



Annual Report 2015

From disease mechanisms to clinical practice



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Overview by the Director

Dear friends, colleagues and supporters of NCMM,

I am proud to present the 2015 Annual Report from NCMM, which summarizes the activities in the 6th full year of operations at NCMM. While NCMM during the first five-year period was building up and grew rapidly in terms of mass and production, 2015 marked the start of the second 5-year period of operations. As described below NCMM now presents as a more mature Centre at steady-state, where groups capitalize on projects, work and investments initiated earlier and where well-established and successful groups rotate out while new groups are being recruited to start new areas of research. This strategy of continuous development of NCMM holds great promise also for the future and should allow NCMM researchers to keep abreast in the area of molecular medicine and translational research.

RECENT PROGRESS - Review of 2015 SCIENCE AND PUBLICATION OUTPUT

NCMM PIs reported around 50 NCMM-affiliated papers published in 2015 and the first quarter of 2016, including papers in Nature Genetics, J. Clin Oncol., EMBO Molecular Medicine, Elife and other journals. NCMM investigators have also filed patents, have started new commercialization projects and report a number of appearances in popular media. The breadth and depth of the research that now goes on in NCMM is very exciting and spans from molecular mechanisms regulating normal physiology and contributing to disease to prognostic studies, looking at association of disease markers and clinical outcome as well as involvement in clinical intervention trials.

TRANSLATIONAL RESEARCH

As of Q1 2016 NCMM PIs lists some 25 **observational or interventional clinical studies** in the areas of therapy and disease mechanisms as well as in the molecular markers, diagnostics and monitoring areas. The extent of clinical collaborations and activity with translational and clinical studies thus continues steadily at a high level.

COLLABORATION AND NETWORKS

As a part of the focus on translational research,

NCMM Group Leaders are all established with **adjunct appointments** in clinical or para-clinical departments at Oslo University Hospital (OUH). This involves increasing interactions and collaborations with Departments of Infectious Diseases, Hematology and Institutes of Experimental Medicine and Cancer Research, illustrating the breadth of application and extension of the molecular medicine research going on in NCMM. Furthermore, NCMM has close links with the Biotechnology Centre as well as additional collaborations across Norway. In fact, NCMM group leaders report more than **45 national collaborations**. The experience after 3-5 years with these affiliations is that they facilitate clinical collaborations, give group leaders better access to patient materials, biobanks and clinical trials and are crucial to facilitate translational research.

A network of **NCMM Associate Investigators** was established in 2010 when the first outstanding researchers and key research groups working across Norway were appointed Associated Investigators (AIs). These appointments, subject to application and evaluation by a Selection Committee, are based on scientific excellence and translational merit as well as added value and compatibility with the NCMM mission. The network was extended in 2011 and 2014 by the appointment of additional new members. Collaborations with this group have been boosted by joint meetings and by a seed money program initiated by the NCMM Board to foster collaborative projects. In 2015 NCMM called for selection of new Associate Investigators in an open call and selected 13 AIs (re-appointed and newly appointed). NCMM has also initiated a **Young Associate Investigator (YAI) program** and the first two NCMM YAIs were appointed at the University of Tromsø in 2014. In an open call in 2015, seven new YAIs were appointed bringing the total associate investigator network of AIs and YAIs to 22 members. The NCMM network meeting in January of 2016 gathered NCMM PIs, new AIs and YAIs and other stakeholders to an interactive programme of talks and active discussions of scientific leadership, funding strategies, research policies, career

development, translational medicine strategies and infrastructure.

On the **European and international arenas**, NCMM investigators enjoy numerous collaborations across the world (more than **40 international collaborations** reported). Research interactions with the three other nodes in the Nordic EMBL Partnership and the EMBL are also increasing rapidly. Implementation at NCMM of the practices of the parent EMBL in recruitment and rotation of staff at all levels also offers the opportunity of recruiting top talent at all levels on an international arena.

FUTURE PROMISE

As NCMM now has started its second 5-year operational period the Centre is at steady state and probably as stable and established as is possible with this model. We are expecting the next 2-3 years should bring significant scientific output from PIs harvesting from strategies set out in their first 5-year appointment period. Gradually, we also now see that NCMM groups rotate, as the Nagelhus group moved out at the end of 2014 and the Mills group is now phasing out since Dr. Ian Mills took up a faculty appointment at Queens University Belfast from 2015. These and coming rotations will involve a second wave of new recruitments and NCMM already recruited a group in bioinformatics from 2016 to be headed by Dr. **Anthony Mathelier** starting in May of 2016.

The Faculty of Medicine hosts NCMM from 2015 and cooperates closely with the Faculty of Mathematics and Science in this endeavor, which has also offered new opportunities, both strategically with the two Faculties and with more alignment and potential for synergies at all levels.

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

April 2016



Kjetil Taskén
Director of NCMM



NCMM history in brief

The **Centre for Molecular Medicine Norway (NCMM)** is part of the **Nordic EMBL Partnership for Molecular Medicine** which was established in 2007 as a joint venture (2008-2012) between the European Molecular Biology Laboratory (EMBL) and the Universities of Helsinki, Oslo and Umeå. A Danish node (Dandrite) joined the Partnership in 2013. The Partnership is dedicated to the growing field of Life Sciences that investigates the molecular basis of disease and explores molecular and genetically based treatments. It capitalizes on regional, complementary strengths in the Nordic countries and each of the four partner nodes brings in a unique set of expertise, skills and facilities encompassing EMBL's recognized research strengths in the areas of molecular, cellular and developmental biology, bioinformatics and structural biology. Altogether, the Nordic EMBL Partnership constitutes a coordinated Nordic infrastructure for enhancing molecular medicine scientific findings through a translational research pipeline, putting scientific discoveries into clinical use in an efficient way and equipping the partners to tackle some of the most challenging problems of biomedicine.

NCMM was formally inaugurated as a joint venture between the University of Oslo (UiO), as host, the Research Council of Norway (RCN) and Health Region South East (HSE) at the end of 2008. The overall objective of NCMM is to conduct cutting edge research in molecular medicine and facilitate translation of discoveries in basic medical research into clinical practice. NCMM focusses particularly on disease mechanisms where Norway has clear strengths and investigates mechanisms of non-communicable diseases such as cancer, cardiovascular and CNS-related disease and immune disorders. NCMM develops and adapts technologies for personalized medical applications and has unravelled new diagnostic methods and drug targets.

NCMM had its first full operational year in 2010 and a midterm evaluation carried out by an external, international committee took place in 2013. The committee recommended that NCMM should be continued for a second five-year period and that funding should be strengthened

to consolidate the success already achieved, to ensure further growth and to build up strategic areas in order to come above critical mass. Funding was therefore committed for a second five-year period (2015-2019) from the consortium partners.

INCOME AND EXPENSES

The **NCMM core funding** in the second five-year period (2015-2019) is 31 million Norwegian kroner (mNOK) (approximately 3.8 mEUR) per year from the 3 consortia partners UiO, Research Council of Norway and Health SouthEast. Furthermore, overhead and production-based income comes in addition. In 2015, NCMM spent 26 mNOK which was less than budgeted due to rotation of groups and lags in hiring. For 2016, NCMM plans to spend 37 mNOK, including transferred funds (see overview of NCMM finances). For the period 2017-2019 we stipulate the NCMM annual core budget expenses to be in the order of 35-38 mNOK (2015-value) with the present level of activity and additional income from overhead and production-based income and including transferred funds.

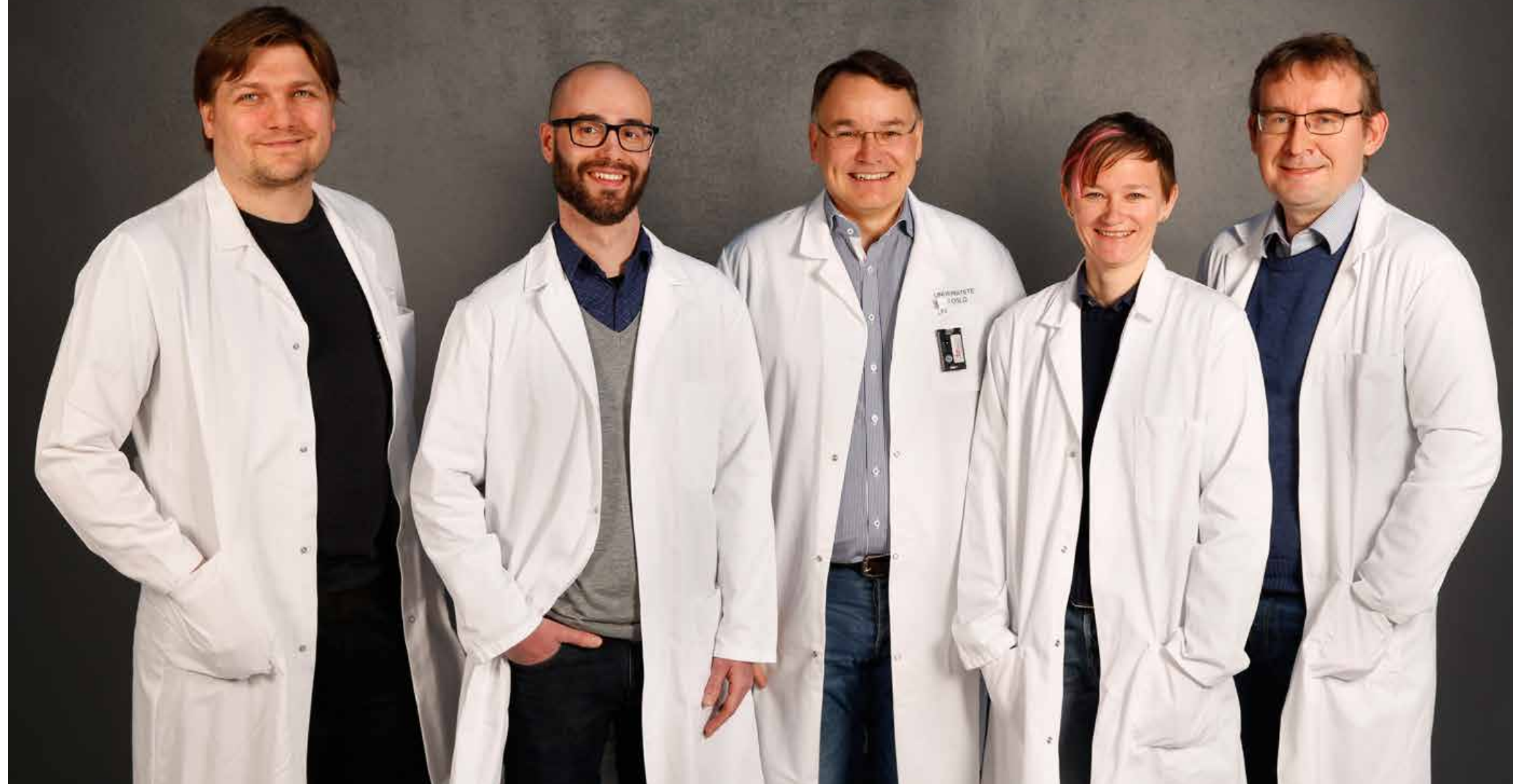
NCMM extramural funding in the form of grants to the group leaders and other competitive funding has increased steadily from 7 mNOK in 2010 to 35 mNOK in 2013. In 2014 NCMM reached 43 mNOK in annual grants and was maintained at this level with 42 mNOK in 2015 although we stipulate a drop to approx. 35 mNOK in 2016 due to rotation of groups. The external funding includes grants from the Research Council of Norway, Norwegian Cancer Society, Health SouthEast, European Commission, competitive grants at UiO and private foundations and organizations such as the Lundbeck Foundation, Novo Nordic Foundation, KG Jebsen Centres, Movember and others.

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

The overall objective of NCMM is to conduct cutting edge research in molecular medicine and facilitate translation of discoveries in basic medical research into clinical practice.

NCMM Group Leaders

From left: J. Preben Morth, Antoni Hurtado, Kjetil Taskén, Judith Staerk and Ian Mills



In the period 2009-11 NCMM hired five new young group leaders. In addition, appointed NCMM Director Kjetil Taskén is leading a research group at NCMM. Group Leader **Erlend Nagelhus** was appointed Professor of Medicine (Physiology) at the University of Oslo in 2013 and therefore rotated out from NCMM when his first five-year contract ended in November 2014. He has now been appointed NCMM Associate Investigator.

Recently, NCMM recruited a new group leader in bioinformatics, **Anthony Mathelier**, and he will start in May 2016. Furthermore, NCMM is in the process of recruiting another group leader that will also function as Assistant Director.

Professor **Kjetil Taskén**, identified by the Research Council as one of the founding members of NCMM, served as Interim Director 2008-10,

was appointed Director from January 2011 and reappointed for a second 5-year period from 2016. His research is in the area of cell signaling and immunomodulation with application in immune diseases, inflammation and tumor immunology.

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

interested in transcriptional and regulatory networks in prostate cancer and aims to better define the interplay between membrane trafficking, metabolism and transcription in prostate cancer as proteins in regulatory hubs for these processes have potential value as cancer biomarkers and therapeutic targets. Mills accepted a position at Queens University of Belfast in 2015 and will leave NCMM in June 2016.

Dr. **Jens Preben Morth** was trained in structural biology at the EMBL Outstation in Hamburg and was recruited from Aarhus University to NCMM in October 2010. His research is in the area of structure and function of membrane transporters. Morth has also started a new program on pH regulation and structure function studies on bicarbonate transporters. His research has relevance to cardiology, neurobiology and kidney diseases. Morth's appointment as group leader was evaluated in 2015 and his position was renewed for a second five-year period (2015-2019).

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

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

Dr. **Anthony Mathelier** is a computer scientist by background who did his PhD at the Pierre and Marie Curie University, Paris. Mathelier was recruited from the University of British Columbia, Vancouver, Canada and will join NCMM from May 2016. He aims at developing cutting-edge bioinformatics tools with immediate application to real-life biological problems and his research group will focus on gene expression regulation and the mechanisms by which it can be disrupted in human diseases such as cancer.

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



Kjetil Taskén

Signaling networks in health and disease

One main focus is to understand why the immune system sometimes turns off its ability to recognize and kill cells in an expanding malignant tumour. We aim to understand how tumours develop immune evasion strategies, what mechanisms operate in different cancers and how we can perturb such immune-inhibitory signals to boost anti-tumour immunity and assist other cancer immunotherapies.

We are starting work with cancer drug sensitivity screening on patient samples looking for efficacious compounds and drug synergies on an individual basis, ultimately aiming to assist clinical decisions in precision oncology and hematology. Other activities focus on the role of the cAMP second messenger system and other signal networks in the regulation of cellular function and its involvement in disease mechanisms in inflammation as well as in infectious, metabolic and cardiovascular diseases.

Description of the Group's Research

The group aims to understand complex intracellular signaling networks and how such networks require anchoring and localization through A kinase anchoring proteins (AKAPs) or other scaffold proteins. The group investigates how these signaling networks mediate hormonally regulated physiological and pathophysiological processes. In the immune system we investigate cAMP- and regulatory T cell-mediated immune-modulation with application in immune diseases, inflammation and tumor immunology. In pursuit

of this understanding the group maps signaling pathways, identifies targets, develops tools to perturb signaling (peptidomimetics, small molecular compounds) and provides “proof-of-principle” experiments using specific disease models.

The Taskén group employs a breadth of techniques in bioinformatics, proteomics, phospho-flow analysis, chemical biology high-throughput screening assays and genetic tools in order to screen new targets for *in vitro* and *in vivo* function. In order to isolate signalling complexes from a variety of targets, including T cells, cardiomyocytes, adipocytes and organelles such as lipid droplets and mitochondria, a chemical genomics approach is used in combination with phospho-proteomics to understand spatiotemporal dynamics of phosphorylation in anchored signaling complexes. Chemical biology screenings identify small molecular compounds for our research. Furthermore, phospho-flow cytometry using fluorescent cell barcoding allows mapping of complex signal networks, assessing how inhibitory signals feed in and examining how small molecules perturb such signal networks. Our recent technology developments now also allow flow-based signalling analyses of adherent cells and high-throughput chemical biology screening by flow cytometry.

The group studies cAMP immunomodulation and involvement of regulatory T cells in HIV, mouse AIDS and various cancers where tumour immunology is of significance. Projects

include studies of regulatory T cells and anti-tumour immune responses in colorectal cancer, pancreatic cancer, cholangiocarcinoma and ovarian carcinoma. In addition, cancer and immune cell signalling analyses are being performed by phospho-flow cytometry to find bio signatures. A recent interest is now to rig drug sensitivity screens to explore the possibility to assist treatment choices in individualized cancer therapy, particularly looking at haematological malignancies. Furthermore, systems biology analyses are applied on the phospho-flow data from single cell signalling as well as from mixed cell populations with Treg immunosuppression.

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

Achievements in 2015

We have studied signalling in immune cells, particularly how regulatory and effector T cell signalling is reciprocally affected during suppression and in collaborative papers how adaptive NK cell signalling involves CD2. Furthermore, we have examined how regulation of platelet functions depend on anchored cAMP signalling pathways.

- Chelappa, S., Lieske, N.V., Hagness, M., Line, P.D., [Taskén, K.](#),[#]Aandahl, E.M.[#] (2016) Activation status of human regulatory T cells controls TCR signaling and susceptibility to suppression in CD4⁺ T cells. *J. Leukocyte Biol.*, in press in “Leading Edge Research” section. ([#]corresponding authors)
- Liu, L., Landskron, J., Ask, E.H., Enqvist, M., Sohlberg, M., Traherne, J., Hammer, Q., Goodridge, J., Larsson, S., Jayaraman, Oei, V.Y.S., Schaffer, M., [Taskén, K.](#), Ljunggren, H.-G., Romagnani, C., Trowsdale, J., Malmberg, K.-J., Béziat, V. (2016) Critical role of CD2 co-stimulation in adaptive NK cell responses revealed in NKG2C-deficient humans. *Cell Reports*, 15: 1–12, May 10, 2016.

- Raslan, Z., Magwenzi, S., Aburima, A., [Taskén, K.](#), Naseem, K.M. (2015) Targeting of Type I Protein Kinase A to lipid rafts is required for platelet inhibition by the cAMP-signaling pathway. *J. Tromb. Haemostasis*, 13:1721–34.
- Landskron, J., [Taskén, K.](#) (2016) Phosphoprotein detection by high-throughput flow cytometry. *Methods in Molecular Biology*, 1355: 275–90.

We have looked at the role of regulatory T cells in tuberculosis and HIV, their activation status as evident from FoxP3 staining and levels of CD147 and the effect of perturbing regulatory T cell activation by MEK inhibitors in collaboration with the Department of Infectious Diseases, Oslo University Hospital (OUH).

- Lieske, N.V., Tonby, K., Kvale, D., Dyrhol-Riise, A.M., [Taskén, K.](#) (2015) Targeting disease-specific regulatory T cells in chronic infectious diseases with MEK/ERK signaling pathway inhibitors. *PLoS One*, 10: e0141903, pp 1–19.
- Stiksrud, B., Lørvik, K.B., Kvale, D., Mollnes, T.E., Ueland, P.M., Trøseid, M., [Taskén, K.](#), Dyrhol-Riise, A.M. Plasma Interferon-inducible Protein10 Levels, T-cell Activation and Regulation are Increased in HIV Immunological Non-Responders. *J. AIDS* in press,

We have characterized regulatory T cells in various cancer types and assessed their involvement in tumor immune evasion.

- Landskron, J., Helland, Ø., Torgersen, K.M., Aandahl, E.M., Gjertsen, B.T. Bjørge, L., [Taskén, K.](#) (2015) Activated regulatory and memory T-cells accumulate in malignant ascites from ovarian carcinoma patients. *Cancer Immunol. Immunother.*, 64: 337–47.
- Santegoets, S.J.A.M., Dijkgraaf, E.M., Battaglia, A., Beckhove, P., Britten, C.M., Gallimore, A., Gouttefangeas, C., de Gruijl, T.D., Koenen, H.J.P.M., Scheffold, A., Shevach, E.M., Staats, J., [Taskén, K.](#), Whiteside, T.L., Kroep, J.R., Welters, M.J.P., van der Burg, S.H. (2015) Monitoring regulatory T cells in clinical samples: consensus on an essential marker set and gating strategy for regulatory T cell analysis by flow cytometry. *Cancer Immunol. Immunother.*, 64:1271–86.
- Chelappa, S., Hugenschmidt, H., Hagness, M.,

“The group aims to understand complex intracellular signaling networks”

Line, P.D., Labori, K.J., Wiedsvang, G., [Taskén, K.](#), Aandahl, E.M. Regulatory T cells that co-express RORγt and FOXP3 are pro-inflammatory and immunosuppressive and expand in human pancreatic cancer. *Oncoimmunol.* In press.

- Chelappa, S., Hugenschmidt, H., Hagness, M., Line, P.D., Labori, K.J., Wiedsvang, G., [Taskén, K.](#), Aandahl, E.M. CD8⁺ T cells that co-express RORγt⁺ and T-bet are functionally impaired and expand in patients with distal bile duct cancer. Resubmitted.
- Chelappa, S., Aandahl, E.M., [Taskén, K.](#) Cancer immunity and immune evasion mechanisms. In Biomarkers of the Tumor Microenvironment: Basic Studies and Practical Applications (Eds. Lars A. Akslen and Randolph S. Watnic, Springer). Accepted for publication.

We earlier demonstrated that regulatory T cells and prostaglandin E₂ (PGE₂) suppresses anti-tumour immune responses in colorectal cancer (Yaqub et al. Cancer Immunol. Immunother. 2008; Brudvik et al., . Cancer Immunol. Immunother. 2012). These observations add to reports that PGE₂ stimulates tumor growth and angiogenesis in colorectal cancer. While COX inhibitors and acetylsalicylic acid may be beneficial to prevent primary colorectal cancer, our findings on the inhibitory effect of PGE₂ on anti-tumor immunity led us to hypothesize that secondary prevention with acetylsalicylic acid may give even further benefit. This appears to hold true in a registry study with data on more than 23,000 patients from the Cancer Registry of Norway coupled with data from the Norwegian Prescription Database. We now plan a clinical intervention trial to assess this finding in a randomized and placebo-controlled setting.

- Bains, S.J., Mahic, M., Myklebust, T.Å., Småstuen, M.C., Yaqub, S., Dørum, L.M., Bjørnbeth, B.A., Møller, B., Brudvik, K.W., [Taskén, K.](#) Aspirin as Secondary Prevention in Patients with Colorectal Cancer - An Unselected Population-Based Study. *J. Clin Oncol.*, in press.

A first report from our cancer drug sensitivity screening approaches in chronic lymphatic leukemia using phospho-flow cytometry to assess effect of targeted therapy drugs is also now out:

- Parente-Ribes, A.^{*}, Skånland, S.S.^{*}, Bürgler, S.^{*}, Os, A., Wang, D., Bogen, B., Tjønnfjord, G.E., [Taskén, K.](#)^{*,#}, Munthe, L.A.^{*,#} Spleen tyrosine kinase inhibitors block CD40L induced proliferation of chronic lymphocytic leukemia cells. *Hematologica*, in press (^{*}=equal contributions, [#]corresponding authors).

Current research also includes examination of cAMP and beta-adrenergic signalling in the heart and in adipocytes with relevance to cardiovascular and metabolic diseases, including studies of an AKAP18 signal complex regulating Ca²⁺ re-uptake in sarcoplasmic reticulum and contractility (Calejo, Østensen). Ongoing work includes chemical biology high-throughput screening, subsequent characterization of hits as well as proof-of-concept studies in animals in vivo both in normal physiology and in ischemia-reperfusion injury. Another ongoing project investigates the function of Opa1 in regulating cAMP signalling in lipid droplets and mitochondria (Rogne, Mylonaku, Dinescu, Chu).

- Calejo, A.I., [Taskén, K.](#) (2015) Targeting protein-protein interactions in complexes organized by A kinase anchoring proteins. *Front. Pharmacol.*, 6:192, pp1–13.

External funding (brief)

In addition to support from NCMM and the Biotechnology Centre of Oslo, the Taskén group has in 2015 had funding from a variety of sources including the Research Council of Norway (FRIPRO, Biotek2021), the Norwegian Cancer Society, Health South-East Regional Health Authority, the EU 7th Framework and ESFRI programmes, Nordforsk, Novo Nordic Foundation as well as from the K.G. Jebsen Foundation that is funding two translational research Centres with Taskén as partner, The K.G. Jebsen Inflammation Research Centre and K.G. Jebsen Centre for Immunotherapy.

Group members

Group members (during 2015 and first quarter of 2016):

Research Scientists:

Einar Martin Aandahl
Johannes Landskron
Sigrid S. Skånland

Postdoctoral fellows:

Ana Isabel Costa Calejo
Dinh-Toi Chu (from Oct. 2015)
Sorina Dinescu (from Jan to May and August to Dec 2015)
Lena Eroukhmanoff (until May 2015)
Morten Hagness (until Sept 2015)
Guro Mørk Johnsen (until March 2015)
Anna Mari Lone
Kristina Berg Lørvik
Maria-Niki Mylanokou (until May 2016)
Deepak Balaji Thimiri Govinda Raj
Vanessa L. Wehbi

PhD Fellows:

Simer Jit Bains (until April 2015)
Aleksandra Đukić
Stalin C. Gunasekaran
Nora V. Lieske (until August 2015)
Kristine Moltu (until August 2015)
Ellen Østensen

MSc students:

Ida Kristin Myhrvold (until May 2016)
Marthe Jøntvedt Jørgensen (from January 2016)

Administrative Officer:

Berit Barkley

Scientific Officers:

Marianne Enger (from February 2016)
Jorun Solheim (until April 2016)
Martine Schrøder (from February 2016)
Gladys Tjørhom

Chemical Biology Platform:

Anne Jorunn Stokka, head
Paul R. Berg (from February 2016)
Eirin Solberg (from January 2016)
David W. McClymont (Until Nov 2015)

Collaborations

We collaborate with more than 20 **international partners**, in 2015 most actively with the groups of Professor John D. Scott, University of Washington, Seattle; Professor Albert Heck, The Netherlands Proteomics Centre, Utrecht; Group leader Klaus Okkenhaug, Babraham Institute, Cambridge, UK; Dr. Guillaume Pidoux, Université Paris Süd; Professor Bodo Grimbacher, Freiburg University; and Dr. Krister Wennerberg, FIMM, Helsinki, Finland.

Nationally the group has in 2015 collaborates with Group Leaders Judith Staerk, J. Preben, Morth and Camila Esguerra Biotechnology Centre / NCMM and Professors Philippe Collas, Jo Klaveness, Arnaldo Frigessi, Bernd Thiede, University of Oslo; Professors Dag Kvale and Anne Ma Dyrhol-Riise, Dept. of Infectious Diseases, Senior Consultants Bjørn Atle Bjørnbeth and Sheraz Yaqub, Gastrosurgical Dept., Professor Ivar Sjaastad, Institute of Experimental Medical Research, Professor Guttorm Haraldsen, Dept. of Pathology, Professor Ludvig Munthe, Institute of Immunology, Professor Geir E. Tjønnfjord Dept. of Hematology Professor Pål Aukrust Dr. Arne Yndestad, Professor Bente Halvorsen and Professor Tom Hemming Karlsen; Inst. of Internal Medicine Research, Professors Johanna Olweus and Professor Kalle Malmberg, Dept of Immunology, Inst. for Cancer Res., Dr. Jorrit Enserink, Dept. of Microbiology and Professor Annetine Staff, Dept Ob-Gyn, Oslo University Hospital; Professor James B. Lorens, University of Bergen, Professors Bjørn Tore Gjertsen, Helga Salvesen and Senior Consultant Line Bjørge, Haukeland University Hospital, Bergen; Professor Anders Sundan, NTNU and Senior Researcher Geir Klinkenberg, SINTEF.

“One main focus is to understand why the immune system sometimes turns off its ability to recognize and kill cells in an expanding malignant tumour”



Ian G. Mills



Prostate Cancer Research Group

Prostate cancer is a high-incidence cancer in men with progression to metastatic disease occurring in around 20-30% of detected cases. Major translational challenges include the development of biomarkers able to predict progression at the time of diagnosis and treatment response/failure as well the need to develop more effective treatment strategies. Our strategy for addressing this has been to explore how transcription factors and chromatin change in transformed cells and how the gene networks that they regulate map back to clinical expression profiles. From the resultant gene networks and pathway enrichments we have identified biological processes that we believe are important to regulate progression and treatment response and have gone on to study these functionally and, with clinical collaborators, to evaluate candidate biomarkers. From this work the main biological focus of the group is on stress response signalling sub-divided broadly into glycosylation and the unfolded protein response/autophagy. In particular, we are focussing on how genes that function in these processes confer resistance to therapeutic and oncogenic stress and how they can be targeted therapeutically.

Description of the Group's Research

1. *Chromatin biology and transcriptional regulation:* Predominantly we employ high-throughput sequencing and transcript profiling to map genome-wide changes in transcription factor recruitment and chromatin compaction in cell-lines and clinical samples. Using these approaches we have found that chromatin opening is a hallmark

of lethal castrate-resistant disease and that the activity of a key transcription factor in prostate cancer, the androgen receptor (AR), is modified by the expression of other oncogenic transcription factors with a focus here principally on c-Myc. Additionally, we have found that regions of open chromatin are hotspots for prostate cancer risk loci.

2. *Autophagy:* Autophagy ('self-eating') is a key stress response that can have pro-survival or pro-apoptotic properties in cancer cells depending on the context and trigger. Whilst this has been recognised by groups worldwide, the desire to achieve clinical translational endpoints through the study of autophagy has led to the over-interpretation of assays and autophagic markers. A key contribution that we are making in this area is to carefully dissect whether autophagic markers are also necessary to drive the functional biology of the autophagic process. We are addressing this by developing and qualifying autophagic assays and then testing the impact of genetic targeting of autophagic factors. With that knowledge in place the program will then move on to explore how these factors affect response to treatments such as anti-androgens.
3. *Glycosylation:* Glycosylation is a bridge between metabolic changes, protein folding capacity and in turn the stability and activity of oncogenes. We realised the potential importance of glycosylation early in the development of our research program based

on clinical profiling and mapping of target genes for the androgen receptor and other transcription factors. In particular, we have been exploring how a pathway called the hexosamine biosynthesis pathway affects the stability of c-Myc and other oncogenes and the response to activators of the unfolded protein response. This pathway is fuelled by metabolites drawn from all of the core metabolic processes in the cell to form a single amino-sugar-nucleotide conjugate – UDP-GlcNAc. Whilst heightened activity of this pathway is required to sustain protein folding in untransformed secretory cells, the same pathway can also confer resistance to environmental stress and consequently the expression and activity of enzymes in the pathway and fuelled by the pathway are retained and amplified in cancer cells.

4. **Biomarkers:** Since prostate cancer progresses in a subset of diagnosed cases to a lethal metastatic disease and the current biomarker, prostate specific-antigen (PSA), is relatively ubiquitous, there is a significant need for biomarkers that flag heightened risk of disease progression. We are evaluating transcripts and proteins as candidate biomarkers focussing predominantly on ‘liquid biopsy’ (urine, blood and circulating tumour cells). Amongst these sample types we have so far made most progress in evaluating markers in blood samples. Since it typically takes 5-10 years from diagnosis to disease progression, blood samples represent a sample type that currently has the longest follow-up time having been biobanked. By contrast urine sample collections are still relatively recent and there remains controversy over the best detection platform for circulating tumour cells. The biomarkers that we have been testing have arisen from three sources. Transcript biomarkers have either been derived from our pre-clinical studies or through collaboration with international research consortia. Protein biomarkers have arisen from proteomic profiling of Janus Serum Bank samples and downstream validation in samples obtained from other Nordic and UK sample collections through collaboration.

Achievements in 2015

Chromatin biology and transcriptional regulation
This work has been driven forward by Alfonso Urbanucci and Stefan Barfeld.

- PhD defense – Stefan Barfeld – ‘The transcriptional role of c-Myc in prostate cancer’

- Myc drives the expression of enzymes in the *de novo* purine biosynthesis pathway and inhibitors of this pathway disassemble nucleoli and enhance response to anti-androgens. This study identified genes that were Myc-dependent, overexpressed in prostate cancer, required to maintain stress resistance and encoding enzymes that are drugable by repurposing clinical approved drugs. Enzymes in the *de novo* purine biosynthesis fulfil these criteria and the study creates the potential for further pre-clinical and clinical evaluation of drugs targeting this pathway to improve response to next-generation anti-androgens.

Barfeld SJ, Fazli L, Persson M, Marijavaara L, Urbanucci A, Kaukonen KM, Rennie PS, Ceder Y, Chabes A, Visakorpi T, **Mills IG** (2015) Myc-dependent purine biosynthesis affects nucleolar stress and therapy response in prostate cancer. *Oncotarget* 6: 12587-602

Other collaborations:

- Divergent androgen regulation of unfolded protein response pathways drives prostate cancer. This study defined the IRE1-XBP1 arm of the unfolded protein response as an AR-driven arm required to support tumorigenesis as well as indicating that the PERK-ATF4 arm is antagonised.

Sheng X, Arnoldussen YJ, Storm M, Tesikova M, Nenseth HZ, Zhao S, Fazli L, Rennie P, Risberg B, Waehre H, Danielsen H, **Mills IG**, Jin Y, Hotamisligil G, Saatcioglu F (2015) Divergent androgen regulation of unfolded protein response pathways drives prostate cancer. *EMBO Mol Med* 7: 788-801

- The androgen receptor controls expression of the cancer-associated sTn antigen and cell adhesion through induction of ST6GalNAc1 in prostate cancer. This study identified an enzyme required for sialylation as an AR-dependent and regulating cell adhesion in prostate cancer.

Munkley J, Oltean S, Vodak D, Wilson BT, Livermore KE, Zhou Y, Star E, Floros VI, Johannessen B, Knight B, McCullagh P, McGrath J, Crundwell M, Skotheim RI, Robson CN, Leung HY, Harries LW, Rajan P, **Mills IG**, Elliott DJ (2015) The androgen receptor controls expression of the cancer-associated sTn antigen and cell adhesion through induction of ST6GalNAc1 in prostate cancer. *Oncotarget* 6: 34358-74

- Slug-dependent upregulation of L1CAM is responsible for the increased invasion po-

tential of pancreatic cancer cells following long-term 5-FU treatment. This study identified L1CAM as a mediator of a pro-metastatic biology in 5-fluorouracil resistant pancreatic cancer cells. We identified the target from transcription profiles.

Lund K, Dembinski JL, Solberg N, Urbanucci A, **Mills IG**, Krauss S (2015) Slug-dependent upregulation of L1CAM is responsible for the increased invasion potential of pancreatic cancer cells following long-term 5-FU treatment. *PLoS One* 10: e0123684

Autophagy

The Autophagy team led by Dr. Nikolai Engedal (Senior Scientist) and Professor Per Seglen (Guest researcher) has continued to make significant progress in dissecting the contribution of LC3 and GABARAPs to autophagy and the relationship between cargo sequestration and fusion of autophagic structures with the lysosome. Some highlights in 2015 have included:

- Evidence that bulk autophagic sequestration does not require LC3 but is dependent on GABARAPs.

Szalai P, Hagen LK, Saetre F, Luhr M, Sponheim M, Overbye A, Mills IG, Seglen PO, and Engedal N. Autophagic bulk sequestration of cytosolic cargo is independent of LC3, but requires GABARAPs. *Exp Cell Res.* 2015;333(1):21-38.

- Further refinements of functional assays for autophagic cargo sequestration to enable their adoption across the research community.

Seglen PO, Luhr M, Mills IG, Saetre F, Szalai P, and Engedal N. Macroautophagic cargo sequestration assays. *Methods.* 2015;75(25-36.

Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A, Adachi H, Adams CM, Adams PD, Adeli K, et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy.* 2016;12(1):1-222.

Glycosylation

This theme has been driven forward by Harri Itkonen.

- UDP-N-acetylglucosamine pyrophosphorylase 1 (UAP1), an enzyme in the hexosamine biosynthesis pathway, inhibits apoptotic responses to drugs that induce protein folding stress. We have previously reported that the hexosamine biosynthesis pathway is an effector for metabolic feedback on oncogenic stability and signalling in prostate cancer and is AR-dependent. Here we show that one enzyme in this pathway modifies the response of prostate cancer cells to drugs that impose folding stress on cells.

Itkonen HM, Engedal N, Babaie E, Luhr M, Guldvik IJ, Minner S, Hohloch J, Tsourlakis MC, Schlomm T, **Mills IG** (2015) UAP1 is overexpressed in prostate cancer and is protective against inhibitors of N-linked glycosylation. *Oncogene* 34: 3744-50

- Targeting OGlcNAc transferase (OGT) creates an opportunity for repurposing clinically approved metabolic inhibitors. A key finding was the targeting OGT, an enzyme we have previously found to be important for the stability and activity of oncogenic transcription factors, enhances the cytotoxic response to mitochondrial inhibitors and to inhibitors of alanine metabolism.

Itkonen HM, Gorad SS, Duveau DY, Martin SE, Barkovskaya A, Bathen TF, Moestue SA, and **Mills IG**. Inhibition of O-GlcNAc transferase activity reprograms prostate cancer cell metabolism. *Oncotarget* 2016 [Epub ahead of print]. doi: 10.18632/oncotarget.7039

Biomarkers and genetic risk factors

This theme has been driven forward by Ingrid Guldvik and Verena Zuber. The predominant focus here has been on further identification and validation of candidate prognostic and predictive prostate cancer biomarkers. Protein-based biomarkers in blood have reached the PCT filing stage (patent) – ‘PROSTATE CANCER MARKERS

RESEARCH GROUPS IAN G. MILLS

AND USES THEREOF' - PCT/US16/12194.

In collaboration with Professor Ole Andreassen (Oslo University Hospitals) and Professor Tere Landi (National Cancer Institutes) we have identified a new genetic cancer risk locus for lung cancer by undertaking a pleiotropy analysis versus blood lipid traits.

Pleiotropic analysis of lung cancer and blood triglycerides identifies a shared genetic locus – Zuber et al., In revision

Other genetic pleiotropy paper in 2015: Andreassen OA, Desikan RS, Wang Y, Thompson WK, Schork AJ, Zuber V, Doncheva NT, Ellinghaus E, Albrecht M, Mattingdal M, et al. Abundant genetic overlap between blood lipids and immune-mediated diseases indicates shared molecular genetic mechanisms. PLoS One. 2015;10(4):e0123057.

External Funding

RCN (Young Talent Grant to Nikolai Engedal)
The Norwegian Cancer Society (Per Seglen)
The Nansen Foundation (Nikolai Engedal)
Lundbeck Foundation PhD Fellowship (Nikolai Engedal in collaboration with Poul Nissen, Aarhus University)
Norwegian Cancer Society/Movember Team Science Award (Mills)
Helse SørØst postdoc grant (Mills)
Norwegian Cancer Society postdoc grant and running costs (Mills)
Helse SørØst and University Oslo Innovation Awards (Mills)
RCN FRIMEDBIO Program Grant (Mills)
RCN FORNY Innovation Award (Inven2/Mills)

Group Members

Nikolai Engedal – Senior Scientist
Professor Per Seglen – Guest Researcher
Ingrid Guldvik – Head Engineer
Frank Saetre – Principal Engineer
Harri Itkonen – Postdoc
Alfonso Urbanucci – Postdoc
Lisa Gerner – PhD Student
Paula Szalai – PhD Student (supervisor: Nikolai Engedal). Successfully defended her Masters' thesis in summer 2015.
Morten Luhr – PhD Student (supervisor: Nikolai Engedal)
Stefan Barfeld – PhD student. Thesis defended successfully autumn 2015
Verena Zuber – Began a new postdoc position at EMBL EBI June 2015

Collaborations

Dr. Wolfgang Lilleby (Oslo University Hospitals) – biomarkers/Ultimovacs clinical trial

Professors Fredrik Wiklund and Henrik Gronberg (Karolinska Institute) – blood-based biomarkers

Professor Fahri Saatcioglu (University of Oslo) – Unfolded protein response and blood-based biomarkers

Dr. Bernd Thiede (University of Oslo) – clinical proteomics

Professor David Neal (Universities of Oxford and Cambridge) – blood-based biomarkers

Professor Suzanne Walker (Harvard Medical School) – OGlcNac transferase inhibitors

Professor Thorsten Schlomm and Dr. Sarah Minner (Hamburg University Medical School/Eppendorff Hospital) – urine and tissue-based biomarkers

Professor Kristin Tasken (Oslo University Hospitals) and the Norwegian Biomarker Consortium – prostate cancer biomarkers

Professor Tere Landi (National Cancer Institutes) – Lung cancer genetic risk factors PRAC-TICAL and ELLIPSE Consortia (UK and global) – Prostate cancer genetic risk factors

Professor Ole Andreassen (NCMM Associate Investigator/Oslo University Hospitals) – pleiotropy and cancer risk loci

Jon Bendik-Thue (MyHere) – development of an app-based risk assessment tool for prostate cancer.

Professor Matthias Wilmanns (EMBL Hamburg) – CAMKK2

Dr. Preben Morth (NCMM) – CAMKK2

Dr. Judith Staerk (NCMM) – chromatin alterations in the haematopoietic lineage

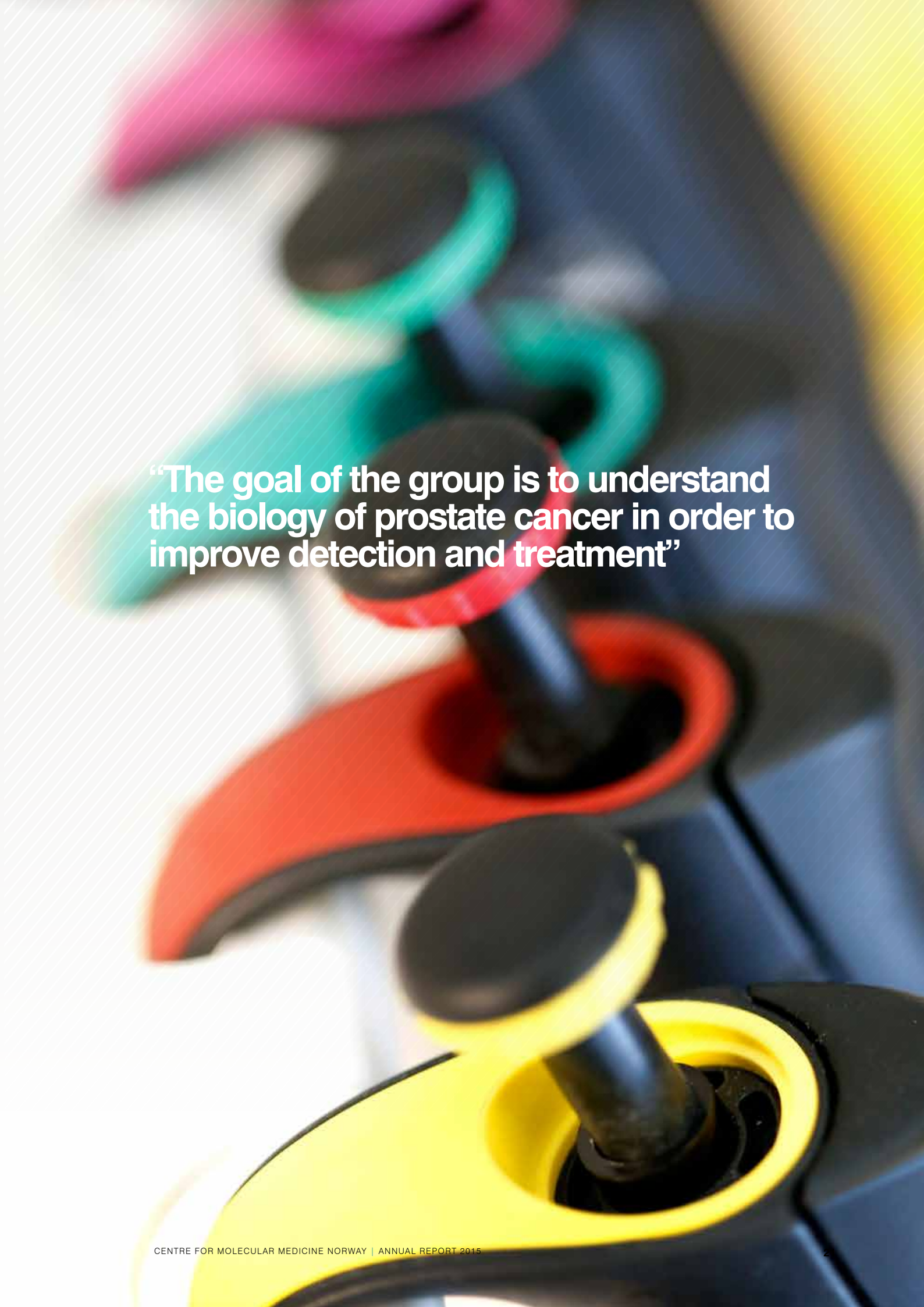
Dr. Toni Hurtado (NCMM) – chromatin looping and alterations in breast and prostate cancers.

Professor Ole Petter Rekvig (NCMM Associate Investigator/University of Tromsø) – lupus genes as cancer biomarkers and drivers

Professor Poul Nissen (Director of DANDRITE and Professor at Aarhus University) – collaboration with Dr. Nikolai Engedal on the SERCA pump and autophagy

Professor Angelo DeMarzo and Professor Srinivasan Yegnasubramanian (Johns Hopkins Medical University) – Myc-dependent biomarkers and gene networks

And many, many others who have contributed in so many ways to the research programs and of course the group itself.



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



Preben Morth



Membrane Transport Group

The Morth group employs a structural systems biology approach to investigate the proteins involved in acid-base homeostasis and metal ion transport across the cellular membrane. A variety of techniques are used in order to identify and characterize both soluble and membrane bound proteins involved in pH regulation. A bioinformatics approach is used to target new proteins and interaction partners of interest. Furthermore, X-ray crystallography and several biophysical methods to obtain structural information as well as biochemical techniques are also used, including activity assays and fluorescence spectroscopic measurements.

Description of the Group's Research

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

The bicarbonate transporters

Acid-base homeostasis is fundamental to our understanding of human physiology and is essential to cellular function. The main buffering system found in the human body is based on bicarbonate. The SLC4 proteins are the main facilitators of bicarbonate transport across the plasma membrane, however, not much is known about the structural basis of function and regulation of these. The N-terminal cytoplasmic domain (NTD) of the sodium-coupled chloride bicarbonate exchanger (NCBE), found predominantly in the choroid plexus of the brain, has been cloned, expressed and purified.

The core domain found centrally in the NTD has been crystallized and the structure determined at 4.0 Å resolution. The NTD of NCBE is found to contain regions of intrinsic protein disorder and these disordered regions are conserved among all bicarbonate transporters of the SLC4 family. The disordered regions coincide with regions of sequence variation, indicating that although sequence is not conserved, the disorder is.

P-type ATPases in infectious diseases

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

Characterization of supramolecular Tankyrase complexes implicated in colorectal cancer, using an intrinsically disordered protein as bait
A translational project focusing on identification

RESEARCH GROUPS PREBEN MORTH

of large supramolecular complexes implicated in the Wnt pathway was initiated by the Morth group. We are performing structural studies of a human ADP-ribosyltransferase tankyrase (TNKS), trying to identify novel direct interaction partners by using a proteomics approach in collaboration with Bernd Thiede (UiO). Tankyrases belong to the poly (ADP-ribose) polymerase (PARP) superfamily and are involved in various cellular functions such as telomere maintenance, centrosome maturation, Wnt signaling, embryonic development and the pathogenesis of Cherubism. We are currently aiming to isolate and characterize proteins that bind to the full length tankyrase enzyme, a protein of more than 1200 residues and with several potential and verified interaction partners. We are therefore combining our structural and biochemical studies with cellular assays, using the strong imaging platforms built up by Oddmund Bakke (UiO).

Achievements in 2015

The magnesium transporter A: a bacterial P-type ATPase dependent on cardiolipin and selectively sensitive to free magnesium in vitro.

This study demonstrates, for the first time, that MgtA is highly dependent on anionic phospholipids and in particular, cardiolipin. The *in vitro* kinetic experiments performed on detergent solubilized MgtA suggest that cardiolipin acts as a magnesium chaperone. We further showed that MgtA is highly sensitive to free Mg^{2+} (Mg^{2+}_{free}) levels in the solution. MgtA is activated when the Mg^{2+}_{free} concentration is reduced below 10 fM and is strongly inhibited above 1 mM, indicating that Mg^{2+}_{free} acts as product inhibitor. Furthermore, co-localization studies confirmed that MgtA is found in the cardiolipin lipid rafts in the membrane. Combined, our findings indicate that MgtA may act as a sensor as well as a transporter of Mg^{2+} (1).

1. Subramani, S., Perdreau-Dahl, H. and Morth, J.P. (2016) The magnesium transporter A is activated by cardiolipin and is highly sensitive to free magnesium in vitro. *Elife*. **5**, 10.7554/eLife.11407

Targeting stress: development of a novel assay based on structural analysis of the manganese dependent enzyme isatin hydrolase.

The product state, mimicked by bound thioisatinate, reveals a water molecule that bridges the thioisatinate to a proton wire in an adjacent water channel and thus allows the proton released by the reaction to escape only when the product is formed. The functional proton wire present in IH-b represents a unique

catalytic feature common to all hydrolases and is here trapped and visualized for the first time (2). Biophysical and structural interpretation of the IHB structure lead to a detection and quantification assay of Isatin in blood based on the recombinant enzyme (3).

2. Bjerregaard-Andersen, K., Sommer, T., Jensen, J.K., Jochimsen, B., Etzerodt, M. and Morth, J.P. (2014) A proton wire and water channel revealed in the crystal structure of isatin hydrolase. *J. Biol. Chem.* **289**, 21351-21359

3. Sommer, T., Bjerregaard-Andersen, K., Simensen, S.M., Jensen, J.K., Jochimsen, B., Riss, P.J., Etzerodt, M. and Morth, J.P. (2015) Enzymatic detection and quantification assay of isatin, a putative stress biomarker in blood. *ACS Chem. Neurosci.* **6**, 1353-1360

External Funding

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

Group members

Postdoctoral fellows:

Kaare Bjerregaard-Andersen (until August 2015)

Kim L. Hein (until August 2015)

Harmonie Perdreau Dahl

Johannes Bauer

PhD fellows:

Saranya Subramani

Theis Sommer

Master Students:

Carolina Alvadia

Stefanie Ruhland (from April 2016)

Principal engineer:

Steffi Munack (until December 2015)

Bojana Damjanovic (from February 2016)

Collaborations

Oddmund Bakke (UiO), Bernd Tiede (UiO), Jan K. Jensen (Aarhus University), Michael Etzerodt (Aarhus University), Ian Mills (NCAMM and Queens University Belfast)

“The group is linking acid-base homeostasis with metal ion transport across the membrane”



Antoni Hurtado



Breast Cancer Group

The main interest of my research is to understand the mechanism of hormone resistance in breast cancer. Breast cancer is a heterogeneous disease and gene expression profiling has classified the tumors into several intrinsic subtypes with distinct prognostic significance. Luminal subtypes are the most frequent (around 70%) and they express Estrogen Receptor alpha (ER). Estrogen-ER interaction induces a transcriptional program, which culminates in proliferation. Estrogen signaling exerts its growth-promoting effects by inducing ER binding to many chromatin sites, which leads to the altered expression of coding and non-coding RNAs. Treatment with anti-ER therapies inhibits its function, reduces tumor growth and improves survival. The anti-estrogen treatments are effective in clinical practice. However, a major clinical limitation is the development of resistance to these therapies and this is the main focus of our research.

Description of the Group's Research

Elucidating the role of cell-signaling pathways controlling FOXA1 functions in Breast Cancer
Previously, we published that FOXA1 expression was key in the response to Tamoxifen-ER (Hurtado, *Nat Genetics* 2011). Hence, a high expression of FOXA1 in primary tumors could predict a good prognosis of ER-positive breast cancer after adjuvant endocrine therapy. However, the expression of ER and FOXA1 is retained in the metastatic sites. We have demonstrated that HER2/HER3 controls the FOXA1-regulated transcriptional program responsible to trigger proliferation and metastases in breast cancer independently of ER (Katika et al, in submission). These results suggest

that FOXA1 mediates proliferation driven by selective cell-signaling pathways. This additional role independent of ER function would at least in part explain resistance to hormone therapy. To test this idea, we have initiated a study with different inhibitors targeting the RTKs Fibroblast Growth Factor Receptor (FGFR) or Janus kinase (JAK) in tamoxifen resistant breast cancer cell lines. JAK is a non-receptor tyrosine kinase that transduces cytokine-mediated signals via the JAK-STAT pathway. Our results show that the inhibition of FGFR or JAK also prevents FOXA1 chromatin interaction. Altogether, these results denote that multiple cell-signaling pathways might be required to control the functions of FOXA1 in hormone-resistant contexts.

We now aim to elucidate which cell-signaling pathways control FOXA1 and to test drugs targeting those pathways as potential inhibitors of tumor growth in hormone-resistant breast cancers. In collaboration with Dr. Anne Jorunn Stokka (responsible for the Chemical Biology Platform at the Biotechnology Center of Oslo) we will apply high-throughput screening to explore the ability of kinases or phosphates inhibitors to control FOXA1 binding in a systematic manner. Moreover, we aim to test how drugs inhibiting FOXA1 chromatin interaction influence tumor growth. In collaboration with Dr. Sørli and Dr. Mælandsmo at the Institute for Cancer Research (Radiumhospitalet, Oslo University Hospital) we will use an ER positive breast tumor model that has been successfully established by implantation of biopsy tissue from primary breast carcinomas in SCID mice. We have recently demonstrated that this model is positive for the expression of FOXA1 (Katika et al.). To validate whether

those inhibitors might be used as a therapeutic alternative for patients with poor response to anti-ER therapies, the most promising drugs will be also tested in animals treated with the anti-ER cancer drug Fulvestrant.

Understanding how Tamoxifen represses estrogen-mediated transcription
Tamoxifen action is thought to occur through its competition with estrogen to interact with ER, which inhibits the ability of the receptor to initiate transcription. However, it has been also described that tamoxifen shows agonistic activity (Frasor, Cancer Res 2006) or an incomplete inhibition of a subset of estrogen-regulated genes (Hurtado, Nat Genetics 2001) in breast cancer cell lines. Yet, the precise mechanism by which tamoxifen executes transcriptional repression or partial induction is still unknown. Previously, we reported that Tamoxifen requires PAX2 to repress the transcription of the oncogene *ErbB2* (Hurtado, Nature 2008). Data of our group point at SNAIL and PAX2 as critical cooperating regulators of transcriptional repression coordinated by Tamoxifen. Interestingly, the interaction of these cooperating transcription factors does not seem to be random. Instead, we have identified that promoter regions of a subset of estrogen-regulated genes (~18%) are enriched with SNAIL in breast cancer cells treated with tamoxifen. We believe that the presence of those cooperating factors might be necessary for tamoxifen repressive action, whereas the absence of those factors might explain the agonistic activity of tamoxifen. All together, we propose that these cooperating factors might be functioning as general ER-associated transcriptional regulators for anti-ER drugs and more importantly, their interaction with ER might dictate tamoxifen outcome. Because fewer than 10% of hormone receptor-positive breast cancers are HER2 positive, the mechanism(s) underlying endocrine resistance remain to be elucidated for the majority of ER-positive breast cancers. We believe that the deregulation of the ER cooperative factors PAX2 and SNAIL might explain the hormone-resistance in ER+/HER2-breast tumors.

Searching for novel mechanisms of action for the anti-ER drugs Fulvestrant and Tamoxifen
The initial understanding of the mechanism of action of anti-ER is based on the idea that those compounds interact exclusively with ER. However, the more we understand about the molecular mechanisms of even targeted drugs, the more we realize that they are generally promiscuous with regard to their biological targets and effects. The simplified view of ‘one drug, one target’ clearly does not hold true. Hitting multiple targets can enable a drug to be applied therapeutically in several potentially unrelated diseases; or, if more than one of the drug’s targets are involved in pathways relevant to a particular disease, the drug may have increased efficacy for this therapeutic application. For instance, the anti-ER drugs Tamoxifen and Fulvestrant also target other proteins than ER. It seems that those drugs increase Bcl-2 levels and inhibit the growth of breast carcinoma cells by modulating PI3K/AKT, ERK and IGF-1R pathways (Long, S et al. JBC, 2006). These results are supported by the fact that a significant number of ER negative patients are responsive to Tamoxifen (Li-Heng Yang, J of Breast Cancer, 2012). Hence, one might think that hormone-resistance might also occur via mechanisms independent of ER.

We propose a multitiered systems-level approach to understand the effect of anti-ER drugs on breast cancer inhibition. We aim to define direct targets of Fulvestrant or Tamoxifen by applying breast cancer cell line protein extracts to Tamoxifen or Fulvestrant affinity matrices and identified binding interactions using LC-MS/MS. This approach has the advantages of examining the entire proteome expressed in the disease-relevant profile (Rix, U. Nat. Chem. Biol. 2009). We believe that with this approach we will be able to surmount the complex action of anti-ER drugs in a hormone-resistant breast cancer context. Moreover, we believe this translational strategy could define a set of Tamoxifen and Fulvestrant interacting proteins, which could be considered as novel targets in breast cancer treatment. Identifying protein mediators of Tamoxifen and Fulvestrant anti-proliferative

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

actions provides an excellent opportunity to understand the mechanism of action of these drugs and therefore has important clinical implications.

Achievements in 2015

- Paper submitted to Nucleic Acids Research (NAR): the work performed by Elisa Fiorito and Yogita Sharma has been very well received by the journal Nucleic Acid Research. Currently, the work is ready for re-submission.
- Best poster prize at the Summer Spetzes School for Nuclear Receptors: Elisa Fiorito was awarded at this FEBS workshop with her CTCF work.
- Selected abstract for EMBO Nuclear Receptor meeting: CTCF work submitted to the journal Nucleic Acids Research was selected for a talk at this meeting.
- Scientia Fellowship award: Sachin Sign has been awarded this fellowship.
- The group was awarded with two new grants: FrimedbIO Young Talent Grant from the Research Council of Norway as well as an Open Project grant from Helse SørØst.

External Funding

The Norwegian Cancer Society (Principal Investigator)
Helse Sør-Øst (Principal Investigator together with Dr. Therese Sørli)
UiO grant (Principal Investigator)
Research Council of Norway, FrimedbIO Young Talent Grant (Principal Investigator)

Group members

Siv Gilfillan - Head of Engineer
Venkata Sateesh - Postdoc.
Sachin Singh - Postdoc.
Elisa Fiorito - PhD student
Shixiong Wang - PhD student
Torbjørn Amundsen Lien - Master student
Signe Helene Kaarstad - Assistant

Three new postdocs will join the group within 2016

Collaborations

Dr. Therese Sørli and Professor Anne-Lise Børresen-Dale (Oslo University Hospital, Oslo, Norway) – Crosstalk between FOXA1 and HER2 breast tumors.

Dr. Anne Jorunn Stokka (The Biotechnology Center, Oslo, Norway) – Identification and characterization of tumor-specific cell signaling pathways regulating FOXA1.

Prof. Vessela Kristensen (Oslo University Hospital, Oslo, Norway) – Breast Cancer susceptibility loci and gene expression.

Dr. Camilla Kaulsrød (Haukeland University Hospital, Bergen) – Role of FoxA1 in endometrial cancers and response to anti-ER therapies.

Dr. Meritxell Bellet (Vall-Hebron Research Institute, Barcelona, Spain) – Analysis of clinical benefit for therapeutic adjuvant treatment with progesterone and vitamin D in breast cancer patients.

Dr. Pere Gascon (IDIPAPS, Hospital Clinic, Barcelona, Spain) – Investigating the role of microenvironment in therapy resistant patients.




Judith Staerk

Stem Cell Group

Our research focuses on deciphering molecular processes during normal and malignant hematopoiesis. Understanding the mechanisms governing blood development is important, both to identify the underlying molecular events that drive lifelong formation of blood cells, as well as to find pathways that are dysregulated in blood disorders. The broad aims of my group are to i) identify epigenetic and genetic events involved in hematopoietic specification and early development, ii) decipher how the nuclear lamina influences hematopoietic development and iii) identify underlying molecular causes of myeloid blood disorders. To achieve these goals we are using human pluripotent stem cells as well as *in vitro* differentiation assays and animal models, along with primary samples isolated from patients suffering from hematopoietic disorders, and combine these assays with genetic and genomic approaches.

Description of the Group's Research

Epigenetic dynamics during blood cell differentiation
Methylation of DNA is a key epigenetic mechanism to regulate gene expression. Recent discovery of TET proteins, which oxidize methylcytosine to 5-hydroxymethylcytosine (5hmC), uncovered a new epigenetic mark. We are interested in defining the role of DNA methylation and 5hmC during human hematopoiesis by assessing how deletion of Tet enzymes in human embryonic stem cells affects early mesoderm and hematopoietic commitment.

Projects with translational impact

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders characterized by impaired hematopoiesis and a predisposition to developing acute myeloid leukemia (AML). The underlying cause for MDS is incompletely understood. We are using prima-

ry patient samples as well as patient-derived induced pluripotent stem cells to analyse the potential of these iPS cells to differentiate into hematopoietic progenitors, and to screen transcription factor and miRNA libraries to identify candidate genes to reverse the potential block in *in vitro* blood cell differentiation.

Chronic lymphocytic leukemia (CLL) is a common hematological cancer in adults and is characterized by clonal B cell expansion. In the past year, we assessed cell cycle defects in CLL, and found that a significant number of CD19⁺ B cells isolated from peripheral blood CLL samples are arrested in cytokinesis. We linked the observed cytokinesis arrest to reduced NuMA and TP53 protein levels, and showed that several proteins known to be crucial for cell division, checkpoint and centromere function were significantly downregulated (manuscript in submission).

Lamin proteins and hematopoiesis

A main focus of our group is to understand how the nuclear lamina influences hematopoietic development. Lamins are the most abundant proteins in the nucleus and form a filamentous meshwork on the nucleoplasmic side of the nuclear envelope. B-type lamins (LMNB) are ubiquitously expressed and have been shown to be essential for cell survival, while A-type lamins (LMNA) are expressed in differentiated cells and seem to be largely absent from early embryonic tissues. Dysfunction of the nuclear envelope is associated with altered nuclear activity, impaired structural dynamics, and altered gene expression. Surprisingly little is known about lamin function and regulation during hematopoiesis. We generated ChIP-Seq data sets to determine whether chromatin binding by LMNA and LMNB1 is blood lineage

RESEARCH GROUPS JUDITH STAERK

and differentiation specific (manuscript in preparation). Additionally, we are investigating whether lamins and the nuclear architecture are affected in myelodysplastic syndrome and chronic myelo monocytic leukemia. Related to these studies we are generating conditional knockout and transgenic animal models to determine the exact role of lamin proteins during hematopoietic development.

Selected Key Publications from PI:

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

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

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

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

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

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

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

External Funding

- 05/2013 - 05/2017: The Norwegian Cancer Society, PhD fellowship
- 04/2014 - 09/2017: Norwegian Research Council, Stem Cell Call
- 09/2014 - 08/2017: The University of Oslo, Postdoctoral fellowship
- 07/2015 - 06/2018: Research Council of Norway, Frimedbjo Young Talent Grant
- 09/2015 - 08/2017 EU FP7-PEOPLE-2013-COFUND, Scientia fellow

Group members

Head Engineer:

Kirsti Præsteng

Postdoctoral fellows:

Safak Caglayan

Artur Cieslar-Pobuda (from February 2016)

Adnan Hashim

Ida Jonson

Marie Rogne

PhD fellows:

Julia Madsen-Østerbye

Oksana Svård

Collaborations

International scientific collaborations

- Stefan N Constantinescu (Ludwig Institute for Cancer Research, Brussels, Belgium). Collaboration on cytokine receptor signaling in normal and malignant hematopoiesis.
- Petr Bartunek (Institute of Genetics, Prague, Czech Republic). Collaboration on cell type specification and zebrafish in vivo models
- Christian Schmees (NMI Reutlingen, University of Tübingen, Germany). Collaboration on generating microRNA libraries from healthy and myelodysplastic syndrome patients

National scientific collaborations

- Geir Tjønnfjord and Ingunn Dybedal, OUS Rikshospitalet, Department of Hematology
- Kjetil Tasken, NCMM, UiO.
- Karl-Johan Malmberg, Dept. of Immunology, Institute for Cancer Research, UiO.

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

Research Collaboration with Oslo University Hospital

The overall objective of NCMM is to conduct cutting-edge research in molecular medicine and facilitate translation of discoveries in basic medical research into clinical practice. In order to enable translational research, NCMM has developed strong links to South-Eastern Norway Regional Health Authority and its subsidiary Oslo University Hospital (OUH).

All NCMM Group Leaders have adjunct positions in clinical or para-clinical departments at OUH. Our experience so far with these affiliations is that they facilitate clinical collaborations, give group leaders better access to patient materials, biobanks and clinical trials and that they are crucial to facilitate translational research. These research collaborations have already resulted in a number of joint publications and NCMM Group Leaders also report on several joint applications for funding of new collaborative projects. NCMM Group Leaders currently hold adjunct appointments at the following departments:

Department of Infectious Diseases (OUH)

The department is the largest of its kind in Norway and covers the entire field of infectious medical conditions, such as tropical medicine, HIV, tuberculosis as well as severe and life threatening bacterial and viral infections.

The Department of Infectious Diseases runs an extensive research programme, especially related to the diseases HIV/AIDS and hepatitis. The department is also responsible for a variety of advanced educational courses in infectious diseases and is organized under the Medicine Division at OUH.

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

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

Cancer Center, organizationally under the Division of Cancer Medicine, Surgery and Transplantation at OUH.

Department of Cancer Genetics, Institute for Cancer Research (OUH)

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

Institute for Experimental Medical Research (OUH)

The Institute for Experimental Medical Research is primarily focusing on heart disease research as well as teaching. In particular, the institute is performing research on congestive heart failure

with a special interest in heart electrophysiology and membrane pumps. The institute is involved in extensive collaborations with other laboratories in clinical departments at the OUH and is interacting with colleagues both nationally and internationally. The institute is organized under the Division of Cardiovascular and Pulmonary Disease at OUH.

Department of Haematology, (OUH)

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

From Disease Mechanisms to Clinical Practice

NCMM group leaders have so far listed some 25 and interventional clinical studies in the fields of therapy and disease mechanisms as well as in the molecular markers, diagnostic and monitoring areas.

On-going development in the area of therapy

- Immunomodulating cAMP antagonists and PKA anchoring disruptors (immunodeficiency and anti-tumor immune responses)
- Disruption of the PKA-AKAP18d-phospholamban-Serca2 complex for cardio-protective effect in ischemia-reperfusion damage
- Small molecule inhibitors of OGG1 and de novo purine biosynthesis enzymes to destabilize oncogenic signaling in prostate cancer
- Bromodomain inhibition to enhance responses to androgen deprivation/anti-androgens in prostate cancer
- Targeting of Na⁺/K⁺-ATPase and Serca2 in neurobiology and heart disease
- Suppression mechanisms by regulatory T cells with application in immune diseases, autoimmunity and cancer
- iPSC disease-modeling of blood disorders
- Assay development and structural analysis of the membrane proteins in virulence operon mgtCBR specific to pathogenic bacteria
- Structural analysis of the membrane proteins linked to the virulence operon mgtCBR specific to pathogenic bacteria
- Structural analysis of bicarbonate transporters and investigation of pH homeostasis
- Enzymatic detection and quantification assay of isatin, a putative stress biomarker in blood.
- Investigation of the Membrane-associated RING finger protein (MARCF1) E3-ligases
- Cancer drug sensitivity screening on patient samples with set of approx. 400 cancer drugs to assist clinical decision on individualized therapy choices in chronic lymphatic leukemia, multiple myeloma and ovarian cancer
- Elucidation of the mechanism of action of medroxyprogesterone injection before surgery as a treatment that improves overall and disease-free survival of ER⁺/HER2⁺ breast cancer patients
- Development of CAMKK2 inhibitors for the treatment of prostate cancer.

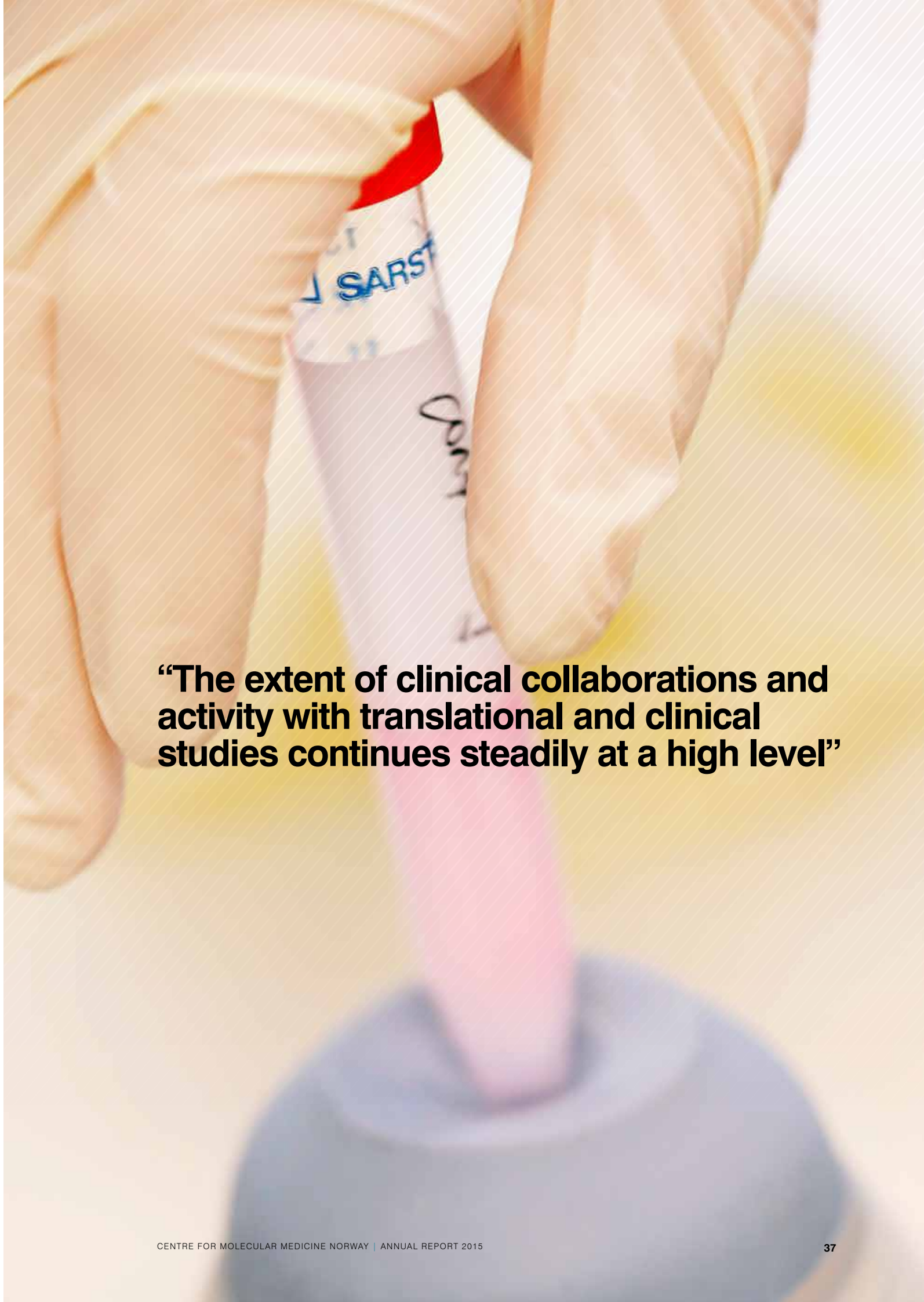
On-going development in the area of diagnostics and monitoring

- Prostate cancer markers – serum/plasma protein biomarkers, overlapping genetic risk factors for prostate cancer and blood lipid traits, transcript-based biomarkers in urine and circulating tumor cells. Evaluation of protein biomarkers in blood samples from patients with prostate cancer undergoing radiotherapy with or without androgen deprivation therapy.
- New biochemical markers for MAO diseases & early screen Parkinson
- Single cell analysis of inflammatory signaling events by fluorescent cell bar-coded phospho-flow cytometry for diagnostics and monitoring
- Regulatory T cell markers in HIV and other immune diseases
- Flow cytometry-based biomarkers in mitogenic signaling pathways for drug sensitivity screens

Proof-of-concept in humans

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

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



“The extent of clinical collaborations and activity with translational and clinical studies continues steadily at a high level”

NCMM Associate Investigators and Young Associate Investigators

NCMM aims to continue to develop its scientific and technological capabilities by establishing strong collaborative links with key scientists and research groups across Norway, thus facilitating translational networking. The Associate Investigator category is meant for outstanding scientists who are currently based in Norway, whose expertise is compatible with the NCMM research areas and who are interested in collaborating with NCMM. Associate Investigators are expected to contribute with their expertise in molecular and translational medicine and be active in mentoring activities towards newly recruited NCMM Group Leaders and Young Associate Investigators.

NCMM has also initiated a Young Associate Investigator program for young talented researchers that are recruited as group leaders at another institution. Young Associate Investigators are identified by one of two routes: either by direct application to NCMM in open calls or where universities and other research institutions that wish to recruit young, talent-

ed group leaders and where the conditions are similar to those offered to NCMM Group Leaders, can offer an affiliation to NCMM during the call. In the latter case NCMM must be contacted beforehand and will assist in the recruitment process of the NCMM Young Associate Investigators. Both Associate Investigators and Young Associate Investigators continue to work at their host institutions but are credited an affiliation to NCMM and the Nordic EMBL Partnership.

NCMM has had twelve Associate Investigators in the first 5-year period. Based on applications, seven Associate Investigators were re-appointed in 2015. In addition, one NCMM group leader was appointed Associate Investigator in 2014 when he rotated out of the Centre. Furthermore, two investigators at the University of Tromsø were appointed NCMM Young Associate Investigators in 2014 in a joint recruitment process between UiT/ University Hospital of North Norway and NCMM. Following an open call announced in the spring 2015, applications for the status as

Associate Investigators and Young Associate Investigators were evaluated by a Selection Committee taking into account scientific excellence, translational merit, compatibility with the NCMM mission and added value for NCMM. The Committee found that the call was highly competitive with excellent applications and in October 2015 the NCMM Board appointed five new Associate Investigators and seven new Young Associate Investigators. Altogether, the NCMM Associate Investigator and Young Associate Investigator network now consists of 22 excellent investigators:

NCMM Associate Investigators:

- Professor **Lars Akslen**, Centre for Cancer Biomarkers (CCBIO), University of Bergen and Haukeland University Hospital (*re-appointed*)
- Professor **Ole A. Andreassen**, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo (*re-appointed*)
- Professor **John-Bjarne Hansen**, KG Jebsen – Thrombosis Research and Expertise Centre

(TREC), Department of Clinical Medicine, UiT, The Arctic University of Norway and University Hospital of North Norway (*newly appointed*)

- Professor **Arne Klungland**, Department of Microbiology, Division of Diagnostics and Intervention, Institute of Clinical Medicine, Oslo University Hospital and Institute for Basic Medical Sciences, University of Oslo (*re-appointed*)
- Professor **Per E. Lønning**, Section of Medicine, University of Bergen and Department of Oncology, Haukeland University Hospital (*re-appointed*)
- Professor **Karl-Johan Malmberg**, Department of Cancer Immunology, Institute for Cancer Research, Oslo University Hospital and Institute for Clinical Medicine, University of Oslo (*newly appointed*)
- Professor **Erlend Nagelhus**, Department of Molecular Medicine, Institute of Basic Medical Sciences, University of Oslo and Department of Neurology, Oslo University Hospital (*appointed 2014*)
- Professor **Pål R. Njølstad**, KG Jebsen Centre for Diabetes Research, University of Bergen and Department of Pediatrics, Haukeland University Hospital (*re-appointed*)
- Professor **Johanna Olweus**, KG Jebsen Center for Cancer Immunotherapy, Department of Cancer Immunology, Institute for Cancer Research, Oslo University Hospital and University of Oslo (*newly appointed*)
- Professor **Ole P. Rekvig**, Department of Medical Biology, University of Tromsø and University Hospital of Northern Norway (*re-appointed*)
- Professor **Helga B. Salvesen**, Department of Clinical Medicine, University of Bergen and Department of Obstetrics and Gynaecology, Haukeland University Hospital (*re-appointed*)
- Professor **Anne Simonsen**, Department of Molecular Medicine, Institute of Basic Medical Sciences, University of Oslo

(*newly appointed*)

- Professor **Anders Sundan**, Department of Cancer Research and Molecular Medicine, Norwegian University for Science and Technology (NTNU) (*newly appointed*)

NCMM Young Associate Investigators:

- Dr. **Sören Abel**, Department of Pharmacy, University of Tromsø and Harvard Medical School (*appointed 2014*)
- Dr. **Thomas Arnesen**, Department of Molecular Biology, University of Bergen and Department of Surgery, Haukeland University Hospital (*newly appointed*)
- Dr. **Lorena Arranz**, Department of Medical Biology, University of Tromsø and Department of Hematology, University Hospital of Northern Norway (UNN) (*appointed 2014*)
- Associate Professor **Simona Chera**, Department of Clinical Science, University of Bergen (*newly appointed*)
- Professor **Trude H. Flo**, Centre of Molecular Inflammation Research (CEMIR) and Dept. of Cancer Research and Molecular Medicine, Norwegian University for Science and Technology (NTNU) (*newly appointed*)
- Dr. **Espen Melum**, Norwegian PSC Research Center, Department of Transplantation Medicine, Oslo University Hospital (*newly appointed*)
- Associate Professor **Siver Mostue**, Department of Circulation and Medical Imaging and Department of Laboratory Medicine, Norwegian University for Science and Technology (NTNU) (*newly appointed*)
- Dr. **Hege Russnes**, Department of Pathology and Department of Cancer Genetics, Institute of Cancer Research, Oslo University Hospital (*newly appointed*)
- Dr. **Pia Abel zur Wiesch**, Department of Pharmacy, University of Tromsø and Yale School of Public Health, US (*newly appointed*)

NCMM Associate Investigators

LARS AKSLEN
Director, Professor of pathology, Senior Consultant

Tumor Biology Research Group



Lars A. Akslen (MD, PhD) is a specialist in surgical pathology. He is directing the Tumor Biology Research Group

(since the establishment in 1995) at Department of Clinical Medicine (University of Bergen). Since 2013, Akslen is also the director of Centre for Cancer Biomarkers (CCBIO), a Norwegian Centre of Excellence (www.ccbio.no). Akslen's team, and now CCBIO, are engaged in translational cancer research with a strong focus on the exploration and validation of novel biomarkers for biologically based classification and grading of malignant tumors as a better guide for more precise and cost-effective cancer treatment.

At present, the team is focusing its efforts in two areas: 1. studies of the tumor microenvironment, especially tumor-vascular interactions and markers of angiogenesis; 2. molecular markers of aggressive tumor behavior, related to proliferation and cell cycle regulation. Gene expression studies are combined with proteomic profiling and single marker validation in patient cohorts. Experimental validation by animal and cell models is done in selected studies. An overall goal is to extend studies of prognostic and predictive biomarkers towards an integrated role in clinical trials and personalized patient management. As examples, the team is now working on trials of anti-angiogenesis treatment (breast and renal carcino-

NCMM ASSOCIATE INVESTIGATORS AND YOUNG ASSOCIATE INVESTIGATORS

ma, malignant melanoma) to explore the potential clinical value of several candidate biomarkers.

The vision of CCBIO is to discover, validate and translate functional cancer biomarkers to improve biological understanding, diagnosis and treatment of aggressive cancer. The research activity is organized in three areas: basic studies and animal models, discovery and validation of new biomarkers in human samples, and clinical studies, in addition to projects on ethics and economy within personalized cancer management. The CCBIO Research School on Cancer Studies has been established to improve education and career development.

OLE A. ANDREASSEN Professor, Director

Translational psychiatry



The group focuses on the relationship between genetic risk, environmental factors and biological variables, and how these are related to clinical disease forms and brain organic relationship in serious mental illness.

Aims: Identify the causes and identify disease mechanisms in schizophrenia and bipolar disorder using a translational approach. The main focus is on genetic factors, since severe mental disorders have a high degree of heredity, but few genetic factors are known. There is also little knowledge about how genetic factors are related to environmental risk factors. Furthermore, the connection to different disease characteristics in patients, including clinical, cognitive and brain organic relationship is unknown. In charting such contexts, the goal is to gain more knowledge

about disease mechanisms. Medications are an important part of treatment of diseases, and targets for the group are to gain more knowledge about how drugs work and how reactions occur.

Research Focus: Discover new disease genes by severe mental disorders through participation in international consortium, with special interest for polygenic effects. Exploring disease genes and examine the context of clinical, cognitive and brain organic changes in well-described clinical material. This operation uses biostatistical methods and analysis. An important part of the activity is to study the mechanism by drugs. The focus is currently on the immune system; which genes affect this, how it is related to psychological symptoms over time, and what role drugs play in this context. We also want to study the differences and similarities between disease groups, thus generating knowledge about what are disease-specific processes and what are phenotype-related processes.

Projects: Polygenic architecture: We use major international genetics studies along with new analysis tools to identify the polygenic contribution to disease development in bipolar disorder, schizophrenia and related disorders. Genotype-phenotype mapping: We identify the clinical and brain organic correlate genetic vulnerability factors in well described national and local cohorts of patients, and how this is related to the proceeding. Immune System: We have a series of studies that explores genetic variants, serum markers, drugs and brain mechanisms related to different aspects of the immune system. Psychosis across disorders: We have several studies on developmental disorders and aging processes

for finding common denominators for the development of psychosis.

ARNE KLUNGLAND Professor and Head of Section

Laboratory for Genome repair and regulation



Arne Klungland did his PhD and post-doctoral training with Erling Seeberg (Oslo) and Nobel prize laureate 2015 Tomas Lindahl (London), two pioneers in the discovery of fundamental processes for the repair of DNA damage. During these years, they focused on the mechanistic insight in the repair of alkylated, deaminated and oxydized bases in DNA and on developing biological systems to assess their endogenous levels and character. Throughout his independent career he has continued to focus on the role of novel modifications in DNA and RNA and to identify genes required for their dynamic regulation. Yet, the focus has been adapted to regulatory modifications and to unravel the biological function of their readers and erasers (EMBO 2006, 2007, Mol Cell 2013, Nat Comm 2011, 2013, Nature 2007, PLoS Gen 2010, Genes & Dev 2015). In 2015 the Klungland group identified 1 more reversible modification in RNA (in review).

Today, the group aims to elucidate new mechanisms of methylation and demethylation for regulation of the mammalian genome and to address genome instabilities associated with cancer development and possible other diseases. The group works closely together with the clinic at Oslo University Hospital. For most projects, novel mutants are designed and tested in cells and model organisms. Current models

also include genes affecting post-translational modifications in RNA and proteins; epigenetic inheritance.

PER E. LØNNING Professor

The Breast Cancer Group



The Breast Cancer Group is located in the Mohn Cancer Research Laboratory at Haukeland University Hospital, Bergen and is headed by Professor Per Eystein Lønning. The research program of the group is translational and assesses different aspects of cancer related to hormonal therapy and chemotherapy as well as cancer risk factors.

Important issues addressed by the group include somatic mutations causing cancer cells to be resistant to treatment, germline factors influencing the risk of cancer affecting clinical progression of cancers and side effects during treatment, hormones and their role in cancer development and treatment of various hormone-sensitive cancers as well as tumor heterogeneity. The work is mainly focused on cancers arising in the breast, but also includes cancers of the ovaries, prostate and the gastrointestinal tract as well as malignant melanomas. The aim is to reveal the mechanisms regulating the behavior of individual cancers, as well as mechanisms of cancer development and therapy resistance. A deeper understanding of cancer cell biology will result in better identification of risk factors and more optimal treatment of patients.

KARL-JOHAN MALMBERG Professor

Natural Killer Cell Biology and Cell Therapy



Karl-Johan Malmberg is a physician-scientist who performs basic, translational and clinical research in the fields of Hematology/Onco-logy and Immunology/Innate immunity. The long-term goal of his laboratory is to advance our fundamental understanding of natural killer (NK) cell development and function, and use this progress to design new immunotherapeutic approaches and clinical trials for patients with cancer. The Malmberg laboratory focuses on basic questions concerning 1) the formation of killer cell immunoglobulin-like receptor (KIR) repertoires and regulation of effector cell function, 2) translational questions of how NK cells may be function-enabled for anti-cancer activity and 3) clinical studies in the context of allogeneic stem cell transplantation (HSCT) and adoptive cell therapy.

In 2012 the group relocated from the Karolinska Institutet (Stockholm) to Oslo University Hospital. At the Institute for Cancer Research, Oslo University Hospital, the Malmberg group has established an interdisciplinary and translational research program aiming at developing cellular therapies for cancer based on new insights into NK cell biology. Since 2015 Malmberg holds a visiting professorship at the Karolinska Institute and leads a Nordic program in NK-cell based immunotherapy.

ERLEND A. NAGELHUS Professor

GliaLab



Erlend A. Nagelhus obtained his MD (1993) and Dr. Med. (1998) at the University of Oslo (UiO). After clinical training he returned to UiO as a postdoc (2004-2005) and senior scientist (2005-2008; Centre for Molecular Biology and Neuroscience, a Norwegian Centre of Excellence). Nagelhus has also been a Research Scholar at Center for Translational Neuromedicine, Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY (2007-2008) and Group Leader at NCMM (2009-2014). Nagelhus was appointed Professor of Physiology at UiO in 2013. In addition, Nagelhus is an Adjunct Professor at the University of Rochester, and holds an adjunct position as research scientist at Department of Neurology, Oslo University Hospital. He is also Head of the Letten Centre.

The GliaLab explores roles of astrocytes – the predominant glial cell type in brain – in health and disease by 2-photon laser scanning microscopy. The group focuses on glial mechanisms for brain waste removal, ionic (dys)-homeostasis and neuron-glia-vascular signaling. Disease models include mesial temporal lobe epilepsy/hippocampal sclerosis, migraine and Alzheimer's disease. The group uses the chronic cranial window preparation in combination with virally delivered genetically encoded fluorescent sensors to shine light on cellular and molecular events in the cerebral cortex and hippocampus of awake behaving mice.

NCMM ASSOCIATE INVESTIGATORS AND YOUNG ASSOCIATE INVESTIGATORS

PÅL R. NJØLSTAD Professor and Consultant Physician

KG Jebsen Center for Diabetes Research



Pål Rasmus Njølstad, MD PhD, is Professor at the Department of Clinical Medicine, University of Bergen and consultant

physician at the Department of Pediatrics, Haukeland University Hospital. Njølstad is also heading the KG Jebsen Center for Diabetes Research. He has had research stays at the University of Chicago (Prof. Graeme I. Bell), Harvard Medical School (Prof. C. Ronald Kahn) and Broad Institute of Harvard and MIT (Prof. David Altshuler).

His KG Jebsen Center consists of some 50 members with competence in epidemiology, clinical investigations and treatment trials, molecular genetics, CRIS-PR, genome-wide association studies, genome sequencing, bioinformatics, cell biology, stem cell research and animal models.

Njølstad's research is focused on monogenic diabetes having described new diabetes syndromes, including MODY8. The group has also revealed that neonatal diabetes can be treated with sulfonylurea tablets instead of insulin. He has achieved competitive research funding, e.g. from the European Research Council (ERC AdG), Novo Nordisk Foundation, the Research Council of Norway as well as the University of Bergen and Helse Vest.

JOHANNA OLWEUS Professor, Head of Department of Cancer Immunology, Institute for Cancer Research, Director K.G. Jebsen Center for Cancer Immunotherapy

Immunotherapy and Antigen presentation



Johanna Olweus received her M.D. and her Ph.D. from the University of Bergen, Norway.

She is a specialist in Immunology and Transfusion medicine and is since 2008 Professor at the University of Oslo as well as Head of Department of Cancer Immunology at the Institute for Cancer Research, Oslo University Hospital Radiumhospitalet. Since 2013 she is also Director of KG Jebsen Center for Cancer Immunotherapy. Olweus and her research group are focusing on the development of new strategies for T-cell based cancer immunotherapy and in-depth mechanistic analyses of the immune responses in clinical immunotherapy trials.

OLE PETTER REKVIK Professor

RNA and Molecular pathology Research Group



Rekvig and his colleagues have developed projects focusing on origin and impact of autoantibodies

against dsDNA and chromatin structures. These studies aim to understand the pathogenesis of lupus nephritis, the most serious manifestation of Systemic lupus erythematosus (SLE). These studies aim to understand tolerance to dsDNA/chromatin structures, how it is controlled and terminated in disease as well as to describe the pathogenesis of lupus nephritis with focus on renal chromatin metabolism.

The group has provided evidence that mammalian B helical dsDNA has an immunogenic potential that depends on the context in which dsDNA is presented to the immune system. The most important is complex formation with immunogenic non-self (viral) DNA/chromatin-binding proteins. These data have generated new paradigms on the origin and pathogenic impact of auto-antibodies to dsDNA/chromatin in SLE.

A central element in the pathogenesis of progressive lupus nephritis relates to an acquired defect of chromatin metabolism in nephritic kidneys. The primary cause for this is a nearby complete and selective shut-down of renal *DNase I* gene expression. Rekvig and colleagues have discovered a new, hitherto unknown function of DNase I. In response to the pro-inflammatory cytokine IL-1 β , DNase I translocates from the cytoplasm into the nucleus in a non-apoptotic context. Upon translocation, DNase I lost its endonucleolytic function, bound to the Fas Receptor promoter region, induced up-regulation of the Fas Receptor and promoted the cells to FasR mediated apoptosis. This extends the function of DNase I to be an *inducer* of apoptosis. This may explain one reason for extensive apoptotic cell death in lupus nephritis.

HELGA B. SALVESEN Professor, Co-Director CCBIO

Bergen Gynecologic Cancer Research Group



The Bergen gynecologic cancer research group has 23 active members focusing on clinical and molecular aspects of gynecologic cancers. The group is embedded in

Haukeland University Hospital, being the first Norwegian ESGO (European Society for Gynecologic Oncology) accredited training center for gynecologic oncology, and the Centre of Excellence CCBIO, co-directed by Prof. Helga B. Salvesen. With breakthroughs published in top-ranked general (Nature, PNAS, NEJM) and specialized cancer journals (JCO, CR, CCR) the research group has contributed to the discovery of new potential treatment targets and markers for individualizing gynecologic cancer care.

Key clinical challenges: gynecologic cancers show significant overlap for histological subtypes and clinical phenotypes, also recently supported by comprehensive molecular tumor profiling. The challenge is now to translate the knowledge into clinically meaningful and applicable tests to improve and individualize patient care. Our research environment is presently in a unique position to take some of this new knowledge to clinical implementation studies.

The group aims to contribute to more precision in gynecologic cancer care. By exploring primary and metastatic lesions, in parallel with comprehensive clinical annotation, advanced imaging and drug testing in preclinical models, the group will define promising targets and conduct molecularly based clinical trials. Individualized treatment and follow-up based on biomarker-determined risk profiles will be implemented as a study in parallel whilst assessing quality of life and costs.

ANNE SIMONSEN Professor

Autophagy Lab



Professor Anne Simonsen received her Dr. Scient degree in 1996 at the University of Oslo, Norway. From 1997-

2004 she was a postdoc at the Norwegian Radiumhospital, Oslo and the Salk Institute of Biological Studies, CA, USA. She is currently a Professor at the Institute of Basic Medical Sciences, University of Oslo, where she heads a research group of eleven people. The overall objective of their research is to characterize the molecular machinery involved in regulation and execution of autophagy at a biochemical and cellular level and to integrate this knowledge in disease-related model systems. The current main focus areas of the research group are; 1) characterization of the membrane remodeling and trafficking events required for autophagosome formation, 2) identification of the molecular machinery involved in selection of cargo for degradation by autophagy and 3) understanding the role of autophagy in fusion-protein-associated leukemia and protein aggregate-associated neurodegenerative disease. Our areas of methodological expertise are high-throughput cell-based assays, bioinformatics, various genome editing approaches, state-of-the art imaging techniques, a range of protein interaction assays, as well as mammalian cell culture systems and in vivo model organisms (Zebrafish).

The team benefits from an extensive interactive network of national and international collaborations. Professor Simonsen is on the Autophagy editorial board and a member

of several national and international committees. She is also leading the Nordic Autophagy Network (2011-2015) and was the main organizer of the 2013 EMBO Autophagy conference.

ANDERS SUNDAN Professor

KG Jebsen Centre for Myeloma Research



The research group consists of 15 people devoted to basic, translational and clinical aspects of the hematological

cancer multiple myeloma. Multiple myeloma is due to malignant transformation of antibody-producing plasma cells in bone marrow, and monoclonal immunoglobulin is used as a biomarker of the disease. Multiple myeloma is considered an incurable disease with a median survival from time of diagnosis of 5-7 years. However the patients show great heterogeneity in response to chemotherapy as well as to the course of the disease. The group has research activities both on the basic and clinical aspects of multiple myeloma. The basic research is centered on how myeloma cell survive in bone marrow and the role of inflammation, oncogenic activation and the clonal evolution of the malignant cells, and how myeloma cells escape immune surveillance. The clinical research is centered on why some patients respond well to chemotherapy whereas others do not, i.e. mechanisms of inherent and acquired resistance to common drugs, and on how the clonal evolution of malignant cells can be monitored in the clinic. The studies are based on extensive use of patient material and in particular bone marrow aspirates taken for diagnostic purposes, as well as mice and in vitro cellular models of myeloma.

NCMM Young Associate Investigators

SÖREN ABEL Group Leader, Visiting Assistant Professor

Infection Biology



Sören Abel received his MSc in biochemistry and molecular biology from the University of Kiel, Germany and during his PhD he studied bacterial second messenger signaling at the University of Basel, Switzerland. He then moved to Harvard Medical School, US, where he developed an interest in next-generation sequencing technologies and applied them to the study of *Vibrio cholerae* infections. In 2015, Abel started his own group as NCMM Young Associate Investigator at the University of Tromsø. He is also a Visiting Assistant Professor in Medicine at Harvard Medical School. The Abel research group is currently in its startup phase: 2 postdocs as well as 2 graduate students (startup and FriPro) were recently hired. Furthermore, the group has funding for an additional postdoc (Helse-Nord) and a shared graduate student with the Optical Nanoscopy group at the University of Tromsø (UiT Strategic Funding).

The Infection Biology research group studies the molecular mechanisms that enable pathogens to adapt to different environmental conditions during infection and transmission. The Abel lab primarily focuses on *Vibrio cholerae*, the causative agent of the severe diarrheal disease cholera and studies how this organism senses and survives the radically different conditions it encounters during the passage through the host

and into the environment. In particular, the group is interested in the c-di-GMP second messenger network that controls important adaptation mechanisms during infection and its impact on population dynamics, bacterial virulence and persistence under changing conditions. They employ deep-sequencing based methods to infer the spread of pathogens within and between hosts and combine it with bacterial genetics and live cell microscopy. Understanding the underlying molecular mechanisms of virulence will help us better understand the important role they play in the fitness of this pathogen. Ultimately, this knowledge might contribute to the development of new interventions against this ancient scourge.

THOMAS ARNESEN Group Leader

Protein N-terminal acetylation



Thomas Arnesen has a PhD in molecular biology from the Department of Molecular Biology (MBI) at the University of Bergen and did his postdoc at the Department of Surgical Sciences, UiB, and at the Department of Biochemistry and Biophysics at the University of Rochester, US. Arnesen is currently group leader of the N-terminal acetylation (NAT) group at MBI. The NAT-group is one of three nodes comprising the ProtMetD (Protein modifications, metabolism and disease) research program at MBI and the group is using eukaryotic model systems like *Saccharomyces cerevisiae*, mammalian cell cultures and *Danio rerio*, combined with *in vitro* biochemical approaches. The Arnesen lab is focusing on the molecular and cellular biology of protein N-terminal acetylation, a major protein

modification in human cells catalyzed by N-terminal acetyltransferases (NATs). Their goals range from defining the NAT-machinery and the molecular mechanisms of N-terminal acetylation to establishing the links between NAT-defects or NAT-overexpression and diseases like cancer and recently discovered syndromes.

Their investigations have contributed to the understanding of the physiological and clinical importance of NATs and N-terminal acetylation. The Arnesen group has revealed that NatA are important for cancer cell survival and has also demonstrated a link between NatA and cancer cell drug sensitization. Furthermore, the lab recently developed the first specific NAT-inhibitors in collaboration with Professor Paul R. Thompson (UMass). These potentially target specific NAT-enzymes and are currently being developed further for cellular and *in vivo* studies for the potential use in cancer chemotherapy. Moreover, the group has been involved in identifying and mechanistically investigating the first genetic disorder caused by a NAT-mutation, the Ogden syndrome. The lethal Ogden syndrome and additional cases and syndromes involving cardiac arrhythmias and intellectual disabilities caused by NAT mutations are currently being functionally studied in the lab. Finally, the Arnesen group is also pursuing links between NATs and metabolism.

LORENA ARRANZ Group Leader

Stem Cell Aging and Cancer



The Stem Cell Aging and Cancer (SAC) research group performs research within the pathophysiology of stem

cells. Taking the hematopoietic system as a primary model, the group aims at understanding the molecular mechanisms of stem cell malignant transformation and the complex interactions of this cell with its surrounding microenvironment, with a focus on inflammation and signaling onco-metabolites. The group's goal is identification of novel therapeutic targets of potential clinical interest.

The group is led by Dr. Lorena Arranz, who graduated in Biology (Biomedicine) and obtained her PhD in Physiology at the Universidad Complutense de Madrid (UCM), Spain. Under the supervision of Professor M. De la Fuente, she studied the contribution of fully differentiated myeloid cells to the aging process, with a focus on oxidation and inflammation. Furthermore, Arranz also became interested in the neuro-endocrine regulation of the immune system during this period. Arranz then moved to Fundacion Centro Nacional de Investigaciones Cardiovasculares (CNIC), where during her first postdoc at Dr. S. Gonzalez' laboratory, she studied the contribution of dysregulated Polycomb proteins in hematopoietic stem cells to both aging and the blood malignancies classified as myeloproliferative neoplasms. From 2012 to 2014 she performed her second postdoc, working in the group of Dr. S. Mendez-Ferrer, where she uncovered the critical role played by the hematopoietic stem cell niche in the pathogenesis of these diseases. This work was published in *Nature* and received an Achievement Award at the congress of the American Society of Hematology (ASH) in 2013. In November 2014, Lorena joined the Department of Medical Biology at the University of Tromsø (UiT) as Group Leader and NCMM Young Associate Investigator,

and was appointed as member of the Department of Hematology at the University Hospital of North Norway (UNN) in January 2015.

Currently, the group consists of two postdocs, two PhD students and a head engineer. Lorena Arranz is supported by a joint meeting among UiT, UNN and the Regional Authorities of Northern Norway (Helse Nord), Young Research Talent grants from the Norwegian Research Council (Stem Cell and FRIPRO programs) and the Norwegian Cancer Society.

SIMONA CHERA Group Leader

Cell fate, ageing and decay



Simona Chera has her background from the regeneration field and her main interest is characterizing the molecular mechanisms controlling regenerative cellular processes. During her PhD she identified and defined a novel level of complexity governing the regeneration response in a classical invertebrate model-system of regeneration (Chera et al., 2010, *Dev. Cell*). Briefly, she demonstrated that an efficient regeneration requires the apoptosis-induced compensatory proliferation promoted by dying cells through a Wnt3a-dependent mechanism. For her postdoctoral studies, she analyzed the cellular and molecular basis of murine pancreatic β -cell regeneration (University of Geneva, Switzerland). During this work she generated a new transgenic model of inducible, specific and total β -cell loss, termed RIP-DTR. By coupling this β -cell ablation model with genetic lineage-tracing tools and transgenic setups allowing the modulation of gene expression, they were the first

to define two distinct, naturally occurring β -cell regeneration mechanisms based on cell-reprogramming and controlled by an age-dependent switch (Thorel et al., 2010, *Nature*; Chera et al., 2014, *Nature*).

Chera is now exploring new strategies aiming at enhancing the β -cell mass in diabetic conditions. Her group also plans to characterize and compare the cellular processes as well as the gene-environment interactions occurring in monogenic diabetes disorders, with emphasis on identifying a general, age-related mechanism of disease onset. She is currently building up her research group at the University of Bergen.

TRUDE HELEN FLO Professor, Co-director

Research group on host-pathogen interactions in mycobacterial and HIV infection



Mycobacterial infections pose a global health challenge with tuberculosis killing more than 1.5 million people each year and disease caused by opportunistic strains is on the rise. Long treatment with antibiotics is required and drug resistant strains are emerging. The group's primary research focus is molecular host defense mechanisms involved in fighting pathogens and virulence strategies employed by mycobacteria to parasitize host cells. The inter-connected roles of trafficking, compartmentalized PRR signaling and iron metabolism for mycobacterial survival make these processes attractive targets for drug development and are currently investigated in our lab both in the host and in the pathogen. The group is currently also studying innate properties of the

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T-cell responses to HIV and mycobacteria. T-cells express PRRs and respond to microbial ligands with cytokine production. The significance of this in disease and also in vaccine design is currently not understood and is something Flo and colleagues are interested in. This basic research strategy may contribute to reveal new therapeutic targets and vaccine development.

The research group is led by Professor Trude H. Flo and includes 2 more research scientists, 4 post docs, 4 PhD students, 2 medical research students and master students. The group has developed expertise, methods and tools to study HIV and mycobacteria and the host innate and adaptive immune defenses both *in vitro* in human primary cells and *in vivo* in mice. The group has strains of *Mtb*, *M. avium* and *M. smegmatis* available with fluorescence and luciferase and performs live imaging of *Mtb* and HIV infections. Furthermore, they have transposon mutant libraries with more than 150 000 mutants in *M. smegmatis*, *M. avium* and *Mtb* available. Finally, the group also pioneer the use of FIB-SEM to establish nanoscale resolution imaging of intracellular mycobacterial infections.

ESPEN MELUM Group Leader / Senior Scientist

Experimental Hepatology



Espen Melum is currently leading the research group Experimental Hepatology which focuses on translational research relevant to the chronic liver disease primary sclerosing cholangitis (PSC). In addition, he is training in clinical gastroenterology

at Oslo University Hospital, Rikshospitalet. In addition to Melum, the group consists of one postdoc, four PhD-students as well as one technician. The group is part of the Norwegian PSC research center located at the Research Institute for Internal Medicine (RIIM) at Oslo University Hospital, Rikshospitalet.

The research interests of the group range from large-scale genetic studies (genome-wide association and deep sequencing studies) to immunological mouse models for bile duct inflammation. The genetic risk factors so far uncovered in the genetic studies in PSC are mainly related to the function of the immune system and the group is therefore increasing their efforts in developing immunologically driven models of bile duct inflammation. The work in these mouse models focuses on understanding the immunological process regulating inflammation in the bile ducts. The group has for the first time demonstrated that the cholangiocytes lining the biliary tree in both mice and humans can present antigens to natural killer T cells (NKT). To expand these findings to *in vivo* mouse models the group has developed a novel mouse model where they introduce a NKT activating antigen into the biliary tree using surgical techniques with development of cholangitis. Furthermore, to expand the knowledge on the importance of NKT cells we are investigating lipid accumulation as a mean to regulate the function of NKT cells during development and activation which can potentially have translational implications.

SIVER MOESTUE Assoc. Professor

MR Cancer Group



Siver Moestue is a member of the MR Cancer Group at the Norwegian University for Science and Technology (NTNU) and his research focuses on cancer metabolism. Moestue also works with functional MR imaging for studies of tumor microenvironment and clinical PET/MR imaging in prostate cancer.

From 2002-2007 Moestue worked at GE Healthcare's Preclinical Biology unit in Oslo, developing novel contrast agents for medical imaging (ultrasound, MRI and PET). After relocating to Trondheim in 2008, he did his PhD working on molecular characterization of breast cancer subtypes. In collaboration with Prof. Anne-Lise Børresen-Dale and Prof. Gunhild Mælandsmo (OUS Radiumhospitalet), he demonstrated novel associations between the molecular background of breast cancers and their metabolic profiles. This knowledge was further expanded in his postdoc period, where he used MR spectroscopy to identify metabolic biomarkers to treatment with PI3K inhibitors. During this period they developed novel ³¹P MRS protocols for therapy monitoring, with high potential for clinical translation.

In 2014, Moestue was awarded a FRIPRO Young Talented Researcher grant, in a project aiming to describe the metabolic plasticity shown by cancer cells following treatment with drugs targeting key energy metabolism pathways. In collaboration with Prof. Ian Mills (NCMM and Univ. of Belfast) and Prof. Mælandsmo, Moestue is now studying metabolic responses to OGT

inhibitors in endocrine resistant breast cancer. His research group, currently comprising 2 postdocs and 3 PhD students, has also developed tools for studying the relationship between metastatic potential, tumor microenvironment and metabolism in cancer using ¹³C NMR tracer flux studies. Moreover, Moestue is responsible for the preclinical projects in the MR Cancer Group, and therefore also works with various MR imaging techniques, in particular DCE-MRI, for studies of tumor vasculature and advanced diffusion-weighted MRI for improved diagnostic imaging and therapy monitoring.

HEGE G. RUSSNES MD, Researcher, Head of Section for Molecular Pathology

Genomic alterations in breast cancer with impact on prognosis, therapy prediction and clinical follow-up



During medical school Hege G. Russnes was involved in cancer research at The Norwegian Radiumhospital supervised by Prof. Jahn M. Nesland, Prof. Anne-Lise Børresen-Dale and Prof. Ragnhild Lothe. Later, after completing 2,5 years training in pathology, Russnes entered the PhD program at

the University of Oslo while continuing her education in pathology. She was also trained in molecular pathology at the Department of Pathology at the Oslo University Hospital (OUS) by Prof. Jan Delabie. Except from an 18 months post-doc period in Prof. Kornelia Polyak's group at Dana-Farber Cancer Institute/Harvard Medical School, Boston, USA the main part of her research activity has been within the Børresen-Dale research group at the Department of Genetics, Institute for Cancer Research (ICR), OUS. From 2015 Russnes entered a joint position as a researcher at Department of Genetics, ICR (50%) and as a senior consultant at Department of Pathology (50%) at OUS. Russnes is since January 2016 Head of the Section for Molecular Pathology.

Russnes has a project group which today consists of one PhD student, two post-docs, two master students and three engineers (<http://ous-research.no/russnes/>).

The main focus of the group is breast cancer research with ongoing projects in the following areas: 1) Molecular classification, 2) Intra tumor heterogeneity, 3) Circulating biomarkers, 4) Tumor evolution and 5) Molecular markers in clinical trials. The group uses a multitude of methods such as microarrays (SNP

arrays, mRNA arrays, miRNA arrays), RNA seq, DNA seq and *in situ* analyses and has trans-disciplinary collaborations, including bioinformaticians and biostatisticians. Finally, Russnes is dedicated in facilitating clinical trials in need of molecular based diagnostics and optimizing study design and sampling to be feasible for translational research.

PIA ABEL ZUR WIESCH Group Leader, Visiting Assistant Professor

Systems Pharmacology



Dr. Abel zur Wiesch studied biochemistry and molecular biology at the University Kiel, Germany, Griffith University, Australia and University Basel, Switzerland. After passing her MSc with distinction, she worked at Roche Diagnostics and was an intern at WHO. She did her PhD in Theoretical Biology at ETH Zurich and received the ETH Medal for an outstanding PhD thesis. During her work as Research Fellow at Harvard and Yale, she held several career development grants from the German Academic Exchange Service and the Swiss National Science Foundation. In 2015, Dr. Abel zur Wiesch became a NCMM Associate Investigator

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and joined the University of Tromsø as a tenure track Associate Professor. She also holds a visiting professorship at Yale School of Public Health, where she spends 20% of her time and employs one postdoc.

The work in Tromsø is supported by a statistician. In addition, one postdoc and PhD-student will start in the spring 2016. The group will use theoretical models in close collaboration with experimentalists and clinicians to explore how we could use both within-host and population-wide drug treatment strategies to minimize human morbidity and mortality. The focus of the research is rationalizing antibiotic treatment by bridging the gap between intracellular reaction kinetics and bacterial population dynamics to improve dosing regimens in tuberculosis therapy. The group links single cell analyses to clinical studies and are funded by the Bill & Melinda Gates foundation. These models are also employed to develop new extended release technologies together with gastroenterologists at Harvard Medical School and MIT. In collaboration with researchers at the Department for Systems Pharmacology, Harvard Medical School, Abel zur Wiesch explores how resistance mechanisms affect bacterial susceptibility. In addition, the team recently developed a method to infer pathogen population dynamics in collaboration with Sören Abel and works on resistance evolution in nosocomial infections and tuberculosis.

IN MEMORY OF HELGA BIRGITTE SALVESEN (1963-2016)



Helga Salvesen was appointed NCMM Associate Investigator in an open call in 2011 and was reappointed in 2015. Her knowledge, passion for science and drive made her a key contributor to building up a national translational network in molecular medicine in Norway. Both the NCMM Centre Director and NCMM group leader Toni Hurtado enjoyed good and fruitful collaborations with her and her colleagues. It was with shock and great sadness we received the message that Helga passed away very unexpectedly in January 2016.

Helga Salvesen was a full-time surgeon at Haukeland University Hospital who also ran a very active research lab. She was a prominent Professor at the University of Bergen (UiB) and was in the forefront internationally in the research field of gynecological cancers. Together with her colleagues, she was responsible for several scientific breakthroughs that have contributed to the discovery of new potential treatment targets and markers for individualizing gynecologic cancer care. In addition, she was the Co-Director of Centre for Cancer Biomarkers (CCBIO), a center of excellence (CoE)

at the Faculty of Medicine and Dentistry, UiB. In 2015, Helga Salvesen received the Health West Research and Innovation Award for her outstanding work related to personalized treatment of gynecological cancer. She was also elected member of the Norwegian Academy of Science and Letters in 2015.

Helga Salvesen was a specialist in gynecology and obstetrics and during her career she had several research stays abroad, including the Dana Farber Cancer Institute at Harvard Medical School, Broad Institute MIT as well as the University of Chicago. In particular, she focused on developing molecular biology tools in her studies of gynecological cancers. Helga Salvesen published more than 130 scientific papers and has supervised a number of PhD fellows.

Although Helga was an impressive clinician and a brilliant cancer researcher, what was most impressive about her was her personal warmth. She was a dedicated and caring physician and researcher and became a role model for many young scientists and doctors. She always had the patients' best interests at heart. NCMM feels honored that Helga Salvesen took the time to be part of the NCMM Associate Investigator network and we value our collaborations over the years.

Research Highlights

PhD fellow and MD Simer Bains presented data on aspirin treatment and colorectal cancer at the 2015 ASCO Conference

The 2015 American Society of Clinical Oncology (ASCO) Meeting took place in Chicago on May 29 - June 2. This annual meeting brings together around 30 000 oncology professionals from around the world to hear the latest news from the world of cancerology. NCMM PhD fellow Simer Bains gave an oral presentation entitled "Impact of aspirin as secondary prevention in an unselected cohort of 23 162 patients with colorectal cancer: A population-based study" for an audience of almost 5000 people. She was the only Norwegian speaker at the meeting and her talk was mentioned both in national media such as by Dagens Medisin: <http://www.dagensmedisin.no/artikler/2015/05/31/asco-debuterte-foran-5000/> and echoed in international discussion and media e.g. in the Medscape note by Professor David Kerr, University of Oxford: <http://www.medscape.com/viewarticle/845146>.

Worldwide, 1.3 million patients are diagnosed with colorectal cancer (CRC) every year and Norway, with a population of 5.1 million, has an annual incidence of approximately 4000 cases. Evidence from randomized controlled trials and experimental and observational studies indicate that aspirin and non-steroid anti-inflammatory drugs (NSAIDs) can decrease the incidence and mortality of CRC, when used prior to diagnosis. However, use of aspirin as primary prevention in the general public is debated as aspirin-induced gastric- and cerebral hemorrhage impact the risk-benefit assessment. In contrast, secondary prevention in patients already diagnosed with CRC may offer more advantage with respect to risk of recurrence as well as a different risk-versus-benefit profile.

At the ASCO meeting Simer Bains presented data from a large cancer registry study coupling data from the Norwegian Cancer Registry and the Norwegian Prescription Database. This population-based, retrospective cohort study included 23 162 patients diagnosed with colorectal cancer in Norway in the period 2004-2011, including 6.102 regular aspirin-users. Bains and her colleagues assessed whether use of aspirin can influence overall survival (OS)



Simer J. Bains (MD, PhD)
Photo : Lisbeth Nilsen, Dagens Medisin

and colorectal cancer-specific survival (CSS) in CRC patients and found that aspirin exposure after the diagnosis of CRC was independently associated with improved CCS as well as OS.

The study was recently published in the Journal of Clinical Oncology revealing that this patient group has a 15% improved cancer-specific survival and 5% improved overall survival compared to those not using aspirin. Furthermore, patients using aspirin both before and after diagnosis had an even further improved CSS and OS. Given the facts that aspirin would be a cheap treatment with few side effects these findings may have potential value for the many patients diagnosed and treated for colorectal cancer every year. The full article "Aspirin as Secondary Prevention in Patients with Colorectal Cancer - An Unselected Population-Based Study" is being published in the Journal of Clinical Oncology in May 2016.

Furthermore, a new multicenter study is being initiated focusing on aspirin effects on patients suffering from colorectal cancer that have also surgically removed liver metastases. This study will be performed in collaboration with Oslo University Hospital (Bjørn Atle Bjørnbeth, Sheraz Yaqub) as well as with colleagues in Stavanger, Bergen, Trondheim and Tromsø.

RESEARCH HIGHLIGHTS

Targeting metabolic feedback pathways to enhance treatment responses and accelerate drug repurposing

As cancers develop they acquire the ability to evolve rapidly to resist therapeutic stress. Over the course of the last few years we have focussed on processes that modulate stress response signalling and the hexosamine biosynthesis pathway as one example. This pathway utilises metabolites from core metabolic processes to create substrates for the modification of proteins to alter their stability and activity. We are collaborating with Professor Suzanne Walker’s group (Harvard Medical School) to characterise novel inhibitors of a conjugating enzyme, O-GlcNAc transferase (OGT) and have also studied the impact of an upstream enzyme, UDP-N-Acetylglucosamine Pyrophosphorylase 1 (UAP1) which generates the substrate for OGT. Reducing UAP1 levels enhances the stress response signalling to chemical stressors of the unfolded protein response in cells – response often activated by radiotherapy and other treatment modalities¹. Targeting OGT sensitises prostate cancer cells to clinically approved drugs such as Metformin, which impose metabolic stress on cells often by impacting in part on mitochondrial function². Working with NCMM Young Associate Investigator Dr. Siver Mostue (NTNU), and his team we were able to identify alanine as a metabolite that was consumed upon targeting OGT to help to maintain cell survival². In addition, targeting OGT significantly upregulated the expression of an important alanine metabolising enzyme, glutamic pyruvate transaminase (Alanine Aminotransferase) 2 (GPT2)². By combining early-stage OGT inhibitors with a clinically approved drug, cycloserine (seromycin) which inhibits GPT2, we achieved an enhanced cytotoxic response in prostate cancer cells². Cycloserine is currently used as a second-line drug to treat tuberculosis. Future work will involve further optimisation of the specificity of OGT inhibitors with a line of set to testing them as enhancers of therapeutic response to standard

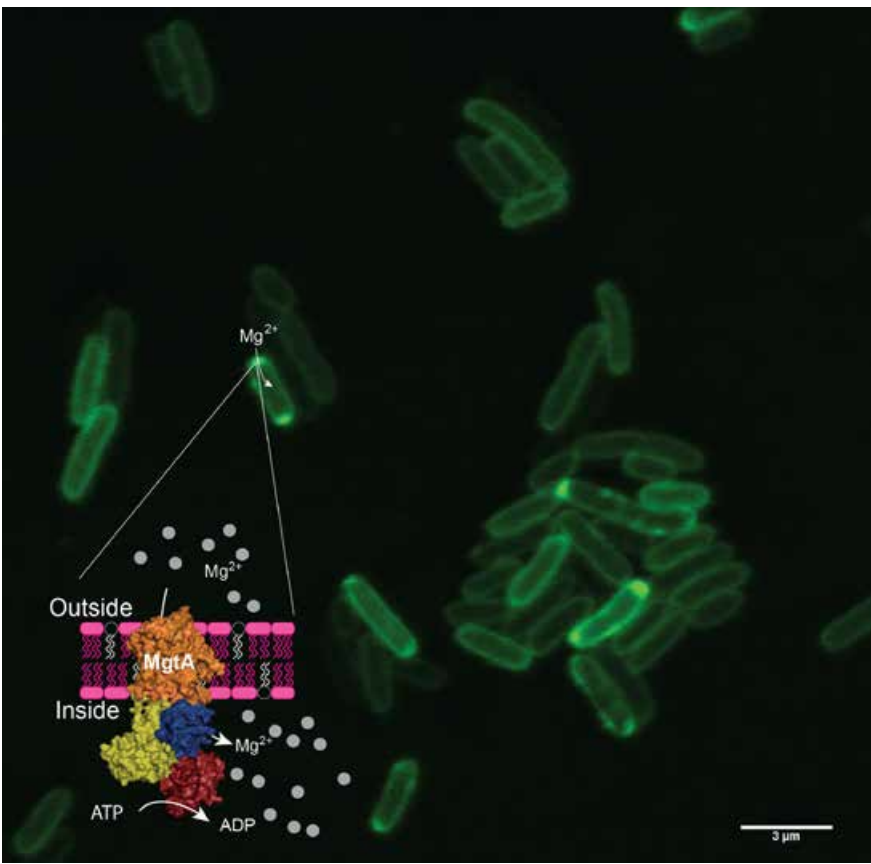
cancer treatments (eg. Radiotherapy) and also to enhance the therapeutic impact of repurposed, clinically approved therapies.

1. Itkonen HM, Engedal N, Babaie E, Luhr M, Guldvik IJ, Minner S, Hohloch J, Tsourlakis MC, Schlomm T, and Mills IG. UAP1 is overexpressed in prostate cancer and is protective against inhibitors of N-linked glycosylation. *Oncogene*. 2015;34(28):3744-50.
2. Itkonen HM, Gorad SS, Duveau DY, Martin SE, Barkovskaya A, Bathen TF, Moestue SA, and Mills IG. Inhibition of O-GlcNAc transferase activity reprograms prostate cancer cell metabolism. *Oncotarget*. 2016.

Bacteria use their own pumps to collect magnesium

Magnesium is found in all living organisms and in humans most magnesium is found in the skeleton. We are supplied with magnesium through our daily diet or as a supplement. Magnesium deficiency is not common, but occurs in patients with intestinal diseases such as Crohn’s disease. These patients often have to live with cramps and various rheumatic illnesses. Other symptoms typical of magnesium deficiency are muscular spasms, cramps, anxiety or abnormal heart rhythms.

Morth and colleagues have recently discovered that the system used by bacteria to transport magnesium is so sensitive that it can detect a pinch of magnesium salt in a swimming pool. They have identified a nano-sized magnesium pump and demonstrated how sensitive the bacteria’s transport system is. The pump was isolated in the plasma membrane from *E. coli*. In addition to the pump itself, the researchers also discovered unique lipid components, in particular cardiolipin, that assist the bacteria in this process. Magnesium deficiency can be deadly for bacteria. This has led to our own cells developing a mechanism that removes magnesium and other metals from bacteria when they start attacking us. In order to counteract this mechanism,



The bacteria are shown in green. The multi-coloured area shows how the pump rests on the bacterial membrane (pink). The ‘machine’ itself inside the membrane is shown in orange. The grey dots are magnesium atoms. Photo: Jens Preben Morth, UiO

bacteria have developed a unique system to detect and attract magnesium. The bacteria manage to do this even if the amounts of magnesium in their environment are only minimal.

Magnesium is bound to several proteins within a cell. For example, it is used by many of the enzymes that are involved when sugar is broken down into energy (glycolysis) and magnesium also stabilises genetic material in both humans and bacteria.

This discovery will hopefully help us to understand some of the molecular systems

that apply when magnesium is identified and absorbed into cells. Not only in the case of bacteria, but also in more advanced organisms. In future we may be able to use this information to create drugs that counteract this process and thus prevent antibiotic resistance. In addition, it will help us understand how bacteria protect themselves against the hostile environments in the human body.

The full article “The magnesium transporter A is activated by cardiolipin and is highly sensitive to free magnesium in vitro” can be found in *eLife*. 2016; 5: e11407. doi: 10.7554/eLife.11407

Events 2015



Photo: J. Landskron, NCMM

March

SAB Visit

The Scientific Advisory Board (SAB) visited NCMM in March 2015. In addition to scientific presentations and discussions with group leaders and the director as well as evaluation of a PI, the SAB also enjoyed a scientific lunch with NCMM PhD fellows and postdocs.

April

Joined the Medical Faculty, UiO

The University Board decided that the Faculty of Medicine should host NCMM from April 2015. The fact that the Faculty of Medicine is now hosting NCMM and cooperates closely with the Faculty of Mathematics and Science in this endeavor offers new opportunities, both strategically with the two Faculties and with more alignment and potential for synergies at all levels.

May

National PhD courses

In May group leader Preben Morth organized a one-week BioStruct PhD course entitled "Membrane Proteins, from isolation to crystals" (MBV9300BTS) at NCMM. The course included both practical lab work and theoretical lessons.

NCMM also organizes a national PhD course in molecular medicine that takes place every year in November (MF9120BTS). Altogether, 33 participants from Norway (Oslo and Trondheim) and Finland (FIMM) attended this two-week course in 2015. The course aims to give its participants insights into the translational and clinical aspects of science.

September

Nordic EMBL Partnership

In September the Danish node Dandrite hosted the 6th annual meeting for the Nordic EMBL Partnership for Molecular Medicine in Aarhus. More than 150 participants from all the four Nordic nodes as well as from the EMBL enjoyed two days of scientific interaction. NCMM PhD student Shixiong Wang was one of two poster award winners. The Nordic EMBL Partnership admin meeting took place in Helsinki in February 2016



NORDIC EMBL
PARTNERSHIP FOR
MOLECULAR MEDICINE



Photos: Dandrite and FIMM



October

Scientific Retreat

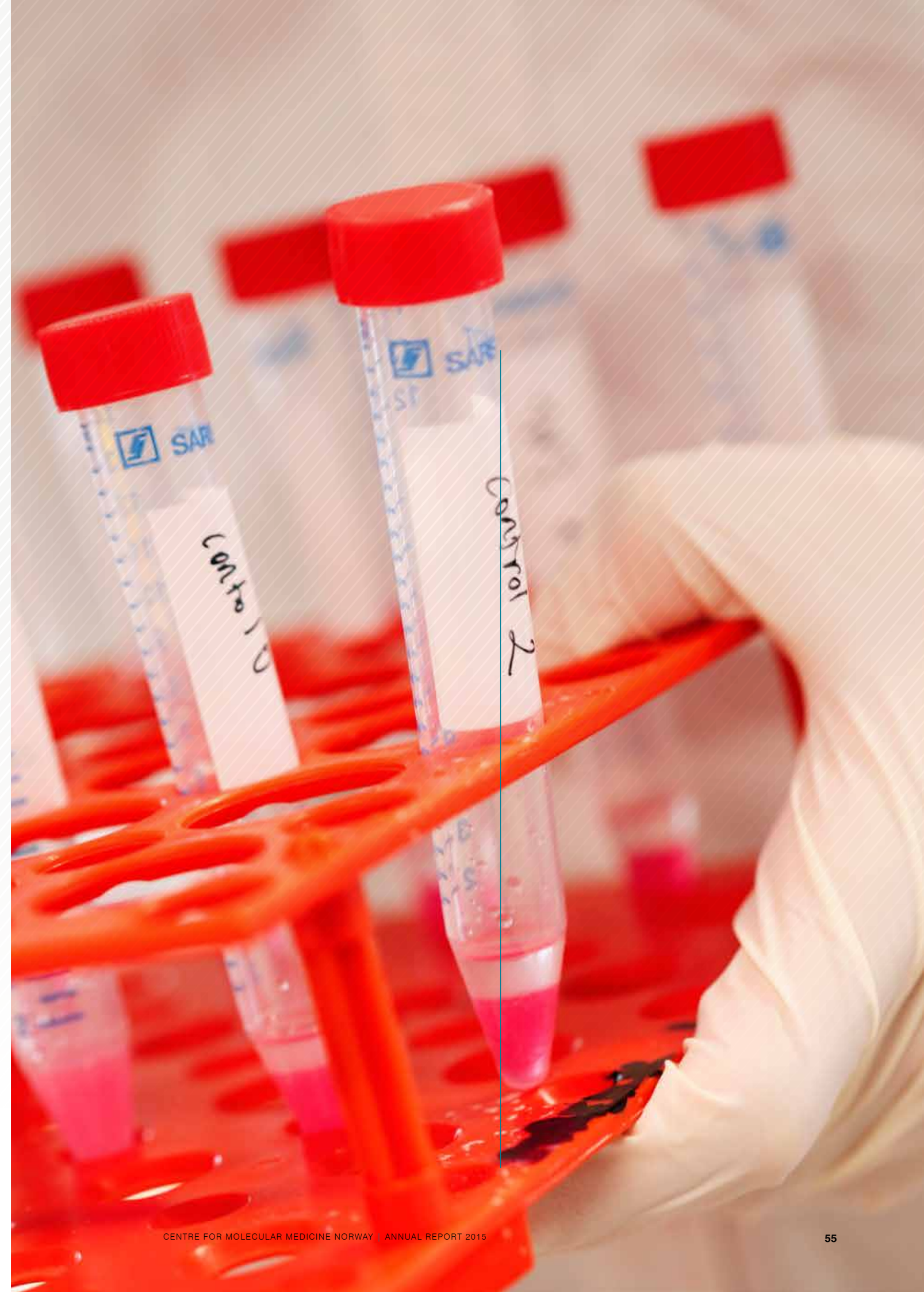
In October NCMM and the Biotechnology Center organized a joint scientific retreat that took place at Holmsbu Spa and Resort, just outside Oslo. This two-day event included scientific talks and discussions, a social dinner and outdoor activities.

King Olav Vs Prize for Cancer Research

In March 2016 the Norwegian Cancer Society announced that Professor Kjetil Taskén will receive the prestigious King Olav Vs Prize for Cancer Research for his work on immunotherapy. King Olav V's Cancer Research Award 2016 is presented by HM King Harald V on behalf of the Norwegian Cancer Society in Oslo on 6 June.

King Olav V's Cancer Research Award is distributed annually to scientists who have distinguished themselves through years of efforts to ensure a better life for many people and the winner receives 1 million NOK. The prize is highly valued among cancer researchers in Norway.

In the press release from the Norwegian Cancer Society it is stated that Kjetil Taskén has contributed greatly to the understanding of immune-oncology and that this research will become even more relevant in the development of next generation immunotherapy. The Secretary General of the Norwegian Cancer Society says "she is especially happy to give the prize to a researcher who works with immunotherapy, which many believe is the future of cancer treatment. Immunotherapy can contribute to a treatment that is tougher against cancer, but easier on the patient". Professor Taskén will receive the prize at a ceremony in Gamle Festsal at the University of Oslo on 6 June 2016.



NCMM Network Meeting



The NCMM Network Meeting was opened by Frode Vartdal, Dean at the Medical Faculty, UiO. Photo: Gang Cheng, NCMM

In the fall 2015 NCMM announced the re-appointment and new appointment of altogether 22 NCMM Associate Investigators and Young Associate Investigators (see separate section). To kick off the extended network program, NCMM organized a network meeting that took place on 18-19 January 2016. This meeting was intended for NCMM group leaders, newly appointed and reappointed NCMM Associate Investigators and Young Associate Investigators, Board members and other stakeholders and scientific leaders.

The first day of the meeting took place at the Norwegian Academy of Science and Letters whereas the second day was organized at the Oslo Science Park and was also open to all NCMM staff. The first day the program included a scientific speed-dating as well as talks covering topics such as team building and top performances, research dissemination and media strategy, creating an international workplace and how to understand cultural differences as well as a debate on private research funding. The



The panel debate on private research funding was chaired by research dean Hilde Nebb, UiO. Panel members from left: Anne Lise Ryel (The Norwegian Cancer Society), Johanna Olweus (OUH/UiO), John-Bjarne Hansen (UiT), Espen Melum (OUH, UiO) and Kåre Rommetveit (Bergen Forskningstiftelse, Stiftelsen Kristian Gerhard Jebsen) Photo: Gang Cheng, NCMM

The panel debate "Innovation in the health care sector – challenges and opportunities" was chaired by Kjetil Storvik, HSØ. Panel members from left: Ketil Widerberg (Oslo Cancer Cluster), Bjarte Reve (Nansen Neuroscience Network), Ole Kristian Hjelstuen (Inven2), Guttorm Haraldsen (NORIN) and Agnete B. Fredriksen (Vaccibody) Photo: Johannes Landskron, NCMM



Clinical trials - implementation of personalized medicine, new drugs and advanced therapeutic medicinal products (ATMPs). Panel members from left: Hans Olav Melberg (UiO), Steinar Madsen (Legemiddelverket), Else Krüger-Hagen (Novartis), Karl-Johan Malmberg (OUH/UiO) and Per E. Lønning (UiB/Haukeland University Hospital) Photo: Johannes Landskron, NCMM

second day the audience was invited to several panel debates covering topics such as research career development at the young group leader stage, new diagnostic possibilities - the road to personalized medicine, clinical trials, innovation in the health care system as well as challenges and benefits of large research infrastructures.

Altogether, 55 participants attended the network meeting and an evaluation after the meeting where approximately one third of the participants

responded, revealed that the participants found the meeting interesting, engaging, inspiring and different. NCMM will therefore aim to have an annual network meeting to further stimulate interaction and collaboration between NCMM and Associate Investigators / Young Associate Investigators and to interact with external stakeholders and to further position NCMM on the national arena.

NCMM PhD dissertations

NCMM has recruited an international group of PhD fellows and currently 15 PhD candidates from eight different countries are working on exciting projects in translational molecular medicine. In 2015 and the beginning of 2016 four NCMM PhD fellows defended their thesis.



Stefan J. Barfeld

Stefan J. Barfeld defended his thesis entitled *“The transcriptional role of c-Myc in prostate cancer”* in October 2015. The work was performed in the research group of Ian Mills and Barfeld defended his thesis at the Department of Biosciences, Faculty of Mathematics and Natural Sciences, UiO.

Every year, about 4,000 men die as a result of prostate cancer in Norway alone. Decades of research have improved detection and treatment options but nonetheless, prostate cancer often remains a fatal disease. Dysregulation of the androgen receptor, a testosterone-binding protein that controls cell proliferation, has been identified as the main cause and driver of the disease. However, a range of other proteins have been shown to play vital roles in prostate cancer. Amongst these, c-Myc is a factor that has been extensively studied in various cancers, especially lymphomas. Surprisingly, the contribution of c-Myc to prostate cancer development and androgen receptor activity has not been thoroughly examined yet.

In his PhD work, Stefan J. Barfeld identified c-Myc to be the driver of a variety of supporting metabolic pathways in prostate cancer, including purine de novo biosynthesis. This pathway is

crucial for rapidly dividing cancer cells, which need large quantities of purines to sustain proliferation. Notably, disrupting this pathway slowed cancer cell growth and induced a cellular stress response. Moreover, the impact of elevated c-Myc levels on androgen receptor activity was examined. Strikingly, c-Myc overexpression dysregulated androgen receptor activity and suppressed a range of well-established androgen receptor targets. These findings have potential implications for future prostate cancer patients as they provide novel insights into the molecular basics of the disease, which could offer treatment alternatives to current therapies.



Kristine Moltu

Kristine Moltu defended her thesis entitled *“Signal network analysis of T cell activation – in human T cells from blood donors and patients with colorectal cancer”* at the Department of Biosciences, Faculty of Mathematics and Natural

Sciences in December 2015. The work was performed in the research group of Kjetil Taskén.

In her PhD work, Kristine Moltu studied different mechanisms that regulate T cell activation both in healthy blood donors and in cancer patients. T cells play an important role in the adaptive immune system and circulate through

the blood and lymphoid tissues, looking for invading microorganisms and cancer cells, also called antigens. T cells are activated when they recognize foreign or harmful antigens and can either destroy foreign elements directly or secrete molecules that mobilize the rest of the immune system. It has been demonstrated that the organization of proteins and lipid components in the plasma membrane influences how effective and precise the T cells are activated. Moltu and colleagues therefore investigated which proteins that are recruited to the plasma membrane upon activation and which proteins that are removed. Such an overview is a good starting point for identifying proteins that can be manipulated in the immune response.

It is very important that activation of T cells is tightly regulated. The immune response needs to be sensitive enough to detect damaging cancer cells but not so sensitive that the immune system attacks the body's own cells. A T cell therefore needs two signals to become fully activated. In her PhD work, Moltu has used a new technology (phospho-flow) that enables identification of signaling cascades inside single cells to study how the second activation signal contributes to regulation of T cell activation.

Some patients with colorectal cancer secrete substances that could prevent activation of T cells and thus elimination of the cancer cells. Moltu has therefore examined which T cell activation signals that are inhibited in colorectal cancer patients compared to healthy blood donors. Insight in these differences could become valuable in the development of future cancer therapies.



MD Simer J. Bains

MD Simer J. Bains defended her thesis entitled *“Malignancy, Metastasis and Immune Modulation – Experimental Tumor Immune Regulation and Observational Clinical Studies in Ovarian and Colorectal Cancer”* in January

2016. The work was performed in the research group of Kjetil Taskén and Bains defended her thesis at the Institute of Clinical Medicine, the Medical Faculty, UiO.

In her PhD work, Simer Bains focused on how cancer develops in interaction with the body's immune system. Furthermore, she focused on different treatment strategies for patients suffering from colorectal cancer.

Aspirin is known as a common pain reliever, a drug used to reduce fever or as blood thinning medication used by heart patients. In an observational study, including 23 162 Norwegian colorectal cancer patients, Bains and colleagues revealed that patients that have been treated with aspirin live significantly longer than patients that did not use aspirin. The data in this study came from the Norwegian Cancer Registry and the Norwegian Prescription Database and included all patients diagnosed with colorectal cancer in Norway in the period 2004-2011. This is an interesting finding since aspirin is an inexpensive drug with few side effects. This information could therefor potentially benefit the 4000 patients that are diagnosed with colorectal cancer in Norway every year. Furthermore, Bains and colleagues demonstrated that colon cancer patients with liver metastases can obtain the same survival rate as patients with only localized disease if the metastases are treated as aggressively as the original tumor, using different surgical methods as well as interventions. Both studies support previous work and may contribute to change the treatment practice in the future.

In addition to the two mentioned studies, Bains examined immune cells from healthy blood

donors and from patients with ovarian cancer to identify specific properties and functions of regulatory T cells (Tregs). This cell type can modulate the immune system and is important to maintain tolerance to self-antigens. However, in connection with cancer, it is not an advantage to have too many Tregs as they can prevent the body's own immune system to fight the disease. Characterizing and understanding these cells may therefore be important to be able to develop new cancer treatments in the future. Furthermore, Bains and colleagues demonstrated that the immediate surroundings of the ovarian cancer tumor inhibit the body's immune system directly. In particular, a specific protein was identified that is being secreted into the environment surrounding the tumor and that down-regulates the immune system.



Elisa Fiorito

Elisa Fiorito has been a PhD fellow in the research group of Antoni Hurtado and defended her thesis entitled "Study of the role of CTCF and FOXA1 in breast cancer" in April 2016 at the Department of Biosciences, Faculty of Mathematics and Natural Sciences, UiO.

Breast cancer is a disease characterized by aberrant growth of the mammary epithelial cells. Its outcome can be affected by specific genetic components and by the activity of proteins influencing cell proliferation and death. In her PhD work, Elisa Fiorito aimed to understand the role of a specific genetic variant and of the transcription factors CTCF and FOXA1 in breast cancer.

Breast cancer is the most common female malignancy in the world, representing the first cause of cancer death among women. In particular, this disease is characterized by uncontrolled proliferation and migration of mammary epithelial cells. Clinical studies have shown that 70% of breast cancer cases express Estrogen Receptor α (ER), which is the main driver of cell proliferation. Upon

the interaction with its ligand estrogen, ER binds the chromatin in the nucleus, where it activates a specific transcriptional program resulting in cell proliferation. Decades of research have improved our knowledge of ER functions and prompted the development of inhibitors commonly used in breast cancer therapy. Moreover, recent studies have characterized a new class of transcription factors, named ER cooperating factors, which tightly modulate ER mediated transcription. Alterations in the functions of these factors and of their chromatin interactions can affect ER activity and breast cancer outcome.

Elisa Fiorito's PhD work aimed at elucidating the functions of ER cooperating factors in breast cancer cells. By employing genomic methods, this study shed light on the molecular mechanism through which a common genetic variant influences ER-positive breast cancer risk. Moreover, Fiorito showed that the transcription factor CTCF can repress a subset of genes related to poor prognosis breast cancer by influencing the formation of long-range chromatin interactions. In addition, Fiorito contributed to the study of FOXA1's role in the activation of genes promoting breast cancer aggressiveness and estrogen-independent cell growth.

Altogether, these findings highlight the importance of cooperating transcription factors and open clinical perspectives on the prediction of breast cancer outcome. Moreover, the development of drugs able to modulate the functions of these factors might be crucial to overcome anti-estrogen resistance and prevent breast cancer progression.





Chair of the NCMM Board, Ragnhild A. Lothe in dialogue with NCMM Director Kjetil Taskén

NCMM Board

The NCMM Board is responsible for, in collaboration with the Director, the Centre's overall coordination and progress. The Board steers and supervises NCMM's activities and finances and does also approve the Center's strategic plans, objectives and budget. The Board's decisions contribute to promote excellence in the Centre's recruitments, research, collaborations and translational value. The Board consists of the Chair and five members representing NCMM's host the University of Oslo and the consortium partner Health South-East Regional Health Authority (HSE) as well as a national representative. The Medical Faculty at UiO in February 2016 appointed a joint Board for NCMM and the Biotechnology Centre of Oslo for the period 2016-2018.

BOARD MEMBERS:

Chair:

- Professor Ragnhild A. Lothe, Oslo University Hospital (OUH) and University of Oslo (UiO)

Members:

- Professor Jan G. Bjålie, Faculty of Medicine, UiO
- Professor Finn-Eirik Johansen, Faculty of Mathematics and Natural Sciences, UiO
- Director Research and Innovation Per Morten Sandset, South-Eastern Norway Regional Health Authority (HSE)
- Professor Jens Petter Berg, Oslo University Hospital
- Maria Perander, UiT The Arctic University of Norway (national representative)

Deputy Members:

- Professor Hilde Nilsen, Faculty of Medicine, UiO and Akershus University Hospital Head of Research Øystein Krüger, Dept. of Research and Innovation, South-Eastern Norway Regional Health Authority (HSE)

Chair R. A. Lothe

"In 2015 NCMM has under the excellent leadership of Director Taskén, strengthened its national position. After a truly competitive selection, new NCMM Associate Investigators were appointed, and in January this year a two day network meeting gathered young and senior Associate Investigators as well as other collaborators for stimulating discussions and laying the ground for new collaborative initiatives."

Recently, Magnar Bjørås, Ole Sejersted and Terje Espevik completed their work as members of the Board. "We are most grateful for your important contributions to the Board's work". We also welcome the new appointed Board members Per Morten Sandset, Maria Perander and Jens Petter Berg, as well as deputy member Hilde Nilsen. The new Board serves as a joint board for the NCMM and the Biotechnology Centre. In line with the recommendations from both Scientific Advisory Board, the Board also supports the merge of the two Centres. We are pleased that the owners are positive to a merge and we foresee a formal decision in the near future. Independent of the outcome of the decision, the Board will continuously work in the best interest of the Centers and their owners"



Photo: J. Landskron, NCMM

Scientific Advisory Board (SAB)

The NCMM Scientific Advisory Board (SAB) was first appointed in 2011 and from 2015 the SAB was appointed as a joint board for NCMM and the Biotechnology Centre of Oslo. The main mission of the SAB is to offer academic and strategic advice as well as benchmark the performance of the groups and Centre internationally. To access recent progress and future strategies, the SAB has therefore decided to meet with NCMM core members every 12-24 months and the fourth site-visit took place in March 2015. The next visit is scheduled for the fall 2016.

MEMBERS OF THE SCIENTIFIC ADVISORY BOARD

The Scientific Advisory Board consists of six internationally renowned scientists:

Professor Leif Groop (Chair)

Head of Lund University Diabetes Centre
Department of Endocrinology
Clinical Sciences Malmö
Lund University, Sweden

Professor Erich Nigg

Director of Biozentrum
Basel, Switzerland

Professor Richard Treisman

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

Dr. Alvis Brazma

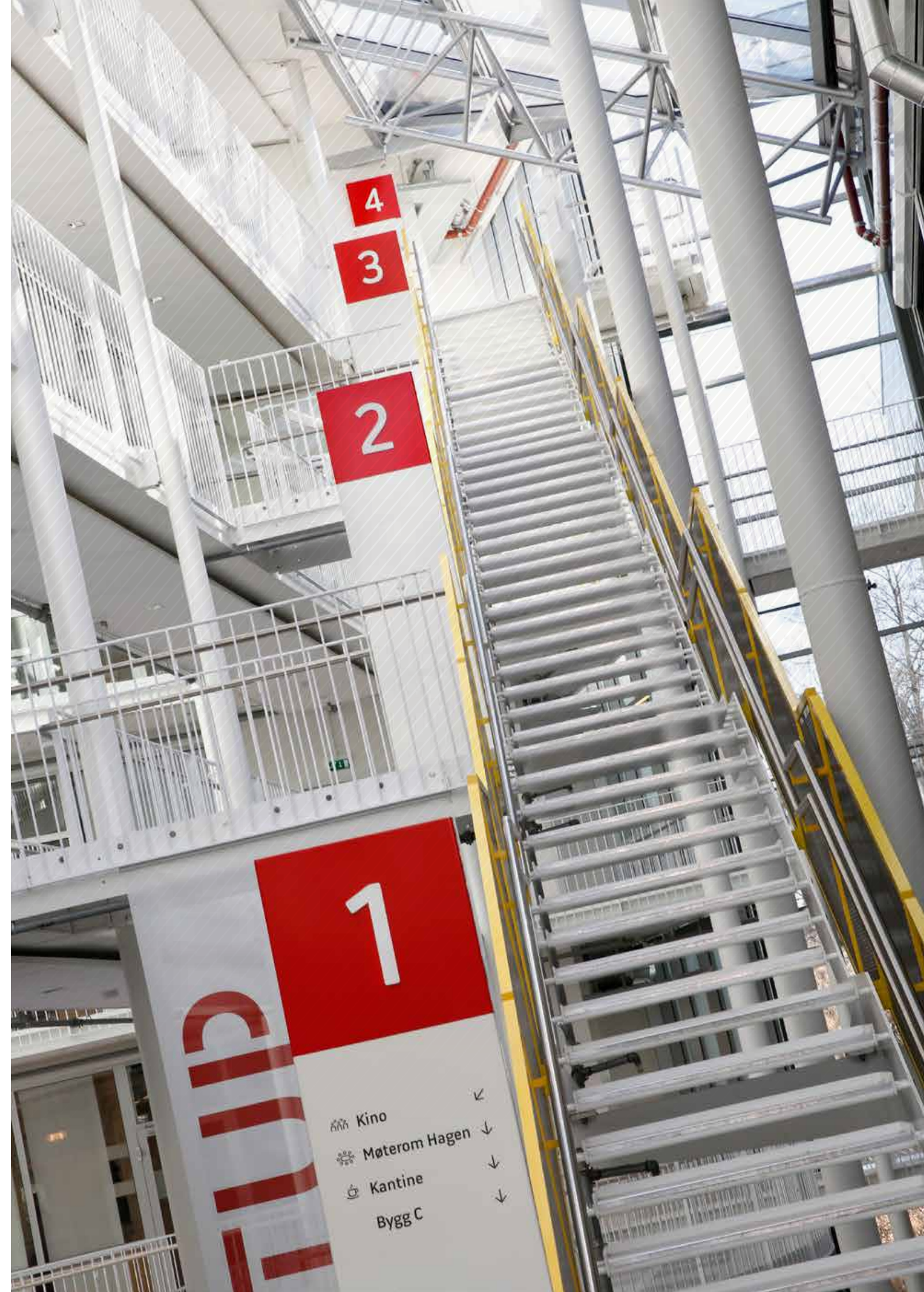
EMBL Senior Scientist & Senior Team Leader
EMBL-EBI Hinxton
Cambridge, UK

Professor Margaret Frame

Epidemiology
Edinburgh Cancer Research Centre
Edinburgh, UK

Professor Nazneen Rahman

Head of the Division of Genetics and
Epidemiology
Institute of Cancer Research
London, UK

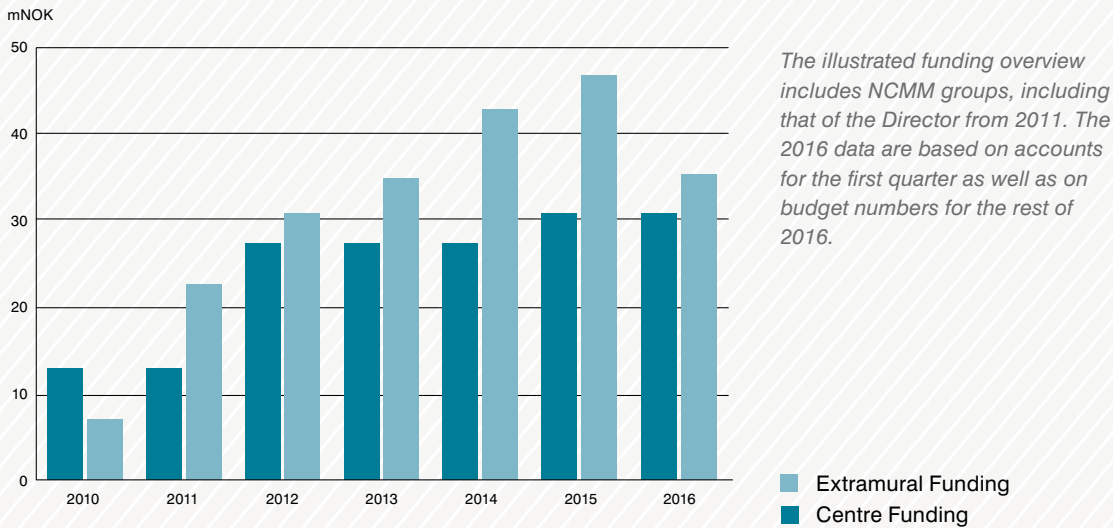


NCMM Funding

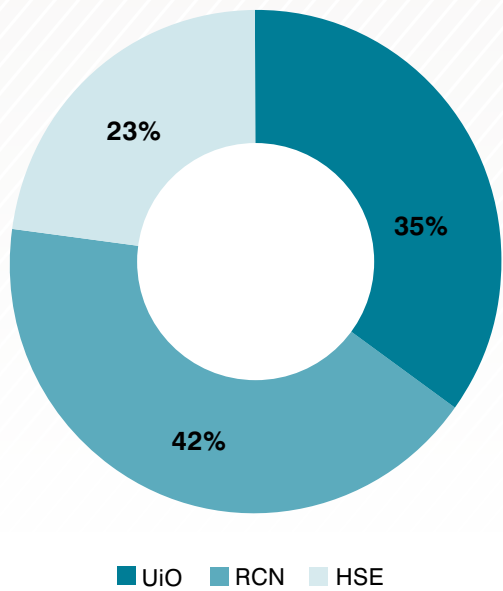
The NCMM core funding in the first five-year period was 27 million Norwegian kroner (mNOK) per year from the 3 consortia partners UiO, the Research Council of Norway (RCN) and Health SouthEast (HSE). Core funding at the same level was also secured for the interim year 2014. A midterm evaluation was carried out by an external, international committee in 2013. After the successful evaluation, NCMM is now set with funding for the period 2015-19. In this period NCMM's partners have committed to fund the Centre with 31 million Norwegian kroner per year. Including transferred funds, NCMM spent 26 mNOK in 2015. This was less than budgeted and due to delays in recruitment of a new research group. For 2016 NCMM has a budget aiming for balance and plans to spend 37 mNOK. For the period 2015-2019 we stipulate the NCMM annual core budget expenses to be in the order of 35-38 mNOK (2015-value) with the present level of activity and including transferred funds.

NCMM extramural funding in the form of grants to the group leaders and other competitive funding has increased steadily from 7 mNOK in 2010 to 43 mNOK in 2014. In 2015 NCMM reached 42 mNOK in annual grants. This includes grants from the Research Council of Norway, the Norwegian Cancer Society, Health SouthEast, , competitive grants at UiO, European Commission and private foundations and organizations such as the Lundbeck Foundation, Novo Nordic Foundation, KG Jebsen Centres, Movember and others. Extramural funding for 2016 is so far stipulated to 35 mNOK. This decrease compared to the last couple of years is a result of two research groups rotating out of the Centre in the period 2015-2016. A new research group is being established from mid-2016 and in addition a second group will be recruited. We therefore expect the amount of extramural funding to increase again from 2017.

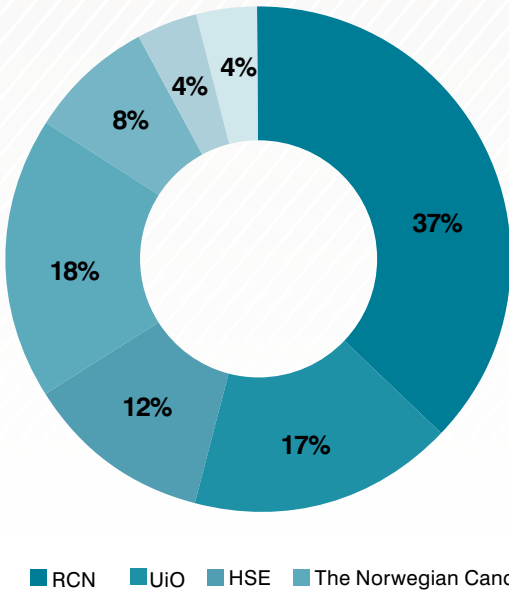
Funding statistics



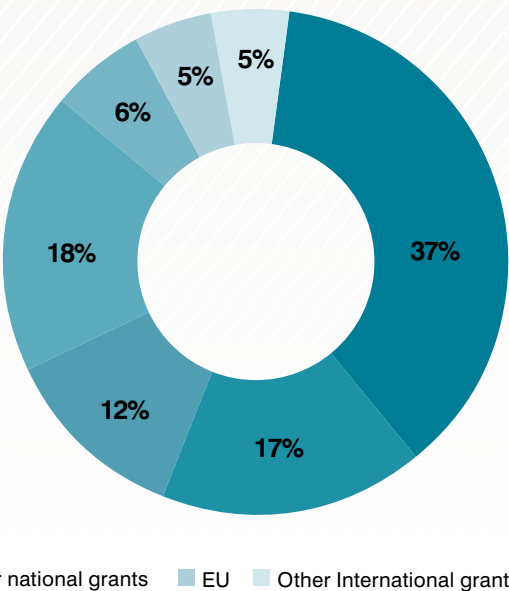
NCMM Core Funding Sources 2015



Extramural Funding Sources 2015



Estimated Extramural Funding Sources 2016



The 2016 overview is an estimate of extramural funding sources based on budget and on secured grants.

NCMM-Affiliated Publications

NCMM publications from 2015

Abundant genetic overlap between blood lipids and immune-mediated diseases indicates shared molecular genetic mechanisms. Andreassen OA, Desikan RS, Wang Y, Thompson WK, Schork AJ, Zuber V, Doncheva NT, Ellinghaus E, Albrecht M, Mattingsdal M, Franke A, Lie BA, Mills IG, Aukrust P, McEvoy LK, Djurovic S, Karlsen TH, Dale A (2015). **PLoS ONE.** 10(4):e0123057. doi: 10.1371/journal.pone.0123057

Myc-dependent purine biosynthesis affects nucleolar stress and therapy response in prostate cancer. Barfeld S, Fazli L, Persson M, Marjavaara L, Urbanucci A, Kaukoniemi KM, Rennie PS, Ceder Y, Chabes A, Visakorpi T, Mills IG (2015). **Oncotarget** 6(14):12587-602.

A differential protein solubility approach for the depletion of highly abundant proteins in plasma using ammonium sulfate. Bollineni RC, Guldvik IJ, Grönberg H, Wiklund F, Mills IG, Thiede B (2015). **The Analyst** 140(24):8109-17. doi: 10.1039/c5an01560j

Targeting protein-protein interactions in complexes organized by A kinase anchoring proteins. Calejo AI, Taskén K (2015). **Frontiers in Pharmacology** 6:192. doi: 10.3389/fphar.2015.00192

Dynamics of ionic shifts in cortical spreading depression. Enger R, Wannan T, Vindedal GF, Jensen V, Helm P, Sprengel R, Looger LL, Nagelhus EA (2015). **Cerebral Cortex** 25(11) 4469-4476. doi: 10.1093/cercor/bhv054

Spatiotemporal regulation of cAMP signaling controls the human trophoblast fusion. Gerbaud P, Taskén K, Pidoux G (2015). **Frontiers in Pharmacology** 6:202. doi: 10.3389/fphar.2015.00202

MicroRNAs enrichment in GWAS of complex human phenotypes. Goulart LF, Bettella F, Sønderby IE, Schork AJ, Thompson KW, Mattingsdal M, Steen VM, Zuber V, Wang Y, Dale A, Andreassen OA, Djurovic S (2015). **BMC Genomics** 16:304. doi: 10.1186/s12864-015-1513-5

Benzo[a]pyrene-induced nitric oxide production acts as a survival signal targeting mitochondrial membrane potential. Hardonniere K, Huc L, Podechard N, Fernier M, Tekpli X, Gallais I, Sergeant O, Lagadic-Gossmann D (2015). **Toxicol In Vitro** 29(7):1597-608. doi: 10.1016/j.tiv.2015.06.010

A Loss-of-Function Variant in a Minor Isoform of ANK3 Protects Against Bipolar Disorder and Schizophrenia. Hughes T, Hansson LJA, Sønderby IE, Athanasia L, Zuber V, Tesli MS, Song J; Hultman CM, Bergen SE, Landen M, Melle I, Andreassen OA, Djurovic S (2015). **Biol Psychiatry** 11. pii: S0006-3223(15)00859-8. doi: 10.1016/j.biopsych.2015.09.021

CIP2A is a candidate therapeutic target in clinically challenging prostate cancer cell populations. Khanna A, Rane JK, Kivinummi KK, Urbanucci A, Helenius MA, Tolonen TT, Saramäki OR, Latonen L, Manni V, Pimanda JE, Maitland N J, Westermarck J, Visakorpi T (2015). **Oncotarget** 14: 6(23):19661-70.

Activated regulatory and memory T-cells accumulate in malignant ascites from ovarian carcinoma patients. Landskron J, Helland Ø, Torgersen KM, Aandahl EM, Gjertsen BT, Bjørge L, Taskén K (2015). **Cancer Immunology and Immunotherapy** 64(3) s.337-347. doi: 10.1007/s00262-014-1636-6

Identifying Novel Gene Variants in Coronary Artery Disease and Shared Genes with Several Cardiovascular Risk Factors. LeBlanc M, Zuber V, Kulle B, Witoelar A, Zeng L, Bettella F, Wang Y, McEvoy LK, Thompso, KW, Schork AJ, Reppe S, Barrett-Connor E, Lighthart S, Dehghan A, Gautvik KM, Nelson CP, Schunkert H, Samani NJ, Ridker PM, Chasman DI, Aukrust P, Djurovic S, Frigessi A, Desikan RS, Dale A, Andreassen OA (2015). **Circ Res.** 118(1):83-94. doi: 10.1161/CIRCRESAHA.115.306629

His499 Regulates Dimerization and Prevents Oncogenic Activation by Asparagine Mutations of the Human Thrombopoietin Receptor. Leroy E, Defour JP, Sato T, Dass S, Gryshkova V, Myat Marlar S,

Staerk J, Constantinescu S, Smith SO (2015). **J Biol Chem.** 291(6):2974-87.

doi: 10.1074/jbc.M115.696534

Targeting tuberculosis and HIV infection-specific regulatory T cells with MEK/ERK signaling pathway inhibitors. Lieske NV, Tonby K, Kvale D, Dyrhol-Riise AM, Taskén K (2016). **PLoS One** 10(11):e0141903. doi: 10.1371/journal.pone.0141903

Slug-dependent upregulation of L1CAM is responsible for the increased invasion potential of pancreatic cancer cells following long-term 5-FU treatment. Lund K, Dembinski JL, Solberg N, Urbanucci A, Mills IG, Krauss S (2015). **PLoS One** 10(4):e0123684. doi: 10.1371/journal.pone.0123684

The androgen receptor controls expression of the cancer-associated sTh antigen and cell adhesion through induction of ST6GalNAc1 in prostate cancer. Munkley J, Oltean S, Vodak D, Wilson BT, Livermore KE, Zhou Y, Star E, Floros VI, Johannessen B, Knight B, McCullagh P, McGrath J, Crundwell M, Skotheim RI, Robson CN, Leung HY, Harries LW, Rajan P, Mills IG, Elliott DJ (2015). **Oncotarget** 6(33):34358-74. doi: 10.18632/oncotarget.6024

Maintaining a Healthy Balance: Targeting TERT to Stem Benign Prostatic Hyperplasia. Pickard A, Mills IG (2015). **Eur Urol** 69(4):555-6. doi: 10.1016/j.eururo.2015.10.028

Anchored PKA as a gatekeeper for gap junctions. Pidoux G, Taskén K (2015). **Commun Integr Biol** 8(4):e1057361. doi:10.1080/19420889.2015.1057361

Targeting of type I protein kinase A to lipid rafts is required for platelet inhibition by the 3,5-cyclic adenosine monophosphate-signaling pathway. **J Thromb Haemost** 13(9):1721-34. doi: 10.1111/jth.13042

Genetic Sharing with Cardiovascular Disease Risk Factors and Diabetes Reveals Novel Bone Mineral Density Loci. Reppe S, Wang Y, Thompson WK, McEvoy LK, Schork, AJ, Zuber Verena, LeBlanc M, Bettella F, Mills IG, Desikan RS, Djurovic S, Gautvik KM, Dale AM, Andreassen OA, GEFOS Consortium (2015). **PLoS One** 10(12):e0144531. doi: 10.1371/journal.pone.0144531

Reduced expression of aquaporins in human intestinal mucosa in early stage inflammatory bowel disease. Ricanek P, Lunde LK, Frye SA, Støen M, Nygård S, Morth JP, Rydning A, Vatn MH, Amiry-Moghaddam M, Tønjum,T (2015). **Clin Exp Gastroenterol** 8:49-67. doi: 10.2147/CEG.S70119

Integration of copy number and transcriptomics provides risk stratification in prostate cancer: A discovery and validation cohort study. Ross-Adams H, Lamb AD, Dunning MJ, Halim S, Lindberg J, Massie CM, Egevad IA, Russel R, Ramos-Montoya A, Vowler SL, Sharma NL, Kay J, Whitaker H, Clark J, Hurst R, Gnanapragasam VJ, Shah NC, Warren AY, Cooper CS, Lynch AG, Stark R, Mills IG, Gronberg H, Neal DE (2015). **EBioMedicine** 2(9):1133-44. doi: 10.1016/j.ebiom.2015.07.017

Monitoring regulatory T cells in clinical samples: consensus on an essential marker set and gating strategy for regulatory T cell analysis by flow cytometry. Santegoets SJAM, Dijkgraaf EM, Battaglia A, Beckhove P, Britten CM, Gallimore A, Godkin A, Gouttefangeas C, de Gruijl TD, Koenen HJPM, Scheffold A, Shevach EM, Staats J, Tasken K, Whiteside TL, Kroep JR, Welters MJP, van der Burg SH (2015). **Cancer Immunol Immunother** 64(10):1271-86. doi: 10.1007/s00262-015-1729-x

Glucocorticoid receptor and Klf4 co-regulate anti-inflammatory genes in keratinocytes. Sevilla LM, Latorre V, Carceller E, Boix J, Vodak D, Mills IG, Pérez P (2015). **Mol Cell Endocrinol** 412:281-9. doi: 10.1016/j.mce.2015.05.015

The Early Effects of Rapid Androgen Deprivation on Human Prostate Cancer. Shaw GL, Whitaker H, Cocoran M, Dunning MJ, Luxton H, Kay J, Massie CE, Miller JL, Lamb AD, Ross-Adams H, Russel R, Nelson AW, Eldridge MD, Lynch AG, Ramos-Montoya A, Mills IG, Taylor AE, Arlt W, Shah N, Warren AY, Neal DE (2015). **Eur Urol** pii: S0302-2838(15)01076-3. doi: 10.1016/j.eururo.2015.10.042

Divergent androgen regulation of unfolded protein response pathways drives prostate cancer. Sheng X, Arnoldussen YJ, Storm ML, Tesikova M, Nenseth HZ, Zhao S, Fazli L, Rennie PS, Risberg BÅ, Wæhre H, Danielsen HE, Mills IG, Jin Y, Hotamisligil GS, Saatcioglu F (2015). **EMBO Mol Med** 7(6):788-801. doi: 10.15252/emmm.201404509

Enzymatic detection and quantification assay of isatin, a putative stress biomarker in blood. Sommer T, Bjerregaard-Andersen K, Simensen SM, Jensen JK, Jochimsen B, Riss P, Etzerodt M, Morth JP (2015). **ACS Chem Neurosci** 6(8):1353-60. doi: 10.1021/cn500346x

Genetic Markers of Human Evolution Are Enriched in Schizophrenia. Srinivasan S, Bettella F, Mattingsdal M, Wang Y, Witoelar A, Schork AJ, Thompson WK, Zuber V, Winsvold BKS, Zwart JAnker, Collier DA, Desikan RS, Melle I, Werge T, Dale A, Djurovic S, Andreassen OA (2015). **Biol Psychiatry.** pii: S0006-3223(15)00855-0. doi: 10.1016/j.biopsych.2015

NCMM-AFFILIATED PUBLICATIONS

Autophagic bulk sequestration of cytosolic cargo is independent of LC3, but requires GABARAPs. Szalai P, Hagen LK, Sætre F, Luhr M, Sponheim M, Øverbye A, Mills IG, Seglen PO, Engedal KN (2015). **Exp Cell Res** 333(1):21–38. doi: 10.1016/j.yexcr.2015.02.003

Augmentation of Ca²⁺ signaling in astrocytic endfeet in the latent phase of temporal lobe epilepsy. Szokol K, Heuser K, Tang W, Jensen V, Enger R, Bedner P, Steinhäuser C, Taubøll E, Ottersen OP, Nagelhus EA (2015). **Front Cell Neurosci** 9:49. doi: 10.3389/fncel.2015.00049

Novel steps in the autophagic-lysosomal pathway. Sætre F, Hagen LK, Engedal KN, Seglen PO (2015). **FEBS J** 282(11):2202–14. doi: 10.1111/febs.13268

Stimulation-evoked Ca²⁺ signals in astrocytic processes at hippocampal CA3-CA1 synapses of adult mice are modulated by glutamate and ATP. Tang W, Szokol K, Jensen V, Enger R, Trivedi CA, Hvalby Ø, Helm PJ, Looger LL, Sprengel R, Nagelhus EA (2015). **J Neurosci** 35(7):3016–21. doi: 10.1523/JNEUROSCI.3319-14.2015.

Transplantation with livers from deceased donors older than 75 years. Thorsen T, Aandahl EM, Bennet W, Olausson M, Ericzon BG, Nowak G, Duraj F, Isoniemi H, Rasmussen A, Karlsen TH, Foss A (2015). **Transplantation** 99(12):2534–42. doi: 10.1097/TP.0000000000000728

Liver transplantation with deceased ABO-incompatible donors is life-saving but associated with increased risk of rejection and post-transplant complications. Thorsen T, Dahlgren US, Aandahl EM, Grzyb K, Karlsen TH, Boberg KM, Rydberg L, Naper C, Foss A, Bennet W (2015). **Transpl Int** 28(7):800–12. doi: 10.1111/tri.12552.

NCMM emerging publications 2016
Choline Kinase Alpha as an Androgen Receptor Chaperone and Prostate Cancer Therapeutic Target. Asim M, Massie CE, Orafidiya F, Pérttega-Gomes N, Warren AY, Esmaeili M, Selth LA, Zecchini HI, Luko K, Qureshi A, Baridi A, Menon S, Madhu B, Escriu C, Lyons S, Vowler SL, Zecchini VR, Shaw G, Hessenkemper W, Russell R, Mohammed H, Stefanos N, Lynch AG, Grigorenko E, D’Santos C, Taylor C, Lamb A, Sriranjana R, Yang J, Stark R, Dehm SM, Rennie PS, Carroll JS, Griffiths JR, Tavaré S, Mills IG, McEwan IJ, Baniahmad A, Tilley WD, Neal DE (2016). **J Natl Cancer Inst** 108(5). pii: djv371. doi: 10.1093/jnci/djv371

Aspirin as Secondary Prevention in 23,162 Patients with Colorectal Cancer - An Unselected Population-Based Study. Bains SJ, Mahic M, Myklebust TÅ, Småstuen MC, Yaqub S, Dørum LM, Bjørneth BA, Møller

B, Brudvik KW, Taskén K (2016). **J. Clin Oncol.** (In Press)

Mapping Protein–DNA Interactions Using ChIP-exo and Illumina-Based Sequencing. Barfeld S, Mills IG (2016). **Methods in Molecular Biology** (In Press)

Regulatory T cells that co-express RORγt and FOXP3 are pro-inflammatory and immunosuppressive and expand in human pancreatic cancer. Chelappa S, Hugenschmidt H, Hagness M, Line PD, Labori KJ, Wiedsvang G, Taskén K, Aandahl EM (2016). **Oncoimmunol** (In Press)

Human regulatory T cells control TCR signaling and susceptibility to suppression in CD4⁺ T cells. Chelappa S, Lieske NV, Hagness M, Line PD, Taskén K, Aandahl EM (2016). **J Leukoc Biol**

pii: jlb.2H10815-334R. [Epub ahead of print]

Inhibition of O-GlcNAc transferase activity reprograms prostate cancer cell metabolism. Ikonen HM, Gorad SS, Duveau DY, Martin SE, Barkovskaya A, Bathen TF, Moestue SA, Mills IG (2016). **Oncotarget** [Epub ahead of print] doi: 10.18632/oncotarget.7039

Phosphoprotein detection by high-throughput flow cytometry. Landskron J, Taskén K (2016). **Methods in Molecular Biology**,1355: 275–90. doi: 10.1007/978-1-4939-3049-4_19

Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozana A, Adachi H, Adams CM, Adams PD, Adeli K, Adhihetty PJ, Adler SG, Agam G, Agarwal R, Aghi MK, Agnello M, Agostinis P, Aguilar PV, Aguirre-Ghiso J, Airolidi EM, Ait-Si-Ali S, Akematsu T, Akporiaye ET, Al-Rubeai M, Albaiceta GM, Albanese C, Albani D, Albert ML, Aldudo J, Algul H, Alirezaei M, Alloza I, Almasan A, Almonte-Beceril M, Alnemri ES, Alonso C, Altan-Bonnet N, Altieri DC, Alvarez S, et al. (2016). **Autophagy** 2;12(1):1–222.

Critical role of CD2 co-stimulation in adaptive NK cell responses revealed in NKG2C-deficient humans. Liu L, Landskron J, Ask EH, Enqvist M, Sohlberg M, Traherne J, Hammer Q, Goodridge J, Larsson S, Jayaraman Oei VYS, Schaffer M, Taskén K, Ljunggren HG, Romagnani C, Trowsdale J, Malmberg KJ, Béziat V (2016). **Cell Reports** (In Press)

The importance of DNA methylation in prostate cancer development. Massie CE, Mills IG, Lynch AG (2016). **The Journal of Steroid Biochemistry and Molecular Biology** (In Press)

The role of glycans in the development and progression of prostate cancer. Munkley J, Mills IG (2016). **Nature Reviews Urology** (In Press)

Glycosylation is an androgen-regulated process essential for prostate cancer cell viability. Munkley J, Vodak D, Livermore KE, James K, Wilson BT, Knight B, McCullagh P, McGrath J, Crundwell M, Harries LW, Leung HY, Robson CN, Mills IG, Rajan P, Elliott DJ (2016). **EBioMedicine** (In Press)

Spleen tyrosine kinase inhibitors block CD40L induced proliferation of chronic lymphocytic leukemia cells. Parente-Ribes A, Skånland SS, Bürgler S, Os A, Wang D, Bogen B, Tjønnfjord GE, Taskén K, Munthe LA (2016). **Hematologica** (In press)

The magnesium transporter A is activated by cardiolipin and is highly sensitive to free magnesium in vitro. Subramani S, Perdreau-Dahl H, Morth JP (2016). **Elife** 5. pii: e11407. doi: 10.7554/eLife.11407

Gene regulatory mechanisms underpinning prostate cancer susceptibility. Whittington T, Gao P, Song W, Ross-Adams H, Lamb AD, Yang Y, Svezia I, Klevebring D, Mills IG, Karlsson R, Halim S, Dunning MJ, Egevad L, Warren AY, Neal DE, Gronberg H, Lindberg J, Wei GH, Wiklund F (2016). **Nat Genet** 48(4):387–97. doi: 10.1038/ng.3523.

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

Press Items
Norwegian Cancer Society: brochure on personalized medicine sent to 600 000 households in Norway, February 2015. NCMM Director Kjetil Taskén main profile in the brochure.

Forskning.no – Ingrid Spilde, March 2015: *Does our immune defence become stronger after infections?* Interview with Kjetil Taskén and Trude Flo (NTNU): <http://forskning.no/2015/02/blir-immunforsvaret-sterkere-etter-sykdom>

Nasjonal Kreftsatsning, March 2015: Klinisk kreftgenomikk – hva skal til? Panel discussions with NCMM group leader Ian Mills: https://www.youtube.com/watch?v=4xMeXIoAJ_U&feature=youtu.be

Nasjonal Kreftsatsning, March 2015: Klinisk kreftgenomikk – hva skal til? Panel discussions with NCMM Director Kjetil Taskén: https://www.youtube.com/watch?v=hN34wFMOG_M

NCMM group leader Preben Morth mentioned in C&EN, 30 April 2015: <http://cen.acs.org/articles/93/>

web/2015/04/Assay-Shed-Light-Potential-Stress.html%20April%2030,%202015

NCMM Director featured on the facebook page “Humans of Oslo Science Park” by Oslo Science Park, May 2015

Dagens Medisin, 30 May 2015: Interview with Simer Bains, PhD fellow NCMM, about her short oral presentation at the 2015 ASCO Meeting in Chicago, on a registry coupling study on secondary preventive effect of aspirin in unbiased population of 25,000 Norwegian colorectal cancer patients.

<http://www.dagensmedisin.no/artikler/2015/05/30/billig-medisin-med-god-effekt-pa-tarmkreft/>

Dagens Medisin, 30 May 2015: Simer Bains at the ASCO 2015 Meeting: <http://www.dagensmedisin.no/artikler/2015/05/31/asco-debuterte-foran-5000/>

Professor David Kerr, Oxford comments on Aspirin registry study above presented at ASCO, 2015 <http://www.medscape.com/viewarticle/845146>

Best of ASCO 2015: The abstract on Aspirin registry study above presented at ASCO, 2015 featured in run-through from meeting, Boston, Jul 31, Aug 1 and San Francisco, Aug 7–8. 2015, in sessions on Gastrointestinal (Colorectal) Cancer: <http://10times.com/asco-boston-meeting> and <http://west-bio.asco.org/program-o>

BMC Medicine report from ASCO on presentation of Aspirin Registry Study: <http://blogs.biomedcentral.com/on-medicine/2015/06/02/advances-insights-clinical-oncology-bmc-medicine-asco-2015/>

Cancer Network Oncology report on presentation of Aspirin Registry Study at ASCO 2015. <http://www.cancernetwork.com/asco-2015-colorectal-cancer/aspirin-may-help-survival-after-colorectal-cancer-diagnosis>

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[tasken-at-the-university-of-oslo-awarded-king-olav-vs-cancer-research-award-2016/](http://occincubator.com/professor-kjetil-tasken-at-the-university-of-oslo-awarded-king-olav-vs-cancer-research-award-2016/)

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Personnel

DIRECTOR AND ADMINISTRATION

Director
Kjetil Taskén

Chief Administrative Officer
Elisa Bjørge

Financial Officer
Anita Skolem

Human Resources Officer
Nina Modahl

RESEARCH GROUPS

Prostate Cancer Group
NCMM Group Leader
Ian Mills

Head Engineers
Ingrid Jenny Guldvik
Frank Sætre

Guest Researcher
Per O. Seglen

Researcher
Nikolai H. Engedal

Postdoctoral Fellows
Harri Itkonen
Alfonso Urbanucci

PhD Fellows
Stefan Barfeld (until October 2015)
Lisa Gerner
Morten Luhr
Paula Szalai (from January 2016)

Membrane Transport Group

NCMM Group Leader
Jens Preben Morth

Principal Engineer
Steffi Munack (until December 2015)
Bojana Damjanovic (from February 2016)

Postdoctoral Fellows
Johannes Bauer
Kaare Bjerregaard-Andersen (until August 2015)
Kim Langmach Hein (until August 2015)
Harmonie Perdreau-Dahl

PhD Fellows
Theis Sommer
Saranya Subramani

MSc Students
Carolina Alvadia
Stephanie Ruhland (from April 2016)

Signaling Networks in Health and Disease

NCMM Group Leader
Kjetil Taskén

Senior Researchers
Einar Martin Aandahl
Johannes Landskron
Sigrid Skånland

Postdoctoral Fellows
Ana Isabel Costa Calejo
Dihn-Toi Chu (from November 2015)
Anna Mari Lone
Kristina Berg Lorvik
Maria-Niki Mylanokou
Deepak B. T. G. Raj (from February 2016)
Vannessa L. Wehbi

PhD Fellows
Simer J. Bains (until January 2016)
Stalin Chelappa
Aleksandra Dukić
Nora Lieske
Kristine Moltu (until December 2015)
Ellen Østensen

MSc students
Ida K. Myhrvold

Scientific Officers
Marianne Enger (from February 2016)
Jorun Solheim (until March 2016)
Martine Schröder (from February 2016)
Gladys Tjørhom (until December 2015)

Administrative Officer
Berit Barkley

Breast Cancer Group

NCMM Group Leader
Antoni Hurtado

Head Engineer
Siv Gilfillan

Postdoctoral Fellow
Venkata S. Somisetty
Sachin Kumar Singh (from June 2015)

PhD Fellow
Elisa Fiorito
Shixiong Wang

MSc student
Torbjørn A. Lien (from March 2016)

Assistant
Signe H. Kaarstad (from March 2016)

Stem Cell Group

NCMM Group Leader
Judith Staerk

Principal Engineer
Kirsti E. Præsteng (from March 2015)

Postdoctoral Fellow
Safak Caglayan
Adnan Hashim
Artur Cieslar-Pobuda (from March 2016)
Ida Jonson
Marie Rogne
Xavier Tekpli (until July 2015)

PhD Fellows
Julia-Kristina Jensen Madsen-Østerbye
Oksana Svärd

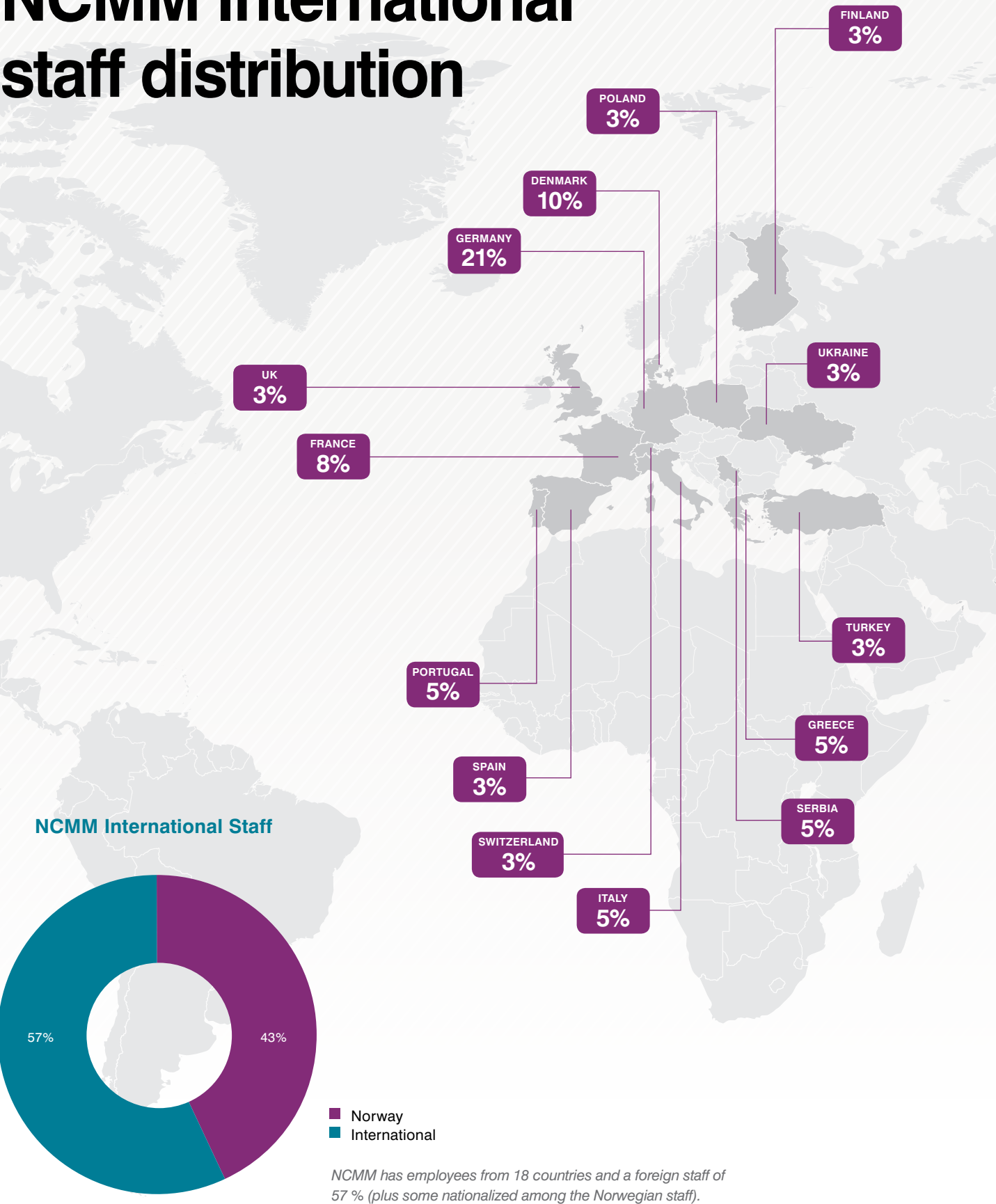
Computational Biology and Gene Regulation

NCMM Group Leader
Anthony Mathelier (from May 2016)

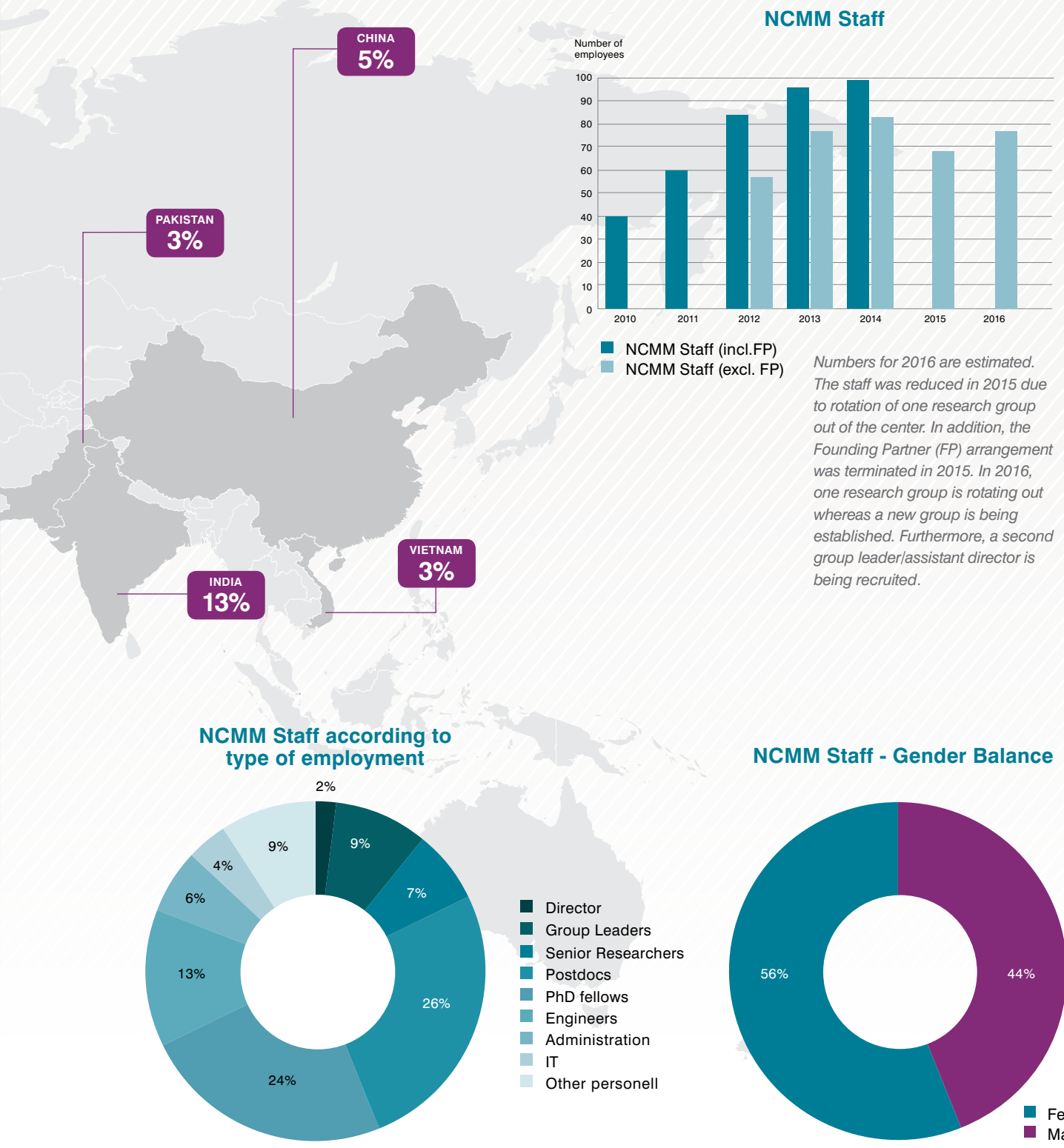
IT Team

Dr. George Magklaras
Gang Cheng
Melaku Tadesse

NCMM International staff distribution



Personnel statistics



NCMM partnerships, collaborations & affiliations

NCMM Partners



UiO : University of Oslo



Nordic EMBL Partnership for molecular medicine



National & international collaborations



www.ncmm.uio

P.O.Box 1137 Blindern, NO-0318 Oslo, Norway

Forskningsparken, Gaustadalleen 21,

0349 Oslo, Norway