NCMM

Centre for Molecular Medicine Norway

Nordic EMBL Partnership for Molecular Medicine

ANNUAL REPORT 2011

Contents

Review by the Director

Professor Kjetil Taskén, Director NCMM
Photo: John Hughes

“Dear friends, colleagues, and supporters of NCMM,

By the end of 2011, its second full year of operation, NCMM was fast approaching 60 employees. The first six groups headed by NCMM founding partners and the newly recruited EMBL-NCMM group leaders were fully operative and both of the final two group leader recruits had either started (Toni Hurtado, fall 2011) or was just about to start (Judith Staerk, beginning 2012). We anticipate that NCMM will continue to grow in 2012. Also expected to grow is the level of extramural funding, which reached 10 million NOK in 2011 and contributed one third of the total NCMM spending (not including founding partner grants, accounted for elsewhere). NCMM principal investigators (PIs) report some 29 NCMM-affiliated papers published in 2011, including several papers in Nature, PNAS, EMBO J., and Blood, and another 15 papers already emerging in the first half of 2012. NCMM investigators have also filed some 4 patent applications and report a number of appearances in popular media. Scientific highlights from NCMM research in 2011 are presented throughout this report. The breath and depth of the research currently in progress at NCMM is very exciting and spans various topics, including molecular mechanisms regulating normal physiology and contributing to disease, prognostic studies looking at the association of disease markers and clinical outcome, and involvement in clinical intervention trials.

As an important component of NCMM’s focus on translational research, all NCMM group leaders have established adjunct appointments in clinical or para-clinical departments at Oslo University Hospital. These appointments involve increasing interactions and collaborations with the Departments of Neurology, Urology, Infectious Diseases, Hematology, and Institutes of Experimental Medicine and Cancer Research (Departments of Cancer Prevention and Genetics), which also illustrates the breath of application and extension of the molecular medicine research taking place at NCMM. The network of NCMM Associate Investigators was further extended in 2011 by the appointment of five new members, 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, activities continuing in 2012.

On the European and international arenas, NCMM investigators now enjoy numerous collaborations around the world. Research interactions with the Finish and Swedish centres in the Nordic EMBL Partnership and the EMBL are also increasing rapidly. NCMM also welcomes the addition of a new Danish centre scheduled to enter the partnership from 2012. The implementation of EMBL practices in recruitment and rotation of staff at NCMM also offers the opportunity to recruit top talent at all levels on an international arena.

The Research Council of Norway Evaluation of

Photo: John Hughes

Biology, Medicine and Health Research in Norway, conducted at the end of 2010 and beginning of 2011, included NCMM in the report. The report from this evaluation highlighted the excellence of the recruits and embraced the initiative of establishing NCMM as a centre with young group leaders. This is encapsulated in the following statements quoted from the Panel 3 Report (page 53); "The organization has been developed in a unique set up in Norway. Young PIs are recruited internationally with a high profile and are offered posts along the model of EMBL, that is 5 years initially and then a renewal for additional years subject to satisfactory performance against a set of criteria. The concept is excellent and could be a blueprint for other initiatives in Norway to overcome the problems associated with recruiting young staff against a widely ageing research staff population across the rest of the university sector. The panel concluded that this programme has serious merits and it is important that it is seen as a way forward". Moreover, the panel noted that "The employment of young staff is a real winner in terms of the age distribution and its consequences elsewhere in Norway. Therefore it is essential to support the venture fully and to have realistic objectives for the team."

The high profile Scientific Advisory Board of NCMM convened for the first time in January 2012 and focused its review on the start-up period of 2010 and 2011. The SAB concluded that they were "impressed by the establishment of the NCMM", which they found to be "a very promising initiative" and highlighted "the need to support these young researchers with appropriate infrastructure and creating possibilities for an academic career".

As evident from the present report, NCMM is still in the building-up phase as a new centre with a focus on young investigators. However, with the excellent set of brilliant young Group Leaders recruited at an international arena, I am sure NCMM is at the start of a very interesting endeavor with great potential for future excellence originating from its own research, clear signs of which are already coming through. Furthermore, 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 the responsibility of building networks and facilitating translational research, NCMM's National Reference Group and Network of NCMM Associate Investigators are tools implemented to foster collaboration and excellence in research; partners across Norway are invited to take ownership and utilise these tools.

June, 2012

Director, Kjetil Taskén

Nordic EMBL Partnership for Molecular Mecidine - An Update on its Progression from the Directors of FIMM and MIMS

The Nordic EMBL Partnership for Molecular Medicine currently comprises three nodes: the Institute for Molecular Medicine Finland (FIMM), the Laboratory for Molecular Infection Medicine Sweden (MIMS), and the Centre for Molecular Medicine Norway (NCMM). In total, this partnership consists of 35 research groups and a total of 330 dedicated employees that share common values and great collaborative potential. This potential will be further expanded in 2012 with the completion of the Danish node in the field of neurosciences.

Professor Olli Kallioniemi
Director of FIMM

FIMM investigates the molecular mechanisms of disease, using genomics and medical systems biology in order to promote human health. Access to unique patient and Biobank materials and state-of-the-art technologies facilitates the performance of high-quality science. There are thirteen research groups at FIMM, including six FIMM-EMBL group leaders, two Finland Distinguished Professors, and five other senior group leaders.

Professor Bernt Eric Uhlin
Director of MIMS

Research at MIMS is focused on the molecular mechanisms of infectious diseases. MIMS has six fully funded MIMS-EMBL group leaders, two partially funded MIMS group leaders, and six mentors/ founding groups.

During the first five years of the Nordic EMBL Partnership, the three nodes have performed joint recruitments for group leaders and PhD students. In addition, all nodes have recruited postdoctoral researchers and other research staff as well as built up the infrastructure to be shared within the partnership. FIMM and MIMS are both funded by their host Universities (Helsinki and Umeå). In addition, MIMS receives governmental funding from the Swedish Research Council for Infrastructure.

The added value of the Nordic EMBL Partnership can be summarised in five points:

1. Participation in an organised structure for collaboration with EMBL and inside the Nordic member countries.
2. Organising a structure to effectively translate discoveries in molecular medicine to clinical practise.
3. Capitalising on Nordic and European investments in molecular biology to extend applications to medicine.
4. Attracting top international talent.
5. Educating specialists in molecular medicine, translational research and personalised medicine.

FIMM
Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

MIMS
Molecular Infection Medicine Sweden
Nordic EMBL Partnership for Molecular Medicine

NORDIC EMBL PARTNERSHIP FOR MOLECULAR MEDICINE - A BRIEF SUMMARY

The Nordic EMBL Partnership for Molecular Medicine was planned and inaugurated in 2007 as a joint venture between the European Molecular Biology Laboratory (EMBL), the Institute for Molecular Medicine Finland (FIMM), the Laboratory for Molecular Infection Medicine Sweden (MIMS), and the Centre for Molecular Medicine Norway (NCMM). This partnership is dedicated to investigating the molecular basis of disease and exploring molecular and genetically based treatments.

Each institute contributes a unique set of expertise, skills and facilities that encompass EMBL's recognised research strengths in the areas of molecular, cellular and developmental biology, bioinformatics and structural biology. These areas are complemented by Norway's expertise in molecular mechanisms of disease, Sweden's focus on microbial pathogenicity and molecular infection medicine, and Finland's strengths in human genomics and medical systems biology, thereby equipping the partners to tackle some of the most challenging questions in biomedicine.

Each partner provides access to scientific infrastructure, including databases, facilities and instrumentation, as well as to clinical materials, networks and training activities, and adopts the EMBL model for international recruitment, staff turnover and scientific reviews. The partnership now also receives support from NordForsk as a Nordic Network of National Centers of Excellence. Collaborations and joint efforts among the centres have increased considerably during 2011.

EMBL

NCMM
Centre for Molecular Medicine Norway
Nordic EMBL Partnership for Molecular Medicine

FIMM
Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

MIMS
Molecular Infection Medicine Sweden
Nordic EMBL Partnership for Molecular Medicine

Photo: John Hughes

Molecular Life Sciences at the University of Oslo

The ability to attract talented researchers has become an important objective for academic institutions, as all prominent research institutions struggle to become more appealing to students and young talents, in international research collaborations, and to investors and society at large. The internationalisation of research and the free movement of researchers and students between countries have lead to the increasing necessity for institutions to compete for the best talents. Evaluations and university rankings contribute to dissimilarities in attractiveness and the research community also faces increasing expectations for providing innovations for business development.

In this picture, we welcome NCMM as an important contributor to the attractiveness of our university; a contribution demonstrated by the long list of applicants for group leader positions and the names of the prestigious institutions from which they come. The advantage of implementing the EMBL model for infrastructure and recruitment is clear, and we are very pleased to take part in this collaborative effort with the institutions of the Nordic EMBL Partnership for Molecular Medicine.

In the administrative governance, NCMM is linked to the Molecular Life Sciences initiative - a multi-faculty priority research area at the University of Oslo. MLS^{UiO} is a strategic body owned by three faculties. The objective is to promote high quality and innovative research within the molecular life sciences and to facilitate interdisciplinary, interfaculty collaboration and other research measures of strategic importance. In this way, NCMM is linked to the owners of MLS^{UiO}, which are the Faculty of Mathematics and Natural Sciences, the Faculty of Medicine and the Faculty of Dentistry, as well as to the South-Eastern Norway Regional Health Authority.

Professor Odd Stokke Gabrielsen, MLS^{UiO} Chair

Our expectation is that the work performed at NCMM will serve as an excellent example of how interdisciplinary research facilitates significant discoveries, with impacts well beyond the traditional disciplines.

Photo: John Hughes

NCMM Research

The overall objective of research at NCMM is to translate basic medical research into clinical practice.

In order to achieve this goal, NCMM researchers collaborate with clinical departments and networks of research groups across the country. This increased access to Nordic biobanks, patient materials, clinical trials and health registries, as well as state-of-the-art techniques, facilitates the investigation of disease mechanisms and promotes the development of more personalised medicine.

There are currently six EMBL-NCMM research groups and two additional founding groups. Each of the research groups is focused on a particular subject area in molecular medicine and these groups are presented in more detail in the following pages.

RESEARCH HIGHLIGHT

Targeting metabolism to treat prostate cancer

Prostate cancer is driven by hormonal signalling and the activity of a transcription factor, the androgen receptor, is a significant driver. NCMM group leader Ian Mills and colleagues recently completed a genomic study to define gene networks that are regulated by the androgen receptor. They showed that the androgen receptor promotes anabolic metabolism and regulates cell cycle checkpoint, collectively contributing to cell growth and proliferation. They demonstrated that a protein, CAMKK2, which is normally abundantly expressed in the brain is aberrantly overexpressed in prostate cancer under the control of the androgen receptor. They also showed that by knocking down the androgen receptor they could reduce the phosphorylation and activity of a critical enzyme for the regulation of energy metabolism, AMP-regulated kinase (AMPK). Furthermore, a small molecule inhibitor of CAMKK2, STO-609, achieved the same results and restricted cell proliferation both of cells in culture and also of xenografted tumours. This inhibitor significantly reduced glucose consumption in the treated cells and the also the activity of a rate-limiting enzyme in glycolysis, phosphofructokinase. When combined with a drug that is commonly used to treat diabetics, Metformin, STO-609 elicited an enhanced apoptotic response in prostate cancer cell-lines in culture. In conclusion, this work strongly suggests that targeting enzymes that regulate energy metabolism may, in the future, be used to restrict prostate cancer development and enhance the cytotoxicity of existing therapies. This is now an emerging focus within the group and the field at large.

The full article can be found in the EMBO Journal, May 2011, Vol. 30, No. 13, Pages 2719-2733.

GROUP TASKÉN - SIGNALLING NETWORKS IN HEALTH AND DISEASE

Group Leader
Kjetil Taskén

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

One main focus is complex intracellular signalling networks, how such networks require anchoring and localisation, and how they mediate hormonally regulated physiological and pathophysiological processes. A second main focus is on cAMP-mediated immune-modulation with application in cancer, immune diseases and inflammation. In pursuit of this understanding, the group maps signalling pathways, identifies drug targets, develops small molecular compounds and provides “proof-of-principle” experiments using specific disease models.

The Taskén group employs a variety of techniques in bioinformatics, proteomics, high-throughput screening assays and genetic tools in order to screen new targets for *in vitro* and *in vivo* function. In order to isolate signalling 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 and then combined with phosphoproteomics to understand spatiotemporal dynamics of phosphorylation in anchored cAMP signalling complexes organised by A kinase anchoring proteins, AKAPs. A key accomplishment in this area in 2011 was the identification on Optic Atrophy 1 (Opa1) as an AKAP on lipid droplets mediating adrenergic control of lipolysis. Furthermore, the group reported the development of transgenic mice expressing a PKA anchoring disruptor in T cells, which inhibits type I PKA anchoring to ezrin and renders effector T cells insensitive to cAMP. This disruptor protects mice from infection with murine leukemia virus that leads to murine AIDS, indicating the importance of cAMP immunomodulation in pathophysiology. The group continues to work with transgenic mice and disease models for *in vivo* proof-of-principle experiments and is currently studying cAMP signalling in tumour models as well as in the heart and adipocytes, in regard to cardiovascular and metabolic diseases.

The use of flow cytometry with a panel of phospho-specific antibodies against signal molecules, in combination with fluorescent cell bar coding (FCB) for high-throughput, has made it possible to obtain a global understanding of signal transduction dynamics at a single cell level. The group’s key accomplishments in this area include the mapping of integrated intracellular signalling maps in T cell activation and in response to prostaglandin E2, which has also unravelled specific regulatory T cell signal pathways involved in immune suppression, cancer and control of inflammation with clinical application.

Key accomplishments in clinical investigations include the report of a phase II clinical intervention trial conducted in collaboration with the Department of Infectious Diseases, OUS (where Taskén has an adjunct appointment) with COX-2 inhibitors that block the prostaglandin E2-cAMP pathway in treatment-naïve HIV patients. Results demonstrated improved immune function and predict clinical benefit (reduced CD38 levels, increased vaccine responses). Furthermore, we report the level of regulatory T cell and prostaglandin E2-mediated suppression of anti-tumour immune responses in patients with metastatic colorectal cancer at the time of liver surgery predict future outcome, testifying to the importance of this pathway also in tumour immunology (study in collaboration with Department of Gastrosurgery, OUS). Clinical studies are on-going both in HIV and cancer.

The improved understanding of signalling 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 maximise their therapeutic value, while minimizing unwanted side-effects.

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, the EU 7th Framework and ESFRI programmes, Nordforsk, and MLS[UiO].

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

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Scientific Officers:
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Gladys Tjørhom

Chemical Biology Platform:
Anne Jorunn Stokka
Niko Sahlberg / Inderjit M. Singh

Selected Key Publications from PI:

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 anchor¬ing 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: 4371-4386Kalland 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.

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

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

(#Corresponding author)

GROUP MILLS - PROSTATE CANCER

Group Leader
Ian G. Mills

Prostate cancer accounts for one third of all male cancer cases in Norway and is the second most significant 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, a steroid hormone-activated transcription factor, and in subtypes of prostate cancer other transcription factors including c-Myc, HIF1alpha and Hes6 become significant. Our research is rooted in the use of chromatin immunoprecipitation coupled with sequencing and transcriptomics to define gene networks driven by these proteins. We use clinical datasets and samples to validate components of these networks as biomarkers in conjunction with clinical collaborators. In addition, we explore the effects of clinically relevant components of these networks on proliferation and viability and work to define new substrates and interacting partners for these proteins.

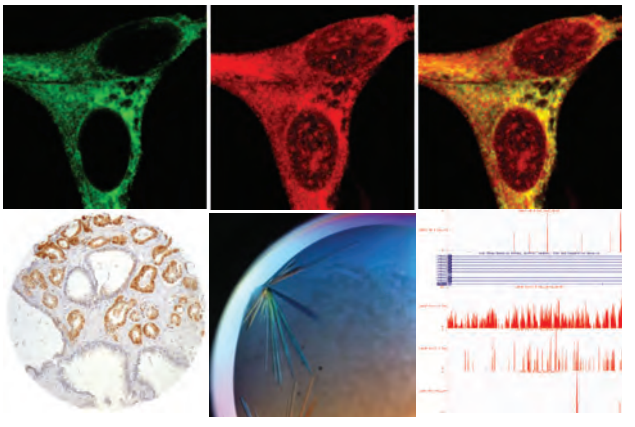
Our work is increasingly showing that localised prostate cancer is characterised by changes in the expression of metabolic enzymes and regulators of metabolism and that in aggressive metastatic disease there is significant cell cycle dysregulation. Localised prostate cancer is a heterogenous and multi-focal disease and much of the mutational burden stems from genomic rearrangement, the so-called chromosome instability phenotype. This takes the form of gene fusions in early-stage prostate cancer and local collaborators are working to identify novel gene fusions in prostate cancer. These have great potential as cancer-specific markers. Metabolic stress can give rise to chromosome instability in models of ageing as well as cancer.

We are beginning to study pathways that are activated in response to metabolic stresses, including autophagy, and how they contribute to drug resistance. Our long-term goal, and the goal of our collaborators and the field at large, is to develop a molecular model for the aetiology of prostate cancer which encompasses the earliest stages linked to oxidative stress, diet and ageing through to the development of metastatic disease. Genomics provides us with signatures for these changes and transcription factors represent the regulators of many of these signature changes. Only by developing such a model can we hope to achieve 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.

Collaborators:

Fahri Saatcioglu (IMBV, UiO), Rolf Skotheim and Ragnhild Lothe (ICR, Oslo), Kristin Tasken, Viktor Berge, Aud Svindland (ICR and OUS, Oslo), Lars Akslen (Bergen), Paloma Perez (Valencia, Spain), Matthias Wilmanns (EMBL, Hamburg), Tapio Visakorpi (Tampere, Finland), Olli Kallioniemi (FIMM, Finland), David Neal (CRUK, Cambridge, UK), Henrik Gronberg (Karolinska, Sweden), Guido Sauter and Thorsten Schlomm (Eppendorff Hospital, Hamburg), Paul Rennie (Prostate Cancer Centre, Vancouver).



External Funding:

In addition to NCMM funding, Mills' group is supported by the Norwegian Cancer Society, Molecular Life Sciences (University of Oslo), National Institutes of Health (USA), Anders Jahre Fond 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.

Photo: John Hughes

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VISITING RESEARCHERS (during 2011/2012)

Victor Latorre
(Instituto de Biomedicina de Valencia, Spain)

Gregor Tevz
(Philips Medical Systems, Netherlands/Pro-Nest-Marie Curie ITN)

Selected Key Publications from PI:

Primary publications

Paulo, P., Ribeiro, F. R., Santos, J., Mesquita, D., Almeida, M., Barros-Silva, J. D., Itkonen, H., Henrique, R., Jerónimo, C., Sveen, A., Mills, I. G., Skotheim, Lothe, R. A., Teixeira, M. R., (2012). Molecular subtyping of primary prostate cancer reveals specific and shared target genes of different ETS rearrangements. Neoplasia. In press.

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Book Chapters

1. Massie, C.E., and Mills, I.G. (2012) Mapping protein-DNA interactions using ChIP sequencing. In Press. Methods Mol Biol. ;809:157-73.

2. Massie, C.E., and Mills, I.G. (2011). Global identification of androgen response elements. Methods Mol Biol. 776:255-73.

GROUP MORTH - MEMBRANE TRANSPORT

Group Leader

Jens Preben Morth

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

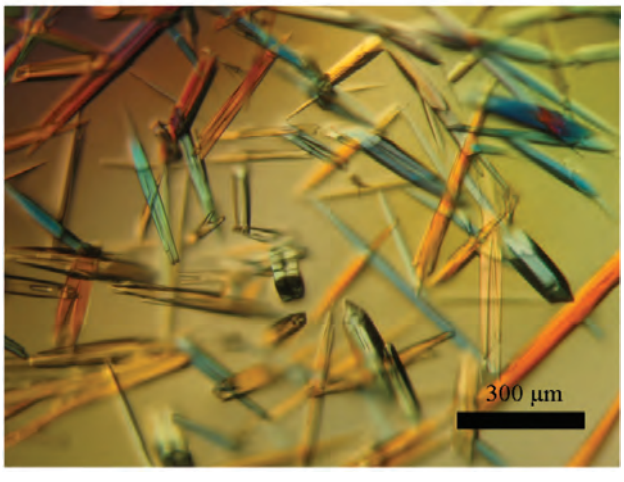
The kidneys are highly complex organs with the vital role of maintaining homeostasis of small organic solutes and minerals in the body. The nephron in the kidney absorbs solutes from the blood and excretes residual products in the urine, and represents the main site for extensive solute exchange in mammals. It is the solute carrier (SLC) transporters that control this exchange.

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

The group is currently developing purification and lipid vesicle reconstitution protocols for the membrane proteins to study their three-dimensional atomic structure and aims to purify and characterise members of the SLC4 and SLC26 family.

A project recently started in the Morth group is focused on bicarbonate transporters from the kidney and brain and will benefit from the experience gained over the last several years of working with P-type ATPases. Bicarbonate transporters are involved in the exchange of acids and tightly control the regulation of intracellular pH across the plasma membrane.

The system is strongly dependent on the ion gradients maintained by the P-type ATPases. The group aims to develop a complete structural model for anion transport and recognition. The structural analysis of P-type ATPases will continue with focus on the prokaryotic Ca2+ ATPases and Mg2+ ATPases, with particular focus on their function as participants in virulence systems.



External Funding:

In addition to NCMM funding, the group is supported by the Lundbeck fondation and the Research Council of Norway.

Photo: John Hughes

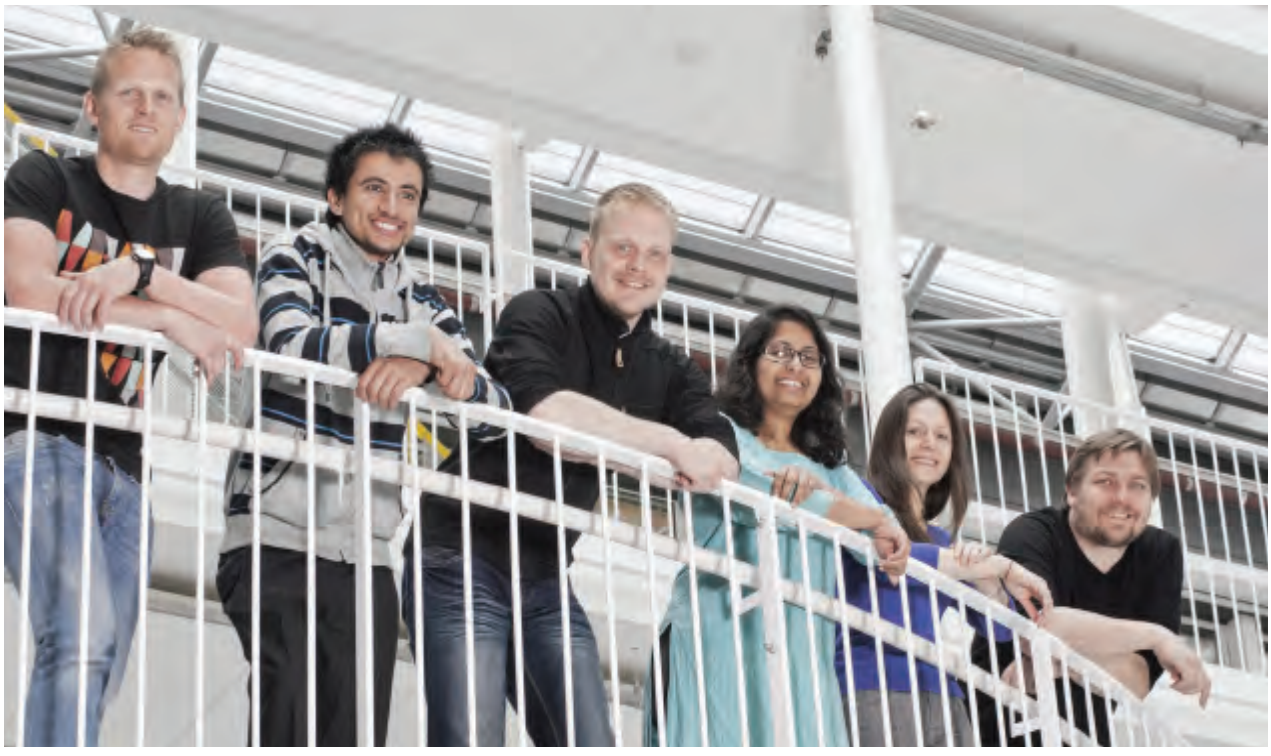


Photo: John Hughes

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Saranya Subramani

MSc Student:
Jayaram Lamsal

Selected Key Publications from PI:

Hein KL, Nissen P, Morth JP. (2012) Purification, crystallization and preliminary crystallographic studies of a PacL homologue from Listeria monocytogenes. Acta Crystallographica section F – Structural Biology and Crystallization Communications. 68: 424-427.

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Andersen JL, Gourdon P, Moller JV, Morth JP, Nissen P. (2011) Crystallization and preliminary structural analysis of the Listeria monocytogenes Ca2+-ATPase LMCA1. Acta Crystallographica section F – Structural Biology and Crystallization Communications. 67: 718-722.

Preu J, Panjikar S, Morth JP, Preben, Jaiswal R, Karunakar P, Tucker PA. (2012) The sensor region of the ubiquitous cytosolic sensor kinase, PdtaS, contains PAS and GAF domain sensing modules. Journal of Structural Biology. 177(2): 498-505.

GROUP NAGELHUS - GLIO-VASCULAR IMAGING

Group Leader
Erlend A. Nagelhus

Nagelhus' research has focused on the molecular characterisation of membrane domains in glial cells, in particular glial end-foot membranes at brain-blood and brain-liquor interfaces. His research group, which joined the NCMM in 2009, is affiliated with the Centre for Molecular Neuroscience and runs its neuroimaging activity in the Letten Centre at the Institute of Basic Medical Sciences, Domus Medica. Nagelhus' group explores the 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 or the thinned skull, the group is able to image the dynamics of neuronal and glial calcium signalling, cell morphology and motility, as well as cerebral blood flow. Currently, the group is using gene knockout strategies to study the roles of glial aquaporins and associated molecules in extracellular volume dynamics, synaptic transmission and signalling at the brain-blood interface. 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.

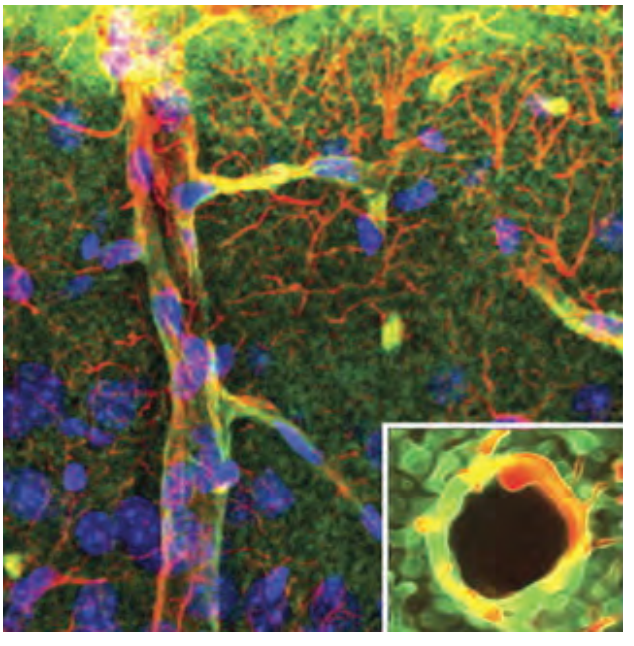
GROUP MEMBERS

Researchers:
Vidar Jensen
Anna Thoren

Postdoctoral Fellows:
John Burkhardt
Karolina Szokol (associate member)
Wannan Tang (EMBO fellow)

PhD Fellows:
Nadia N. Haj-Yasein
Alexander S. Thrane
Vinita R. Thrane
Gry F. Vindedal

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



External Funding:

In addition to NCMM funding, the group is supported by the Research Council of Norway.

Photo: John Hughes

Selected Key Publications from PI:

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Haj-Yasein NN, Jensen V, Vindedal GF, Gundersen GA, Klungland A, Ottersen OP, Hvalby OC, and Nagelhus EA. (2011) Evidence that compromised K+ spatial buffering contributes to the epileptogenic effect of mutations in the human Kir4.1 gene (KCNJ10). Glia 59(11): 1635-42.

Nagelhus EA, Horio Y, Inanobe A, Fujita A, Haug FM, Nielsen S, Kurachi Y, Ottersen OP. (1999) Immunogold evidence suggests that coupling of K+ siphoning and water transport in rat retinal Muller cells is mediated by a coenrichment of Kir4.1 and AQP4 in specific membrane domains. Glia 26:47-54.

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Photo: John Hughes

GROUP HURTADO - BREAT CANCER (NEW EMBL-NCMM GROUP)

Group Leader

Antonio Hurtado

The Breast Cancer group at NCMM was initiated in August of 2011 and is currently comprised of three members: Siv Gilfillan (engineer; started in September, 2011), Elisa Fiorito (PhD student; started November, 2011) and Madhu Katika (joint postdoc, shared with the group of Anne-Lise Børresen-Dale and Kristine Kleivi; started March, 2012).

The group's research is focused on breast cancer tumours, and in particular the role of the Estrogen Receptor (ER). ER is expressed in most breast tumours and mediates the actions of both estrogen and anti-ER therapy. ER is currently the best clinical target for blocking proliferation induced by estrogen-ER complexes. Although anti-ER therapy is successful in many patients, at least one third of patients show no benefit from these treatments. Therefore, the goal of our research is to identify the pathways dysregulated in hormone resistant breast cancer tumours.

Our group is currently using genomic and proteomic methods in combination with systems biology analyses to address three main questions. The first involves the identification and characterisation of partners modulating ER repression and how they can be influenced by anti-ER treatments. The second is to study how non-nuclear factors (kinases and phosphatases) influence ER function in hormone resistance phenotypes. The third involves the analysis of the expression of all ER cooperating factors that influence ER-therapy and the correlation of their expression with clinical information in order to identify phenotypes of patients that benefit to the endocrine therapy. Ultimately this work will help to improving diagnosis and patient-targeted treatment.

Photo: John Hughes

GROUP MEMBERS

Postodoctoral Fellow:
Madhu Katika

Head Engineer:
Siv Gilfillan

PhD Fellow:
Elisa Fiorito

Selected Key Publications from PI:

Gilfillan S, Fiorito E and Hurtado A. Functional genomic methods to study Estrogen Receptor activity. (2012) J Mammary Gland Biol Neoplasia. Epub ahead of print, 2012 May 16.

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

Hurtado A, Holmes KA, Ross-Innes CS, Schmidt D and Carroll JS. FoxA1 is a key determinant of estrogen receptor function and endocrine response. Nature Genetics, 2011 Jan;43(1):27-3.

Schmidt D, Schwalie PC, Ross-Innes CS, Hurtado A, Brown GD, Carroll JS, Flicek P, Odom DT. A CTCF-independent role for cohesin in tissue-specific transcription. Genome Res. 2010 May;20(5):578-88.

Holland D, Burleigh A, Git A, Suet-Feung C, Hurtado A, Bruna A, Ali R, Greenwood W, Dunning M, Samarajwa S, Menon S, Rueda O, Lynch A, Mackinney S, Ellis I Eaves C, Carroll J, Curtis C, Aparicio S and Caldas C. ZNF703, a luminal breast cancer oncogene, is a transcriptional repressor and differentially regulates luminal and basal progenitors in human mammary epithelium. EMBO Mol Med, 2011 3(3):167-80.

GROUP STAERK - STEM CELLS (NEW EMBL-NCMM GROUP)

Group Leader
Judith Staerk

Embryonic stem (ES) cells are pluripotent cells that can theoretically differentiate into any cell type of the adult body, a feature that makes these cells an important source for regenerative medicine. The term hematopoiesis describes the sustained production of blood cells. This is guaranteed by the presence of hematopoietic-specific stem cells (HSCs) that have the capacity to self-renew and to produce daughter cells that differentiate into progenitors and give rise to mature blood cells throughout life. The recent discovery that ectopic transcription factors, Oct4, Klf4, c-Myc and Sox2 induces pluripotency in various human somatic cell types provides great possibilities to derive patient-specific ES-like cells (induced pluripotent stem (iPS) cells). Suitable protocols are now needed to differentiate human iPS and ES cells into somatic cell types that can be used for tissue repair and to generate model systems for human development.

We will work with mouse models, somatic cell reprogramming and proteomics combined with biochemical assays to decipher processes during normal and malignant hematopoiesis.

The broad aims of our research are:

1. To identify the transcriptional networks of human hematopoietic specification with the ultimate goal to derive long-term repopulating HSCs from human ES cells *in vitro*.
2. To identify underlying mechanisms of impaired blood cell differentiation during hematopoiesis using *in vivo* mouse models and patient-derived iPS cells.
3. To identify protein interactions during thrombopoietin receptor signaling in blood progenitor proliferation and megakaryocyte differentiation.

Photo: John Hughes

GROUP MEMBERS

Postdoctoral Fellow:
Xavier Tekpli

Principal Engineer:
Mustapha Lamkhannat

Selected Key Publications from PI:

Staerk J, Dawlaty MM, Gao Q, Maetzel D, Hanna J, Sommer CA, Mostolovsky G, Jaenisch R. Reprogramming of human peripheral blood cells to induced pluripotent stem cells. Cell Stem Cell. 2010 Jul 2; 7(1):20-4. Preview: Cell Stem Cell. 2010 Jul 2;7(1):1-2.

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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. Pan-Src Family Kinase Inhibitors Replace Sox2 during the Direct Reprogramming of Somatic Cells. Angew Chem Int Ed Engl. 2011 Jun 14;50(25):5734-6. (*equal contribution).

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UNIT FOR CELL SIGNALLING (FOUNDING GROUP)

Group Leader
Stefan Krauss

The unit for cell signaling works on druggable interference points in Hh and Wnt/ β-catenin signalling. In the last 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 tested on cancer and stemcell models *in vitro* and *in vivo*. Furthermore, we analyse the role of β-catenin, p120 and other armadillo proteins in specific cancer cells using ZFN based knock outs, and we study links between Hh and Wnt signaling.

Selected Key Publications from PI:

Waaler J, Machon O, Tumova L, Dinh H, Korinek V, Wilson S R, Paulsen J E, Pedersen N M, Eide T J, Machonova O, Gradl D, Voronkov A, von Kries J P, 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.

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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.

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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.

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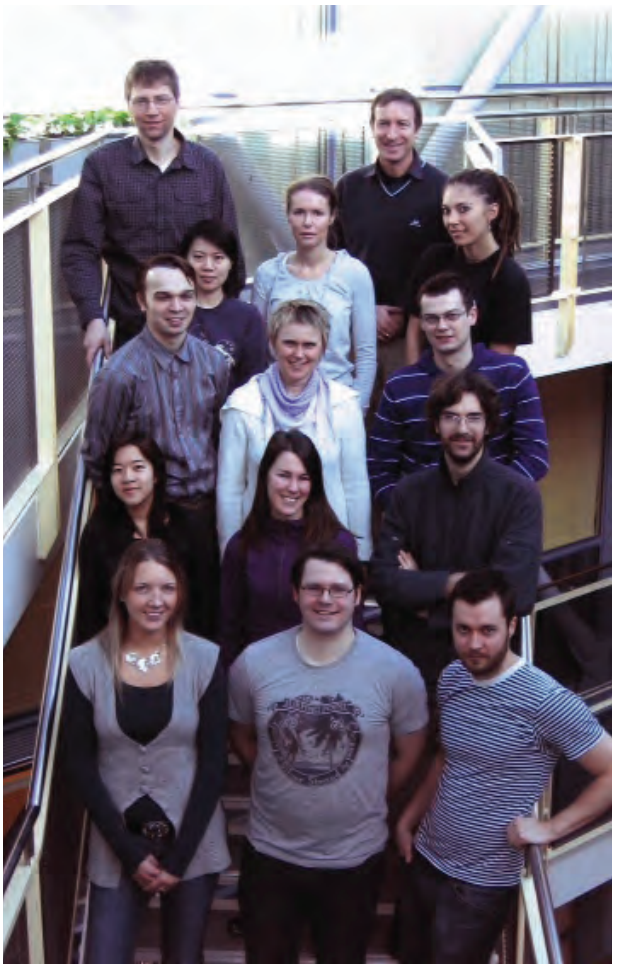

Photo: CAST

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.

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Wilson SR, Strand MF, Krapp A, Rise F, Petersen D, Krauss S (2010). Hedgehog antagonist cyclopamine isomerizes to less potent forms when acidified. J Pharm Biomed Anal. 52(5): 707-13.

GROUP MEMBERS

Postodoctoral Fellows:
Petter A. Olsen
Ondrej Machon
Jennifer Dembinski
Nina T. Solberg
Andrey Voronkov

MSc Students:
Anders Grimsmo
Khahn Huynh
Tore Vehus

PhD Fellows:
Jo Waaler
Martin F. Strand

Engineers:
Olga Machonova
Huyen Mong Thi Dinh
Monika Gelazauskaite

Administrative:
Bie Ekblad
Line Mygland

LABORATORY FOR MOLECULAR NEUROSCIENCE (FOUNDING GROUP)

Group Leader

Mahmood Amiry-Moghaddam

The Laboratory for Molecular Neurosciences (LMN) investigates the molecular mechanisms involved in physiological processes such as brain volume regulation and osmosensing, the physiopathological roles of aquaporins in the brain, mechanisms governing the maintenance of astrocyte polarity, blood-brain-barrier integrity and roles of the brain extracellular matrix in health and disease. The aim is to use this knowledge to unravel the molecular basis for cell death and oedema development in stroke and other neurological conditions, and to explore the pathophysiology of temporal lobe epilepsy, Alzheimer's disease and other neurodegenerative disorders.

The long term goals of the LMN are to identify new mechanisms of disease and new molecular targets for the treatment of neurological diseases.

Selected Key Publications from PI:

Yang J, Lunde LK, Nuntagij P, Oguchi T, Camassa LM, Nilsson LN, Lannfelt L, Xu Y, Amiry-Moghaddam M, Ottersen OP, Torp R. Loss of astrocyte polarization in the tg-ArcSwe mouse model of Alzheimer's disease. J Alzheimers Dis.2011;27(4):711-22.

Jacobsen Ø, Maekawa H, Ge NH, Görbitz CH, Rongved P, Ottersen OP, Amiry-Moghaddam M, Klaveness J. Stapling of a 3(10)-helix with click chemistry. J Org Chem. 2011 Mar 4;76(5):1228-38. Epub 2011 Jan 28.

Benfenati V, Caprini M, Dovizio M, Mylonakou MN, Ferroni S, Ottersen OP,Amiry-Moghaddam M. 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. 2011 Feb 8;108(6):2563-8. Epub 2011 Jan 24.

Stahl K, Mylonakou MN, Skare Ø, Amiry-Moghaddam M, Torp R. Cytoprotective effects of growth factors: BDNF more potent than GDNF in an organotypic culture model of Parkinson's disease. Brain Res. 2011 Mar 10;1378:105-18.

GROUP MEMBERS

Researcher:
Reidun Torp

Postdoctoral Fellow:
Henning Boldt

PhD Fellows:
Laura Camassa
Lisa K. Lunde
Eystein Hoddevik
Katja Stahl

Engineers:
Bjørg Riber
Karen-Marie Gujor
Jorunn Knutsen
Bashir Hakim

Physicist:
Johannes Helm

MD/PhD students:
Faraz Hameed Khan
Gry-Helen Enger Syverstad

Visiting Scientist:
Shirin Katoozi

Professors Emeriti:
Eric Rinvik
Finn-Morgens Haug

Research Collaboration with Oslo University Hospital

Collaboration

NCMM's overall objective is to translate basic medical research into clinical practice.

In order to facilitate translation of its research, NCMM has developed strong links to South-Eastern Norway Regional Health Authority and its subsidiary Oslo University Hospital. Furthermore, adjunct appointments in clinical or paraclinical departments in Oslo University Hospital have been established and all NCMM group leaders hold 20% adjunct appointments at different departments at the hospital.

Adjunct appointments

Department of Haematology

- 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. Research is conducted in most of the areas in which treatment is provided at the department.

Department of Infectious Diseases

- 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, and severe and life threatening bacterial and viral infections. The Department of Infectious Diseases runs an extensive research program, especially related to the diseases HIV/AIDS and hepatitis. The department is also responsible for a variety of courses in continuing education in infectious diseases.

Institute for Experimental Medical Research

- Group leader Preben Morth

The Institute for Experimental Medical Research is primarily focused on heart disease research and teaching, especially congestive heart failure with great interest in heart electrophysiology and membrane pumps. The institute is involved in extensive collaborations with other laboratories and clinical departments at the hospital, and with colleagues both nationally and internationally.

Department of Neurology

- 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 and has outpatient clinics, hospital wards, and laboratories at Ullevål and Rikshospitalet. The areas of research at 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, and painful disorders of the peripheral nerves.

Department of Urology

- 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 specialised knowledge and high-tech surgical techniques. The development of new treatments in this field is rapid, and consequently research and education are important foci of the department.

Photo: John Hughes

Institute for Cancer Research

Department of Cancer Prevention - Group leader Ian Mills (10%)

The Institute has strong international research groups within biochemistry, cell and tumour biology, genetics, radiation biology, immunology and cancer prevention. For more than 30 years there has been a close interaction between researchers at the Institute and cancer surgeons, oncologists and pathologists. This 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, organisationally under the Division of Surgery and Cancer Treatment at Oslo University Hospital.

Department of Genetics - Group leader Toni Hurtado

The institute's goal is to follow the linear time course of predisposition, initiation, early stages and advanced disease, dissect the molecular mechanisms triggered at each stage and follow the multidimentional interactions at various levels in a systems biology approach to better perform risk estimation, prognostication and prediction.

NCMM Events

BiO-NCMM Retreat

In September of 2011, the Biotechnology Centre of Oslo and the Centre for Molecular Medicine Norway met at Thorbjørnrud Hotel in Jevnaker, Norway, for three days of scientific discussions and social activities.

This provided the researchers and administrative staff with the opportunity to get to know one another both socially and professionally, improving not only moral but also helping to create a more effective and collaborative working atmosphere.

Thorbjørnrud Hotel, Jevnaker, Norway. Photo: Rachel Thomas

Nordic Molecular Medicine Network (NMMN)

The Nordic nodes of the EMBL Nordic Partnership in Molecular Medicine are supported by Nordforsk for a Nordic Network of National Centres of Excellence (NCE). This network, known as the “Nordic Molecular Medicine Network” (NMMN), promotes collaboration and exchange among the EMBL and the three NCE/Nordic nodes (the Institute for Molecular Medicine Finland (FIMM), Centre for Molecular Medicine Norway (NCMM), Laboratory for Molecular Infection Medicine Sweden (MIMS)).

The establishment of the network is an important part of the Nordic EMBL partnership and is essential to promote sustainable long-term collaboration. The NMMN meets once annually, with the three nodes acting as alternating hosts. The NMMN network also provides financial support to PhD students and post-docs for travel to the other partners for collaborations, workshops and courses.

The Second Nordic Molecular Medicine Network (NMMN) meeting was held in Helsinki, September 29th to 30th, 2011. At this conference, nearly 150 participants of the Nordic EMBL Partnership for Molecular Medicine (FIMM, NCMM, MIMS, and EMBL) came together for a scientific program including technology-based Meet-the-Experts sessions, group discussions, and tours of the FIMM facilities.

NCMM Associate Investigators

In order to further develop its scientific and technological capabilities, the NCMM has established strong collaborative links with key scientists and research groups working across Norway through the appointment of Associate Investigators.

These appointments, evaluated by a Selection Committee, are based on scientific excellence and translational merit, as well as added value and compatibility with NCMM mission.

There have thus far been two calls for Associate Investigators affiliated with NCMM and the Nordic EMBL Partnership in Molecular Medicine, the first in the autumn of 2009 and the second in the Spring of 2011.

The NCMM Associate Investigators are presented in the following pages.

Photo: John Hughes

BJARNE BOGEN - NCMM Associate Investigator

Cellular and Molecular Immunology Research Group, Institute of Clinical Medicine, University of Oslo

The Bogen group is focused on immunoglobulins (Ig), in particular how they may be recognised by T cells and 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 summarised 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 recognise 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 2011 we began investigating this pathogenic mechanism in patients with Chronic Lymphatic Leukaemia (CLL) and systemic Lupus Erythematosus (SLE) and extending our studies of the basic mechanisms by establishing new strains of transgenic and knock-in mice.

2. Novel vaccine molecules for cancer and infectious diseases

Key accomplishments in 2011 on vaccine development projects have been to extend the application of Vaccibody molecules to influenza, HIV and tuberculosis. In 2012 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.

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

The 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 2012 will focus on immunoediting of tumours and how tumour cells escape killing by CD4+ T cells.

GROUP MEMBERS

Assistant Professor:
Ludvig Munthe

Senior Researcher:
Keith Thompson
Alex Corthay

Postdoctoral Fellows:
Agnete B. Fredriksen
Ranveig Braathen
Inger Øynebråten
Anders A. Tveita
Even Fossum
Simone Bürgler
Johanne Jacobsen

Research Technicians:
Peter Hofgaard
Hilde Omholt
Elisabeth Vikse
Mona Lindeberg

PhD Fellows:
Gunnveig Grødeland
Kristin Aas-Hanssen
Kristina Lorvig
Ole A.W.Haabeth
Fredrik Schjesvold
Anna P. Ribes
Marta Baranowska
Heidi Spång

Medical Students:
Ane Anderson
Henriette Jodal

MSc Students:
Aram Andersen
Marte Fauskanger
Arnar Gudjonsson

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 cytokines that are regulated in heart failure and to study those that promote myocardial hypertrophy and cardiac dysfunction. Using microarray technology to identify regulated cytokines in hypertrophied and failing myocardium following myocardial infarction, the group has reported close to twenty cytokines not previously assigned a role in heart failure. For example, interleukin (IL)-18 was found to be strongly upregulated in our pulmonary heart disease model and following myocardial infarction. We have shown that the role of IL-18 in the phosphorylation of certain intracellular proteins is important in the development of diastolic dysfunction, with possible therapeutic and diagnostic implications. Furthermore, recent data from mouse model experiments indicate that blocking IL-18 effects via IL-18 binding protein can result in a reduction in diastolic dysfunction.

The group has also identified a putative stress-sensor, syndecan-4, which acts in concert with cytokines. 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. In order to ensure the relevance of the identified stress-sensor for human disease, the group is currently analyzing its regulation in patients.

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 (Prof. P. Aukrust, Prof. L. Gullestad) provides a unique opportunity to verify findings from experimental models by analyzing cytokine regulation in material from patients with different types of chronic heart failure.

Christensen is also 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 Regional Health Authority. In collaboration with the Department of Cardiology at Akershus University Hospital (Prof. T. Omland/PhD student H. Røsjø) we have filed a patent on granins as biomarkers of cardiac disease based on studies in mice and humans. Collaboration with NCMM, in particular the Morth group, has also been important in the granin work and in the syndecan project.

GROUP MEMBERS

Researcher:
Cathrine Carlson

Postdoctoral Fellows:
Ståle Nygård
Ida Gjervold Lunde

PhD Fellows:
Anne Wæhre
Kate Herum
Mari Elen Strand
Maria Vistnes

Research Engineers:
Dina Behmen
Hilde Dishington
Almira Hasic
Marita Mathisen
Bjørg Austbø
Hilde Jarstadmarken
Heidi Kvaløy

Research Curriculum Student:
Vigdis Hillestad

OLE PETTER REKVIG - NCMM Associate Investigator

Human and Murine Lupus Nephritis - Molecular Biology, Genetics and Epigenetics, 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 explains the factors that account for the 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 shut-down 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.

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 effect of proinflammatory cytokines on the expression of renal DNaseI and is also currently generating a human renal DNaseI transgenic mouse. The transgene will be expressed in two mouse strains that spontaneously develop classical lupus nephritis. Since the transgene will be randomly incorporated in the genome at several positions, the autologous DNaseI, but not the human transgenic DNaseI, will be down-regulated in the context of disease progression. According to the hypothesis, the wild-type mouse will die from lupus nephritis, while the transgenic mouse will be protected from disease progression by the constitutive expression of the human DNaseI. Since human lupus nephritis is in principle indistinguishable from the murine form, this transgenic mouse model will demonstrate the therapeutic value of preventing the down-regulation of renal DNaseI.

The group is investigating several genetic and epigenetic mechanisms in order to explain the basis for the clinically dangerous renal DnaseI shut-down and are prioritizing the following topics:

1. Transcriptional interference between DnaseI and the convergently encoded and overlapping Trap1 genes.
2. The role of DNA methylation and histone modifications in distinguishing transcriptionally active from inactive chromatin.
3. The expression and impact of miRNAs targeting DnaseI mRNA.

Preliminary results indicate the importance of transcriptional interference with Trap1. The group is using miRNA profiling to analyse the up-regulated miRNAs that target DnaseI mRNA in both human and murine forms of the disorder. New information on central check-points in the signalling cascades that regulate DnaseI gene expression will be used to develop new aim-directed and causal therapy modalities. The project represents a translational study performed in parallel in autoimmune lupus-prone mice and in humans.

GROUP MEMBERS

Professors:
Elin Mortensen
Henrik Nielsen

PhD Fellows:
Silje Fismen
Natalya Seredkina
Annica Hedberg
Dhivya Thiyagarajan
Stine Figenschau

Senior Scientist:
Kristin A Fenton

Technician:
Kanapathippillai Premasany

ANNE-LISE BØRRESEN-DALE - NCMM Associate Investigator

Department of Genetics, Institute for Cancer Research, Oslo University Hospital, Norwegian Radium Hospital

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 (http://ous-research.no/kgjebsen/), the aim is to integrate molecular data at all levels, from both tumours and healthy tissue from large cohorts of breast cancer cases. 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.

GROUP MEMBERS

Project Group Leaders:
Anita Langerød
Kristine Kleivi Sahlberg

Postdoctoral Fellows:
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Marit Krohn
Suvi Katri Leivonen
Hege Elisabeth Gjercksky Russnes

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Sandra Nyberg
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Hans Kristian Moen Vollan
David Quigley

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Gry Aarum Geitvik

Biomedical Laboratory Scientist:
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Eldri Undlien Due
Anita Halvei
Laila Jansen
Daniel Nebdal
Cathrine Pedersen
Anja Valen
Veronica Okkenhaug Vang
Phuong Vu

Medical Students:
Ivan Olegovich Potapenko

IN CLOSE COLLABORATION WITH:

The Cancer Genome Variation Group
Headed by Professor Vessela N. Kristensen
The Tumor Initiating Cells in Breast Cancer Progression Group
Headed by Therese Sørlie

OLE A. ANDREASSEN - NCMM Associate Investigator

TOP Study Group, 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 part of the new KG Jebsen Centre for Psychosis Research (www.med.uio.no/klinmed/forskning/grupper/top), which runs a large and ongoing collaborative study of clinical characteristics, neurocognitive functioning and brain biology of psychotic disorders. The overall goal is to identify underlying mechanisms and genetic susceptibility.

The TOP Study Group is the largest psychiatric research organisation in Norway, with a total of 20 research fellows/PhD students, 8 post docs, and 10 senior faculties. The organisation leads a psychosis research network in Norway, and participates in the EU 7th framework programs ENBREC and PsychDPC. The research is currently focused on genotype-phenotype mapping, using clinical and neurocognitive characteristics, with a specific emphasis on brain imaging.

The TOP Research Program is headed by Ole Andreassen, with expertise in psychiatric genetics, neuroscience and brain imaging, and is organised into sub-projects at all university hospitals in Oslo. Patients are recruited using a common study protocol, and all samples and data are collected into common biobank and database. All sub-projects are using the infrastructure for neurocognitive testing, MR neuroimaging, molecular genetic laboratory facilities and database service. The program is organised into the following groups:

1. The TOP Clinical Unit, headed by Ingrid Melle, runs the clinical research projects, focusing on longitudinal first episode studies.
2. The TOP neurocognitive group, headed by Kjetil Sundet, thoroughly investigates patients with a standard neuropsychological test battery for thorough phenotyping.
3. The TOP MRI group, 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. We use 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 TOP MolGen group, headed by Srdjan Djurovic, has both regular equipment for SNP genotyping and Solexa Genome Analyzer (Illumina).

GROUP MEMBERS

Senior Scientists:
Thomas Espeseth
Jimmy Jensen
Anders Dale

Postdoctoral Fellows:
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Anja Vaskinn

PhD Fellows:
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Christine Lycke Brandt
Ingrid Dieset
Luiz Fernando Goulart
Greg Reckless
Kristina Skåtun
Martin Tesli
Morten Mattingsdal
Elen Gjevik
Kathrine Wirgenes

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Elin Inderhaug
Eivind Bakken
Niels Petter Sigvartsen
Thomas Doug Bjella

Centre Administration:
Linn Kleven
Ragnhild B. Storli
Trude C. Steen

VIDAR STEEN - NCMM Associate Investigator

Center for Medical Genetics and Molecular Medicine, the University of Bergen

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, serious psychiatric disorders affecting approximately one percent of the population during the course of a lifetime. Below is a brief description of some selected findings during 2011.

Although both schizophrenia and bipolar disorder have a high estimated heritability, only a limited number of genetic susceptibility variants have been verified thus far. We reported on a novel association between complement-related genes (CSMD1 and CSMD2) and risk for schizophrenia (Håvik et al 2011), supporting the observed link between immunity and schizophrenia. Since cognitive dysfunctions are often seen in patients with psychotic disorders, we also study cognition in health and disease, and contributed to a milestone paper demonstrating the polygenic underpinnings of IQ (Davies et al 2011). Treatment with some types of antipsychotic drugs (e.g., clozapine and olanzapine) may lead to major metabolic adverse effects, such as weight gain and lipid disturbances. The underlying mechanisms are not completely understood. We have demonstrated that antipsychotics may turn on cellular lipid biosynthesis through activation of the SREBP transcription system, both *in vivo* and *in vitro*. During 2011, we reported that olanzapine-induced weight gain in the rat is associated with orexigenic neuropeptide signalling in the hypothalamus (Fernø et al 2011) and found that certain variants in genes encoding energy homeostasis genes may predict the risk of weight gain in antipsychotic-treated patients with schizophrenia (Jassim et al 2011).

The research group is also responsible for running the UiB node of the Norwegian Microarray Consortium, a national FUGE platform for large-scale genomic analysis (www.genomics.no).

GROUP MEMBERS

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Bjarte Håvik

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ARNE KLUNGLAND - NCMM Associate Investigator

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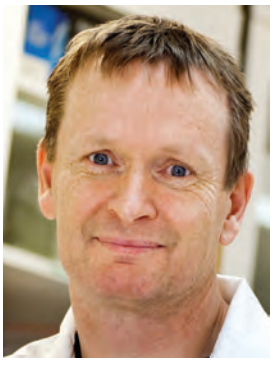

The Klungland research group has two main foci: 1) to identify and characterise novel hydroxylases for genome and epigenome regulation, and 2) to be in the forefront of methods related to the analysis of genome and epigenome base modifications. These foci are explained in more detail below.

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 tumourigenesis. Currently, we are analysing four enzymes that were identified through their specific interactions with 5-hmC containing DNA.

Recently, functional RNAs and reversible RNA modifications have entirely changed the scientific community's view on RNA. 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 other enzymes that putatively can reverse the 6-mA modifications and we are currently analysing the role of 6-mA in meiosis and certain diseases.

Although the importance of DNA methylation (e.g., 5-mC) in epigenetic regulation and reprogramming has been well established, the exact role(s) of 5-hmC remains elusive. 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; thus, there is 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.

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PÅL R. NJØLSTAD - NCMM Associate Investigator

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

Njølstad is Principal Investigator at the KG Jebsen Center for Translational Diabetes Research in Bergen. 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 individualised 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. Find new genetic risk factors for diabetes and its complications.
2. Reveal novel disease mechanisms in diabetes development.
3. Develop and implement improved targeted treatment of diabetes.

Professor Pål R. Njølstad was recently awarded an ERC Advanced Grant on the genetics of childhood obesity and diabetes using the Norwegian Mother and Child Cohort.

GROUP MEMBERS

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Ottar Nygård

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Project Advisor:
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HELGA B. SALVESEN - NCMM Associate Investigator

Department of Clinical Medicine, University of Bergen and Department of Obstetrics and Gynaecology, Haukeland University Hospital

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). 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 (MoMaTEC).

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. 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.

GROUP MEMBERS

Postdoctoral Fellows:
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Ingfrid Haldorsen (imaging)
Maria Ræder
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Kanthida Kusanmano

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Study Nurse:
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PhD Fellows:
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Even Birkeland
Mari K Halle
Henrica Werner
Jenny Husby (imaging)
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Medical Students:
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Siv Mjøs
Hilde Engerud

ROLF BJERKVIG - NCMM Associate Investigator

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

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 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.

Specifically, our research aims are to:

1. Advance our understanding of biological mechanisms driving brain tumour initiation and progression by discovering bona fide cancer genes/pathways that either promote initiation or drive cancer progression and metastasis. We will collect and integrate genomic (DNA copy number and exome sequence), epigenomic (DNA methylation pattern), transcriptomic (coding and non-coding RNA profiling) and proteomic data from our unique brain tumour models and biobanks.
2. Establish platforms for large scale screening of FDA-approved drug libraries for candidates with anti-tumour efficacy, either as monotherapy or in combination with cytotoxic agents or radiotherapy. The platform is based on *in vitro* cultures of large series of patient glioma biopsies and state-of-the art animal models. In addition to already approved drugs (for non-cancer indications), the platform will screen for novel drug targets and be used for biomarker discovery (predicting treatment response).
3. Perform clinical trials for assessment of drugs with promising anti-tumour efficacy.

GROUP MEMBERS

Group Leaders:
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Hrvoje Miletic
Per Øyvind Enger
Frits Thorsen

Senior Investigators:
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Renate Grüner

Postdoctoral Fellows:
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Kai-Ove Skaftnesmo
Per Øystein Sakariassen
Ivana Manini (visiting scientist)

Senior Tecnhician:
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Clinicians:
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Dorota Goplen
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Agnete Svendsen
Krishna Talasila
Gro Røsland
Eskil Eskilsson
Liliane Hansen
Linda Sleire
Inger Anne Netland
Bente Skeie
Lina Leiss
Inderjit Kaur Daphu
Olivier Keunen (visiting)

PER EYSTEIN LØNNING - NCMM Associate Investigator

Section of Medicine, University of Bergen, and 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.

GROUP MEMBERS

Senior Scientists:
Stian Knappskog
Hans Petter Eikesdal
(consultant oncologist)

Postdoctoral Fellow:
Elisabet Ognedal Berge

Senior Tecnhicians:
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Synnøve Yndestad
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Anne Hege Straume

LARS A. AKSLEN - NCMM Associate Investigator

The Gade Institute, Section for Pathology, University of Bergen

Professor Akslen is a specialist in surgical pathology. He has been the head of the Tumour Biology Research Group since the establishment in 1995 at the Gade Institute, University of Bergen, and is also a senior consultant at Haukeland University Hospital. His team is currently engaged in translational cancer research and is focused on the exploration and validation of novel biomarkers for more biologically based classification and grading of malignant tumours of different tumour types (e.g., breast, prostate, melanoma, gynaecologic cancer). At present, the research team is focusing its efforts in two areas:

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

The team recently reported that HSP27 appears to represent a critical regulator and biomarker of angiogenesis and tumour dormancy as shown in studies of breast cancer models with clinical validation (Straume et al., PNAS 2012). Akslen and co-workers have also reported several novel angiogenesis markers, such as glomeruloid microvascular proliferation (GMP) and vascular proliferation index (VPI). In breast cancer studies, the team has found that angiogenesis, indicated by several markers, is particularly increased in the aggressive basal-like subtype. Further clinical validation of these markers is on-going. The team 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 the assessment of tumour 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 personalised patient management. The team has extensive national and international collaboration.

GROUP MEMBERS

Senior Researchers:
Jarle B. Arnes (pathologist)
Karin Collett (pathologist)
Ingeborg M. Bachmann (dermatologist)
Ole Johan Halvorsen (pathologist)
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Gøril Knutsvik
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Hanne Puntervoll
Cornelia Schuster
Kristi Anne Veien
Elisabeth Wik

Pre-PhD Projects:
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Emilia Hugdahl (dermatologist)
Kristi Krüger (medical student)
Henrik Svendsen (plastic surgeon)

Technicians:
Gerd Lillian Hallseth
May Britt Kalvenes

National & International Infrastructure Collaborations

NCMM is involved in a number of institutional level collaborations and infrastructure initiatives, with the objective of scientific integration and facilitating translational research. Both the breadth of internationally recognised co-operation partners and the access to Norwegian, Nordic and European resorces provide the NCMM with the infrastructure tools to achieve excellence in translational medical research. The national and international infrastructure collaborations in which NCMM is involved are outlined below.

NATIONAL

NCMM is a joint venture among the University of Oslo (hosting institution), the Research Council of Norway (Forskningsrådet) and South-Eastern Norway Regional Health Authority (Helse Sør-Øst). Its location in the Oslo Research Park provides overlap and co-localisation with the Biotechnology Centre of Oslo and the nearby Centre for Molecular Biology and Neuroscience provide extensive access to infrastructure and instrumentation in addition to both theoretical and technical expertise.

The Biotechnology Centre of Oslo also hosts the Chemical Biology Platform, a high throughput screening facility that offers competence and technologies that enable researchers to study the effect of chemical compounds on biological function. The platform is part of a larger Norwegian network (ChemBioNet Norway / NOR-OPENSCREEN), which brings together leading chemists, biologists and informaticians from complementing units located in Tromsø, Trondheim, Bergen and Oslo, and thereby provides access to a host of national infrastructure tools. The Norwegian platform is a full partner of the European ChemBioNet and thereby has access to their chemical libraries.

EUROPEAN

During the period from 2008 to 2010, NCMM acted as a national host for the Preparatory Phase of the project EATRIS, the European Advanced Translational Research Infrastructure in Medicine, with Professor Kjetil Taskén as the scientific partner representing Norway. EATRIS is an international research infrastructure initiative aimed at strengthening health research and development (R&D) in Europe in order to allow the more efficient transfer of research discoveries into new clinical applications for disease pre-

EU FP7 RESEARCH PROJECT

PROSTATE RESEARCH ORGANIZATION-NETWORK OF EARLY STAGE TRAINING (PRO-NEST)

PRO-NEST is an FP7 Marie Curie Initial Training Network investigating the initiation and progression of prostate cancer on a molecular level, and ultimately aims to improve diagnosis, treatment and prevention by identifying new biomarkers and therapeutic targets. As a training program, PRO-NEST provides young scientists with the tools they need to become independent and versatile prostate cancer researchers, with both a broad knowledge base and specific expertise in basic, clinical and applied research. PRO-NEST is an integrated European training program involving respected scientists from more than 16 institutions in 9 different European countries, and the multi-disciplinary approach trains skills in specific technical areas as well as in project management and the communication of science.

EU FP7 RESEARCH PROJECT

NATURAL PRODUCTS FROM MARINE FUNGI FOR THE TREATMENT OF CANCER (MARINE FUNGI)

MARINE FUNGI is an FP7 project that aims to explore the potential anti-cancer properties of compounds naturally produced by various strains of marine fungi collected off the coasts of Elba, Chile, and Indonesia. Eleven partner institutions from seven countries have joined the MARINE FUNGI project. Each partner was specifically chosen for their expertise in the various fields needed, such as the collection, isolation and fermentation of marine fungi strains, identification and characterisation of active secondary metabolites, screening of these compounds for biological activity against a panel of human cancer cell lines, and the eventual large scale production of these products.

vention, diagnosis and treatment. The infrastructure includes expertise in technology transfer, regulatory affairs and product development, training programs, and translation centers with state-of-the-art facilities for complete R&D development pipelines for different product types. Effectively, EATRIS will operate to increase the return on the investments made in publicly funded biomedical research by removing existing bottlenecks to translation, quickly bringing new discoveries closer to the clinic ('bench-to-bedside') and to society in general.

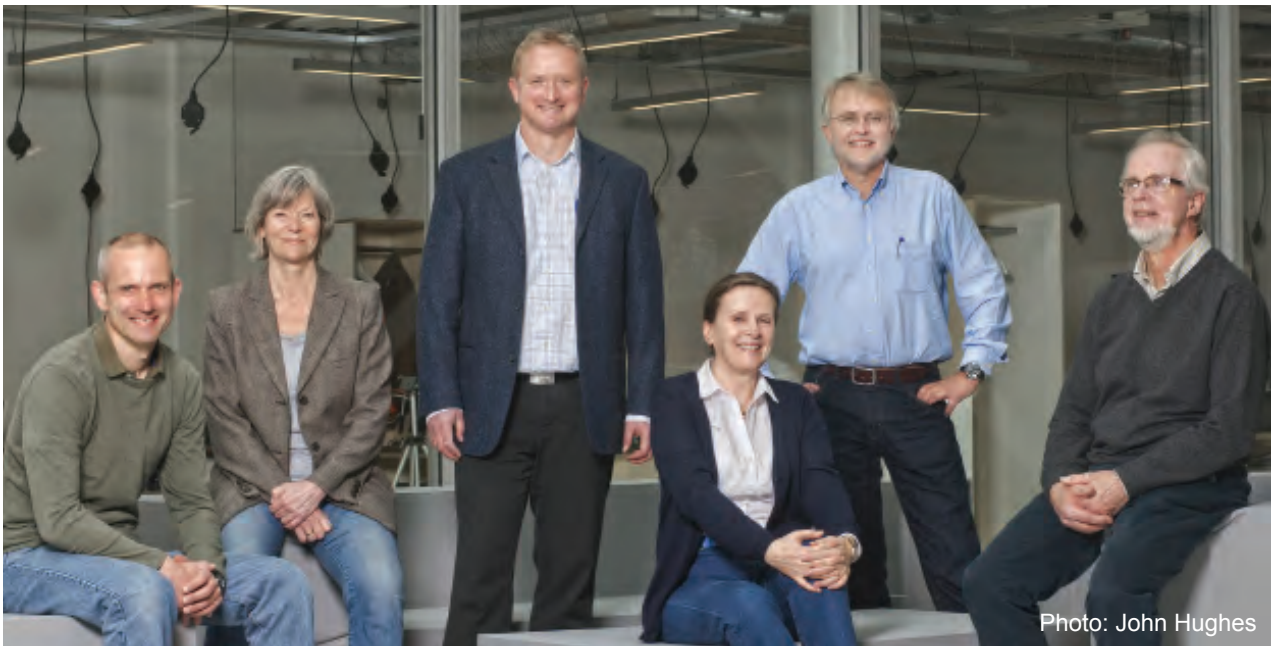
The EATRIS Preparatory Phase was funded with €4.2 million by the European Community's 7th Framework Programme, supporting the formation of a consortium consisting of ten countries: Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden and the UK. NCMM was responsible for the preparation of a grant application to the Norwegian Research Council (NRC) for support to build a Norwegian EATRIS node (an EATRIS Centre), submitted in 2010, and was short listed by the NRC to submit a revised application.

In the second-round decision, the Norwegian EATRIS node was awarded 2 million NOK to cover the fees for participation in the project at the European level over the next two years. The EATRIS member states have also agreed to apply for European Research Infrastructure Consortium (ERIC) status to the European Commission, expecting formal establishment of the ERIC late 2012/early 2013. The formal decision of Norway's continued participation will, however, have to await funding decisions for 2013 to 2016.

The European Infrastructure of Open Screening Platforms for Chemical Biology (EU-OPENSCREEN) consists of 20 partners from 17 European countries. EU-OPENSCREEN aims to build an association of screening centres with the most advanced technology, to be used by European researchers for identifying new compounds and targets in a variety of fields in Life Sciences (e.g. human and veterinary medicine, systems biology, biotechnology, agriculture and nutrition). These association centres will include high-throughput screening platforms, chemical libraries, chemical resorces for hit discovery and optimisation, bio- and chem-informatics support, and a publicly accessible database containing screening results, assay protocols, and chemical information. The Chemical Biology Platform at the Biotechnology Centre of Oslo is part of the Norwegian participation in the EU-OPENSCREEN (ChemBioNet Norway/ NOR-OPENSCREEN, with Professor Kjetil Taskén as a Norwegian partner and Steering Committee member), thereby giving NCMM access to leading chemistry, biology and informatics resources.

NCMM Board

The 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 research and collaboarations, recruitment, translational value and economy.



Left to right: Finn-Erik Johansen, Guro Valen, John Torgils Vaage, Ragnhild A. Lothe, Terje Espevik, Ole Sejersted

Members of the Board

Professor Ragnhild A. Lothe, Norwegian Radium Hospital, Oslo University Hospital/University of Oslo

Professor Finn-Eirik Johansen, Faculty of Science and Mathematics, University of Oslo

Professor Jan G. Bjålie, Faculty of Medicine University of Oslo

Director of Research, Professor John Torgils Vaage*, Department of Research and Innovation, South-Eastern Norway Regional Health Authority

* to be replaced from 2012 by Director of Research, Professor Magnar Bjørås, Department of Microbiology, Oslo University Hospital

Head of the Institute for Experimental Research, Professor Ole Sejersted, Oslo University Hospital

Professor Terje Espevik, Norwegian University of Science and Technology (Representative from National Reference Group)

Special Adviser Marianne Grønsleth, Research Council of Norway (Observer to NCMM Board proceedings)

Deputy Members of the Board

Professor Guro Valen, Faculty of Medicine, University of Oslo

Assistant Professor Ingvild Mikkola, University of Tromsø (Representative from National Reference Group)

Head of Research Øystein Krüger, Department of Research & Innovation, South-Eastern Norway Regional Health Authority (from 2012)

NOTES FROM THE CHAIR OF THE BOARD

Ragnhild A. Lothe
Chair

The recruitment of NCMM's group leaders, based on scientific excellence, was finalised last year and their success is already visible as highlighted elsewhere in this report and the review by the Director.

The Scientific Advisory Board (SAB) convened at NCMM for the first time in 2011 and their visit included a discussion session with the Board. The SAB was impressed with the Centre and all that the Director and staff have already achieved, a statement certainly pleasing to the Board. It was also agreed that the main challenges in the near future are to ensure a close integration with the clinical institutions in Oslo and to fulfill the coming bioinformatics needs of the NCMM groups. Several initiatives are already in place to meet these challenges.

As a national Centre, it is not only important to establish nation-wide networks but also to actively utilise and support collaborations within such networks. With this in mind, the National Reference Group is represented in the Board and the NCMM Associate Investigators are located across the country. These networks will require further attention and development in order to maximise the benefit to all parties involved.

The composition of the Board has recently changed, as the University of Oslo appointed two new members, professors Jan G. Bjålie and Finn-Erik Johansen - thank you both for accepting this role and we look forward to continued successful collaboration. My sincere thanks also go to Professors Heidi Kiil Blomhoff and Sigbjørn Fossum for serving as Board members during the first phase of NCMM - your constructive discussions and assistance in getting NCMM "up and running" during this period are highly appreciated. Finally, my personal thanks go to the entire Board, both past and present, for your valuable work.

On behalf of the Board, the very best collaboration with the Director and chief administrative officer, Elin Kaurstad, is appreciated and is important for our work to be successful.

Professor
Jan G. Bjålie
Faculty of Medicine
University of Oslo

Assistant Professor
Ingvild Mikkola
Department of Pharmacy
University of Tromsø

Special Adviser
Marianne Grønsleth
Research Council of Norway

Scientific Advisory Board (SAB)

The NCMM Scientific Advisory Board (SAB) was appointed by the NCMM Board on June 10th, 2011 and had its first meeting in January of 2012.

The main task of the SAB is to critically investigate the scientific performance of NCMM, in relation to the research plan as outlined in the project proposal, and to advise on the further development of NCMM. This board will meets once annually with the NCMM core members in order to assess recent progress and future strategies.

Left to right: Leif Groop, Alvis Brazma, Erich Nigg, Annika Lindblom, Richard Treisman

SAB Members

Professor Leif Groop, Head of Lund University Diabetes Centre, Department of Endocrinology, Clinical Sciences Malmö, Lund University, SAB Chair

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

Professor Erich Nigg, Director of Biozentrum, Basel, Switzerland

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

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

National Reference Group

The National Reference Group is responsible for national coordination and ensuring that other regions can benefit from the academic and recruitment opportunities represented by the EMBL node.

Assistant Professor
Ingvild Mikkola
Department of Pharmacy
University of Tromsø
Deputy member of the NCMM Board

Professor
Terje Espevik
Norwegian University of Science and Technology
Member of the NCMM Board

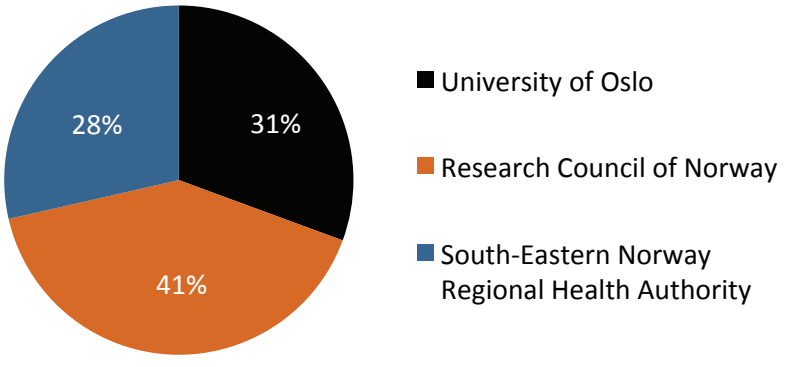
Professor
Vidar Steen
Institute for Clinical Medicine
University of Bergen

Professor
Anne-Brit Kolstø
Faculty of Mathematics and Natural Sciences
University of Oslo

NCMM Funding

The sorces of funding for NCMM operations can be seen in the pie chart below. Total NCMM funding is approximately 24.5 million NOK per year (approximately 3.3 million EURO).

Additional external funding is provided to the groups by individual grants (10 million NOK in 2011). Sources of external funding include the Norwegian Cancer Society, the Research Council of Norway, the Lundbeck Foundation, and EU grants.



NCMM-Affiliated Publications

NCMM publications from 2011

1. Review: Spatiotemporal dynamics of hCG/cAMP signaling and regulation of placental function. Weedon-Fekjaer MS, Tasken K. (2012, Epub 2011) Placenta. 33 Suppl: S87-91.
2. Anti-tumor Immune Responses Associate with Clinical Outcome in Patients with Liver Metastasis from Colorectal Cancer. Brudvik KW, Henjum K, Aandahl EM, Bjørnbeth BA, Taskén K. (2012, ePub 2011) Cancer Immunology, Immunotherapy. 61: 1045-1053.
3. Modulation of T cell immune functions by the prostaglandin E(2) - cAMP pathway in chronic inflammatory states. Brudvik KW, Tasken K. (2012, Epub 2011) British Journal of Pharmacology. 166 (2): 411-9.
4. Correlation analysis of p53 protein isoforms with NPM1/FLT3 mutations and therapy response in acute myeloid leukemia. Anensen N, Hjelle SM, Van Belle W, Haaland I, Silden E, Bourdon JC, Hovland R, Tasken K, Knappskog S, Lonning PE, Bruserud O, Gjertsen BT. (2012, Epub 2011) Oncogene. 31 (12): 1533-45.
5. 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, and Nagelhus EA. (2012, Epub 2011) Acta Ophthalmologica.
6. Critical role of aquaporin-4 (AQP4) in astrocytic Ca2+ signaling events elicited by cerebral edema. Thrane AS, Rappold PM, Fujita T, Torres A, Bekar LK, Takano T, Peng W, Wang F, Thrane VR, Enger R, Haj-Yasein NN, Skare O, Holen T, Klungland A, Ottersen OP, Nedergaard M, Nagelhus EA. (2011) Proceedings of the National Academy of Sciences of the United States of America. 108(2): 846-51.
7. CD147 (Basigin/Emmprin) identifies FoxP3+CD45RO+CTLA4+-activated human regulatory T cells. Solstad T, Bains SJ, Landskron J, Aandahl EM, Thiede B, Tasken K, Torgersen KM. (2011) Blood. 118(19): 5141-51.
8. Androgen receptor driven transcription in molecular apocrine breast cancer is mediated by FoxA1. Robinson JL, Macarthur S, Ross-Innes CS, Tilley WD, Neal DE, Mills IG, Carroll JS. (2011) The EMBO Journal. 30(15): 3019-27.
9. Optic atrophy 1 is an A-kinase anchoring protein on lipid droplets that mediates adrenergic control of lipolysis. Pidoux G, Witczak O, Jarnaess E, Myrvold L, Urlaub H, Stokka AJ, Kuntziger T, Tasken K. (2011) The EMBO journal. 30(21): 4371-86.
10. An exploratory trial of cyclooxygenase type 2 inhibitor in HIV-1 infection: downregulated immune activation and improved T cell-dependent vaccine responses. Pettersen FO, Torheim EA, Dahm AE, Aaberge IS, Lind A, Holm M, Aandahl EM, Sandset PM, Tasken K, Kvale D. (2011) Journal of Virology. 85(13): 6557-66.
11. Analysing phosphorylation-based signalling networks by phospho flow cytometry. Oberprieler NG, Tasken K. (2011) Cellular Signalling. 23(1): 14-8.
12. Cyclic AMP-mediated immune regulation--overview of mechanisms of action in T cells. Mosenden R, Tasken K. (2011) Cellular Signalling. 23(6): 1009-16.
13. Mice with disrupted type I protein kinase A anchoring in T cells resist retrovirus-induced immunodeficiency. Mosenden R, Singh P, Cornez I, Heglind M, Ruppelt A, Moutschen M, Enerback S, Rahmouni S, Tasken K. (2011) Journal of Immunology (Baltimore, Md : 1950). 186 (9): 5119-30.
14. Effects of type I protein kinase A modulation on the T cell distal pole complex. Mosenden R, Moltu K, Ruppelt A, Berge T, Tasken K. (2011) Scandinavian Journal of Immunology. 74(6): 568-73.
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17. The androgen receptor fuels prostate cancer by regulating central metabolism and biosynthesis. Massie CE, Lynch A, Ramos-Montoya A, Boren J, Stark R, Fazli L, Warren A, Scott H, Madhu B, Sharma N, Bon H, Zecchini V, Smith DM, Denicola GM, Mathews N, Osborne M, Hadfield J, Macarthur S, Adryan B, Lyons SK, Brindle KM, Griffiths J, Gleave ME, Rennie PS, Neal DE, Mills IG. (2011) The EMBO Journal. 30(13): 2719-33.

18. T cell-signaling network analysis reveals distinct differences between CD28 and CD2 costimulation responses in various subsets and in the MAPK pathway between resting and activated regulatory T cells. Kalland ME, Oberprieler NG, Vang T, Taskén K, Torgersen KM. (2011) Journal of Immunology (Baltimore, Md : 1950). 187(10): 5233-45.

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22. Principles for the post-GWAS functional characterization of cancer risk loci. Freedman ML, Monteiro AN, Gayther SA, Coetzee GA, Risch A, Plass C, Casey G, De Biasi M, Carlson C, Duggan D, James M, Liu P, Tichelaar JW, Vikis HG, You M, Mills IG. (2011) Nature Genetics. 43(6): 513-8.

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24. P-type ATPases at a glance. Bublitz M, Morth JP, Nissen P. (2011) Journal of Cell Science. 124(Pt 15): 2515-9.

25. Protein kinase A antagonist inhibits beta-catenin nuclear translocation, c-Myc and COX-2 expression and tumor promotion in Apc(Min/+) mice. Brudvik KW, Paulsen JE, Aandahl EM, Roald B, Tasken K. (2011) Molecular Cancer. 10: 149.

Photo: John Hughes

26. Phosphodiesterases as targets for modulating T-cell responses. Bjorgo E, Moltu K, Tasken K. (2011) Handbook of Experimental Pharmacology. 204: 345-63.

27. Crystallization and preliminary structural analysis of the Listeria monocytogenes Ca2+-ATPase LMCA1. Andersen JL, Gourdon P, Moller JV, Morth JP, Nissen P. (2011) Acta Crystallographica section F – Structural Biology and Crystallization Communications. 67: 718-722.

28. Stereoselective synthesis of (RP)-8-substituted-N-acylated and N-alkylated adenosine-3',5'-cyclic phosphorothioic acids as cAMP antagonists. Andrei M, Bakkebo T, Klaveness J, Tasken K, Undheim K. (2011) European Journal of Medicinal Chemistry. 46(12): 5935-40.

29. Structural insights into the high affinity binding of cardiotonic steroids to the Na+,K+-ATPase. Yatime L, Laursen M, Morth JP, Esmann M, Nissen P, Fedosova NU. (2011) Journal of Structural Biology. 174(2): 296-306.

NCMM emerging publications 2012

1. Dynamic interaction between lymphoid tyrosine phosphatase and C-terminal Src kinase controls T cell activation. Vang T, Liu WH, Delacroix L, Wu S, Vasile S, Dahl R, Yang L, Francis D, Landskron J, Taskén K, Tremblay ML, Lie BA, Page R, Mustelin T, Rahmouni S, Rickert RC, Tautz, L. (2012) Nature Chemistry. Biol. 8: 437-46.
2. Heterogeneity in the Activation Requirements of Human Regulatory T cells. Hagness M, Henjum K, Landskron J, Brudvik KW, Bjørnbeth BA, Foss A, Taskén K, Aandahl, E.M. (2012) Journal of Immunology. 188: 5459-66.
3. Modulation of proximal signaling in normal and transformed B cells by transmembrane adaptor Cbp/PAGs. Kalland ME, Solheim SA, Skånland SS, Taskén K, Berge T. (2012) Experimental Cell Research. 318: 1611-9.
4. Creating order from chaos: Cellular regulation by kinase anchoring. Scott JD, Dessauer CW, Taskén K. Annu. Rev. Pharmacol. Toxicol. (in press).
5. Loss of Kir4.1 potassium channels in hippocampus of patients with mesial temporal lobe epilepsy. Heuser K, Eid T, Lauritzen F, Thoren AE, Vindedal GF, Taubøll E, Gjerstad L, Spencer SS, Ottersen OP, Nagelhus EA, de Lanerolle N. Journal of Experimental Neurology and Neuropathology. (in press).
6. 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.
7. Aquaporin-4 and epilepsy (review). Binder DK, Nagelhus EA, and Ottersen OP. (2012) Glia. 60(8): 1203-14.
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10. Both El Tor and classical cholera toxin bind blood group determinants. Heggelund, Julie Elisabeth; Haugen, Espen; Lygren, Birgitte; Mackenzie, Alasdair; Roclöv, Åsa Holmner; Vasile, Francesca; Reina, José J.; Bernardi, Anna; Krengel, Ute. (2012) Biochemical and Biophysical Research Communications. 418(4): 731-35.
11. LYP inhibits T-cell activation when dissociated from CSK. Vang, Torkel; Liu, W.H.; Delacroix, L.; Wu, S.; Vasile, S.; Dahl, R.; Yang, L.; Francis, D.; Landskron, Johannes; Tasken, Kjetil; Tremblay, M.L.; Lie, B.A.; Mustelin, T.; Rahmouni, S.; Rickert, R.C.; Tautz, L. (2012) Nature Chemical Biology. 8: 437-46.
12. IFPA Meeting 2011 workshop report III: Placental immunology; epigenetic and microRNA-dependent gene regulation; comparative placentation; trophoblast differentiation; stem cells. Ackerman WE, Bulmer JN, Carter AM, Chaillet JR, Chamley L, Chen CP, Chuong EB, Coleman SJ, Collet GP, Croy BA, de Mestre AM, Dickinson H, Ducray J, Enders AC, Fogarty NME, Gauster M, Golos T, Haider S, Heazell AE, Holland OJ, Huppertz B, Husebekk Anne, John RM, Johnsen Guro Mørk, Jones CJP, Kalionisv B, König J, Lorenzon AR, Moffett A, de Mello JC Moreira, Nuzzo AM, Parham P, Parolini O, Petroff MG, Pidoux G, Ramírez-Pinilla MP, Robinson WP, Rolfo A, Sadoysky Y, Soma H, Southcombe JH, Tilburgs T, Lash GE (2012) Placenta. 33: s.S15-22.
13. The sensor region of the ubiquitous cytosolic sensor kinase, PdtaS, contains PAS and GAF domain sensing modules. Preu J, Panjikar S, Morth JP, Preben, Jaiswal R, Karunakar P, Tucker PA. (2012) Journal of Structural Biology. 177(2): 498-505.
14. A brain-wide glio-vascular pathway facilitates 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. Science Translational Medicine (in press).
15. Real-time analysis of microglial activation and motility in hepatic and hyperammonemic encephalopathy. Thrane VR, Thrane AS, Chang J, Alleluia V, Nagelhus EA, Nedergaard M. (2012) Neuroscience. 2012 Jun 21 [Epub ahead of print].

Patents filled 2011 - 2012

1. Method and compositions for identifying activated regulatory T cells. Inventors: Taskén K, Solstad TS, Torgersen KM, Aandahl EM, Thiede B, Bains SJ, Landskron JR, Hagness M, Henjum K, Foss AE, Bjørnbeth BA. U.S. Provisional Patent Application Serial No. 61/502,993, Filed: 30-Jun-2011.
2. Methods and compositions for inhibition of activation of regulatory T cells. Inventors: Taskén K, Kalland ME, Oberprieler NG, Vang T, Torgersen KM. U.S. Provisional Patent Application Serial No. 61/502,989, Filed: 30-Jun-2011.
3. The A kinase anchoring protein ezrin interacts with connexin 43 to facilitate protein kinase A control of gap junction communication in cell fusion. Inventors: Taskén K, Pidoux G, Lygren B, Evain-Brion D. U.S. Provisional Patent Application Serial No, Filed: 15-May-2012.
4. Chemical Compounds [that target the AKAP18d-phospholamban interaction]. Inventors: Taskén K, Lygren B, Østensen E, Klaveness J. U.K. Patent Application, Filed: 18-May-2012.

RESEARCH HIGHLIGHT

Old Drugs New Tricks
How some anti-inflammatory drugs can be used to treat HIV

The Taskén group has published a study indicating that treatment with celecoxib, a drug commonly used to treat pain and arthritis, can improve the outcomes for HIV patients that have not been treated with any anti-retroviral drugs. This finding may be particularly relevant for HIV patients with limited access to the expensive HIV treatments or for those with poor responses to current therapies.

“These types of anti-inflammatory drugs are cheaper and easier to administer than current anti-retroviral medications,” said Professor Kjetil Taskén, a lead researcher in this study. “If they can be used to slow the progression to AIDS, and therefore delay the need for anti-retroviral drugs, this could decrease the cost of treatment and improve access to patients world-wide.”

Celecoxib has a similar effect as anti-inflammatory drugs like Ibuprofen and it is precisely celecoxib’s impact on inflammation that makes it so interesting for HIV treatment. Much of the complications seen in HIV infection are not caused by the actual virus but by the immune system’s response. Because the immune system cannot clear the virus, it can become permanently “activated”, and this is linked to a faster progression to AIDS. Drugs like celecoxib can reduce this chronic activation, improve responses to vaccines and likely improve the overall prognosis of patients.

The full article can be found in the Journal of Virology, July 2011, Vol. 85, No. 13, Pages 6557-66.

Photo: John Hughes

RESEARCH HIGHLIGHT

Astrocytes and the blood-brain barrier

Astrocytes have enjoyed a renaissance over recent years, boosted by new insight regarding their intimate coupling to synaptic transmission and a number of neurological disorders. It has long been surmised that the involvement of astrocytes in physiological and pathophysiological processes depends on their key roles in brain water homeostasis. A question that has intrigued neuroscientists for years is what mechanisms are responsible for regulating brain interstitial fluid dynamics and extracellular space volume.

In the paper Haj-Yasen et al., Proc Natl Acad Sci USA 2011 Oct 25;108(43):17815-20, Nagelhus and co-workers provide evidence that the astrocytic water channel aquaporin-4 (AQP4) facilitates resorption of brain interstitial fluid and thus regulates baseline extracellular volume.

The authors generated a glial-conditional Aqp4 knockout mouse line to demonstrate that the astrocytic end-foot pool of AQP4 regulates water exchange at the blood-brain interface. Compared with litter controls, glial-conditional Aqp4 knockout mice showed a 31% reduction in brain water uptake after systemic hypo-osmotic stress and a delayed postnatal resorption of brain water. The authors also concluded that endothelial cells are devoid of AQP4.

These findings change our view of the blood-brain barrier in a fundamental way, as they indicate that perivascular astrocytic endfeet may acquire a barrier function. The findings also imply that any drugs engineered to target AQP4 for therapeutic purposes will have to be designed to permeate the endothelial cell layer.

The full article can be found in Proc. Nat. Acad. Sci. USA. Oct 2011. Vol. 108, No. 43, Pages 17815-20.

Personnel

ADMINISTRATION

Director
Professor Kjetil Taskén

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Elin K. Kaurstad
Chief Financial Officer
Anita Skolem

Senior Consultants
Nina Modahl
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Head Engineer
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NCMM-Group Leader
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Vidar Jensen
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Vinita Rangroo Thrane
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George Andreas Gundersen
Martine Eilert-Olsen
Cecilie E. Bugge
Wannam Tareg (EMBO fellow)

Membrane Transport Group
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Hanne Guldsten
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Kim Langmach Hein
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Jayaram Lamsal

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Ellen Østensen
Administrative Officer:
Berit Barkley
Scientific Officers:
Jorun Solheim
Gladys Tjørhom
Chemical Biology Platform:
Anne Jorunn Stokka
Niko Sahlberg / Inderjit M. Singh

Photo: John Hughes

Stem Cell Group
NCMM-Group Leader
Judith Staerk
Principal Engineer
Mustapha Lamkhannat
Post Doctoral Fellow
Xavier Tekpli

NATIONALITIES REPRESENTED AT NCMM (2011)

Listed in alphabetical order


Canada

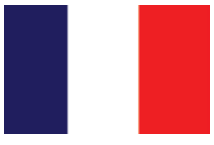

Israel


Denmark


Italy


Finland


Norway


France


Poland


Germany


Spain


Greece


Sweden


India


United States of America

NCMM Partnerships, Collaborations & Affiliations

Nordic EMBL Partnership for Molecular Medicine:

EMBL

MIMS Molecular Infection Medicine Sweden

FIMM Institute for Molecular Medicine Finland

NCMM Centre for Molecular Medicine Norway

NCMM Partners:

UiO : University of Oslo

The Research Council of Norway

HELSE SØR-ØST

National & International Collaborations:

Centre for Molecular Biology and Neuroscience

EU-OPENSCREEN ESFRI ROADMAP 2008

BiO The Biotechnology Centre of Oslo

ChemBioNet

ESFRI

EATRIS European Advanced Translational Research Infrastructure in Medicine

EMBL | UiO : University of Oslo | HELSE SØR-ØST | The Research Council of Norway

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