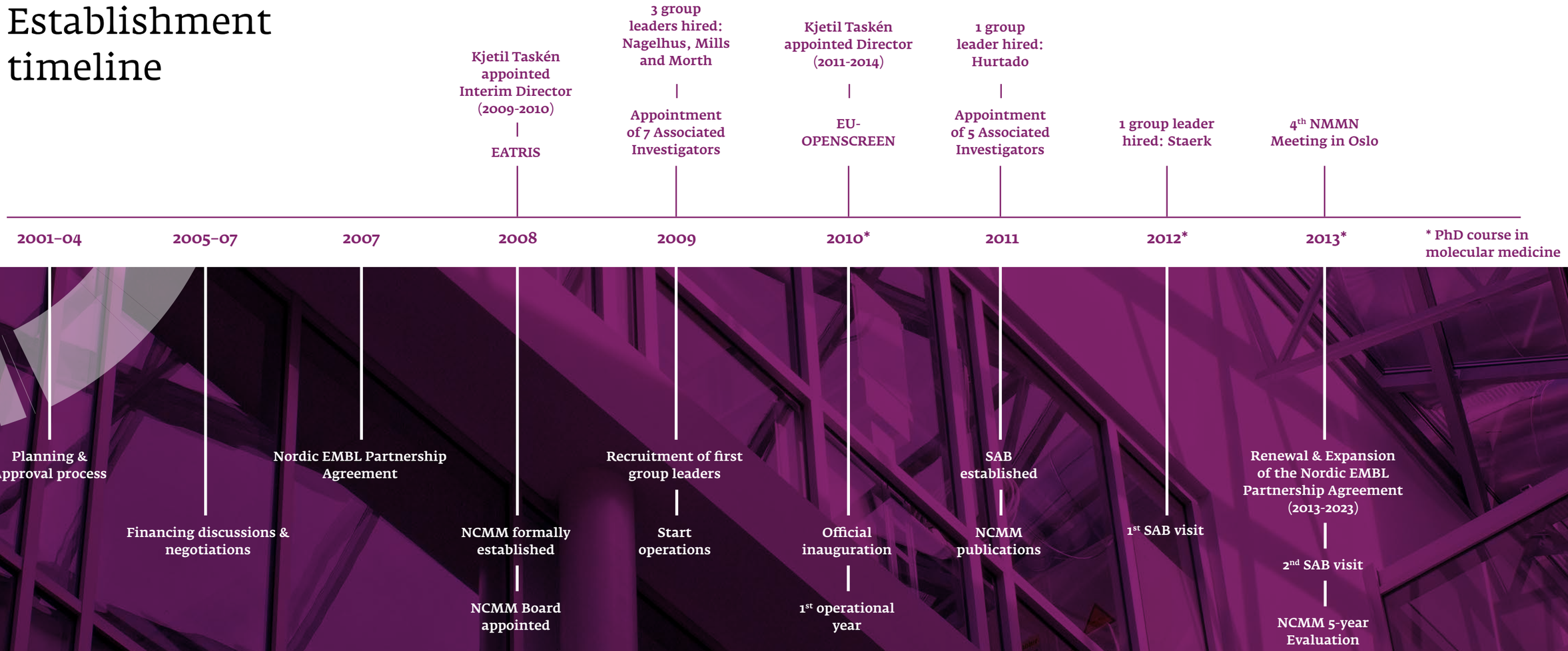
European research collaboration and attracting funding from the EU and the European Research Council are prioritized by UiO. NCMM has been very active in this respect and score well above the average. NCMM was a door-opener for Norway being invited to participate in the European infrastructure program EATRIS. NCMM is also taking part in the development of other ESFRI initiatives.

Together, all these excellent activities are building visibility and scientific excellence, making NCMM a highly appreciated instrument for the strategy of UiO. NCMM has shown through its activities that it is able to meet UiO's great expectations and ambitions, and contribute significantly to the visibility of our university. We are very much looking forward to the report from the international evaluation committee, and we are confident that it will be strong and supportive, confirming that NCMM is on a very positive track.

On behalf of MLS^{UiO}

Professor
Odd Stokke Gabrielsen,
MLS^{UiO} Chair

Establishment timeline



Group Leader:
Erlend Nagelhus

Erlend Nagelhus – GLIO-VASCULAR IMAGING GROUP

The Nagelhus group explores roles of glia in neurological disorders by *in vivo* two-photon laser scanning microscopy. This minimally invasive technique offers real-time imaging of physiological and pathophysiological processes in the brains of living animals. Through a cranial window of the thinned skull, the group studies brain-fluid dynamics, calcium signaling in cellular microdomains, cell morphology and motility as well as cerebral blood flow. The overall aim is to gain insight into mechanisms underlying glial control of neurons and the vasculature. Understanding neuronal-glial-vascular interactions may provide new treatment strategies for brain disorders involving perturbed circulation and water homeostasis. A major break-through came with the 2012 discovery of the aquaporin-4 dependent para-vascular pathway for cerebrospinal fluid circulation and clearance of interstitial fluid and waste.

The research of Nagelhus has focused on molecular specialization of glial endfoot membranes at brain-blood and brain-liquor interfaces. His research group, which joined the NCMM in 2009, runs its neuroimaging activity in the Letten Centre at the Institute of Basic Medical Sciences (IMB), Domus Medica. In 2013 Nagelhus was appointed Professor in Medicine at the Department of Physiology, IMB. He is now establishing a brand new laboratory (GliaLab) in the Annex of Domus Medica, accommodating equipment funded by the Research Council of Norway through NORBRAIN: A Large-scale Infrastructure for 21st century Neuroscience.

Photo: John Hughes

GROUP MEMBERS

SENIOR ENGINEER
P. Johannes Helm

RESEARCHERS:
Vidar Jensen
Anna Thoren

POSTDOCTORAL FELLOWS:
John Burkhardt
Karolina Szokol (associate member)
Wannan Tang (EMBO fellow)

PHD FELLOWS:
Vigdis Andersen Eidsvaag (associate member)
Rune Enger
Georg Andreas Gundersen
Alexander S. Thrane
Vinita R. Thrane
Gry F. Vindedal

Students enrolled in the Medical Student Research Program:
Cecilie E. Bugge

SELECTED KEY PUBLICATIONS FROM PI:

Nagelhus EA, Ottersen OP (2013) *Physiological roles of aquaporin-4 in brain*. **Physiol Rev**, Review, in press.

Thrane AS, Takano T, Rangroo Thrane V, Wang F, Peng W, Ottersen OP, Nedergaard M, Nagelhus EA (2013) *In vivo NADH fluorescence imaging indicates effect of aquaporin-4 deletion on oxygen microdistribution in cortical spreading depression*. **J Cereb Blood Flow Metab** Apr 24. doi: 10.1038/jcbfm.2013.63. [Epub ahead of print]Thrane AS, Rangroo Thrane V, Zeppenfeld D, Lou N, Xu Q, Nagelhus EA, Nedergaard M (2012) *General anesthesia selectively disrupts astrocyte calcium signaling in the awake mouse cortex*. **Proc Natl Acad Sci U S A** 109(46):18974-9.

Enger R, Gundersen GA, Haj-Yasein NN, Eilert-Olsen M, Thoren AE, Vindedal GF, Petersen PH, Skare Ø, Nedergaard M, Ottersen OP, Nagelhus EA (2012) *Molecular scaffolds underpinning macroglial polarization: an analysis of retinal Müller cells and brain astrocytes in mouse*. **Glia** 60(12):2018-26.

Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA, Nedergaard M (2012) *A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β*. **Sci Transl Med** 4(147):147ra111. doi: 10.1126/scitranslmed.3003748.

Heuser K, Eid T, Lauritzen F, Thoren AE, Vindedal GF, Taubøll E, Gjerstad L, Spencer DD, Ottersen OP, Nagelhus EA, de Lanerolle NC (2012) *Loss of perivascular Kir4.1 potassium channels in the sclerotic hippocampus of patients with mesial temporal lobe epilepsy*. **J Neuropathol Exp Neurol** 71(9):814-25.

Haj-Yasein NN, Jensen V, Østby I, Omholt SW, Voipio J, Kaila K, Ottersen OP, Hvalby Ø, Nagelhus EA (2012) *Aquaporin-4 regulates extracellular space volume dynamics during high-frequency synaptic stimulation: a gene deletion study in mouse hippocampus*. **Glia** 60(6):867-74.

Group Leader: Ian G. Mills[1]

Ian Mills – PROSTATE CANCER GROUP

Prostate cancer accounts for one third of all male cancer cases in Norway and is the second most signifcant cause of cancer mortality in men in Europe. The goal of the group is to understand the biology of prostate cancer in order to improve detection and treatment. Prostate cancer is driven by the androgen receptor and also characterized by genomic mutations and rearrangements. In the course of the last twelve months we have discovered that a subgroup of androgen receptor binding sites associated with aggressive metastatic prostate cancers are tissue-specific[1]. Motif co-enrichment at tissue-specific androgen receptor binding in metastatic disease also suggests that the androgen receptor may be co-recruited along with pro-inflammatory (NF-kB and STATs) and stem cell-associated (c-Myc and GATA) transcription factors. Genes associated with these sites provide a prognostic signature for progression and include genes regulated by endoplasmic reticulum stress (ER stress) response pathways. ER stress pathways can promote survival or apoptosis in cells in response to stressors ranging from hypoxia to drug treatments and depending on the magnitude of the stress and signaling pathways activated downstream of ER stress induction. We have shown in a recent collaboration on lymphoma that the activation of one arm of the ER stress response is necessary for maintaining the transforming capacity of oncogenic c-Myc[2]. Based on the prognostic gene signature in prostate cancer we are interested in determining whether ER stress response pathways play similar roles in maintaining the transforming capacity of the androgen receptor and other transcription factors. Our work focuses therefore in part on the interplay between the AR and these factors and ER stress pathway activation. One potentially cytoprotective consequence of ER stress induction is macroautophagy ('self-eating'). In the lymphoma study this did indeed account for at least part of the pro-transforming interplay between c-Myc and ER stress response induction[2]. To explore this relationship in prostate cancer cells we have developed assays for each step in the autophagic response. We have also obtained small-molecule inhibitors that perturb c-Myc expression and the activation of ER stress response pathways. This will allow us to dissect more carefully the interplay between these factors and AR function in prostate cancer as a step towards combination therapies and the discovery of new biomarkers that can act as surrogates for the activity of these pathways and transcription factors. Biomarker validation is supported in part by funds from Movember as part of their Global Action Plan for biomarker development.

In previous work we have reported that the AR can promote aerobic glycolysis and anabolic metabolism[3]. We are now exploring how changes in metabolic flux can affect the glycosylation status and activity of transcription factors, in effect forming a feedback loop connecting metabolism to the regulation of gene expression and phenotype. Changes in metabolic flux and gene expression can also occur due to the accumulation of somatic mutations in the course of cancer progression. Intriguingly we collaborated with a group at the Karolinska Institute who have been sequencing prostate cancers and found a significant subset of tumours with predominantly somatic mitochondrial mutations[4]. More age-matched cases are now being sequenced to determine whether there is a preferential enrichment for mutations in certain regions of the mitochondrial and an association with oxidative stress. Mitochondrial mutations can also accumulate in the ageing process, however this study included samples from cancer tissue cores, benign tissue and blood samples with called mutations arising only in the cancer cores. Mitochondrial mutations also arise as part of the ageing process and prostate cancer is amongst the most strongly age-associated cancers of epithelial origin. Further work is needed to determine whether a spectrum of somatic mutations exists that

KEY PUBLICATIONS REFERENCED IN THE TEXT

1 Sharma, N. L. *et al*. The androgen receptor induces a distinct transcriptional program in castration-resistant prostate cancer in man. *Cancer Cell* **23**, 35-47, doi:10.1016/j.ccr.2012.11.010 (2013).

2 Hart, L. S. *et al*. ER stress-mediated autophagy promotes Myc-dependent transformation and tumor growth. *J Clin Invest* **122**, 4621-4634, doi:10.1172/JCI62973 (2012).

3 Massie, C. E. *et al*. The androgen receptor fuels prostate cancer by regulating central metabolism and biosynthesis. *Embo J* **30**, 2719-2733, doi:10.1038/emboj.2011.158 (2011).

4 Lindberg, J. *et al*. The Mitochondrial and Autosomal Mutation Landscapes of Prostate Cancer. *Eur Urol*, doi:10.1016/j.eururo.2012.11.053 (2012).

OTHER PUBLICATIONS 2012/2013

1 Lindberg, J. *et al*. Exome sequencing of prostate cancer supports the hypothesis of independent tumour origins. *Eur Urol* **63**, 347-353, doi:10.1016/j.eururo.2012.03.050 (2013).

2 Paulo, P. *et al*. Molecular subtyping of primary prostate cancer reveals specific and shared target genes of different ETS rearrangements. *Neoplasia* **14**, 600-611 (2012).

3 Mills, I. G. Nuclear translocation and functions of growth factor receptors. *Semin Cell Dev Biol* **23**, 165-171, doi:10.1016/j.semcdb.2011.09.004 (2012).

4 Massie, C. E. & Mills, I. G. Mapping protein-DNA interactions using ChIP-sequencing. *Methods Mol Biol* **809**, 157-173, doi:10.1007/978-1-61779-376-9_11 (2012).

5 Lilleby, W., Stensvold, A., Mills, I. G. & Nesland, J. M. Disseminated tumor cells and their prognostic significance in non-metastatic prostate cancer patients. *Int J Cancer*, doi:10.1002/ijc.28002 (2012).

6 Itkonen, H. & Mills, I. G. Chromatin binding by the androgen receptor in prostate cancer. *Mol Cell Endocrinol* **360**, 44-51, doi:10.1016/j.mce.2011.09.037 (2012).

7 Hoefer, J. *et al*. PIAS1 is increased in human prostate cancer and enhances proliferation through inhibition of p21. *Am J Pathol* **180**, 2097-2107, doi:10.1016/j.ajpath.2012.01.026 (2012).

spans the ageing process, the emergence of localized prostate cancer and progression to metastasis. Evidence from our study and other groups suggests that mutations in p53 are associated with aggressive/poor prognosis cases and that somatic mutations in epigenetic regulators are also significant during the course of the development of prostate cancers. Data arising from sequencing studies and indeed genome-wide association studies will form the basis of a significant number of functional follow-up projects and the development of new disease models over the coming years.

Collectively this work is critical to achieving the twin goals in prostate cancer research:

1. To distinguish ageing tissue from cancer destined to progress to aggressive disease.

2. To restrict the transition from age-associated tissue changes to aggressive prostate cancer.

Photo: John Hughes

GROUP MEMBERS AND PROJECTS

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

HEAD ENGINEER:
Ingrid Jenny Guldvik – biomarker validation

PHD FELLOWS:
Lisa Gerner – structure/function studies on CAMKK2
Harri Itkonen – glycosylating enzymes and pathways in prostate cancer
Stefan Barfeld – transcriptional regulation by the AR and other transcription factors

MSC STUDENTS:
Morten Luhr

EXTERNAL FUNDING
In addition to NCMM funding, Mills' group is supported by the Norwegian Cancer Society, Molecular Life Sciences (University of Oslo), and two EU FP7 programs: P-CUBE (Infrastructure for Protein Production Platforms) and PRO-NEST (Prostate Research Organizations-Network of Early Stage Training, an EU/Marie Curie Training Network grant. National Institutes of Health (USA), Movember Foundation

Photo: Ola Sæther, UiO

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Photo: John Hughes

Photo: John Hughes

Photo: Ola Sæther, UiO

Photo: John Hughes

Group Leader:
Jens Preben Morth

J. Preben Morth – MEMBRANE TRANSPORT GROUP

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

A variety of techniques are used in order to identify and characterize both soluble and membrane bound proteins involved in pH regulation. A bioinformatics approach is used to target new proteins and interaction partners of interest. X-ray crystallography and several biophysical obtain structural information and 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.

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

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

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

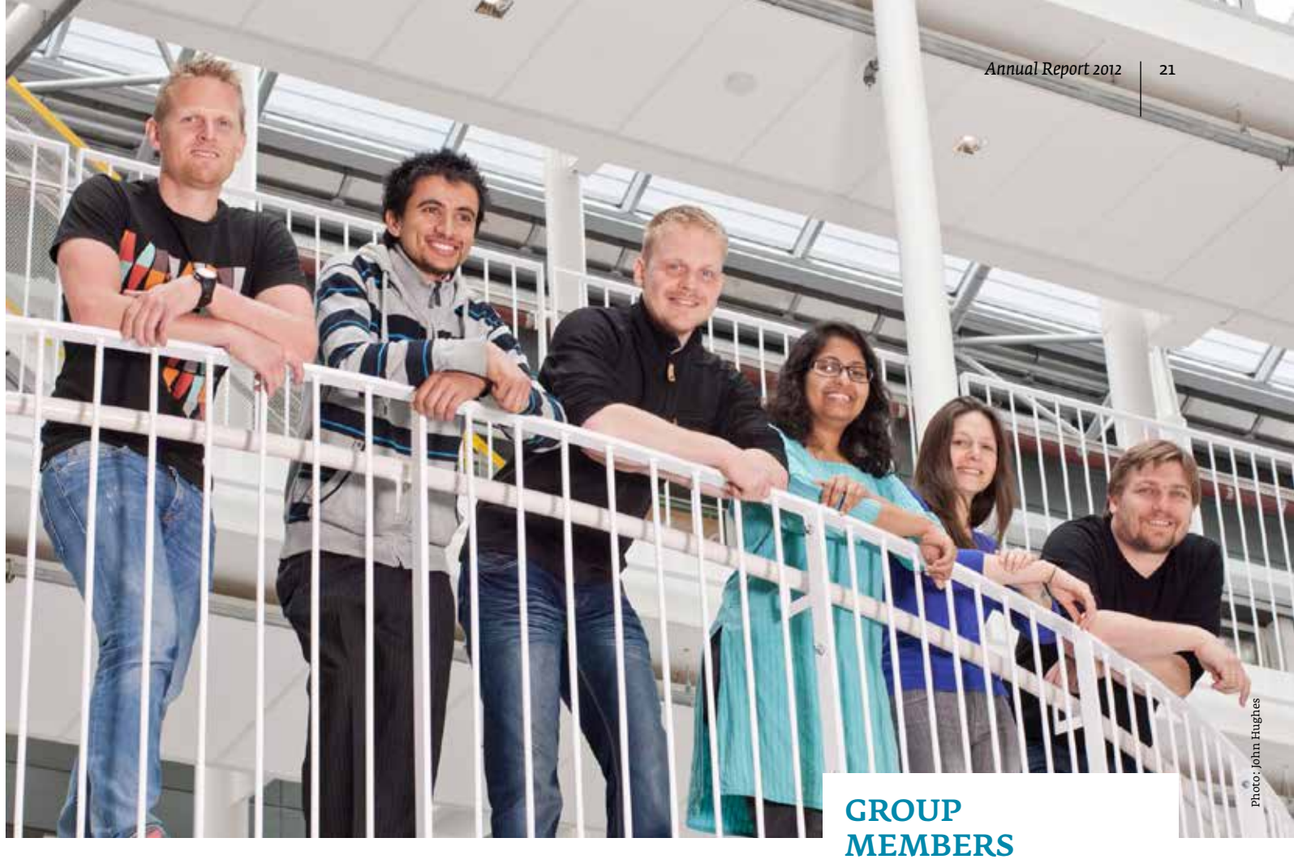


Photo: John Hughes

GROUP MEMBERS

POSTDOCTORAL FELLOWS:
Harmonie Perdreau Dahl
Kim Langmach Hein

PHD FELLOWS:
Kaare Bjerregaard-Andersen
Saranya Subramani
Theis Sommer

MASTER STUDENTS:
Jayaram Lamsal
Sazzad Toushik
Nina Fagernes

PRINCIPAL ENGINEER:
Hanne Guldsten

SELECTED KEY PUBLICATIONS FROM PI:
Voronkov A, Holsworth DD, Waaler J, Wilson SR, Ekblad B, Perdreau-Dahl H, Dinh H, Drewes G, Hopf C, Morth JP, Krauss S. Structural Basis and SAR for G007-LK, a Lead Stage 1,2,4-Triazole Based Specific Tankyrase 1/2 Inhibitor (2013). **J Med Chem**. 11;56(7).
Gourdon P, Liu XY, Skjørringe T, Morth JP, Møller LB, Pedersen BP and Nissen P (2011) Crystal structure of a copper-transporting PIB-type *ATPase*. **Nature**, 475, 59-64.
Gourdon P, Andersen JL, Hein KL, Bublitz M, Pedersen BP, Liu X-Y, Yatime L, Nyblom M, Claus Olesen C, Møller JV, Nissen P and Morth JP (2011) *HiLiDe—Systematic Approach to Membrane Protein Crystallization in Lipid and Detergent*. **Cryst. Growth and Design**. 11:2098-2106.
Jensen JK, Thomson LC, Nissen P, Gettins PWG, Peterson CB, Andreasen PA and Morth JP (2011) *Crystal structure of plasminogen activator inhibitor-1 in an active conformation with normal thermodynamic stability*. **J. Biol. Chem**.286:29709-17.
Morth J P, Pedersen BP, Toustrup-Jensen MS, Sorensen TL, Petersen J, Andersen JP, Vilsen B and Nissen P (2007) *Crystal structure of the sodium-potassium pump*. **Nature** 450, 1043-1049.

Group Leader:
Antoni Hurtado

Antoni Hurtado – BREAST CANCER GROUP

The Breast Cancer group at NCMM was initiated in August 2011 and is currently comprised of three members: Siv Gilfillan (engineer; started in September 2011), Elisa Fiorito (PhD fellow since November 2011) and Madhu Katika (joint post-doc between my group and the groups of Anne-Lise Børresen-Dale and Kristine Kleivi Sahlberg; started in March of 2012). Furthermore, three more people will join the team soon: Yogita Sharma (bioinformatician, June 2013), Siri Norhagen (master student, June 2013) and Elena Gonzalez (research assistant, August 2013). We are also in the process of employing an additional postdoc.

RESEARCH OF THE GROUP:

The interest of our group is mainly focused on the study of breast cancer. Breast cancer is a heterogeneous disease and the most frequent tumors are positive for the expression of Estrogen Receptor (ER) and/or human epidermal growth factor receptor 2 (HER2), the main regulators of proliferative processes in these tumors. These breast cancer subtypes are treated with anti-ER or anti-HER2 therapies. However, treatment-resistance occurs at least in 40% of the patients treated with any of these therapies. Therefore, the main goals of my research are to provide alternative therapies for these patients as well as to identify patients who will have a positive outcome of the existing treatments. Our group aims to address three main objectives in a comprehensive manner by using state-of-the-art technologies:

1) Identification and characterization of the factors that dictate the response to anti-ER and anti-HER2 therapies.
2) Applications of findings from aim 1 to medical practice. We wish to develop methods to predict the outcome for anti-ER therapies.
3) Development of mouse models that mimic the human pathology to be used as pre-clinical tools. We wish to validate the findings from aim 1 by using *in vivo* models.

RESEARCH COLLABORATION:

To date, the group has established a total of six collaborations with national and international groups. These collaborations are very important for the success of our research. At the national level, one of the most important collaborators is Prof. Anne-Lise Børresen-Dale (Dept. of Genetics, Institute of Cancer Research, OUH-Radiumhospitalet), who is an Associated Investigator of NCMM. The interaction with clinicians and basic researchers in Prof. Børresen-Dale's group provides an excellent atmosphere for a synergistic collaboration between both teams. Another significant collaboration has been established with Associate Investigator Prof. Helga Salvesen (Haukeland University Hospital, Bergen). Her clinical experience in endometrial cancer is crucial for this collaboration. Both teams are interested in understanding the role of FOXA1 in endometrial cancers and its association with the poor response to tamoxifen therapy. Finally, the group has initiated links with the team of Prof. Bernd Thiede (The Biotechnology Center of Oslo), who is an outstanding investigator in the field of proteomics. At the international level, my group has established collaborative projects with two groups. The contribution of Dr. Meritxell Bellet (Vall-Hebron Research Institute, Barcelona, Spain) is very important for our research. Both groups are interested in the development of quantitative methods to predict the response to tamoxifen treatment. The team of Dr. Bellet provides an extensive series of human samples of patients treated with tamoxifen for a long period of time. The access to human material complemented with clinical information is crucial for the progress of the project. Finally, the group of Dr. Julio Saez-Rodriguez (EBI-EMBL, Cambridge, UK) and my team are interested to develop a computational model of transcription factor activity by cell signaling pathways.

Photo: John Hughes

EXTERNAL FUNDING:

In addition to NCMM funding, the laboratory is supported by the Norwegian Cancer Society (Kreftforeningen).

GROUP MEMBERS

POSTDOCTORAL FELLOWS:
Madhu Katika

PHD FELLOWS:
Elisa Fiorito

HEAD ENGINEER:
Siv Gilfillan

SELECTED KEY PUBLICATIONS FROM PI:

Katika MR, Hurtado A (2013) A functional link between FOXA1 and breast cancer SNPs. **Breast Cancer Res**. 18;15(1):303. Epub ahead of print

Fiorito E, Katika MR, Hurtado A (2013) Cooperating transcription factors mediate the function of estrogen receptor. **Chromosoma**. 122(1-2):1-12.

Gilfillan S, Fiorito E, Hurtado A (2012) Functional genomic methods to study estrogen receptor activity. **J Mammary Gland Biol Neoplasia** 17(2):147-53.

Hurtado A, Holmes KA, Ross-Innes CS, Schmidt D and Carroll JS (2011) FoxA1 is a key determinant of estrogen receptor function and endocrine response. **Nature Genetics** 43(1):27-33.

Hurtado A, Holmes KA, Geistlinger TR, Hutcheson IA, Nicholson RI, Brown M, Jiang J, Howat W, Ali S and Carroll JS (2008) Regulation of ERBB2 by oestrogen receptor-PAX2 determines response to tamoxifen. **Nature** 456:663-7.

Group Leader: Judith Staerk

Judith Staerk – STEM CELL GROUP

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

The broad aims of our research are to:

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

Photo: John Hughes

GROUP MEMBERS

POSTDOCTORAL FELLOWS:
Xavier Tekpli

PHD FELLOWS:
Julia-Kristina Jensen Madsen-Østerbye
Oksana Rogovchenko

ENGINEER:
Hasina Hossain

SELECTED KEY PUBLICATIONS FROM PI:

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.

Staerk J*, Defour JP*, Pecquet C, Leroy E, Poirel HA, Brett I, Itaya M, Smith SO, Vainchenker W, Constantinescu SN (2011) *Orientation-Specific Signaling by Thrombopoietin Receptor Dimers*. **EMBO J**. 30(21):4398-413. (*equal contribution).

Staerk J*, Lyssiotis CA*, Medeiros LA, Bollong M, Foreman RK, Zhu S, Garcia M, Gao Q, Bouchez LC, Lairson LL, Charette BD, Supekova L, Janes J, Brinker A, Cho CY, Jaenisch R, Schultz PG (2011) *Pan-Src Family Kinase Inhibitors Replace Sox2 during the Direct Reprogramming of Somatic Cells*. **Angew Chem Int Ed Engl**. 50(25):5734-6. (*equal contribution).

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

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

James C, Ugo V, Le Couedic J-P, Staerk J, Delhommeau F, Lacout C, Berger R, Garcon L, Raslova H, Bennaceur A, Villeval J-L, Constantinescu S.N, Casadevall N, Vainchenker W (2005) *A unique clonal JAK2 mutation leading to constitutive signaling causes polycythemia vera*. **Nature** 434(7037):1144-8.

Group Leader:
Kjetil Taskén

Kjetil Taskén – SIGNALING NETWORKS IN HEALTH AND DISEASE

(Founding group)

A major goal of the Taskén group is to understand the role of the cAMP second messenger system 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. A 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, placenta cells and organelles such as lipid droplets and mitochondria, a chemical genomics approach is used in combination with phospho-proteomics to understand spatiotemporal dynamics of phosphorylation in anchored cAMP signaling complexes organized by AKAPs. Chemical biology screenings identify small molecular compounds for our research. Furthermore, phospho-flow cytometry using fluorescent cell barcoding allows processing of up to 64 samples with different stimulations and perturbations in the same run. Setups and antibody panels are established for mapping T cell signaling pathways, signaling by prostaglandins, cytokines and other inflammatory mediators as well as regulatory T cell pathways that allow mapping of complex signal networks, assessing how inhibitory signals feed in and examining how small molecules perturb such signal networks.

The group studies cAMP immunomodulation and involvement of regulatory T cells in HIV, mouse AIDS and various cancers where tumor immunology is of significance. Projects include studies of regulatory T cells and anti-tumor immune responses in colorectal cancer and ovarian carcinoma. In addition, cancer and immune cell signaling analyses are being performed by phospho-flow cytometry to find biosignatures. Systems biology analyses are applied on the phospho-flow data from single cell signaling as well as from mixed cell populations with Treg immunosuppression.

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

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

In terms of clinical investigations, a fourth clinical intervention study with COX-2 inhibitor in HIV patients (Taskén co-PI) is on-going in collaboration with the Department of Infectious Diseases, Oslo University Hospital (OUH). Furthermore, a clinical intervention study with use of NSAID to block the observed effects of PGE_2 in metastatic colorectal cancer is currently under development to assess the secondary prophylactic effect (collaboration with the Dept. of Gastrosurgery, OUS).

EXTERNAL FUNDING:

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

COLLABORATORS:

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

Photo: John Hughes

GROUP MEMBERS

(during 2012 and starting 2013):

RESEARCH SCIENTISTS:
Einar Martin Aandahl
Torunn Berge (leave of absence 2013)
Elisa Bjørgo (until April 2013)
Johannes Landskron

POSTDOCTORAL FELLOWS:
Lena Eroukhmanoff
Guro Mørk Johnsen
Anna Mari Lone (from Feb. 2013)
Maria-Niki Mylanokou
Marie Rogne
Sigrid Skånland
Susanne Weedon-Fekjær

PHD FELLOWS:
Aleksandra Đukić (started May 2013)
Stalin C. Gunasekaran
Morten Hagness (Thesis submitted)
Karen Henjum (Thesis defended Oct. 2012)
Maria Kalland (Thesis defended Sept. 2012)
Nora Lieske
Kristine Moltu
Kristoffer Watten-Brudvik
(Thesis defended June 2012)
Ellen Østensen

MD/PHD & MSC STUDENTS:
Anders Egeland (graduated May 2012)
Lise-Lotte Flage-Larsen (started April 2013)
Grunde Wibetoe (graduated May 2012)

ADMINISTRATIVE OFFICER:
Berit Barkley

SCIENTIFIC OFFICERS:
Jorun Solheim
Gladys Tjørhom

CHEMICAL BIOLOGY PLATFORM:
Anne Jorunn Stokka
Inderjit M. Singh/David McClymont

SELECTED KEY PUBLICATIONS FROM PI:

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).

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

Photo: John Hughes

Photo: Ola Sæther, UiO

Photo: Ola Sæther, UiO

Photo: John Hughes

Group Leader:
Stefan Krauss

Stefan Krauss – UNIT FOR CELL SIGNALING

(Founding group)

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

GROUP MEMBERS

POSTDOCTORAL FELLOWS:
Petter A. Olsen
Jennifer Dembinski
Nina T. Solberg
Andrey Voronkov

PHD FELLOWS:
Jo Waaler
Martin F. Strand

MSC STUDENTS:
Anders Grimsmo
Khahn Huynh
Tore Vehus

ENGINEERS:
Huyen Mong Thi Dinh
Monika Gelazauskaite

ADMINISTRATIVE:
Bie Ekblad
Line Mygland

SELECTED KEY PUBLICATIONS FROM PI:

Voronkov A, Holsworth DD, Waaler J, Ekblad B, Perdreau H, Drewes G, Schuler H, Morth JP, Krauss S (2013) *Structural basis and SAR for Go07-LK*, a lead stage 1,2,4-triazole based specific Tankyrase1/2 inhibitor. **J Med Chem**. 56(7): 3012-23.

Voronkov A, Krauss S (2013) *Wnt/beta-catenin signaling and small molecule inhibitors*. **Curr Pharm Des**. 2013;19(4):634-64.

Waaler J, Machon O, Tumova L, Dinh H, Korinek V, Wilson SR, Paulsen JE, Pedersen NM, Eide TJ, Machonova O, Gradl D, Voronkov A, von Kries JP, Krauss S (2012) *The novel tankyrase inhibitor JW55 decreases canonical Wnt signaling in colon carcinoma in vitro and reduces tumor growth in conditional APC mutant mice in vivo*. **Cancer Research** 72(11):2822-32.

Roberg-Larsen H, Strand MF, Grimsmo A, Olsen PA, Dembinski JL, Rise F, Lundanes E, Greibrokk T, Krauss S, Wilson, SR (2012) *High sensitivity detection of active oxysterols with automated filtration/filter backflush (AFFL)-SPE-LC*. **J Chromatogr A**. 1255: 291-7.

Solberg N, Machon O, Machovna O, Krauss S (2012) *Mouse Tcf3 represses canonical Wnt signaling by either competing for beta-catenin binding or through occupation of DNA binding sites*. **Mol Cell Biochem**. 365 (1-2): 53-63.

Solberg N, Machon O, Krauss S (2012) *Characterization and functional analysis of the 5'-flanking promoter region of the mouse Tcf3 gene*. **Mol Cell Biochem**. 360(1-2):289-99.

Strand MF, Wilson SR, Dembinski JL, Holsworth DD, Khvat A, Okun I, Petersen D, *Krauss S* (2011) *A novel synthetic smoothened antagonist transiently inhibits pancreatic adenocarcinoma xenografts in a mouse model*. **PLoS One** 6 (6), e19904.

Jing Y, Machon O, Hampl A, Dvorak P, Xing Y, *Krauss S* (2011) *In vitro differentiation of mouse embryonic stem cells into neurons of the dorsal forebrain*. **Cell Mol Neurobiol**. 31 (5):715-27.

Waaler J, Machon O, von Kries JP, Wilson SR, Lundenes E, Wedlich D, Gradl D, Paulsen JE, Machonova O, Dembinski JL, Dinh H, Krauss S (2011) *Novel synthetic antagonists of canonical Wnt signaling inhibit colorectal cancer cell growth*. **Cancer Research** 71 (1):197-205.

Dembinski JL, Krauss S (2010) *A Distinct Slow-Cycling Cancer Stem-like Subpopulation of Pancreatic Adenocarcinoma Cells is maintained in vivo*. **Cancers** 2(4):2011-2025.

Wilson SR, Strand MF, Krapp A, Rise F, Herstad G, Malterud KE, Krauss S (2010) *Hedgehog antagonists cyclopamine and dihydroveratramine can be mistaken for each other in Veratrum album*. **J Pharm Biomed Anal**. 53 (3):497-502.

Group Leader:
Mahmood Amiry-Moghaddam

Mahmood Amiry-Moghaddam – LABORATORY FOR MOLECULAR NEUROSCIENCE (Founding group)

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

RECENT ACHIEVEMENTS

- Unraveling the role of AQP4 in cell volume regulation and calcium signaling in astrocytes (Benfenati et al, PNAS 2011).
- Unraveling the roles of water transporting co-transporter NKCC1 in formation of arachnoid cysts in human (Exp Neurol. 2010, Cerebrospinal Fluid Res. 2010) and edema formation in mice (Neurocrit Care. 2010).
- Designing and synthesis of synthetic peptides potentially binding to AQP4 (Jacobsen et al. Org Biomol Chem. and J Org Chem In 2011).
- Establishing the loss of astrocyte polarity as a common denominator in Alzheimer's disease and epilepsy (Yang et al. J Alzheimer's disease 2011, Alvestad et al. Epilepsy Research 2013).
- Unraveling the beneficial role of AQP4 for survival in cerebral malaria (Promeneur et al. PNAS 2013)

Photo: Gunnar F. Lothe

GROUP MEMBERS

RESEARCHER:
Reidun Torp

POSTDOCTORRAL FELLOWS:
Henning Boldt
John Kudolo
PhD fellows:
Laura Camassa
Lisa Lunde
Eystein Hoddevik
Katja Stahl
Shirin Katoozi

MD/PHD & MSC STUDENTS:
Faraz Hameed Khan
Gry-Helen Enger Syverstad
Agnete Prydz

ENGINEERS:
Bjørg Riber
Karen-Marie Gujor Jorunn Knutsen
Bashir Hakim
Paul Johannes Helm

PROFESSOR EMERITI:
Finn-Mogens Haug
Eric Rinvik (passed away in March 2013)

SELECTED PUBLICATIONS FROM 2009-2013

* Corresponding author

Mylonakou MN, Petersen PH, Rinvik E, Rojek A, Valdimarsdottir E, Nielsen S, Ottersen OP, Amiry-Moghaddam M* (2009) Analysis of mice with targeted deletion of AQP9 gene provides conclusive evidence for expression of AQP9 in neurons. **J Neurosci Res** 87: 1310-1322.

Benfenati V, Caprini M, Dovizio M, Mylonakou MN, Ferroni S, Ottersen OP, Amiry-Moghaddam M* (2011) An aquaporin-4/transient receptor potential vanilloid 4 (AQP4/TRPV4) complex is essential for cell-volume control in astrocytes. **Proc Natl Acad Sci U S A** 108: 2563-2568

Alvestad S, Hammer J, Hoddevik EH, Skare O, Sonnewald U, Amiry-Moghaddam M*, Ottersen OP (2013) Mislocalization of AQP4 precedes chronic seizures in the kainate model of temporal lobe epilepsy. **Epilepsy Res**. Doi: 10.1016/j.eplepsyres.2013.01.006

Promeneur D, Lunde LK, Amiry-Moghaddam M, Agre P (2013) Protective role of brain water channel AQP4 in murine cerebral malaria. **Proc Natl Acad Sci U S A** 110: 1035-1040.

Amiry-Moghaddam M & Ottersen OP (2013) Immunogold cytochemistry in neuroscience. **Nature Neuroscience** (In Press)

Photo: John Hughes

Research Collaboration with Oslo University Hospital

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

Furthermore, adjunct appointments in clinical or para-clinical departments in OUH have been established for all NCMM Group Leaders and they hold 20% adjunct appointments at different departments at OUH. The experience after 1-3 years 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. The adjunct positions also facilitate interactions not only for the Group Leaders but also for their PhD and postdoctoral fellows as well as incoming clinical researchers in the NCMM groups, thus securing a more diverse and dynamic research environment.

Adjunct Appointments

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.

DEPARTMENT OF INFECTIOUS DISEASES (OUH)

- Group Leader Kjetil Taskén

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

DEPARTMENT OF UROLOGY (OUH)

- Group Leader Ian Mills (10%)

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

DEPARTMENT OF CANCER PREVENTION, INSTITUTE FOR CANCER RESEARCH (OUH)

- Group leader Ian Mills (10%)

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

DEPARTMENT OF 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 at OUH-Ullevål and OUH-Rikshospitalet. Research areas within the department include movement disorders, epilepsy, stroke and diseases of the brain's blood supply, MS and other inflammatory diseases of the central nervous system, disorders of the neck and back as well as painful disorders of the peripheral nerves.

DEPARTMENT OF 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 an clinical departments at the OUH and are interacting with colleagues both nationally and internationally.

Disease Mechanisms and Translation

Photo: John Hughes

Although the Centre has only been fully operational for three years, NCMM group leaders recently listed 24 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-AKAP18δ-phospholamban-Serca2 complex for cardio-protective effect in ischemia-reperfusion damage
- Targeting of CAMKK2 for metabolic regulation 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

PROOF-OF-CONCEPT IN HUMANS

- Effect on CD38 and vaccine responses in HIV-infected humans by anti-inflammatory drug (COX-2 inhibitor Phase IIA)
- Vaccine and radiation in prostate cancer

ON-GOING DEVELOPMENT IN THE AREA OF DIAGNOSTICS AND MONITORING

- Prostate cancer markers – androgen receptor regulome
- 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

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

Photo: F. Saggio, UiO

Research Highlights

PROSTATE CANCER TISSUE STUDY: COULD REVOLUTIONIZE FUTURE TREATMENT OF ADVANCED CANCER PATIENTS

The androgen receptor is an accepted driver for the emergence and progression of prostate cancer. Numerous studies have defined androgen receptor target genes in using chromatin immunoprecipitation and transcript profiling in *in vitro* models with the aim of defining clinically relevant gene networks. NCMM group leader Ian Mills and colleagues recently published the first study to do so directly in clinical samples representing a spectrum of prostate cancers, from treatment-responsive disease to castrate-resistance. They have identified a distinct set of androgen receptor binding sites that are common to castrate-resistant cases and distinct from those found in *in vitro* models and other stages of the disease. Binding motifs for cell cycle/oncogenic (c-Myc and E2Fs) and inflammatory (NF-kB and STATs) transcription factors co-enrich with this distinct castrate-resistant signature of androgen receptor binding sites. This provides clues to collaborating transcription factors that may facilitate reprogramming of androgen receptor recruitment during prostate cancer progression. By integrating transcriptomic data with this binding site signature Mills and colleagues have derived a discrete 16-gene signature capable of discriminating between localized prostate cancer and castrate-resistant disease. This prognostic signature is now being tested in additional cohorts at the protein and transcript level.

The full article "The androgen receptor induces a distinct transcriptional program in castration-resistant prostate cancer in man", where Dr. Ian Mills is a co-senior co-author, can be found in **Cancer Cell**, Vol. 23, Issue 1, 14 January 2013, Pages 35-47.

SUGAR-COATED ONCOGENES ARE NOT NECESSARILY SO SWEET

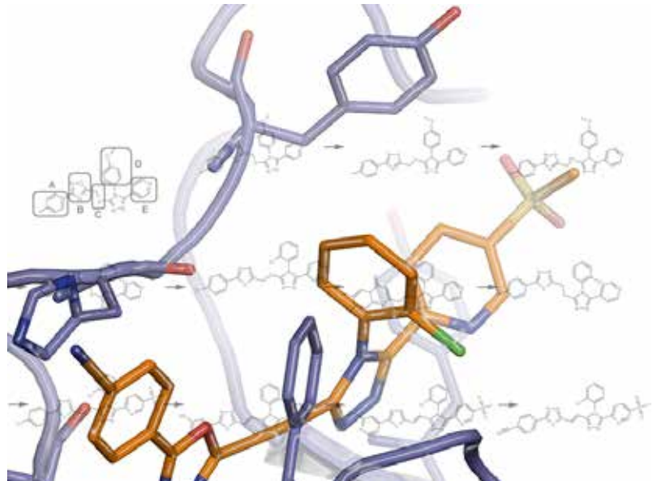
NCMM group leader Ian Mills and colleagues have previously reported that the androgen receptor contributes to prostate cancer development by altering the expression of a network of metabolic genes and regulators. Strikingly, many of the metabolic targets and pathways regulated by the androgen receptor are also targets for other oncogenic transcription factors, including c-Myc and Hypoxia-inducible factor 1alpha (HIF1A). This led the research group of Ian Mills and their collaborators at the Oslo University Hospital to ask whether a single pathway within this network could sense and respond to metabolic reprogramming and, in turn, affect the stability or activity of transcription factors. They now report that the hexosamine biosynthesis pathway, fuelled by metabolites from glucose, amino acid, nucleotide and fatty acid metabolism, is androgen-regulated and generates an amino-sugar conjugate called UDP-N-acetylglucosamine. This is used by O-GlcNAc transferase (OGT) to glycosylate and increase the stability of c-Myc and other proteins. Furthermore, Mills and colleagues show that by using a small-molecule inhibitor of OGT, the levels of this important oncogenic transcription factor can be significantly reduce. The impact of treatment is a reduction in cell proliferation associated with the suppression of the expression cell cycle genes and induction of the unfolded protein response. In clinical samples increased OGT expression associates with prostate cancer progression assessed biochemically. OGT expression also correlates with copy number amplification at the c-Myc locus on chromosome 8q24. In conclusion, hexosamine biosynthesis, and in particular OGT, provides a feedback-loop, linking metabolic flux to transcriptional regulation and a possible intervention point for cancer treatment.

The full article "O-GlcNAc transferase integrates metabolic pathways to regulate the stability of c-MYC in human prostate cancer" can be found in **Cancer Res.**, 29 May 2013, [Epub ahead of print] doi:10.1158/0008-5472.CAN-13-0549.

TARGETING TANKYRASES TO TREAT TUMORS

Excessive signaling by the Wnt-pathways drives cell regeneration in a range of solid tumors, including colorectal cancer. Tankyrases belong to the poly (ADP-ribose) polymerase (PARP) superfamily and are involved in various cellular functions, including attenuating Wnt/b-catenin signaling. Thus, Tankyrase 1 and 2 (TNKS1/2) are promising pharmacological biotargets with possible applications for the development of novel anti-cancer therapeutics. NCMM founding partner Stefan Krauss and colleagues have developed a new class of tankyrase inhibitors that target the adenosine binding site, unique to tankyrases. Recently, a focused structure-activity-relationship (SAR) study was conducted in collaboration with NCMM group leader Preben Morth and his team to find potent derivatives of the novel tankyrase inhibitor candidate. Chemical analoging of this substance resulted in a highly specific, potent and metabolically stable TNKS1/2 inhibitor that is not recognized by other PARP family members. Furthermore, the molecule inhibits tankyrase activity both in cell cultures and *in vivo* in mouse models. In the study, Morth and his team co-crystallized the PARP domain of TNKS 2 binding the inhibitor, revealing the structural basis for the specificity and high-affinity observed with this type of compounds. The novel tankyrase inhibitor provides an excellent tool for analyzing the functions of TNKS1/2 and Wnt/b-catenin signaling in cell biology, cancer and disease models.

The full article "Structural basis and SAR for G007-LK, a lead stage 1,2,4-triazole based specific tankyrase 1/2 inhibitor" can be found in **Journal of Medical Chemistry**, Volume 56, 11 April 2013, Pages 3012-23.



WASTE CLEARANCE IN THE BRAIN DEPENDS ON WATER CHANNELS

Throughout most of the body the lymphatic system transports excess fluids and waste from the interstitial spaces between cells to the blood. However, the brain lacks such a lymphatic circulation and it has therefore been unclear how the interstitial fluid here is cleared of waste. NCMM group leader Erlend Nagelhus and his colleagues at the University of Rochester Medical Center, New York, recently revealed a new clearance system in the brain that serves a lymphatic-like function. In this study, the researchers investigate the fluid flow in the brain of living mice by means of *in vivo* two-photon imaging and small fluorescent tracer molecules, demonstrating that cerebrospinal fluid (CSF) enters the parenchyma along para-vascular spaces that surround penetrating arteries and that brain interstitial fluid is cleared along para-venous drainage pathways. Furthermore, mice lacking the water channel protein Aquaporin 4 (AQP4) in astrocytes, showed a slowed CSF influx through this system and a significant reduction in interstitial solute clearance, indicating that astrocytic water transport mediates this flux. These finding could have relevance for understanding or treating neurodegenerative diseases that involve mis-accumulation of soluble proteins, such as amyloid β in Alzheimer's disease. Amyloid β is expressed continuously in the brain and needs to be removed effectively to avoid an accumulation that could damage the nerve cells. Nagelhus and colleagues therefore injected fluorescent-tagged amyloid β into the brain tissue and observed that deletion of the AQP4 gene did indeed suppress clearance of soluble amyloid β, suggesting that this pathway may remove amyloid β from the central nervous system.

The full article "A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including Amyloid β" can be found in **Science Translational Medicine**, Volume 4, 15 August 2012, Pages 147ra111.

Future prospects for personalized medicine

SUMMARY OF PRESENTATION ON PERSONALIZED MEDICINE GIVEN BY NCMM DIRECTOR KJETIL TASKÉN

Traditionally, clinical diagnosis and treatment has been based on the patient's symptoms, medical and family history as well as results from laboratory samples. However, the post-genomic era has led to fundamental changes in biology and medicine. Personalized medicine is an emerging field of medicine, using an individual's genetic and biomarker profile to guide decisions made in regard to prevention, diagnosis as well as treatment of disease. Genetic or other biomarker information will enable decisions such as who should receive certain types of therapies or specific doses of a given therapy or can reveal who is predisposed to a particular safety risk and should be monitored extra carefully.

Future medical treatment aims to be able to predict diseases based on knowledge of all disease genes and complex disorders (predictive medicine). Furthermore, based on systems biology, functional genomics and molecular epidemiology and by using population-wide bio banks and health registers, physicians will be able to prevent development to disease at the level of specific populations or individuals (preventive medicine). Finally, individual genetic makeup and biomarker profile can be used to tailor individual treatments (personalized medicine). Molecular medicine, not only surveying biomarkers but also focussing on disease mechanisms and translational research will be crucial to obtain the understanding and knowledge necessary to offer more individual-based treatments and therapies.

Personalized medicine includes genetic profiling, classification as well as correlation to prognosis and treatment response. Furthermore, extraction of biomarker sets in diagnostic tests could be useful to select between several treatment options. Examples of such selection schemes for available therapies are already available for some indications in oncology and a similar development is observed in other disease areas such as cardiovascular diseases, diabetes and metabolic diseases as well as cognitive disorders. In the future, the individual biomarker status could be used in selection of an optimal treatment with good effect. Furthermore, companion diagnostics are increasingly being developed to both select treatment and monitor treatment effect. This has lead to increasing stratifications of the patient populations (stratified medicine, precision medicine) and will ultimately lead to a situation for example in cancer where we have one disease in each patient as we will know the cancer genetics and the molecular cause of the disease in each patient. This will challenge our diagnosis systems as well as the orphan drug system. Furthermore, the implications are "n-of-one" medicine or fully individualized treatment and this will challenge the way we normally think about evidence-based medicine and documentation in placebo controlled studies.

The on-going international development in this area will lead to demands for national, publicly funded diagnostics and treatment and this requires building up infrastructures, expertise and trust in national health care systems. Introduction of personalized medicine challenges national health authorities with respect to what should be publicly funded and not and will require insight and competence to reach good solutions in each case, considering patient benefit, society benefits and health economics. Furthermore, while introduction of personalized medicine and tailored treatments may imply higher costs for each patient treated it also implies good treatment effect (and hence god "return on investment") in those treated as well as not treating those who would not have effect. Hence, it should also be possible to showcase that personalized medicine actually can save costs and improve health economics – this if the upside can be balanced between industry as compensation for reduced market size and the health care providers (society). However, independently of what the Norwegian Health Authorities do we will see an increasing public demand for new therapies. Thus, there is a need to invest in the development and maintenance of competitive medical and high-tech research clusters with international level competence. Moreover, such environments are necessary to produce knowledge of specific genetic risk factors that pertain to each specific population and for development of personalized medicine nationally. Funding of research to bring forward personalized medicine could therefore be considered as an investment cost in a health economy perspective.

In summary, the introduction of personalized medicine will redefine the concept of evidence-based medicine as not only will it be possible to say whether a treatment is effective, but also for whom it is effective.

NCMM Director Taskén was an invited speaker at the debate conference "Cancer and Priorities" organized by Dagens Medicine at OUH-Radiumhospitalet on April 10 2013 where he presented a talk entitled "Skreddersydd medisin: dyrt og eksklusivt eller investering i fremtidig pasient-nytte og bedre helseøkonomi?"

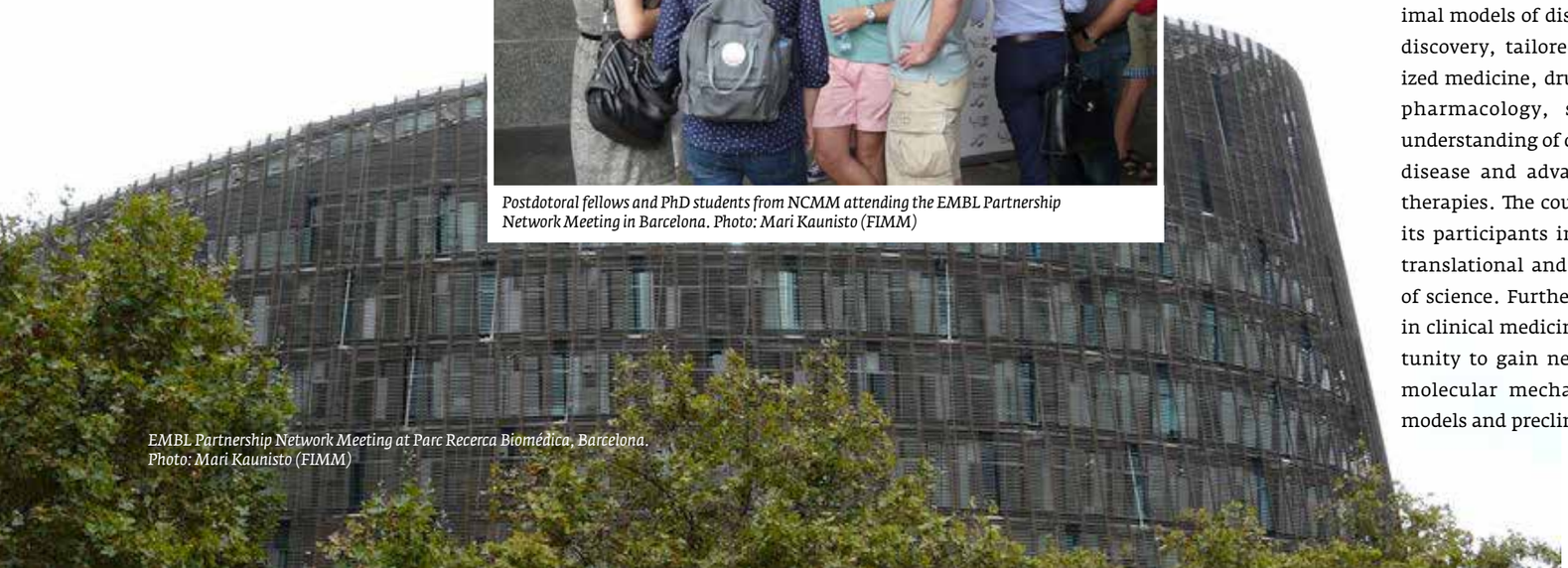
NCMM Events

EMBL PARTNERSHIP EVENT - PERSPECTIVES IN TRANSLATIONAL MEDICINE

In September 2012, the EMBL organized an EMBL Partnership network meeting entitled "Perspectives in Translational Medicine" that took place in Barcelona. In total, 150 participants from all the Nordic EMBL Partnership nodes as well as from France (EMBL-Grenoble), Italy (EMBL-Monterotondo), UK (EMBL-EBI), Germany (Heidelberg/Hamburg) and Spain (Barcelona, Centre for Genomic Regulation) attended this three-day event. NCMM had representatives from all their eight groups (newly recruited and founding groups) and group leaders and postdoctoral fellows as well as PhD students attended the conference. The conference aimed at introducing the different partners and their research. In addition to many interesting lectures, networking between the different nodes was also facilitated by a separate Nordic Node Group Leader Meeting, poster sessions and a separate PhD/postdoc meeting. In 2012, the Barcelona network conference replaced the annual Nordic Molecular Medicine Network (NMMN) meeting that was organized by Umeå and Helsinki in 2010 and 2011, respectively. The next NMMN meeting will take place in Oslo in September 2013.

The EMBL Partnership has now reached a stage of maturity that opens up for closer collaborations and it is timely to start building bridges between the individual partner institutes. The feed-back after the Barcelona meeting was very positive and enthusiastic and the EMBL is therefore currently considering making the partnership meeting a regular event. For future events, the specialization and focus will be increased, enabling concrete scientific discussions and spearheading collaborations.

Postdotoral fellows and PhD students from NCMM attending the EMBL Partnership Network Meeting in Barcelona. Photo: Mari Kaunisto (FIMM)



EMBL Partnership Network Meeting at Parc Recerca Biomédica, Barcelona. Photo: Mari Kaunisto (FIMM)

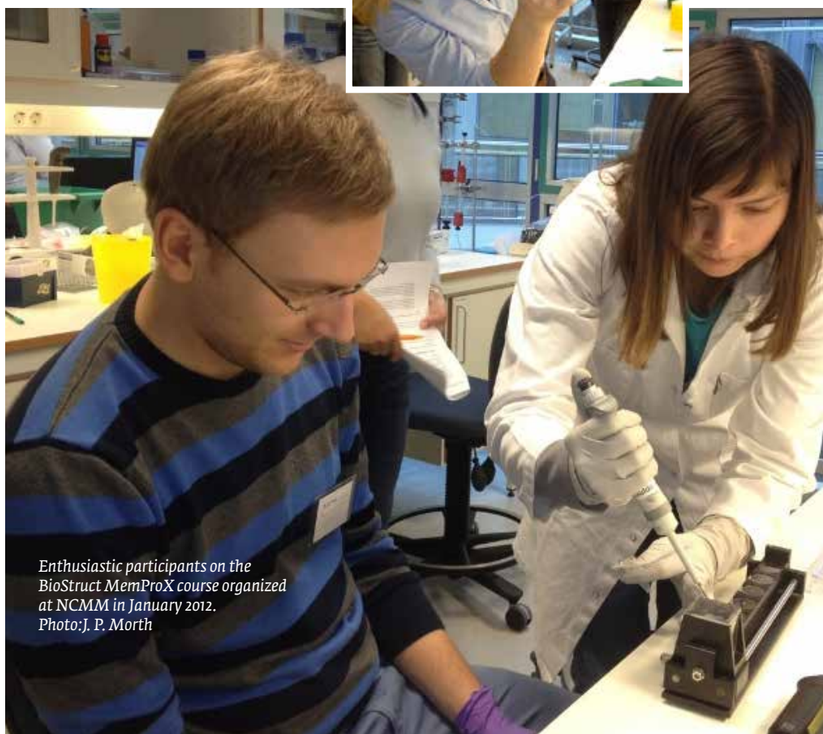
NCMM SCIENTIFIC RETREAT

In December 2012, NCMM organized its second retreat that took place in Asker, just outside Oslo. In addition to NCMM staff, Associated Investigators were invited to attend this two-day event with both scientific discussions 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 a 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 2012, topics of the course included disease mechanisms, animal models of disease, biomarker discovery, tailored and personalized medicine, drug targeting and pharmacology, structure-based understanding of disease, imaging disease and 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.

The Research Council of Norway (RCN) launched five national research schools in 2009 that were granted money for eight years, pending on a successful midterm evaluation. NCMM Group Leader Preben Morth is a board member of the National Graduate School in Structural Biology (BioStruct) that is hosted by the University of Tromsø and where UiO is one of the partners. BioStruct was recently granted money for three more years as a result of a positive evaluation. Fourteen PhD courses are offered on a biannual basis and in 2012, Morth organized a one-week BioStruct course entitled "Membrane Proteins, from isolation to crystals" (MBV9300BTS) at NCMM. The course included both practical lab work and theoretical lessons and focused on methodology and decision processes involved in membrane protein crystallization. Altogether, 14 participants from Norway (Bergen and Oslo), Finland and Sweden attended the course.



Enthusiastic participants on the BioStruct MemProX course organized at NCMM in January 2012. Photo:J. P. Morth

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 to compete here in Oslo.

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

NCMM Board

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

MEMBERS OF THE BOARD

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

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

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

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

Chair Ragnhild A. Lothe.
Photo: John Hughes

Greetings from the Chair of the Board

2012 has been an active and successful year for NCMM and its scientific groups. They have documented an impressive scientific production, including several publications in prime journals, and consequently the group leaders have been granted extensive extramural funding. The international atmosphere in the Centre continues to exist through the recruitment of skilled young scientists and through the extensive international network. In agreement with the Centre strategy the PIs conduct translational research projects and participate in several interventional and observational clinical studies.

The optimism of this joint venture for the three consortium partners, University of Oslo – host Institution, the South East Regional Health Authorities and the Norwegian Research Council, is reflected among their board representatives. We have the best confidence in the Director and the Centre members to continue their success and compete in the international arena of molecular medicine.

On behalf of the Board,
Ragnhild A. Lothe

From left to right:
Richard Treisman, Annika Lindblom, NCMM Director Kjetil Taskén, SAB Chair Leif Groop, Alvis Brazma and Erich Nigg.
Photo: John Hughes

Scientific Advisory Board (SAB)

The NCMM Scientific Advisory Board (SAB) was appointed by the Board in June 2011 and conducted their first site-visit at NCMM in January 2012. 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 second site-visit took place in February 2013.

After the second visit, the SAB acknowledged "the excellent scientific progress, the many national and international collaborations created as well as increasing number of joint NCMM projects, staff members, funding and publications". Furthermore, their general feeling was that "NCMM is on very successful upward trajectory, and that recruitment of the 5 group leaders has been a very successful endeavor".

MEMBERS OF THE SCIENTIFIC ADVISORY BOARD
The Scientific Advisory Board consists of five internationally renowned scientists:

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

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

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

Professor Erich Nigg
Director of Biozentrum
Basel, Switzerland

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

National Reference Group

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

THE REFERENCE GROUP CURRENTLY CONSISTS OF:




From left to right: Professor Terje Espevik, Norwegian University of Science and Technology, NTNU (Member of the NCMM Board), Assistant Professor Ingvild Mikkola, Dept. of Pharmacy, University of Tromsø (Deputy member of the NCMM Board), Professor Vidar Steen, Center for Medical Genetics and Molecular Medicine, University of Bergen and KG Jebsen Centre for Psychosis Research (Norwegian CoE, 2013) and Professor Anne-Brit Kolstø, Faculty of Mathematics and Natural Sciences, UiO.

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 senior or younger scientists who are currently based in Norway, whose expertise is compatible with the NCMM research areas and who are interested in collaborating with NCMM and in contributing to the building of an NCMM Molecular Medicine and Translational Research Network. Associated Investigators continue to work at their host institutions but are credited an affiliation to NCMM and the Nordic EMBL Partnership.

These appointments, subject to application and evaluation by a Selection Committee, are based on scientific excellence and translational merit. In the first two calls (Autumn 2009 and Spring 2011), a total of 12 Associated Investigators have been appointed. Nominations are being made for a time period of three years but are renewable.

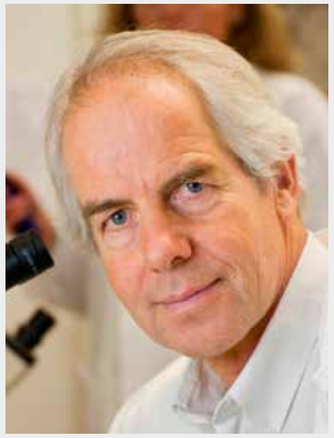
The NCMM Associated Investigators are presented in the following pages.

Photo: John Hughes

Illustrating photos on the following right pages are taken at NCMM.

BJARNE BOGEN – NCMM Associate Investigator

Centre for Immune Regulation (CIR, Centre of Excellence since 2007) and Cellular and Molecular Immunology Research Group, Institute of Clinical Medicine, University of Oslo



The Bogen group has an interest in immunology of T and B lymphocytes, autoimmune diseases, immunosurveillance of cancer and development of more powerful vaccines. More specifically, the group is focusing on immunoglobulins (Ig) and how they may be recognised by T cells as well as the use of parts of Ig modules for the group's development of novel vaccine molecules.

Three main projects comprise the group's research, each of which is briefly summarized below:

1. Idiotype-driven T cell-B cell collaboration and its role in health and disease

B lymphocytes require two separate signals in order to become activated, proliferate and differentiate. These signals are delivered via binding of the antigen-specific B cell receptor and specific helper T cells. Over the last 25 years, Bogen and co-workers have painstakingly established a novel type of interaction between T and B lymphocytes, in which T cells recognize Ig variable region-derived idiotypic (Id) peptides presented on the Major Histocompatibility Class II molecules on the surface of B cells. Our previous work has shown that if the B cell receptor is specific for a self-antigen and receives help from such Id-specific T cells, its activation may cause immune dysregulation, autoimmunity and B lymphoma development in mice. In 2012 we began investigating this pathogenic mechanism in patients with Chronic Lymphatic Leukaemia (CLL) and systemic Lupus Erythematosus (SLE). Furthermore, we are extending our studies of the basic mechanisms by establishing new strains of transgenic and BCR knock-in mice that we recently have established.

2. Novel vaccine molecules for cancer and infectious diseases

Key accomplishments in 2012 on vaccine development projects have been to extend the application of Vaccibody molecules to influenza, HIV and tuberculosis. In 2013 we will continue these studies and also try to develop more potent versions of the molecules. We will also try to develop vaccine molecules for human application.

Photo: F. Saggio, UiO

3. The mechanism by which CD4+ T cells can reject cancer cells

A main accomplishment in 2011 on tumour immunology projects was the demonstration that inflammation promotes the rejection of tumour cells by CD4+ T cells (Nature Communications, 2011). Efforts in 2013 will focus on immune-editing of tumours and how tumour cells escape killing by CD4+ T cells.

GROUP MEMBERS

ASSISTANT PROFESSOR:
Ludvig Munthe

SENIOR RESEARCHER:
Keith Thompson

POSTDOCTORAL FELLOWS:
Ranveig Braathen
Inger Øynebråten
Anders A. Tveita
Even Fossum
Simone Bürgler
Johanne Jacobsen
Ole Audun Haabeth

PHD STUDENTS:
Gunnveig Grødeland
Kristin Aas-Hanssen
Fredrik Schjesvold
Anna P. Ribes
Marta Baranowska
Heidi Spång
Anna Lysen

RESEARCH TECHNICIANS:
Peter Hofgaard
Hilde Omholt
Elisabeth Vikse
Mona Lindeberg

MEDICAL STUDENTS:
Ane Anderson
Henriette Jodal

MSC STUDENTS:
Aram Andersen
Marte Fauskanger
Arnar Gudjonsson

OLE A. ANDREASSEN – NCMM Associate Investigator

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

The Thematically Organized Psychosis (TOP) Study group is located in the KG Jebsen Centre for Psychosis Research (www.med.uio.no/klinmed/forskning/grupper/top/) and is part of a large and on-going collaborative study of clinical characteristics, neurocognitive functioning and brain biology of psychotic disorders. The overall goal is to identify underlying mechanisms and genetic susceptibility of schizophrenia and bipolar disorders.

The KG Jebsen Centre for Psychosis Research is the largest psychiatric research centre in Norway, with a total of 40 research fellows/PhD students, 14 post docs, and more than 10 senior faculties. The Centre leads a psychosis research network in Norway, and participates in several NIH and EU funded projects. The TOP Study is currently focused on phenotyping, including clinical and neurocognitive characteristics, with a specific emphasis on brain imaging and genetic analysis.

The KG Jebsen Centre for Psychosis Research is headed by Ole Andreassen. The Centre has expertise in psychiatric genetics, neuroscience and brain imaging, and runs the TOP Study which is organized into sub-projects at all university hospitals in Oslo and across collaborative sites in Norway. Patients are recruited using a common study protocol, and all samples and data are collected in a common biobank and databases. All sub-projects have access to a common infrastructure for neurocognitive testing, MR neuroimaging, molecular genetic laboratory facilities and database service. These groups at the KG Jebsen Centre are briefly described below:

1. The Clinical Unit, headed by Ingrid Melle, has extensive experience in clinical research in psychotic disorders, primarily longitudinal first episode studies.
2. The Neurocognitive Unit, headed by Kjetil Sundet, thoroughly investigates patients with a standard neuropsychological test battery.
3. The MRI Unit, headed by Ingrid Agartz in collaboration with Anders M. Dale, has extensive experience in MRI brain imaging methods and in studies in severe mental disorders. The Research Scanners include a 1.5T MRI scanner (Siemens) and a 3T MRI scanner (General Electric). We have developed automatic brain imaging analytical tools for detecting gene-brain phenotypes, enabling analyses of large datasets.
4. The MolGen group, headed by Srdjan Djurovic, has both regular equipment for SNP genotyping and Solexa Genome Analyzer (Illumina).
5. The KG Jebsen Centre also includes Prof Vidar M. Steen and Stephanie Le Hellard at University of Bergen, who are responsible for the Functional Genetics Unit and the Bioinformatics Unit, respectively.

Photo: John Hughes

The **key accomplishments** in 2012/first Q 2013 have been to elucidate new genetic mechanisms of neurocognitive dysfunction and dementia (Jonsson et al Nature 2012, Jonsson et al NEJM 2012) and brain structure variation (Stein et al. Nat Genetics 2012). We have also contributed with new methods to improve gene discoveries in complex disorders, including schizophrenia and bipolar disorders (Schork et al. PLoS Genetics 2013, Andreassen et al AJHG 2013, Andreassen et al. PLoS Genetics 2013, Liu et al. Nat Genetics 2013).

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ANNE-LISE BØRRESEN-DALE – NCMM Associate Investigator

KG Jebsen Centre for Breast Cancer Research and Department of Genetics, Institute for Cancer Research, Oslo University Hospital-Radiumhospitalet

The Børresen-Dale's research group is mainly focused on exploring the systems biology of breast cancer. In the K.G. Jebsen Center for Breast Cancer Research, of which she is the director, the aim is to integrate molecular data at all levels, from both tumours and healthy tissue from large cohorts of breast cancer patients. This includes deep sequencing data of tumours and metastases, DNA and RNA profiling as well as protein and metabolic profiling. In the integrated analyses, the group explores the genes, pathways, and networks involved in basic processes such as the cell cycle, DNA repair, apoptosis, and immune response, as well as their impact on breast cancer development, progression and response to therapy. The aim of performing longitudinal studies of samples at different stages of the disease and characterising such patient materials in full molecular details is to develop more individual treatment protocols.

A collaborative project was started in 2012 between a project group leader in Børresen-Dales group, Kristine Kleivi Sahlberg, and NCMM group leader Toni Hurtado examining the signalling pathways in HER2 positive breast cancers and their crosstalk with the estrogen receptor (ER). Together the groups will investigate the deregulated signalling pathways in HER2+ cancers in relation to treatment response and investigate the molecular interactions of ER and HER2 pathways using *in silico* studies in combination with state of the art technologies in prospective cell and clinical samples. Madhu Katika has been hired as a shared post doc between the two groups to work on this project. The Børresen-Dale group has a close collaboration with the groups of Cancer Genome Variation headed by Professor Vessela N. Kristensen and Tumor Initiating Cells in Breast Cancer Progression headed by Therese Sørlie.

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VIDAR STEEN – NCMM Associate Investigator

Center for Medical Genetics and Molecular Medicine, University of Bergen and KG Jebsen Centre for Psychosis Research (Centre of Excellence 2013)

Vidar Steen is the head of "Dr Einar Martens Research Group for Biological Psychiatry" at the Center for Medical Genetics and Molecular Medicine, the University of Bergen. The research group aims to identify biological and genetic factors involved in the aetiology, pathophysiology and treatment of bipolar disorder and schizophrenia, which are serious psychiatric disorders affecting approximately one percent of the population during the course of a lifetime. Below is a brief description of some selected events during 2012.

The Martens group is part of the KG Jebsen Centre for Psychosis Research that was officially opened in September 2012. It is headed by AI Ole A. Andreassen at UiO/OUS, and the research activities are mainly focused on the genetics and disease mechanisms of schizophrenia and bipolar disorder. In November, we were informed by the Research Council of Norway that our joint UiO/UOS/UiB-based NORMENT application (Norwegian Centre for Mental Disorders Research) had been granted funding as a new Centre of Excellence from 2013. Our research group is also responsible for running the UiB Genomics Core Facility, which is part of the Norwegian Microarray Consortium, a national FUGE platform for large-scale genomic analysis (www.genomics.no). During 2012, we have published several papers on metabolic adverse effects of antipsychotic drugs, exploring and establishing their mechanisms of action in a rat model (e.g., Skrede et al Int J Neuropsychopharmacol 2012, Jassim et al Psychopharmacol 2012, Skrede et al PLoS One 2012). We have also contributed substantially to the fields of cognition- and psychiatric genetics. Of special importance, we published a new method for interpretation of GWAS data (Christoforou et al Am J Hum Genet 2012). We also contributed to a large international study on the genetics of hippocampal volume (Stein et al Nat Genet 2012).

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Kari M. Ersland (dissertation June 2012)
Goran Jassim (dissertation October 2012)
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LARS A. AKSLEN – NCMM Associate Investigator

The Gade Institute, Section for Pathology, University of Bergen and Centre for Cancer Biomarkers (CCBIO, Centre of Excellence 2013)

Professor Akslen, a certified specialist in surgical pathology, has been directing the Tumor Biology Research Group at the Department of Clinical Medicine, University of Bergen since its establishment in 1995. Akslen is also since 2013 the director of Centre for Cancer Biomarkers, CCBIO, a Norwegian Centre of Excellence awarded by the Research Council of Norway. The Akslen team and now CCBIO are engaged in translational cancer research with a strong focus on the exploration and validation of novel biomarkers for more biologically based classification and grading of malignant tumors, as a better guide for targeted treatment.

At present, the team is focusing its efforts in two areas:

1. Studies of the tumor microenvironment, especially tumor-vascular interactions and angiogenesis.
2. Genetic and molecular markers of aggressive tumor behavior, especially related to cell cycle regulation and proliferation (e.g. Axl, EZH2, Nestin, P16, Stathmin).

Recently, the team reported that HSP27 appears to represent a critical regulator and biomarker of angiogenesis and tumor dormancy as shown in studies of breast cancer models with clinical validation (Straume et al., PNAS 2012). Furthermore, in collaboration with researchers at Harvard Medical School and Cornell University, the team has recently demonstrated how a tumor-secreted protein might induce a metastasis-resistant environment (niche) and inhibit metastatic spread (Catena et al., Cancer Disc 2013). Akslen and co-workers have previously reported several novel angiogenesis markers that might provide better grading of malignant tumors and provide important information for targeted treatment. In breast cancer studies, the team has found that angiogenesis, by several markers, is particularly increased in the aggressive basal-like subtype. The Akslen group is currently exploring predictive markers in the setting of anti-angiogenesis treatment of metastatic melanoma (Schuster et al., PLoS One 2012).

An important approach of the team has been to combine basic studies with assessment of tumor samples from patients, through the use of biobanks and registry data. The current aim is to extend studies of prognostic and predictive biomarkers towards an integrated role in clinical trials and personalized patient management. The team has extensive national and international collaboration.

Photo: John Hughes

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PÅL R. NJØLSTAD – NCMM Associate Investigator

The KG Jebsen Center for Diabetes Research, University of Bergen and Haukeland University Hospital

The Njølstad group is one of five research groups (nodes) located at the KG Jebsen Center for Diabetes Research. Diabetes affects five percent of the Norwegian population and its prevalence is increasing epidemically. The disease is a great burden due to both its acute and long-term complications. The vision of the KG Jebsen Center is to uncover novel disease mechanisms in diabetes development and to establish tools for differentiating specific subgroups of patients, thus facilitating individualized care.

The Center will achieve this vision by integrating the findings from large-scale genetic investigations and model systems with clinical research. Diagnostic tools will be developed based on genetic and non-genetic biomarkers, which will be validated in population-based data samples and processed for clinical application and dissemination.

Three major areas of research have been defined, which will provide a foundation for improvement in clinical care:

1) Identification of new genetic risk factors for diabetes and its complications
2) Identification and understanding of novel disease mechanisms in diabetes development
3) Development and implementation of improved targeted treatment of diabetes.

Professor Pål Njølstad leads the Clinical Medicine Node at the KG Jebsen Center for Translational Diabetes Research. The main aims of this node are:

1. Identification and characterisation of novel subtypes of diabetes. The knowledge gained through this project will be used to improve diagnostics and the targeted treatment of diabetes.
2. Obtain pluripotent stem cells (iPSC) from patients with monogenic diabetes. These iPSC will then be used as a research tool for therapeutic uses.

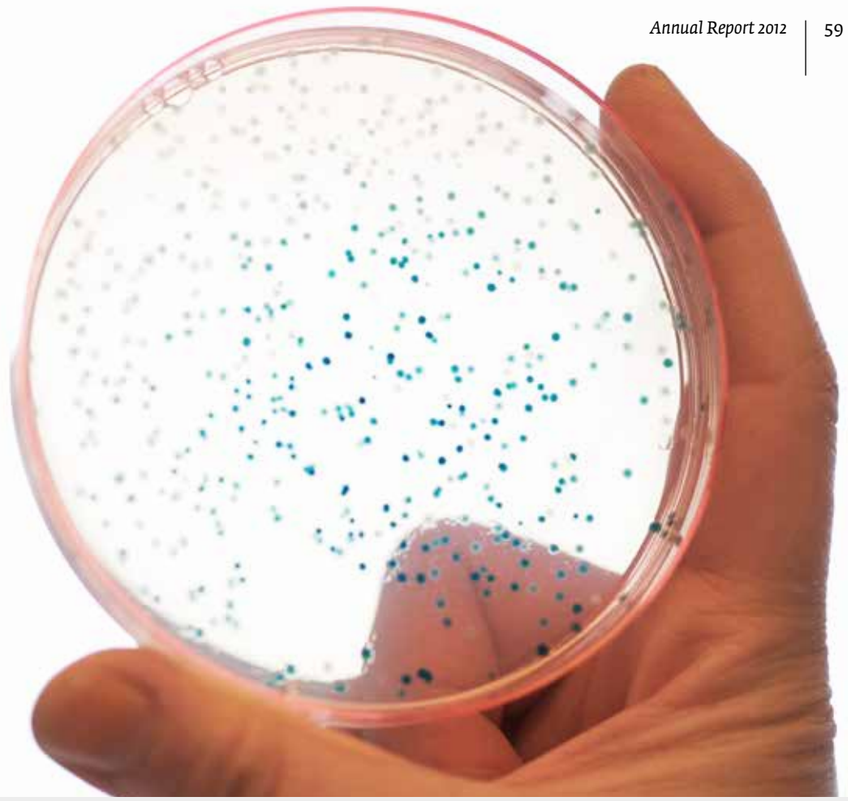

Photo: F. Saggio, UiO

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ARNE KLUNGLAND – NCMM Associate Investigator

Genome Repair and Regulation, Molecular Biology Research Group, Department of Molecular Medicine, Oslo University Hospital and Department for Basic Medical Sciences, University of Oslo

The Klungland research group has two main foci: 1) to identify and characterise novel reversible modifications in DNA and RNA, and 2) to be in the forefront of methods related to the analysis of genome and epigenome base modifications. These foci are explained in more detail below.

Studying the code of chemical modifications in DNA and RNA is important for understanding fundamental biological processes in health and disease. DNA has been the main focus for studying genome and epigenome base modifications. One of our major projects is related to the "6th" base in DNA, 5-hydroxymethylcytosine (5-hmC). 5-hmC is generated by the TET enzymes, which hydroxylate 5-methylcytosine (5-mC). Our preliminary data support the suspected roles of 5-hmC in transcription regulation, in addition to its apparent roles in epigenetic reprogramming and as an intermediate in the conversion of 5-mC to cytosine (C). The 5-hmC modification was recently shown to be absent in cancerous cells. This finding leads to the interesting hypothesis that the 5-hmC modification is essential for normal cellular processes and the loss of this modification may be a hallmark for tumorigenesis. Currently, we are analysing four enzymes that were identified through their specific interactions with 5-hmC containing DNA.

The exact role(s) of 5-hmC remains elusive although the importance of DNA methylation (e.g. 5-mC) in epigenetic regulation and reprogramming has been well established. 5-hmC has been detected in the DNA of embryonic stem cells as well as many other cell types. Surprisingly, brain tissue DNA contains the highest levels of 5-hmC. Bisulfite sequencing cannot distinguish between 5-mC and 5-hmC and there is thus a great need for methods that can identify 5-hmC. Currently, several methods are available for the identification of 5-hmC. These methods include 5-hmC antibodies, antibodies raised against cytosine 5-methylenesulfonane (CMS), single-molecule real-time sequencing relying on DNA polymerase kinetics, restriction enzymes resistant or sensitive to 5-hmC or β-glu-5-hmC, and two other methods that take advantage of β-gt (references in Robertson et al., Nature Protocols 2012, 7:340-50). The Quest 5-hmC™ DNA Enrichment Kit, patented by us, features J-base binding protein (JBP) for specific enrichment of 5-hmC containing DNA. The workflow makes the procedure reliable for robust analysis of multiple samples. The sensitive and selective 5-hmC enrichment obtained is competitive to all other methods established for enriching 5-hmC containing genomic DNA. At the time of this report, no study has yet provided a direct comparison of the methods.

Recently, functional RNAs and reversible RNA modifications have changed the scientific community's view on RNA entirely. The fat mass and obesity-associated dioxygenase FTO/ALKBH9 reverses 6-methyladenine (6-mA) modifications in RNA. The role of 6-mA in mRNA is currently unknown. We have identified an AlkB homolog, ALKBH5, that efficiently reverse the 6-mA modifications and that results in infertility in mice. We are currently analysing the role of 6-mA in meiosis and human diseases. Today, our focus is on reversible marks in RNA.

Photo: F. Saggio, UiO

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GEIR CHRISTENSEN – NCMM Associate Investigator

Cellular and Molecular Biology of Myocardial Hypertrophy and Heart Failure, Institute for Experimental Research, Oslo University Hospital Ullevål and University of Oslo

Chronic heart failure is a frequent outcome of several disease states. The leading etiological causes are hypertension, valvular disease and ischemic heart disease, including myocardial infarction. Despite recent advances in treatment options for heart failure, the syndrome is still a major cause of death.

The aim of the Christensen group is to develop novel therapeutic approaches and better diagnostic tools for heart failure through new knowledge about the molecular mechanisms involved. The group's main strategy is to identify genes that are regulated in heart failure and to study those that promote myocardial hypertrophy and cardiac dysfunction. Using microarray technology to identify regulated genes in hypertrophied and failing myocardium following myocardial infarction and aortic stenosis, the group has reported several genes not previously assigned a role in heart failure. In particular, several proteoglycans have over recent years been identified as regulated with important pathophysiological roles during development of heart failure.

Proteoglycans are highly glycosylated proteins localized in the extracellular matrix (ECM) or bound to cell membranes. Traditionally, proteoglycans are considered structural molecules of connective tissues and thus have been investigated in bone and cartilage. New results from our laboratory indicate an active role for proteoglycans as signal mediators determining myocardial fibrosis and diastolic dysfunction in the heart. We have shown that the membrane-bound proteoglycan syndecan-4 acts as a mechanical stress-sensor in cardiac fibroblasts inducing down-stream pro-fibrotic signalling resulting in increased myocardial stiffening. An array of experiments performed in collaboration with researchers at Harvard University has shown that syndecan-4 interacts with calcineurin, considered to be one of the most important signaling molecules for stress-induced myocardial hypertrophy. Furthermore, the ECM-localized proteoglycan lumican was found to have a direct effect on cardiac fibroblast activity triggering pro-fibrotic signalling. In order to ensure the relevance of the identified proteoglycans for human disease, the group has also analysed regulation of these molecules in biopsies from patient hearts.

The Christensen group is involved in several collaborations that provide access to samples and techniques to facilitate their research. For example, access to patient samples from the Research Institute for Internal Medicine and the Department of Cardiology at Oslo University Hospital Rikshospitalet (Professors Pål Aukrust and Lars Gullestad) provides a unique opportunity to verify findings from experimental models by analyzing gene regulation in material from patients with different types of chronic heart failure. Moreover, in collaboration with the Department of Cardiology at Akershus University Hospital (Professor Torbjørn Omland/Head of Research Helge Røsjø) we have filed a patent on granins as biomarkers of cardiac disease based on studies in mice and humans. Christensen is the head of the Center for Heart Failure Research, which comprises a close network of thirteen research groups in the Oslo region and in South-Eastern Norway Health Region. He has also recently become head of the newly established Norwegian PhD School of Heart Research.

Photo: John Hughes

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HELGA B. SALVESEN – NCMM Associate Investigator

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 Salvesen's research is focused on molecular alterations in gynaecologic cancer, to define potential targets for new therapies and develop reliable biomarkers for individualised therapy. The goal is to perform a comprehensive molecular profiling of primary- and metastatic lesions from cervical, endometrial- and ovarian carcinomas in order to improve trials with molecularly targeted therapy. This project represents clinical research with a strong focus on translational aspects. The study is part of a collaborative platform with Harvard, Dana Farber Cancer Institute, and MIT working towards the global characterisation of molecular alterations in metastatic gynaecologic cancer.

Through this work we have identified potentially targetable genetic alterations that are prevalent in aggressive gynaecologic disease (PNAS 2008 and 2009, Nature 2013). Based on this background, we have launched a prospective multicentre study to reduce morbidity, promote individualised treatment and facilitate the implementation of molecularly based targeted therapy for women with gynaecologic cancer. Tissue from primary tumours is collected nationally from several hospitals in the region and internationally through members of the Nordic Society for Gynaecologic Oncology and from European Cancer centres (MoMaTEC1).

During this project we plan to take our previous studies of global molecular classification of primary tumours to a new level, with global characterisation of genetic alterations in fresh tissues from corresponding metastatic lesions. The project will focus on molecular alterations in paired samples from primary tumours and metastatic lesions from the same patient with the goal of identifying targetable molecular alterations in metastatic lesions not present in the primary tumours.

Photo: John Hughes

A unique sample collection with freshly frozen primary-metastatic sample pairs will be used as an investigation set, and larger series with paired primary-metastatic formalin fixed paraffin embedded lesions will be used for clinical validation. The ultimate goal is to apply the new knowledge regarding distribution of genetic alterations in metastatic lesions to improve the design of trials with molecularly targeted therapy.

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ROLF BJERKVIG – NCMM Associate Investigator

NorLux Neuro-Oncology, Department of Biomedicine, University of Bergen and Centre de Recherche Public de la Santé, Luxembourg

Photo: John Hughes

The Bjerkvig group focuses on malignant tumours of the central nervous system (CNS), in particular glioblastoma and brain metastases, which represent a major unsolved clinical challenge. Primary malignant brain tumours can be regarded as a local disease within the CNS where the aggressive infiltrative tumour growth into the normal brain makes complete surgical resection impossible. Also, secondary brain tumours that result from metastatic disease represent a formidable problem.

Our research environment includes both research scientists and clinicians within the international laboratory NorLux (established in Norway and Luxembourg; www.norlux.lu). The NorLux Neuro-Oncology laboratory has built up a critical mass of competitive scientists within the major fields of biomedical brain tumour research (basic science and translational research towards clinical application). Through identification of new therapeutic targets within brain cancer and through the design of new treatment strategies, the laboratory is pro-active in the development of biotechnology and has close relations to pharmaceutical industry.

Our main mission is to translate key findings from our activities in basic and preclinical research into clinical application. To achieve this goal, basic and translational research are connected to clinical practice in order to verify new biological mechanisms in clinical material and to translate new therapeutic principles into clinical application. The laboratory has thus close relationships to clinical departments, which we think is fundamental for a translational research centre. The group is divided into four independent research teams focusing on fundamental aspects of brain tumour biology. In addition, researchers in five clinical departments (Oncology, Neuropathology, Neuroradiology, Dermatology and Neurosurgery) are active in implementing the new therapeutic principles that have been developed in our laboratories.

Based on recent research, our major focus is on identifying how tumour cells adapt to therapeutic intervention and in particular anti-angiogenic treatment. We have shown that this adaptive response is associated with a change in tumour metabolism. To determine in detail metabolic pathways in the tumours, we inject ^{13}C-labelled glucose into glioblastoma patients before neurosurgery. Upon tissue collection, we can assess in detail ^{13}C-labelled metabolites in the tumour samples by a technique termed metabolomic flux analysis. Based on information obtained from these studies, the group is, in collaboration with foreign institutions, developing new inhibitors targeting glycolysis in brain tumours.

Another research area is on tumour-host cellular interactions, cancer stem cells and validation of drug candidates for malignant brain tumours. In particular, we are performing research on how normal brain cells are re-programmed by cancer cells to promote tumour growth. The group has also developed a novel gene therapy approach based on lentiviral vectors that has shown promising results in preclinical studies. A strategy for taking this therapeutic principle into the clinic is under development. Furthermore, we have developed a research programme focusing on elucidating the mechanisms involved in brain metastasis from secondary tumours, with a particular focus on melanomas.

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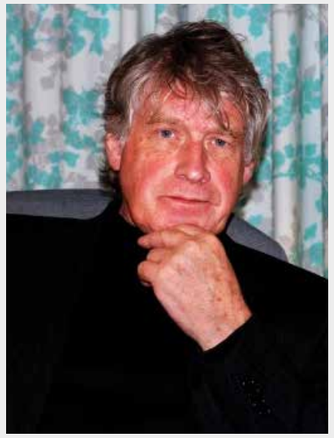
OLE PETTER REKVIG – NCMM Associate Investigator

Systemic lupus erythematosus and cancer – Regulation of the gene pair Trap 1 and DNaseI by transcriptional interference. RNA and molecular Pathology Research Group, Department of Medical Biology, Faculty of Health, University of Tromsø



The Rekvig group has generated a new evidence-based model that identifies factors that account for initiation and progression of human and murine lupus nephritis. Data from on-going studies demonstrate that antibodies against dsDNA lead to early deposition of chromatin fragments in the glomerular mesangial matrix, while progression of the disease is executed by a sudden and rapid shutdown of the renal nuclease DnaseI gene with an almost complete loss of DNaseI enzyme activity. In the absence of DnaseI, chromatin is not appropriately degraded; instead, chromatin is retained in glomerular basement membranes (GBM) in association with chromatin-reactive IgG autoantibodies. This confers to a serious progression of renal inflammation.

In order to understand why DNaseI is down-regulated in nephritic kidneys and why the loss of renal DNaseI executes severe progression of lupus nephritis, the group is analysing the regulation of the renal DNaseI gene. The effect of certain pro-inflammatory cytokines has been identified. The effect of silenced DNaseI gene will be directly demonstrated in a human renal DNaseI transgenic mouse. The transgene will be expressed out of regulatory context in two mouse strains that spontaneously develop classical lupus nephritis. According to the hypothesis, the transgene will protect against development of lupus nephritis.

In context of the results that appeared when analysing DNaseI in lupus nephritis, we developed a growing interest in regulating DNaseI in context of transcriptional interference.

Transcriptional interference usually refers to the direct negative impact of transcription of one gene on transcription of another gene provided the genes are transcribed in opposite directions and that the two genes overlap with each other. Transcriptional interference is potentially widespread throughout biology; therefore, it is timely to assess exactly its nature, significance and operative mechanisms especially in clinical medicine.

Photo: F. Saggio, UiO

Key achievements in 2012 include the demonstration that renal DNaseI is regulated by a convergent and overlapping gene that expresses the anti-apoptotic survival protein tumor necrosis factor receptor-associated protein 1 (Trap1). Trap 1 is up-regulated during stress and inflammation, and was observed to be up-regulated in severe lupus nephritis in situations where the DNaseI gene was nearby completely silenced. In detailed studies we could demonstrate that the two proteins are inversely expressed during progressive lupus nephritis.

The group is investigating regulation of DNaseI gene in lupus nephritis and Trap1 in cancer through a newly established collaboration with PI NCMM Ian Mills. Preliminary data demonstrate that Trap 1 is up-regulated in e.g. prostate cancer. The main prediction from data obtained in 2012 is therefore that high Trap 1 expression in kidneys confers to progression of lupus nephritis because of down-regulated DNaseI, while in prostate cancer high Trap 1 expression may indicate cancer cell survival due to its anti-apoptotic activity.

New information on central checkpoints in the signalling cascades that regulate DnaseI and Trap 1 gene expression will be used to develop new causal therapy modalities. The project represents a translational study performed in parallel in cell cultures, animal models and in humans.

The project group received a new financial funding for 3 years and a new post doc.

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PER EYSTEIN LØNNING – NCMM Associate Investigator

Section of Medicine, University of Bergen, & Department of Oncology, Haukeland University Hospital

The key focus of our team is to identify potential mechanisms of therapy resistance toward endocrine treatment and chemotherapy, with an emphasis on breast cancer. Our team works in the area of translational research, studying these mechanisms in tissue collected from human breast cancers undergoing treatment.

Endocrine therapy has been a focus of interest over several years and the group has delivered key studies concentrating on the mechanisms of action of endocrine therapy in breast cancer. Most of our work has been related to estrogen disposition in postmenopausal women and, in particular, endocrine effect of inhibitors of estrogen synthesis, the so-called aromatase inhibitors.

With regards to studying resistance to chemotherapy, our main focus has been disturbances related to the function of the "p53 pathway" as a cause of resistance toward important cytotoxic compounds like the anthracyclines. Thus, apart from mutations affecting the TP53 gene itself, we have identified defects in multiple other genes involved in the p53 or redundant pathways, including CHEK2, ATM and the Retinoblasoma gene.

In addition, on-going work is concentrated on the effects of gene polymorphisms and epigenetic mechanisms influencing cancer risk. While genetic risk factors in relation to frequent cancer diseases like breast and colorectal cancers have been studied through so-called Genome-Wise Association Studies (GWAS) exploring multiple variants across the genome, in 2011 we could show that two adjacent SNPs (located only 24bp apart) counteracted the effects of each other with respect to ovarian, breast and endometrial cancer risk. This effect was overlooked in a general GWAS model. Thus, we believe similar phenomena may occur with respect to key genes involved in cellular processes like apoptosis and DNA repair, and we are currently studying several genes of relevance and perform detailed studies on the biological mechanisms involved.

Our aim for the next years is to implement novel second-generation gene sequencing (and epigenetic analysis) studying multiple gene disturbances in concert.

Photo: John Hughes

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NordForsk

Nordic Molecular Medicine Network

The Nordic Molecular Medicine Network (NMMN) is a Nordic Network of National Centres of Excellence and is supported by Nordforsk (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. Åke Forsberg, Umeå University, acts as NMMN project manager.

Establishment of the network is an important part of the Nordic EMBL Partnership and is essential to promote sustainable long-term collaborations. The first two NMMN meetings were organized by MIMS and FIMM in 2010 and 2011, respectively. In 2012, the annual NMMN meeting was replaced by an EMBL Partnership event in Barcelona (see NCMM Events section), organized by EMBL and including EMBL partners also from outside the Nordic countries. The fourth networking meeting will take place in Oslo in September 2013.

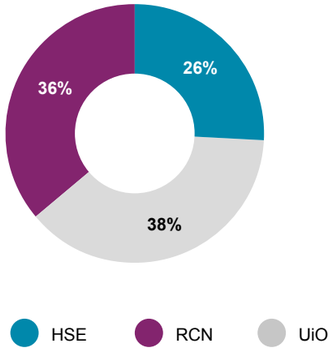
NCMM Funding

The annual *NCMM core funding* is 27 million Norwegian kroner (mNOK) (approx. 3.6 mEUR) per year from the 3 consortia partners UiO (10 mNOK), the Research Council of Norway (10 mNOK) and Health SouthEast (7 mNOK), originally for the period 2008-2012. However, due to delays in the start-up period, some funding was redistributed to 2013 and 2014. In addition to the core funding, the centre receives some overhead and production-based income from UiO (1.8 mNOK in 2012). Including transferred funds, NCMM spent 31 mNOK in 2012 on its core budget and plans to spend 31.3 mNOK in 2013 and 2014, drawing on transferred funds inside the first 5-year period if the consortia partners continue their commitment in 2014 which at the moment is not fully financed.

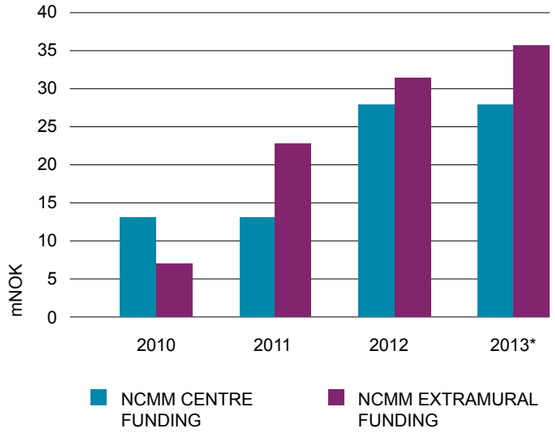
For the period 2015-2019 we stipulate the NCMM annual core budget expenses to be in the order of 35 mNOK annually (2015-value, averaged for 2015-19) with the present level of activity, when adjusting for price and salary increases from when NCMM was planned and including the national function which was not budgeted for in the first 5-year period.

NCMM extramural funding in the form of grants to the group leaders and other competitive funding (ex. Founding Partners that are accounted elsewhere) was approx. 7 mNOK in 2010, 23 mNOK in 2011, 30 mNOK in 2012 and is stipulated to exceed 35 mNOK in 2013. This includes grants from the Research Council of Norway (7), Norwegian Cancer Society (6), Health SouthEast (2), European Commission (5), NIH (1), competitive grants at UiO (4) and private foundations and organizations such as the Lundbeck Foundation, Novo Nordic Foundation, Carlsberg Foundation, KG Jebsen Centres (3), Movember and others. Furthermore, the Nordic nodes within the EMBL Nordic Partnership in Molecular Medicine are also supported by Nordforsk as a Nordic Network of National Centres of Excellence. This network “Nordic Molecular Medicine Network” (NMMN) has promoted collaboration and exchange between FIMM, NCMM, MIMS and EMBL.

NCMM CORE FUNDING SOURCES 2012



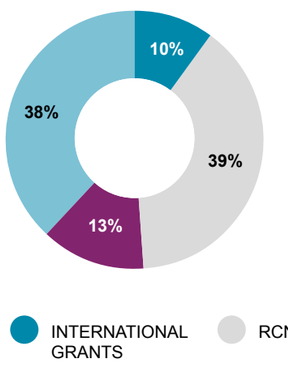
NCMM CENTRE FUNDING VS. EXTRAMURAL FUNDING



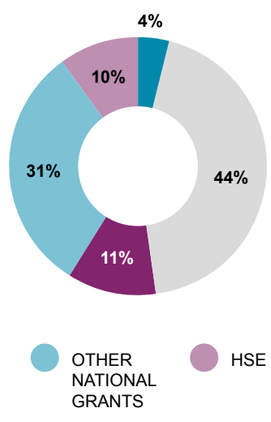
FUNDING STATISTICS

The funding overview illustrated above includes only NCMM groups, including that of the Director from 2011. Finances of the Founding Partners not accounted at NCMM have not been included. The 2013 data are based on accounts for the first half and on budget numbers for the second half of 2013.

EXTRAMURAL FUNDING SOURCES 2012



ESTIMATED EXTRAMURAL FUNDING SOURCES 2013



The overview of extramural funding sources includes NCMM groups but not finances of the Founding Partner groups accounted elsewhere. The 2013 overview below is an estimate of extramural funding sources for the whole 2013 based on budget sending on secured grants.

NCMM-Affiliated Publications

NCMM publications from 2012

- Mislocalization of AQP4 precedes chronic seizures in the kainate model of temporal lobe epilepsy. Alvestad S, Hammer J, Hoddevik EH, Skare O, Sonnewald U, Amiry-Moghaddam M, Ottersen OP. (2013) **Epilepsy Res**. doi: 10.1016/j.eplepsyres.2013.01.006. [Epub ahead of print]
- Review: Aquaporin-4 and epilepsy. Binder DK, Nagelhus EA, Ottersen OP. (2012) Glia 60(8): 1203-14.
- Regulatory T-cell-mediated inhibition of antitumor immune responses is associated with clinical outcome in patients with liver metastasis from colorectal cancer. Brudvik KW, Henjum K, Aandahl EM, Bjørnbeth BA, Taskén K. (2012) **Cancer Immunol Immunother**. 61(7):1045-53.
- Modulation of T cell immune functions by the prostaglandin E2 - cAMP pathway in chronic inflammatory states. Brudvik KW, Taskén K. (2012) **Brit. J. Pharmacol**. 166 411–419.
- EGF signalling and rapamycin-mediated mTOR inhibition in glioblastoma multiforme evaluated by phospho-specific flow cytometry. Cornez I, Joel M, Taskén K, Langmoen IA, Glover JC, Berge T. (2013) **J Neurooncol**. 112(1):49-57 (Epub 2013 Jan 9).
- Deletion of aquaporin-4 changes the perivascular glial protein scaffold without disrupting the brain endothelial barrier. Eilert-Olsen M, Haj-Yasein NN, Vindedal GF, Enger R, Gundersen GA, Petersen PH, Haug FMS, Skare Ø, Adams ME, Froehner SC, Burkhardt JM, Thoren AE, Nagelhus EA. (2012) **Glia** 60(3):432-40.
- Molecular scaffolds underpinning macroglial polarization: an analysis of retinal Müller cells and brain astrocytes in mouse. Enger R, Gundersen GA, Haj-Yasein N., Eilert-Olsen M, Thoren AE, Vindedal GF, Petersen PH, Skare Ø, Nedergaard M, Ottersen OP, Nagelhus EA. (2012) **Glia** 60(12):2018-26.
- Cooperating transcription factors mediate the function of estrogen receptor. Fiorito E, Katika M, Hurtado A. (2013) **Chromosoma** 122(1-2):1-12 (Epub 2012 Nov 29).
- Review: Functional genomic methods to study estrogen receptor activity. Gilfillan S, Fiorito E, Hurado A. (2012) **J Mammary Gland Biol Neoplasia** 17(2):147-53.
- Genetic and functional analyses implicate the NUDT11, HNF1B, and SLC22A3 genes in prostate cancer pathogenesis. Grisanzio C, Werner L, Takeda D, Awoyemi BC, Pomerantz MM, Yamada H, Sooriakumaran P, Robinson B, Leung R, Schinze AC, Mills IG, Ross-Adams H, Neal DE, Kido M, Yamamoto T, Petrozziello G, Stack E, Lis R, Kantoff PW, Loda M, Sartor OA, Egawa S, Tewari AK, Hahn WC, Freedman ML. (2012) **Proc Natl Acad Sci USA** 109(28):11252-7 (Epub 2012 Jun 22).
- Kinetics and activation requirements of contact-dependent immune suppression by human regulatory T cells. Hagness M, Henjum K, Landskron J, Brudvik KW, Bjørnbeth BA, Foss A, Taskén K, Aandahl EM. (2012) **J Immunol**. 188(11):5459-66.
- Aquaporin-4 regulates extracellular space volume dynamics during high-frequency synaptic stimulation: a gene deletion study in mouse hippocampus. Haj-Yasein NN, Jensen V, Østby I, Omholt S, Kaila K, Voipio J, Ottersen OP, Hvalby Ø, Nagelhus EA. (2012) **Glia** 60(6):867-74 (Epub 2012 Mar 14).

- ER stress-mediated autophagy promotes Myc-dependent transformation and tumor growth. Hart LS, Cunningham JT, Datta T, Dey S, Tameire F, Lehman SL, Qiu B, Zhang H, Cerniglia G, Bi M, Li Y, Gao Y, Liu H, Li C, Maity A, Thomas-Tikhonenko A, Perl AE, Koong A, Fuchs SY, Diehl JE, Mills IG, Ruggero D, Koumenis C. (2012) **J Clin Invest**. 122(12):4621-34 (Epub 2012 Nov 12).
- Purification, crystallization and preliminary crystallographic studies of a PacL homologue from Listeria monocytogenes. Hein KL, Nissen P, Morth JP. (2012) Acta Crystallogr Sect F Struct Biol **Cryst Commun**. 68 (Pt 4):42.
- Loss of perivascular Kir4.1 potassium channels in the sclerotic hippocampus of patients with mesial temporal lobe epilepsy. Heuser K, Eid T, Lauritzen F, Thoren AE, Vindedal GF, Taubøll E, Gjerstad L, Spencer DD, Ottersen OP, Nagelhus EA, de Lanerolle NC. (2012) **J Neuropathol Exp Neurol**. 71(9):814-25.
- PIAS1 is increased in human prostate cancer and enhances proliferation through inhibition of p21. Hoefer J, Schäfer G, Klocker H, erb HH, Mills IG, Hengst L, Puhr M, Culig Z. (2012) **Am J Pathol**. 180(5):2097-107. doi: 10.1016/j.ajpath.2012.01.026 (Epub 2012 Mar 23).
- Transducin-like enhancer protein 1 mediates estrogen receptor binding and transcriptional activity in breast cancer cells. Holmes KA, Hurtado A, Brown GD, Launchbury, R, Ross-Innes CS, Hadfield J, Odom DT, Carroll JS. (2012) **Proc Natl Acad Sci USA** 109(8):2748-53.
- Recent Advances in Wnt/beta-Catenin Pathway Small-Molecule Inhibitors. Holsworth DD, Krauss S. (2012) Annu. Rep. Med. Chem., 47, 393-409.
- A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Nagelhus EA, Nedergaard M. (2012) **Sci Transl Med**. 4(147):147ra111. doi: 10.1126/scitranslmed.3003748.
- Modulation of proximal signaling in normal and transformed B cells by transmembrane adapter Cbp/PAG. Kalland ME, Solheim SA, Skånland SS, Taskén K, Berge T. (2012) **Exp Cell Res**. 318(14):1611-9.
- Is the brain water channel aquaporin-4 a pathogenetic factor in idiopathic intracranial hypertension? Results from a combined clinical and genetic study in a Norwegian cohort. Kerty E, Heuser K, Indahl UG, Berg PR, Nakken S, Lien S, Omholt SW, Ottersen OP, Nagelhus EA. (2013) **Acta Ophthal** 91:88-91.
- NF-κB activity in perinatal brain during infectious and hypoxic-ischemic insults revealed by a reporter mouse. Kielland A, Camassa LM, Døhlen G, Munthe LA, Blomhoff R, Amiry-Moghaddam M, Carlsen H. (2012) **Brain Pathol**. 22(4):499-510.
- Disseminated tumor cells and their prognostic significance in non-metastatic prostate cancer patients. Lilleby W, Stensvold A, Mills IG, Nesland JM. (2013) **Int J Cancer**. 133(1):149-55. doi: 10.1002/ijc.28002 (Epub 2012 Dec 22).
- Exome sequencing of prostate cancer supports the hypothesis of independent tumour origins. Lindberg J, Klevebring D, Liu W, Neiman M, Xu J, Wiklund P, Wiklund F, Mills IG, Egevad L, Grönberg H. (2012) **European Urology** 63(2):347-53. doi: 10.1016/j.eururo.2012.03.050 (Epub 2012 Mar 31).
- The mitochondrial and autosomal mutation landscapes of prostate cancer. Lindberg J, Mills IG, Klevebring D, Liu W, Neiman M, Xu J, Wikstrom P, Wiklund P, Wiklund F, Egevad L, Gronberg H. (2013) **European Urology** 63(4):702-8 (Epub 2012 Dec 5).
- Mapping protein-DNA interactions using ChIP sequencing. Massie CE, Mills IG. (2012) **Methods Mol Biol**. 776:255-73 (Book Chapter).
- Peri-pubertal gonadotropin-releasing hormone analog treatment affects hippocampus gene expression without changing spatial orientation in young sheep. Nuruddin S, Wojniusz S, Ropstad E, Krogenæs A, Evans NP, Robinson JE, Solbakk AK, Amiry-Moghaddam M, Haraldsen IR. (2012) **Behav Brain Res**. 242:9-16.
- Molecular subtyping of primary prostate cancer reveals specific and shared target genes of different ETS rearrangements. Paulo P, Ribeiro FR, Santos J, Mesquita D, Almeida M, Barros-Silva JD, Itkonen H, Henrique R, Jerónimo C, Sveen A, Mills IG, Skotheim RI, Lothe RA, Teixeira MR. (2012) **Neoplasia** 14(7):600-11.

- Thrombopoietin receptor down-modulation by JAK2 V617F: restoration of receptor levels by inhibitors of pathologic JAK2 signaling and of proteasomes. Pecquet C, Diaconu CC, Staerk J, Girardot M, Marty C, Royer Y, Defour JP, Dusa A, Besancenot R, Giraudier S, Villeval JL, Knoops L, Courtoy PJ, Vainchenker W, Constantinescu SN. (2012) **Blood** 119(20):4625-35.
- Interleukin-33 drives a proinflammatory endothelial activation that selectively targets nonquiescent cells. Pollheimer J, Bodin J, Sundnes O, Edelmann RJ, Skånland SS, Sponheim J, Brox MJ, Sundlisaeter E, Loos T, Vatn M, Kasprzycka M, Wang J, Küchler AM, Taskén K, Haraldsen G, Hol J. (2013) **Arterioscl. Thromb. Vasc. Biol**. 33(2):e47-55 (Epub 2012 Nov 15).
- The sensor region of the ubiquitous cytosolic sensor kinase, PdtaS, contains PAS and GAF domain sensing modules. Preu J, Panjikar S, Morth JP, Jaiswal R, Karunakar P, Tucker PA. (2012) **J Struct Biol**. 177(2):498-505.
- Protective role of brain water channel AQP4 in murine cerebral malaria. Promeneur D, Lunde LK, Amiry-Moghaddam M, Agre P. (2013) **Proc Natl Acad Sci USA** 110(3):1035-40 (Epub 2012 Dec 31).
- Real-time analysis of microglial activation and motility in hepatic and hyperammonemic encephalopathy. Rangroo Thrane VR, Thrane AS, Chang J, Alleluia V, Nagelhus EA, Nedergaard M. (2012) **Neuroscience** 220:247-55.
- High sensitivity measurements of active oxysterols with automated filtration/filter backflush-solid phase extraction-liquid chromatography-mass spectrometry. Roberg-Larsen H, Strand MF, Grimsmo A, Olsen PA, Dembinski JL, Rise F, Lundanes E, Greibrokk T, Krauss S, Wilson SR. (2012) **J Chromatogr A**. 1255:291-7.
- Review: Cell signalling analyses in the functional genomics era. Rogne M, Taskén K. (2013) **N Biotechnol**. 30(3):333-8 (Epub 2013 Jan 28).
- Aquaporin-1 in cardiac endothelial cells is downregulated in ischemia, hypoxia and cardioplegia. Rutkovskiy A, Bliksøen M, Hillestad V, Amin M, Czibik G, Valen G, Vaage J, Amiry-Moghaddam M, Stensløkken KO. (2012) **J Mol Cell Cardiol**. 56:22-33 (Epub 2012 Dec 10).
- Aquaporin-4 in the heart: expression, regulation and functional role in ischemia. Rutkovskiy A, Stensløkken KO, Mariero LH, Skrbic B, Amiry-Moghaddam M, Hillestad V, Valen G, Perreault MC, Ottersen OP, Gullestad L, Dahl CP, Vaage J. (2012) **Basic Res Cardiol**. 107(5):280.
- Creating order from chaos: cellular regulation by kinase anchoring. Scott JD, Dessauer CW, Taskén K. (2013) **Annu Rev Pharmacol Toxicol**. 53:187-210 (Epub 2012 Oct 8).
- The androgen receptor induces a distinct transcriptional program in castration-resistant prostate cancer in man. Sharma NL, Massie CE, Ramos-Montoya A, Scott HE, Lamb A, MacArthur S, Stark R, Warren AY, Mills IG*, Neal DE*, (2013) **Cancer Cell**. 23(1):35-47. (Epub 2012 Dec 20). (*Authors contributed equally)
- Mouse Tcf3 represses canonical Wnt signaling by either competing for β-catenin binding or through occupation of DNA-binding sites. Solberg N, Machon O, Machonova O, Krauss S. (2012) **Mol Cell Biochem**. 365(1-2):53-63.
- Characterization and functional analysis of the 5'-flanking promoter region of the mouse Tcf3 gene. Solberg N, Machon O, Krauss S. (2012) **Mol Cell Biochem**. 360(1-2):289-99.
- Luciferase assay to study the activity of a cloned promoter DNA fragment. Solberg N, Krauss S. (2012) **Methods Mol Biol**. 977:65-78.
- The JAK-STAT pathway and hematopoietic stem cells from the JAK2V617F perspective. Staerk J, Constantinescu SN. (2012) **JAK-STAT**. Volume 1:3.
- General anesthesia selectively disrupts astrocyte calcium signaling in the awake mouse cortex. Thrane AS, Thrane VR, Zeppenfeld D, Lou N, Xu Q, Nagelhus EA, Nedergaard M. (2012) **Proc Natl Acad Sci USA** 109(46):18974-9.
- A bimodular mechanism of calcium control in eukaryotes. Tidow H, Poulsen L,R, Adreeva A, Knudsen M, Hein KL, Wiuf C, Palmgren MG, Nissen P. (2012) **Nature** 491(7424):468-72 (Epub 2012 Oct 21).
- LYP inhibits T-cell activation when dissociated from CSK. Vang T, Liu WH, Delacroix L, Wu S, Vasile S, Dahl R, Yang L, Musumeci L, Francis D, Landskron J, Tasken K, Tremblay ML, Lie BA, Page R, Mustelin T, Rahmouni S, Rickert RC, Tautz L. (2012) **Nature Chem Biol**. 8(5):437-46.

- The autoimmune-predisposing variant of lymphoid tyrosine phosphatase favors T helper 1 responses. Vang T, Landskron J, Viken MK, Oberprieler N, Torgersen KM, Mustelin T, Tasken K, Tautz L, Rickert RC, Lie BA. (2013) **Hum Immunol**. 74(5):574-85 (Epub 2013 Jan 17).
- Wnt/beta-catenin signaling and small molecule inhibitors. Voronkov A, Krauss S. (2012) **Curr Pharm Des**. 19(4):634-64.
- A novel tankyrase inhibitor decreases canonical Wnt signaling in colon carcinoma cells and reduces tumor growth in conditional APC mutant mice. Waaler J, Machon O, Tumova L, Dinh H, Korinek V, Wilson SR, Paulsen JE, Pedersen NM, Eide TJ, Machonova O, Gradl D, Voronkov A, von Kries JP, Krauss S. (2012) **Cancer Res**. 72(11):2822-32.
- p53 isoforms β/γ correlate with prognostic NPM1/FLT3 mutations and therapy response in acute myeloid leukemia. Ånensen N, van Belle W, Hjelle SM, Haaland I, Bourdon J-C, Hovland R, Tasken K, Knappskog S, Lønning PE, Bruserud Ø, Gjertsen BT. (2012) **Oncogene** 31:1533-45.

NCMM EMERGING PUBLICATIONS 2013

- Aggressive treatment of patients with metastatic colorectal cancer increases survival. Brudvik KW, Bains SJ, Seeberg LT, Labori KJ, Waage A, Taskén K, Aandahl EM, Bjørnbeth BA (2013) **HPB Surg**., in press.
- Mobilizers of intracellular calcium potently block autophagy. Autophagy. Engedal KN, Torgersen ML, Guldvik IJ, Barfeld S, Bakula D, Saetre F, Hagen LK, Proikas-Cezanne T, Seglen PO, Simonsen A, Mills. (2013) **Autophagy**, In Press.
- N-Linked Glycosylation Supports Cross-Talk between Receptor Tyrosine Kinases and Androgen Receptor. Itkonen HM, Mills IG. (2013) **PLoS One** published 28 May 2013 | PLOS ONE 10.1371/journal.pone.0065016
- O-GlcNAc transferase integrates metabolic pathways to regulate the stability of c-MYC in human prostate cancer. Itkonen HM, Minner S, Guldvik IJ, Sandmann MJ, Tsourlakis MC, Berge V, Svindland A, Schlomm T, Mills IG. (2013). **Cancer Res**. Published OnlineFirst May 29, 2013; doi:10.1158/0008-5472.CAN-13-0549
- A functional link between FOXA1 and breast cancer SNPs. Katika M, Hurtado A. (2013) Breast Cancer Res. 15(1):303. [Epub ahead of print]
- Probing Determinants of Cyclopiazonic acid Sensitivity of Bacterial Ca2+ -ATPases. Kotsubei A, Gorgel M, Morth JP, Nissen P, Adersen JL. (2013) **FEBS J**. [Epub ahead of print].
- CD147 in regulatory T cells. Landskron J, Taskén K. (2013) Cell Immunol. 282(1):17-20 [Epub ahead of print].
- A Novel Tankyrase Small-Molecule Inhibitor Suppresses APC Mutation-Driven Colorectal Tumor Growth. Lau T, Chan E, Callow M, Waaler J, Boggs J, Blake RA, Magnuson S, Sambrone A, Schutten M, Firestein R, Machon O, Korinek V, Choo E, Diaz D, Merchant M, Polakis P, Holsworth DD, Krauss S, Costa M. (2013) **Cancer Res**. 73(10):3132-3144 (Epub 2013 Mar 28).
- Tankyrases as Drug Targets. Lehtiö L, Chi NW, Krauss S. (2013) **FEBS J**. doi: 10.1111/febs.12320. [Epub ahead of print]
- Proinflammatory and immunoregulatory role of eicosanoids in T cells. Lone AM, Taskén K. (2013) **Front. Immunol**. (T cell biology), in press.
- A proteomic approach to screening of dynamic changes in detergent-resistant membranes from activated human primary T cells. Moltu K, Bjørgo E, Solstad T, Berge T, Thiede B, Taskén K. (2013) **J Proteomics Bioinf**. In Press.
- Review: Physiological roles of aquaporin-4 in brain. Nagelhus EA, Ottersen OP. (2013) Physiol Rev.
- *In vivo* NADH fluorescence imaging indicates effect of aquaporin-4 deletion on oxygen microdistribution in cortical spreading depression. Thrane AS, Takano T, Rangroo Thrane V, Wang F, Peng W, Ottersen OP, Nedergaard M, Nagelhus EA. (2013) **J Cereb Blood Flow Metab**. Apr 24. doi: 10.1038/jcbfm.2013.63 [Epub ahead of print].

- Structural basis and SAR for G007-LK, a lead stage 1,2,4-triazole based specific tankyrase 1/2 inhibitor. Voronkov A, Holsworth DD, Waaler J, Wilson SR, Ekblad B, Perdreau-Dahl H, Dinh H, Drewes G, Hopf C, Morth JP, Krauss S. (2013) **J Med Chem**. 56(7):3012-23 (Epub 2013 Mar 29).

PATENTS FILED IN 2012

Method to regulate connexin 43 gap junction communication. Inventors: Taskén, K., Pidoux, G., Lygren, B. Evain-Brion, D. U.S. Provisional Patent Application, Filed: 15-May-2012.

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

PRESS ITEMS:

- Nature Chemical Biology, News & Views, April 17, 2012: Immunology, Csk keeps Lyp on a leash (Comment on Vang et al., Nat Chem Biol. Paper: www.nature.com/nchembio/journal/v8/n5/full/nchembio.940.html)
- Forskning.no, September 5, 2012: Vannkanaler renser hjernen (Nagelhus, www.forskning.no/artikler/2012/september/332452)
- Forskningsrådet, September 11, 2012: Vannkanaler holder hjernen ren (Nagelhus, www.forskningsradet.no/prognett-nevronor/Nyheter/Vannkanaler_holder_hjernen_ren/1253980053252/p1224698072633)
- UiO, Det Medisinske Fakultet, November 6, 2012: Et vindu til hjernens mysterier (Nagelhus, www.med.uio.no/om/aktuelt/aktuelle-saker/2012/internasjonalisering/erlend-nagelhus.html)
- Cancer Research UK, Science Update Blog, December 20, 2012: Tissue study turns tables on prostate cancer (based on Sharma et al., Cancer Cell. Paper, Mills co-senior author: www.scienceblog.cancerresearchuk.org/2012/12/20/tissue-study-turns-tables-on-prostate-cancer/)
- TheInformationDaily.com, December 20, 2012: Prostate cancer tissue study could revolutionise treatment (based on Sharma et al., Cancer Cell. Paper, Mills co-senior author: www.theinformationdaily.com/2012/12/20/prostate-cancer-tissue-study-could-revolutionise-treatment)
- UiO, Institutt for Klinisk Medisin, Ferbruary 26, 2013: Nye KG Jebsen sentre (www.med.uio.no/klinmed/om/aktuelt/aktuelle-saker/2013/nye-k-g-jebsen-sentre.html)
- Stiftelsen Kristian Gerhard Jebsen, 2013: Satsing på betennelsesforskning (www.stiftkgj.no/?page_id=328)
- UiO, March 22, 2013: Kan immunsystemet kurere kreft slik det kurerer influensa? (www.uio.no/om/aktuelt/arrangementer/uio-festivalen/arrangementer/livsvitenskap/kan-immunsystemet-kurere-kreft.html)
- Stiftelsen Kristian Gerhard Jebsen, 2013: Når immunsystemet ikke klarer å bekjempe kreft
- VG, April 5, 2013, pp 10-11: 6 nye våpen mot kreft (kilde: skreddersydd medisin, Taskén)
- Dagens Medisin, April 11, 2013: Skreddersydd kreftbehandling utfordrer diagnosesystemene w(Taskén, www.dagensmedisin.no/nyheter/skreddersydd-kreftbehandling-utfordrer-diagnosesystemene/)
- Science-Business eXchange (SciBX), April 18, 2013: Targeting Tankyrase (Morth, Cover Story, www.biocentury.com/scibx/coverstory/2013-04-18/cover-story-targeting-tankyrase-s1)

Personnel

DIRECTOR AND ADMINISTRATION

Director
Professor Kjetil Taskén

Chief Administrative Officer
Elin Kaurstad (until March 2013)

Chief Administrative Officer
Dr. Elisa Bjørgo (from April 2013)

Financial Officer
Anita Skolem

Personnel Officer
Nina Modahl

RESEARCH GROUPS

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NCMM Group Leader
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Head Engineer
Ingrid Jenny Guldvik

Postdoctoral Fellows
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Dr. Alfonso Urbanucci
Dr. Verena Zuber

PhD Fellows
Harri Itkonen
Lisa Gerner
Stefan Barfeld

MSc Student
Morten Luhr

Glio-vascular Imaging Group
NCMM Group Leader
Professor Erlend A. Nagelhus

Senior Engineer
P. Johannes Helm

Senior Researchers
Dr. Vidar Jensen
Dr. Anna Thoren
Postdoctoral Fellows
Dr. John Burkhardt
Dr. Karolina Szokol
Dr. Wannan Tang

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Rune Enger
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Gry F. Vindedal

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Cecilie E. Bugge

Membrane Transport Group
NCMM Group Leader
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Principial Engineer
Hanne Guldsten

Postdoctoral Fellows
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Dr. Kim Langmach Hein

PhD Fellows
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Saranya Subramani
Theis Sommer

MSc Students
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Sazzad Toushik
Nina Fagernes

Signaling Networks in Health and Disease
NCMM Group Leader
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Senior Researchers
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Dr. Torunn Berge
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Dr. Elisa Bjørgo (until April 2013)
Dr. Johannes Landskron

Postdoctoral Fellows
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Dr. Guro Mørk Johnsen
Dr. Anna Mari Lone (from Feb. 2013)
Dr. Maria-Niki Mylanokou
Dr. Marie Rogne
Dr. Sigrid Skånland
Dr. Susanne Weedon-Fekjær

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Stalin C. Gunasekaran
Morten Hagness
Karen Henjum (until Oct. 2012)
Maria Kalland (until Sept. 2012)
Nora Lieske
Kristine Moltu
Kristoffer Watten-Brudvik
(until June 2012)
Ellen Østensen

MD/PhD & MSc students
Anders Egeland (until May 2012)
Lise-Lotte Flage-Larsen
(from April 2013)
Grunde Wibetoe (until May 2012)

Scientific Officers
Jorun Solheim
Gladys Tjørhom

Administrative Officer
Berit Barkley

Chemical Biology Platform
Dr. Anne Jorunn Stokka
Dr. Inderjit M. Singh
(until Oct. 2012)
David McClymont
(from Feb. 2013)

Photo: John Hughes

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Dr. Siv Gilfillan

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Dr. Madhu Katika

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Elisa Fiorito

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NCMM Group Leader
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Postdoctoral Fellow
Dr. Xavier Tekpli
PhD Fellows
Julia-Kristina Jensen Madsen-Østerbye
Oksana Rogovchenko
(from May 2013)

Unit for Cell Signaling
NCMM Founding Group
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Monika Gelazauskaite

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Dr. Jennifer Dembinski
Dr. Nina T. Solberg
Dr. Andrey Voronkov

PhD Fellows
Jo Waaler
Martin F. Strand

MSc students:
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Khahn Huynh
Tore Vehus

Administrative:
Bie Ekblad
Line Mygland

Lab for Molecular Neuroscience
NCMM Founding Group
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Senior Researcher
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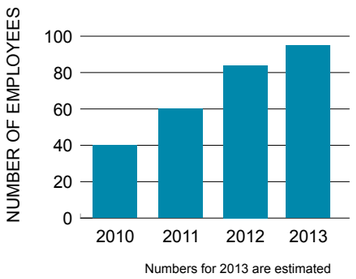
Karen-Marie Gujor Jorunn Knutsen
Bashir Hakim

Postdoctoral Fellows
Dr. Henning Boldt
Dr. John Kudolo
PhD Fellows
Laura Camassa
Lisa Lunde
Eystein Hoddevik
Katja Stahl (from 2013)
Shirin Katoozi (from 2013)

MD/PhD & MSc students:
Faraz Hameed Khan
Gry-Helen Enger Syverstad
(from 2013)
Agnete Prydz (from 2013)

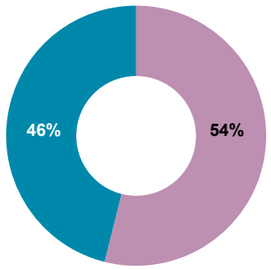
PERSONNEL STATISTICS

NCMM STAFF IN THE PERIOD 2010–2013

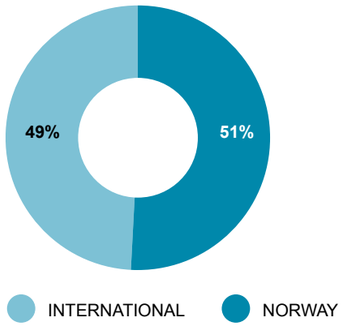


Numbers for 2013 are estimated

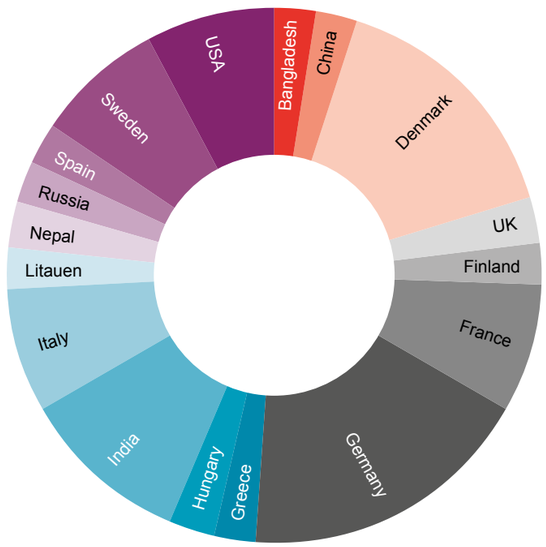
NCMM STAFF 2012: GENDER BALANCE



NCMM STAFF 2012: INTERNATIONAL STAFF



NCMM INTERNATIONAL STAFF DISTRIBUTION



NCMM Partnerships, Collaborations & Affiliations

NCMM Partners:

UiO : University of Oslo

The Research Council of Norway

HELSE SØR-ØST

Nordic EMBL Partnership for molecular medicine:

FIMM Institute for Molecular Medicine Finland

MIMS Molecular Infection Medicine Sweden

NCMM Centre for Molecular Medicine Norway

DANDRITE Danish Research Institute of Translational Neuroscience

EMBL

National & international collaborations:

BIO The Biotechnology Centre of Oslo

Centre for Molecular Biology and Neuroscience

ESFRI

EU-OPENSCREEN Chemical keys for life's locks

EATRIS

EMBL

The Research Council of Norway

UiO : University of Oslo

HELSE SØR-ØST

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