

Centre for Cancer Biomedicine

2007–2017

2007



2008

2009

2010

2011

2012

2013

2014

2015

2016

2017

Uniting forces against cancer

We would like to thank everyone involved in CCB for 10 truly amazing years of high-level research combined with enthusiasm and a friendly and collegial environment.

	3
Comments by the directors	4
2007	8
2008	10
2009	13
2010	16
2011	20
2012	25
2013	36
2014	41
2015	46
2016	54
2017	58
Research groups	64
PhD/MSc degrees in CCB	76
The CCB organisation	80

TEN YEARS WITH CCB – A SUCCESS STORY

Harald Stenmark
Director

Ragnhild A. Lothe
Co-Director

The 10th annual symposium at Farris Bad Hotel 28-29 August 2017 marked the end of Centre for Cancer Biomedicine (CCB) as a Norwegian Centre of Excellence (CoE). Here we provide some reflections about the achievements of CCB, as well as the continuation of the centre's research.

The realization of a vision

The initiative to propose a CoE in cancer research was taken by the late Sjur Olsnes, a proponent for excellence in science. CCB's vision, in simplified terms, was to "unite basic and translational cancer research for the benefit of the patient". CCB has remained faithful to this vision, and has delivered top-level multidisciplinary research results from which innovations have emerged and clinical studies and trials have been initiated.

Genuine collaborations across disciplines

Even though added scientific value through interdisciplinary collaborations was the principal idea of CCB, it became clear that such collaborations rarely happen spontaneously, and during the early phase of CCB considerable effort was put into stimulating joint projects. These efforts have been rewarded with a number of successful projects that were ground-breaking because they combined patient-oriented discoveries with cell biological insights. Examples of this are provided

in this report. CCB's biostatisticians have had a prominent role in the joint projects since their expertise has enabled analyses of big data from cancer genomics and proteomics studies as well as interpretations of imaging data and biochemical analyses from cell biology.

Educating and training the next generation of cancer researchers

In the project proposal, CCB promised to graduate 50 PhDs during the centre period, an ambitious goal. Now that status can be made, we are proud to announce that as many as 61 PhDs have graduated from CCB, two of these with the prestigious H.M. the King's Gold Medal. CCB's group leaders have not used any of the CoE funding to reduce their teaching duties. On the contrary, CCB has financed as many as 5 adjunct (associate) professorships at the University of Oslo, which have contributed significantly to training in cancer research at the Faculties of Medicine and Mathematics & Natural Sciences. Furthermore, CCB's course



The director of CCB Harald Stenmark with co-director Ragnhild A. Lothe.

on "Advanced cancer biology", led by CCB young PI Guro E. Lind, has been very well attended and has received excellent ratings from students. CCB has also taken responsibility for the education of 51 master degrees, and for training of postdocs and early-career researchers, especially in the form of courses in leadership and laboratory management. Some of this training has occurred as part of CCB's programme for equal opportunities, and the percentage of female project leaders in CCB has indeed increased from 20% in 2007 to 43% in 2017.

Achievements that have pushed the frontiers of science

The long-term funding as a CoE has given CCB the opportunity to embark on ambitious projects that have pushed the frontiers of science. As exemplified in this report, CCB scientists have identified characteristics of cancers that enable us to diagnose cancer at an early stage and tailor therapy to the individual patient. CCB scientists have also uncovered fundamental molecular mechanisms of cancer suppression and development that provide new opportunities for diagnosis and therapy. Ground-breaking discoveries are often, but not always, published in the most prestigious scientific journals. If we use publications in the world-leading interdisciplinary journals Nature and Science as a benchmark, CCB is among the most successful Norwegian CoEs with 13 papers in these journals of which CCB scientists are senior authors of 8.

43%

The percentage of female project leaders in CCB has increased from 20% in 2007 to 43% in 2017

Group leader Rolf I. Skotheim, co-director Ragnhild A. Lothe, and group leader Guro E. Lind.



CCB is among the most successful Norwegian CoEs.

CCB has also had a significant publication rate in other top-ranked journals such as New England Journal of Medicine, Cancer Cell, Nature Genetics, Journal of Clinical Oncology, Cancer Discovery, Nature Cell Biology, and Gastroenterology.

Innovations that benefit patients and medical personnel

An important step in bringing a scientific discovery from bench to bedside is to secure intellectual property rights. As exemplified elsewhere in this report, CCB scientists have been very active in making scientific innovations. CCB scientists have filed as many as 36 patent applications. For instance, the Lothe group holds 8 patents for novel cancer biomarkers whereas the Danielsen group holds 9 patents for novel informatics and bioinformatics tools and apps for smartphones. The commercialization of these innovations may ultimately benefit health care personnel as well as cancer patients.

Making an impact that is visible for a wide audience

It has been a goal for CCB that its science has an impact on cancer research and treatment that is noticed beyond the scientific community. CCB has published as many as 655 papers, many of which have been dedicated covers and editorials in major international research journals. Major discoveries have also been covered in popularized format in TV, radio, podcasts, newspapers and magazines, and CCB's web pages with research news have been frequently visited. The many awards, recognitions and prizes to CCB's junior and senior scientists (examples are given in this report) have also contributed to make CCB's research achievements visible to a wide audience.

Making footprints that last into the future

Even though CCB's time as a Norwegian CoE is over, the major scientific achievements made in CCB will continue to influence Norwegian cancer research, and CCB's scientists are already engaged in new centres and projects with high ambitions. For example, Harald Stenmark will lead a new CoE, Centre for Cancer Cell Reprogramming, in which three previous CCB project leaders – Anne

– a key to unlocking the secrets of the DNA (de)methylation machinery“ and “FRIPRO” project, “Transcript variation in multifocal prostate cancer”, respectively, by the Research Council of Norway. All these new projects and centres are based on scientific discoveries made in CCB and are the best testimony that CCB has been making a lasting impact on science in Norway.

Acknowledgements

We would like to thank everyone involved in CCB for 10 truly amazing years of high-level research combined with enthusiasm and a friendly and collegial environment. This goes to our lab assistants, technicians, students, postdocs, researchers, PIs, associate members, and visiting professors. We are particularly grateful to our clinical associates, professors Arild Nesbakken, Harald Holte and Karol Axcróna for their valuable contributions to the patient-oriented research and training of young scientists. We thank CCB's excellent scientific advisory board, professors Olli Kallioniemi, Manuel Sobrinho-Simões, David Kerr, Lena Claesson-Welsh and Marja Jäätelä, who have given extremely helpful advice, especially in the critical early phase of the centre. The Board of CCB, first chaired by Sigbjørn Fossum and later by Hilde Nebb, has been genuinely supportive and provided important information and advice during the whole centre period. CCB's two host institutions, the University of Oslo and Oslo University Hospital, have likewise been professional and supportive hosts of the centre, and the centre's access to cutting-edge research infrastructure has been a key to its success. Obviously we would like to thank the Research Council of Norway for substantial funding and for giving us the opportunity to follow our scientific visions. We would also like to thank our sponsors, in particular the Norwegian Cancer Society, the South-Eastern Norway Regional Health Authority, the European Research Council, and the National Institutes of Health. Finally, we would like to acknowledge all cancer patients who have allowed CCB's research on clinical samples through written informed consent.

Simonsen, Tor Erik Rusten and Jørgen Wesche – will be among the PIs. Ragnhild A. Lothe is director of the K.G. Jebsen Colorectal Cancer Research Centre and leads “SMART- colorectal cancer”, one of five priority areas at Oslo University Hospital. She was also recently granted the “Toppforsk” project “Modeling tumor heterogeneity in colorectal cancer management” by the Research Council and the University of Oslo. Håvard E. Danielsen leads “DoMore!”, a “Lighthouse” project of the Research Council, which focuses on innovative information technology in cancer diagnosis and prognosis. Another CCB PI, Knut Liestøl, is a central co-applicant in this high-profile venture. Kirsten Sandvig leads the large-scale national nanotechnology project of the Research Council, “Biodegradable nanoparticles in cancer diagnosis and therapy”. Erlend B. Smeland leads a project of the Norwegian Cancer Society entitled “Translational research in B-cell lymphoma” and a “FRIPRO” project of the Research Council, “New diagnostic markers and targets for therapeutic intervention in B-cell lymphoma”. The two elected CCB young PIs, Guro E. Lind and Rolf I. Skotheim, have received a Young Research Talent grant “Methylation supernegative colorectal cancers

2007

Selected publications

Autophagy paper from CCB researchers highlighted in Science

A paper from Anne Simonsen and co-workers entitled "Promoting basal levels of autophagy in the nervous system enhances longevity and oxidant resistance in adult *Drosophila*" published in the journal *Autophagy*, 4 (2), 176-84 - showing that induction of autophagy in the neurons of aging flies strongly increases their life span - was dedicated an editorial (Editor's choice) in the December 14 issue of *Science*. Simonsen was the leader of the project group "Autophagy in health and disease" at Centre for Cancer Biomedicine, Institute for Cancer Research.

Prizes / Awards

Dr. Ragnar Mørk legacy prize to Anne Simonsen

In 2007 the Dr. Ragnar Mørk legacy prize was awarded to Anne Simonsen from the Centre for Cancer Biomedicine at the Norwegian Radium Hospital. The Dr. Ragnar Mørk legacy prize is distributed annually to a scientist who has achieved excellent results throughout years of outstanding research. The award is personal, and amounts to NOK 200,000.

For several years Anne Simonsen has been trying to understand how the enzyme PI 3-kinase regulates intracellular transport. She was project leader for "Autophagy in health and disease". This project aimed to clarify how autophagy is regulated, and how faulty regulation of autophagy can lead to diseases such as cancer and neurodegenerative illness.

The Dr. Ragnar Mørk legacy prize is distributed annually to a scientist who has achieved excellent results throughout years of outstanding research. The award is personal, and amounts to NOK 200,000.

Selected publications

Editorial in Cell highlights paper from Tor Erik Rusten and co-workers

The December 28 issue of "Cell" had an editorial about autophagy. Here, recent important publications that had contributed to our understanding of this process by identifying new molecular players and new ways to manipulate autophagic pathways, were discussed. Among these was an article from Tor Erik Rusten and co-workers entitled "ESCRTs and Fab1 regulate distinct steps of autophagy" (*Curr Biol*, 17 (20), 1817-25).

The cellular process of autophagy (literally self-eating) is important during development and in the normal physiology of an organism. During autophagy, cellular components destined for degradation are enclosed in a double-membraned vesicle (the autophagosome), which then fuses with a lysosome where the contents are degraded and mostly recycled. Dysregulation of autophagy occurs in many diseases including cancer and neurodegeneration. Several papers contribute to our understanding of autophagy by identifying new molecular players in this process and new ways to manipulate autophagic pathways.



Project leader Tor Erik Rusten studies fruit flies.

Several papers contribute to our understanding of autophagy by identifying new molecular players in this process and new ways to manipulate autophagic pathways.

2008

Selected publications

CCB group leader Erlend Smeland contributed to paper on oncogenic mutation in DLBC Lymphoma published in Science, and to a New England Journal of Medicine article that links gene expression signatures to survival in lymphoma patients.

Erlend B. Smeland and Jan Delabie co-authored an article entitled “Oncogenic CARD11 mutations in human diffuse large B cell lymphoma”, published in Science in March 2008. These important findings came as a result of an international collaborative effort involving prominent scientists from cancer centres in the USA, Canada, Germany, Spain and Norway.

Lenz G, Davis RE, Ngo VN, Lam L, George TC, Wright GW, Dave SS, Zhao H, Xu W, Rosenwald A, Ott G, Muller-Hermelink HK, Gascoyne RD, Connors JM, Rimsza LM, Campo E, Jaffe ES, Delabie J, Smeland EB, Fisher RI, Chan WC, Staudt LM (2008) Oncogenic CARD11 mutations in human diffuse large B cell lymphoma Science, 319 (5870), 1676-9.

The results of a large study of B-cell lymphoma patients by Smeland and collaborators published in New England Journal of Medicine, showed that survival after combined chemotherapy was determined by differences in immune cells, fibrosis, and angiogenesis in the tumour microenvironment. This was reflected in the gene expression signatures.

Lenz G, Wright G, Dave SS, Xiao W, Powell J, Zhao H, Xu W, Tan B, Goldschmidt N, Iqbal J, Vose J, Bast M, Fu K, Weisenburger DD, Greiner TC, Armitage JO, Kyle A, May L, Gascoyne RD, Connors JM, Troen G, Holte H, Kvaloy S, Dierickx D, Verhoef G et al. (2008) Stromal gene signatures in large-B-cell lymphomas N Engl J Med, 359 (22), 2313-23.

Prizes / Awards

Dr. Ragnar Mørk legacy prize to Tor Erik Rusten

The 2008 prize from Dr. Ragnar Mørk’s legacy went to Tor Erik Rusten, senior scientist in CCB.

The Dr. Ragnar Mørk legacy prize is awarded annually to a scientist who has achieved excellent results throughout years of outstanding research. The award is personal and amounts to NOK 200,000.

Rusten was leading a project group on “Phosphatidylinositol kinase signaling and disease” where the focus was to investigate the functions of the at that time identified Tumour Suppressor Enzyme Complex termed PI3K-III, to gain novel insight into carcinogenesis.

Selected publications

CCB scientist published findings about entry of nanoparticles into cells

Senior CCB scientist Tore-Geir Iversen published a paper entitled “Cellular trafficking of quantum dot-ligand bioconjugates and their induction of changes in normal routing of unconjugated ligands” in the June 21st issue of Nano Letters.

Tekle C, Deurs Bv, Sandvig K, Iversen TG (2008) Cellular trafficking of quantum dot-ligand bioconjugates and their induction of changes in normal routing of unconjugated ligands Nano Lett, 8 (7), 1858-65.

Tore Geir Iversen, project leader working with nanoparticles, and Alicia Llorente, project leader working with exosomes.





2009

Funding

ERC Advanced Grant to CCB director Harald Stenmark

Harald Stenmark from the Department of Biochemistry at the Institute for Cancer Research was awarded an Advanced Grant from the European Research Council (ERC) amounting to 2.27 mill Euro over a 5-year period for running the project “The PI3K-III complex: Function in cell regulation and tumour suppression”.

Selected publications

Prizes / Awards

Joint CCB review presented on the cover of Molecular Oncology

A review written jointly by members of two CCB groups was presented on the cover of the August 2009 issue of Molecular Oncology, a thematic issue dedicated to “Endocytosis, signaling and cancer”.

The review was entitled “Autophagy in tumour suppression and promotion” and was co-authored by Andreas Brech, Terje C. Ahlquist, Ragnhild A. Lothe and Harald Stenmark. It dealt with autophagy, a catabolic process that functions tumour suppressive under basal conditions but can be exploited by tumour cells to promote their survival once carcinogenesis has been initiated. This paper was an example of the interdisciplinary collaborations that constitute the basis of CCB. Stenmark’s group studied autophagy genes at the cellular level whereas Lothe’s group studied these genes at the patient level, and the two groups had a joint project that combined these studies.

Brech A, Ahlquist T, Lothe RA, Stenmark H (2009) Autophagy in tumour suppression and promotion Mol Oncol, 3 (4), 366-75.

Polish-Norwegian Research Fund grant to CCB project leader Antoni Wiedlocha

Antoni Wiedlocha’s group was awarded a 900,000 Euro grant for the project “Translocation of fibroblast growth factors 1 and 2 to the cytosol and nucleus” from the Polish-Norwegian Research Fund over a period of 2.5 years. This project was a cooperation with Prof. Jacek Otlewski at the University of Wroclaw, Poland, and the total project funding amounted to 1,800,000 Euro.

CCB project leader Rolf I. Skotheim received Dr. Ragnar Mørk’s prize 2009

The Dr. Ragnar Mørk’s legacy award for 2009 went to Rolf Skotheim, working at the Department of Cancer Prevention at the Institute for Cancer Research. This award is distributed annually to a scientist who has achieved important results. Skotheim is involved in research where DNA and RNA from various cancers types are analyzed by integrated computational and laboratory based approaches. The award is personal and amounts to NOK 200,000.

The aim of Skotheim’s research is to identify and characterise critical genes involved in the cancer development. Such genes may serve as biomarkers in diagnostics and targets for future molecularly tailored therapy. The studies are primarily focused on testicular and colorectal cancer.

This paper is an example of the interdisciplinary collaborations that constitute the basis of CCB.

CCB SCIENTISTS WITH REVIEW IN NATURE

Selected publications

Camilla Raiborg and Harald Stenmark published a review in Nature about the functions of endosomal sorting complex required for transport (ESCRT) proteins in endosomal sorting of ubiquitylated membrane proteins.

In the review, the authors discussed that selective trafficking of membrane proteins to lysosomes is required for proper cell signalling and metabolism. Ubiquitylation signals this by specifying protein transport to the lysosome lumen via the multivesicular endosome pathway. The ESCRT machinery sorts ubiquitylated cargo into invaginations of endosome membranes and, through a highly conserved mechanism also employed in cytokinesis and viral budding, mediates abscission of the cargo-containing intraluminal vesicles from the perimeter membrane. The involvement of

the ESCRT machinery in suppressing diseases such as cancer, neurodegeneration and infections underscores its importance in cell biology and physiology.

Raiborg C, Stenmark H (2009) [The ESCRT machinery in endosomal sorting of ubiquitylated membrane proteins](#) Nature, 458 (7237), 445-52.

The involvement of the ESCRT machinery in suppressing diseases underscores its importance in cell biology and physiology.

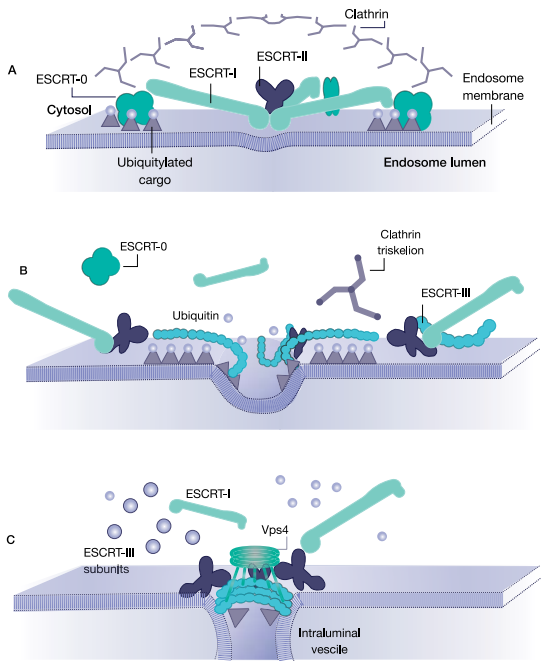


The ESCRT machinery in endosomal sorting of ubiquitylated membrane proteins

a) Cargo sorting into clathrin-coated microdomains. Initial recognition of ubiquitinated cargo (ubiquitin shown in red) is mediated by ESCRT-0, which is concentrated in microdomains through interaction with a clathrin coat (violet). ESCRT-0 also serves to recruit ESCRT-I. The elongated ESCRT-I recruits ESCRT-II and possibly contributes to membrane involution (indicated by black shadow).

b) Membrane deformation. ESCRT-III is recruited by binding to the two Vps25 subunits of ESCRT-II and forms spiral-shaped filaments that gate cargo into invaginations that are caused by the ESCRT-III filaments. During this process, cargo is deubiquitinated by proteases that are recruited by ESCRT-III, but the diffusion of cargo is strictly limited by the ESCRT-III filaments.

c) Membrane abscission. As ESCRT-III filaments assemble into circular arrays, the membrane continues to invaginate. Vps4 enters into the invagination to disassemble ESCRT-III filaments, ensuring that filaments only assemble at the neck of the forming ILV. Vps4 may also serve to remove subunits of the neck filaments, thereby contributing to construction of the neck which ultimately causes membrane abscission.



2010

Selected publications

Molecular mechanisms and clinical classification of B-cell lymphomas published in Nature
CCB, represented by Erlend Smeland’s group, has actively been participating in a prestigious and highly successful large international collaborative project regarding molecular profiling of B cell lymphomas as one of four European groups (LLMPP, headed by Dr. Louis Staudt at NCI). These studies have led to a series of publications in top-ranked international journals. So far, the consortium has characterised several major subgroups of B-NHL by expression profiling. These studies led to the discovery of 3 previously unrecognised, distinct subgroups of diffuse large B cell lymphoma (DLBCL) - ABC, GCB and primary mediastinal B cell lymphoma (PMBL), which have distinct molecular profiles and different prognosis. A LLMPP study demonstrated that the adaptor protein CARD11, which is involved in NF-κB activation, is activated by somatic mutation in the coiled-coil region in a subset of ABC DLBCLs, and hence is a novel oncogene (Lenz et al, Science 2008). These findings were extended, and it was demonstrated that ABCs are dependent on chronic B cell receptor signalling and demonstrated frequent somatic mutations in the BCR associated molecules CD79a and b (Davis et al, Nature, 2010). B cell receptor signaling can be responsible for NF-κB activation in many ABC DLBCLs, which lack activating mutations in CARD11 (the latter are only observed in 10% of ABCs, while practically all ABCs demonstrate NF-κB activation). The LLMPP consortium applied for new NIH grants to support a development and validation of diagnostic tools based on the obtained results in the project.



Davis RE, Ngo VN, Lenz G, Tolar P, Young RM, Romesser PB, Kohlhammer H, Lamy L, Zhao H, Yang Y, Xu W, Shaffer AL, Wright G, Xiao W, Powell J, Jiang JK, Thomas CJ, Rosenwald A, Ott G, Muller-Hermelink HK, Gascoyne RD, Connors JM, Johnson NA, Rimsza LM, Campo E et al. (2010) **Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma** Nature, 463 (7277), 88-92.

Prizes / Awards

Sir Hans Krebs Medal to CCB director Harald Stenmark

At the 2010 FEBS Congress in Gothenburg, Harald Stenmark from the Centre for Cancer Biomedicine and the Institute for Cancer Research was awarded the Sir Hans Krebs Medal.

Selected publications

This silver medal is awarded annually by the Federation of European Biochemical Societies for “outstanding achievements in Biochemistry and Molecular Biology or related sciences”. The Sir Hans Krebs medal was awarded for the first time in 1968 and since then, 15 of the 38 awardees have also received the Nobel Prize. Recent awardees include Nobel laureates Aaron Ciechanover (2006) and Tim Hunt (2008).

After receiving the medal, Stenmark presented a plenary lecture entitled “How a lipid mediates tumour suppression”.

Identification of a high risk group among patients with malignant nerve sheath tumors

In an interdisciplinary multicentre study, including University of Lund, Portuguese Oncology Institute, University Hospital of Groningen and Oslo University Hospital, the Lothe group identified a high risk group among patients with malignant nerve sheath tumors (MPNST).

In an unbiased manner the DNA copy number variation throughout the tumor genome was examined for suitability as surrogate markers for survival. Variations at each of three chromosomal sites in the tumor identified a high risk group with only 11% 10 year disease specific survival. In contrast, the patients without any of these tumor changes had 74% 10 year survival. Multivariate analyses including NF1 status, tumor location, size, grade, sex, complete remission, and initial metastatic status showed that the genomic high-risk group was the most significant predictor of poor survival. Several genes whose expression was affected by the DNA copy number aberrations were identified.

Brekke HR, Ribeiro FR, Kolberg M, Agesen TH, Lind GE, Eknaes M, Hall KS, Bjerkehagen B, van den Berg E, Teixeira MR, Mandahl N, Smeland S, Mertens F, Skotheim RI, Lothe RA. (2010) **Genomic changes in chromosomes 10, 16, and X in malignant peripheral nerve sheath tumors identify a high-risk patient group** J Clin Oncol. 2010 28:1573-82.

The Sir Hans Krebs medal was awarded for the first time in 1968 and since then, 15 of the 38 awardees have also received the Nobel Prize.

11% 74%

Variations at each of three chromosomal sites in the tumor identified a high risk group with only 11% 10 year disease specific survival.

In contrast, the patients without any of these tumor changes had 74% 10 year survival.

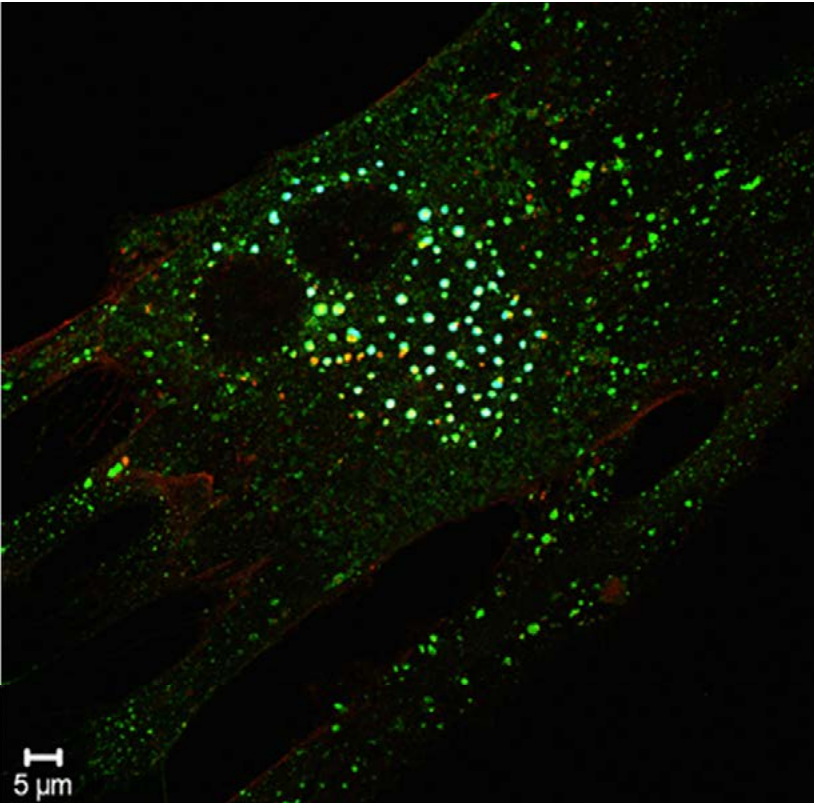
INTEGRIN DEGRADATION AND CELL MIGRATION

**Selected
publications**

One of the hallmarks of cancer cells is their ability to invade tissues outside the site of the initial tumour. In cancer research there is therefore a lot of interest in mechanisms that regulate the ability of cells to move. Integrin molecules are membrane proteins that mediate the traction between cells and the extracellular matrix, and it is well known that their internalisation and recycling are required for cell migration. CCB PhD student Viola Lobert and her co-workers made the unexpected observation that degradation of integrin molecules is important for cell migration. This degradation is induced by a component of the extracellular matrix, which triggers ubiquitination of the integrin molecules. Ubiquitinated integrins are recognised by the so-called endosomal sorting complex required for transport (ESCRT), which sorts the integrins to lysosomes for degradation (Lobert et al., Developmental Cell, 2010). This mechanism ensures that internalised integrin molecules that contain portions of extracellular matrix are not recycled to the plasma membrane where they would otherwise have made dysfunctional adhesion sites. This project was a collaboration between two CCB groups, and the paper was dedicated a “Highlight” in Nature Reviews in Molecular Cell Biology and an editorial comment on the Nature Cell Migration Gateway.

Lobert VH, Brech A, Pedersen NM, Wesche J, Oppelt A, Malerød L and Stenmark H (2010). Ubiquitination of $\alpha 5 \beta 1$ integrin controls fibroblast migration through lysosomal degradation of fibronectin-integrin complexes Dev. Cell 19: 148-159.

Figure legend: Integrin trafficking requires the ESCRT machinery. Here, integrin (in red) accumulates at early endosomes (labeled by EEA1, in blue) together with ubiquitin (green) upon depletion of the ESCRT machinery.





2011

Highlights

Centre for Cancer Biomedicine ranked “Exceptionally Good” in the Centre of Excellence mid-term evaluation

In 2011 the Research Council of Norway completed a midterm evaluation of 8 Centres of Excellence that were inaugurated in 2007. We are pleased to announce that Centre for Cancer Biomedicine was ranked with the highest obtainable score, “exceptionally good”. Consequently CCB’s CoE status was extended with another 5-year period, i.e. until 31 August 2017.

Conclusion from the international evaluation panel, led by professor Sten Grillner, The Nobel Institute for Neurophysiology, Karolinska Institute, Stockholm:

“CCB is delivering, at a very high level, what is expected from a national CoE – clear international scientific impact combined with a societal impact in the form of better cancer patient care.”

“CCB is delivering, at a very high level, what is expected from a national CoE – clear international scientific impact combined with a societal impact in the form of better cancer patient care.”

2011

21

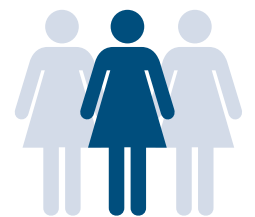
Extracts from the CCB evaluation report:

“The research quality of the centre is internationally forefront. The consortium has been able to step up its quality work by strong internal links, the main objective of a national CoE. The multi-faceted approach from cell biology through systems biology to clinical research has led to excellent outcomes, and the infrastructure from technological platforms to biobanks serve the consortium well.”

“The CoE has been extremely productive when it comes to publications in top-tier journals and specialized ones. The internal links have resulted in joint publications, demonstrating the strengths of the individual groups, as well as the added value of the consortium of excellent groups with complementary competencies.”

“The CoE has created an impressive network of international and national collaborators and attracted international grants. Several out-going and in-coming visitors fertilize the research with new ideas. The core CoE funding of the Research Council of Norway appears to have provoked the desired domino effect, as more than 80% of funding is from other sources.”

“The CoE is engaged in researcher training, the PhD degree output appears to be good, and international postdocs from prestigious institutions have been attracted. The CoE has paid serious attention to the gender issue, and attracted excellent women group leaders.”



The CoE has paid serious attention to the gender issue, and attracted excellent women group leaders



Selected publications

39%

A LLMPP collaborative study discovered that MyD88, a central adaptor protein in Toll-like receptor signaling, was mutated in 39% of Activated B-cell like diffuse large B-cell lymphoma.

Identification of new mutations in B-cell lymphoma

CCB, represented by Erlend Smeland’s group, is actively participating in a prestigious and highly successful large international collaborative project regarding molecular profiling of B cell lymphomas (LLMPP, headed by Dr. Louis Staudt at NCI). These studies have led to a series of publications in top-ranked international journals. So far, the consortium has characterised several major subgroups of B-NHL by expression profiling. These studies led to the discovery of 3 previously unrecognised, distinct subgroups of diffuse large B cell lymphoma, which have distinct molecular profiles and different prognosis. The ABC subgroup is characterised by NF-κB activation, and several mechanisms leading to NFκB activation in this subgroup has been unravelled by the LLMPP consortium. Recently, the LLMPP group demonstrated that activating mutations in the adapter protein MyD88 were found in 39% of ABC DLBCL (Ngo et al, Nature. 470(7332):115-9). The article demonstrated for the first time that MyD88 is an oncogene and the high mutation frequencies in ABC DLBCL suggest the possibility for development of novel therapeutic strategies in this type of lymphoma.

Ngo VN, Young RM, Schmitz R, Jhavar S, Xiao W, Lim KH, Kohlhammer H, Xu W, Yang Y, Zhao H, Shaffer AL, Romesser P, Wright G, Powell J, Rosenwald A, Muller-Hermelink HK, Ott G, Gascoyne RD, Connors JM, Rimsza LM, Campo E, Jaffe ES, Delabie J, Smeland EB, Fisher RI, Braziel RM, Tubbs RR, Cook JR, Weisenburger DD, Chan WC, Staudt LM. (2011) **Oncogenically active MYD88 mutations in human lymphoma** Nature. 470(7332):115-9.

Selected publications

IDENTIFICATION OF NEW PHENOTYPE IN CRC

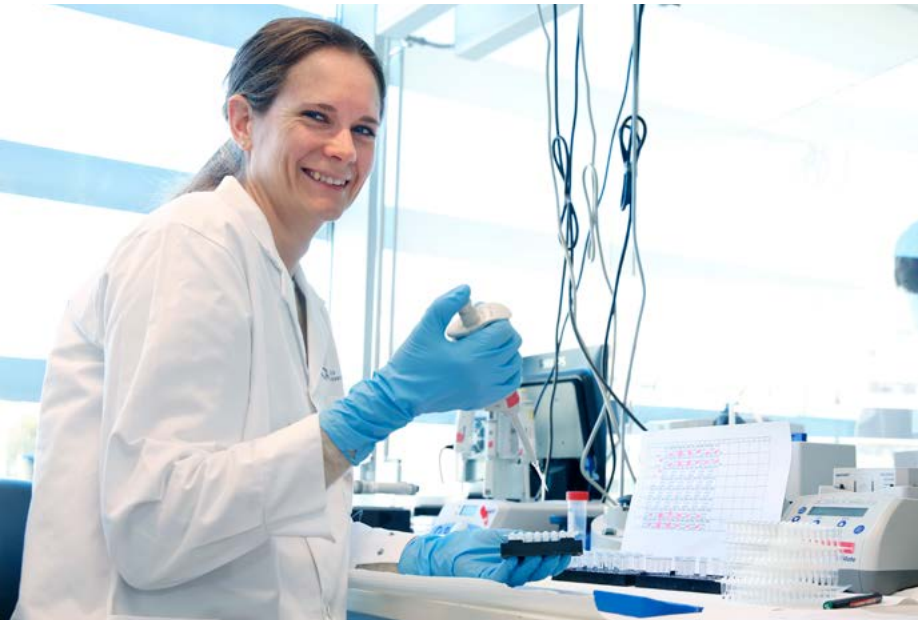
Colorectal cancer (CRC) is commonly characterized by inherent genomic instabilities such as chromosome instability and micro-satellite instability.

Sveen, Ågesen and co-workers at CCB analyzed genome-wide disruption of pre-mRNA splicing, and proposed transcriptome instability as a characteristic that is analogous to genomic instability on the transcriptome level. Exon microarray profiles from two independent patient series, including a total of 160 CRCs, were investigated for their relative amounts of alternative splicing differences. Each exon in each sample was assigned an alternative splicing score, and amounts of deviating exon usage per sample were derived from exons with extreme splicing scores.

There was great heterogeneity within both patient series in terms of sample-wise amounts of deviating splicing. This was strongly associated with the expression levels

of approximately half of 280 splicing factors. Samples with high or low amounts of deviating exon usage, associated with overall transcriptome instability, were almost completely separated into their respective groups by hierarchical clustering analysis of splicing factor expression levels in both sample series. Samples showing a preferential tendency towards deviating exon skipping or inclusion were associated with skewed transcriptome instability. There were significant associations between transcriptome instability and reduced patient survival in both sample series. In the test series, patients with skewed transcriptome instability showed the strongest prognostic association ($P = 0.001$), while a combination of the two characteristics showed the strongest association with poor survival in the validation series ($P = 0.03$).

Sveen A, Ågesen TH, Nesbakken A, Rognum TO, Lothe RA, Skotheim RI. (2011) **Transcriptome instability in colorectal cancer identified by exon microarray analyses: Associations with splicing factor expression levels and patient survival** Genome Med. 3(5):32.



Prizes / Awards

CCB congratulates Professor Sverre Heim with The King Olav V's Cancer Research Award 2011
Professor Sverre Heim received King Olav V's Cancer Research Award in a ceremony on the 14th of June where His Majesty King Harald V handed over the prestigious cancer prize to Sverre Heim, the prize winner from Centre for Cancer Biomedicine.
Sverre Heim is one of the world's leading experts within cancer cytogenetics with 30 years' experience within this field. He was head of the Section for Cancer Cytogenetics at the Institute for Medical Informatics, Oslo University Hospital.
The prestigious prize is awarded annually by the Norwegian Cancer Society, and the winner receives NOK 750,000.

Camilla Raiborg receives Dr. Mørk's prize for 2011 for her outstanding research on mechanisms of downregulation of growth factor receptors
The Ragnar Mørk's Legacy prize for 2011 went to Camilla Raiborg. This award is distributed annually to a scientist who has achieved important results. Raiborg is currently a project leader in Harald Stenmark's group at the Institute for Cancer Research and Centre for Cancer Biomedicine.
Raiborg has been central in the identification and functional characterization of the mammalian endosomal sorting complex required for transport (ESCRT) machinery. She showed that a key component of this machinery, HRS, is recruited to endosomes via binding to the membrane lipid phosphatidylinositol 3-phosphate (Raiborg et al., Journal of Cell Science, 2001).
A key finding was her discovery that HRS binds ubiquitinated membrane proteins in endosome membranes and mediates their targeting to the lysosome for degradation (Raiborg et al., Nature Cell Biology, 2002). She also showed that HRS recruits the coat protein clathrin to endosomes (Raiborg et al., EMBO Journal 2001), and that this causes concentration of the ESCRT machinery to facilitate efficient cargo sorting (Raiborg et al., Journal of Cell Science, 2006). Importantly, both HRS and more downstream components of the ESCRT machinery are required for ligand-mediated downregulation of epidermal growth factor receptors (Raiborg et al., Experimental Cell Research, 2008), which is interesting in light of the well-known fact that too high levels of these receptors are associated with cancer development.
Raiborg's leading role in studies of the ESCRT machinery is illustrated by the fact that she has been contributing reviews and commentaries on this topic in top journals such as Nature (2009) and Science (2011).

Kaisa Haglund awarded prestigious grant from Helse Sør-Øst
In December 2011, project leader Kaisa Haglund in Harald Stenmark's group was awarded a prestigious career grant ("utvidet forskerstipend") from Helse Sør-Øst for the proposal "Mechanisms of cytokinesis in development and carcinogenesis". The grant amounted to NOK 2 million per year and ran from April 2012 to March 2016.

The Ragnar Mørk's Legacy prize for 2011 went to Camilla Raiborg

2012

Innovation

Selected publications

Prizes / Awards

New prognostic tests for colorectal cancer stage II and III
Researchers at the Centre for Cancer Biomedicine, Oslo University Hospital, have developed gene signatures that may be developed into prognostic tests for patients with stage II and III colorectal cancer.
The tests have been named ColoGuideEx and ColoGuidePro and can predict at time of diagnosis the expected disease outcome. The signatures have been developed through advanced statistics on gene expression measurements of all human genes from cancer patients treated at the hospital.
ColoGuideEx and ColoGuidePro measures the activity of 13 and 7 genes, respectively, in the cancer tissue, and each gene contributes with prognostic information. The robustness of the signatures have been validated in independent series of patient samples from Norway and from USA and Australia.
The research behind the ColoGuides was published on January 2nd 2012, in the journals GUT and Clinical Cancer Research. This work was led by Professor Ragnhild A. Lothe, and is part of an interdisciplinary research programme "prognostic and predictive biomarkers of colorectal cancer" within Oslo University Hospital.
Both ColoGuide signatures became innovation projects through Inven2, the TTO of OUH and U of Oslo.

Agesen TH, Sveen A, Merok MA, Lind GE, Nesbakken A, Skotheim RI, Lothe RA. (2012) ColoGuideEx: a robust gene classifier specific for stage II colorectal cancer prognosis Gut. 61 (11), 1560-7.
Sveen A, Ågesen TH, Nesbakken A, Meling GI, Rognum TO, Liestøl K, Skotheim RI, Lothe RA. (2012) ColoGuidePro: a prognostic 7-gene expression signature for stage III colorectal cancer patients Clin Cancer Res. 18(21):6001-10.

Alicia Llorente and Kirsten Sandvig publish potential biomarkers for prostate cancer
Alicia Llorente and Kirsten Sandvig, Department of Biochemistry, Institute for Cancer Research and Centre for Cancer Biomedicine, have published a proteomic analysis of microvesicles released from a human prostate cancer cell line in the journal Molecular and Cellular Proteomics.
Potential new non invasive biomarkers:
Most of the 266 proteins identified have previously been reported to be present in vesicles released from other cell types, but several proteins seem to be specific for prostate cancer cells. Since microvesicles can reach biological fluids, these proteins are thus potentially useful as new non invasive biomarkers for detection, diagnosis and/or prognosis of prostate cancer.

Sandvig K, Llorente A. (2012) Proteomic analysis of microvesicles released by the human prostate cancer cell line PC-3 Mol Cell Proteomics. 11(7):M111.012914.
Prestigious career grant for research on cancer biomarkers to Guro E. Lind
In December 2012, group leader Guro E. Lind was awarded a prestigious career grant from Helse Sør-Øst for the proposal "Epigenetic biomarkers in cancer - their function and clinical importance". The grant amounted to NOK 2 million per year and ran for 4 years.

WEB BASED CANCER ENCYCLOPEDIA

Highlights

Oncolex.org is a web based cancer encyclopedia for health care providers worldwide, published by the Institute for Medical Informatics (IMI) at Oslo University Hospital. IMI is headed by Håvard E. Danielsen, and is part of the Center for Cancer Biomedicine.

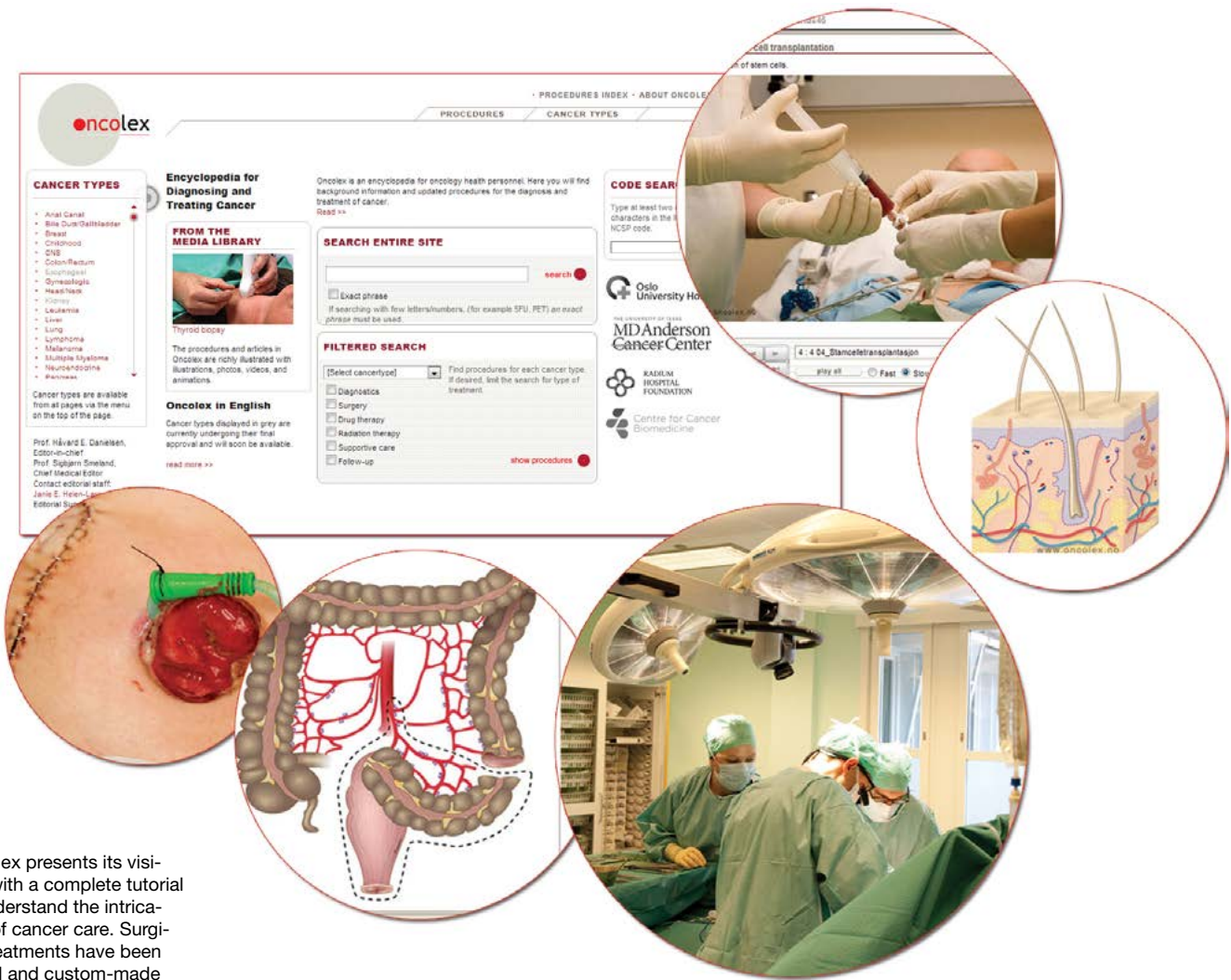
www.oncolex.org is a free, comprehensive online resource for cancer diagnostics, treatment and supportive care. The encyclopedia contains extensive material for 44 cancer types including explanatory texts, illustrations, animations, photos and video footage. As a resource in continual progress, it keeps track of novel procedures and technology transforming the field of cancer diagnostics and treatment.

Oncolex was initially released to the Norwegian-speaking public in 2006, featuring articles and procedures related to gynecological cancers. By the end of 2009, it contained thorough explanations and procedures for 44 cancer types, supplying health care providers in Norway with updated and detailed information on cancer care, sourced directly from acclaimed medical specialists at the Norwegian Radium Hospital and Rikshospitalet.

As the use of the encyclopedia augmented, the possibility of making an English version

was explored and defined as relevant development of the site. The project team had chosen Sitecore as the technical platform, and it proved a wise choice as adding a second language based on the Norwegian structure was feasible. Translation to English was performed by a native speaker in the editorial staff.

In 2011 another significant step in the development of oncolex.org took place when Håvard E. Danielsen made an agreement with experts at MD Anderson Cancer Center in Houston, Texas – one of the most renowned cancer centres in the world - about co-signing and reviewing the English language texts. Oncolex.org was presented at MD Anderson’s 2012 GAP conference in Oslo from 14th-16th of May. This was the first time the annual conference for the MD Anderson “Global Academic Programme” (GAP) was held outside Texas.



Oncolex presents its visitors with a complete tutorial to understand the intricacies of cancer care. Surgical treatments have been filmed and custom-made illustrations and animations help explain procedures.

The encyclopedia contains extensive material for 44 cancer types including explanatory texts, illustrations, animations, photos and video footage.

Selected publications

Breaking advances in prognostic testing of colorectal cancer

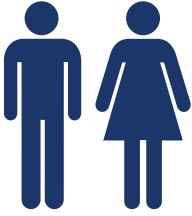
Results from colorectal cancer research at CCB, Department of Cancer Prevention, Institute for Cancer Research and Department of Gastrointestinal Surgery have been highlighted from recent cancer literature as “Breaking Advances” in the AACR journal Cancer Research on 15th of October 2012.

Important findings and clinical challenges:

The colorectal cancer gene signatures addressed above remained significant across technology platforms, in multivariate analyses, and were independent of treatment. The latter opens for guidance in who may benefit from surgery alone and can avoid chemotherapy and side effects thereof. Similar signatures have recently been published by others, but none are yet implemented in the clinic. All studies were reviewed by Sveen and coworkers in Clinical Cancer Research 2013. Although a good prognosis is predicted for a stage III patient and therefore, adjuvant treatment with chemotherapy is seemingly not necessary, this cannot be implemented at this stage since removal of a treatment option would require 100 % certainty. We also need predictive factors for chemotherapy: who will be the responders to this treatment?

400

patients from 3 independent clinical series were included in Dr. Anita Sveen's study.



Sveen A, Nesbakken A, Ågesen TH, Guren MG, Tveit KM, Skotheim RI, Lothe RA. (2013) Anticipating the clinical use of prognostic gene expression-based tests for colon cancer stage II and III: is Godot finally arriving? Clin Cancer Res. 19(24):6669-77.

CCB Principal Investigator Erlend B. Smeland co-authored Nature article on Burkitt lymphoma

Erlend B. Smeland from the Department of Immunology at the Norwegian Radium Hospital, co-authored an article published in Nature entitled “Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics”

Novel therapeutic targets in Burkitt's lymphoma: In collaboration with the LLMP consortium, Erlend Smeland's group has used high-throughput RNA sequencing and RNA-interference screening in order to discover essential regulatory pathways in Burkitt's lymphoma that cooperate with MYC, the defining oncogene of this cancer. The transcription factor TCF3, its negative regulator ID3, phosphoinositide 3-kinase, and cyclin D3 were identified as important regulators of oncogenesis in Burkitt's lymphoma. These molecules thus represent novel opportunities for pharmacological targeting in Burkitt's lymphoma.

Schmitz R, Young RM, Ceribelli M, Jhavar S, Xiao W, Zhang M, Wright G, Shaffer AL, Hodson DJ, Buras E, Liu X, Powell J, Yang Y, Xu W, Zhao H, Kohlhammer H, Rosenwald A, Kluin P, Müller-Hermelink HK, Ott G, Gascoyne RD, Connors JM, Rimsza LM, Campo E, Jaffe ES, Delabie J, Smeland EB, Ogwang MD, Reynolds SJ, Fisher RI, Braziel RM, Tubbs RR, Cook JR, Weisenburger DD, Chan WC, Pittaluga S, Wilson W, Waldmann TA, Rowe M, Mbulaiteye SM, Rickinson AB, Staudt LM. (2012) Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics Nature. 490(7418):116-20.



As of 2013
Medinsight has:

170
implemented registries

600
users

40
different disease
areas covered

MEDINSIGHT

– a conceptual framework to provide standardized development of medical registries, developed by Håvard Danielsen and the Institute for Medical Informatics

Medinsight registries allow monitoring of patients and treatments in a way that has previously been impossible using other medical record systems.

Background: National strategies for improving the quality of health services have led to an increased need for documentation of the results of diagnostics and treatment. Medinsight was developed by the Institute for Medical Informatics (IMI) in 2004, in response to clinicians’ requirements to carry out quality assurance of patient treatment, as well as to cover researchers’ needs for storage and collation of research results. As of 2013 Medinsight has over 170 implemented registries, 600 users and 40 different disease areas are covered.

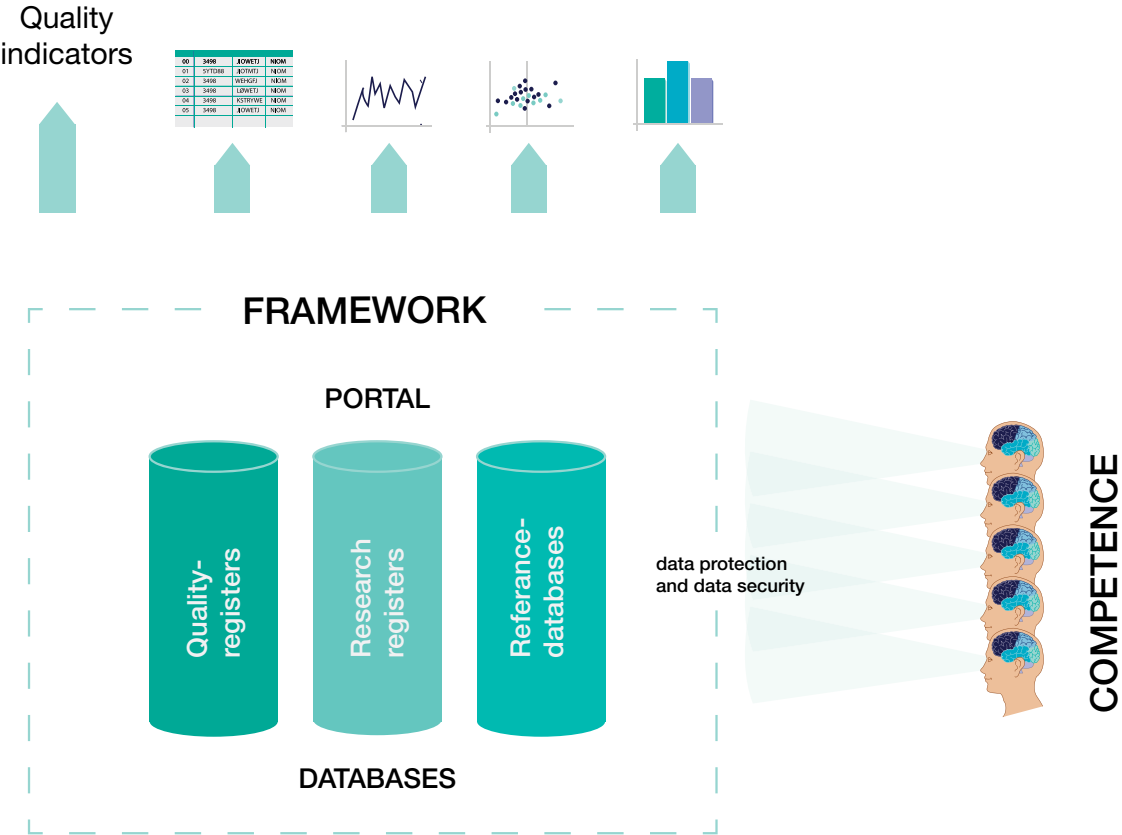
Medinsight registries: Medinsight registries are custom built databases based on the individual user’s requirements, and are connected to any legal accessible data sources via the Medinsight portal. Technically, Medinsight can contain any type of registry (quality-, research-, biobank-, trial- or clinical registry). Existing data from other types of databases such as DataEase, Access, Excel and SPPS can all be converted into a Medinsight registry.

Medinsight framework: Medinsight is created as a Windows program, which is installed centrally. Access to the registries is controlled through a role-based user filter in the framework. All the registries are stored in a standardized format in SQL Server with secure routines for backing up of all data.

New registries may be implemented using functionality stored in the framework. The principles of data quality, data accessibility, security and simple reporting are principles IMI believes are necessary in order to carry out successful quality improvement and research.

With Medinsight, reports can be created without help from database specialists. Key elements in the report module are functions for counting, filtering and analysis, survival curves and age distribution. Data may be transferred to statistics tools such as SPSS if more advanced analyses are required. Developers at IMI and healthcare providers work closely together, establishing user-friendly registers adapted to each user’s requirements, whether in terms of quality assurance or research.

- Medinsight is an important contribution for:**
- Systematic registration of data to be used in the evaluation and improvement of patient treatment
 - A tool for regular reporting of quality with respect to medical parameters
 - Quality assured data for research
 - Quality assurance of multiple data sources through a portal



Medinsight CORE , a licenced version of Medinsight, has been available since 2012. Medinsight Core allows hospitals outside Oslo University Hospital use of this unique tool for medical registries.

Prizes / Awards

CGB scientists awarded prize for Excellent Research Article

A study carried out in Edward Leithe’s project group at Department of Cancer Prevention was awarded the Excellent Research Article prize by the Oslo University Hospital on 26th October. The prize carries an award of 50,000 NOK.

Novel mechanism for regulation of intercellular communication: In this study, a novel mechanism for regulation of direct intercellular communication has been identified; SUMOylation of the channel protein connexin43. The findings may have important implications for our understanding of the molecular basis underlying the dysregulation of this type of intercellular communication during cancer development. The first author of

the article is Ane Hansen Kjenseth. The study was published in the May 4th issue of Journal of Biological Chemistry and was featured on the cover of the journal.

Kjenseth A, Fykerud TA, Sirnes S, Bruun J, Yohannes Z, Kolberg M, Omori Y, Rivedal E, Leithe E. (2012) The gap junction channel protein connexin 43 is covalently modified and regulated by SUMOylation J Biol Chem. 287(19):15851-61.



Innovation

SECURING EXCLUSIVE RIGHTS TO BIOMARKERS

– British biotech company signed agreement with Inven2 to secure exclusive rights to biomarkers identified in the Lothe group

The 8th of February 2012 Inven2, the Hospital’s technology transfer office (TTO), signed a licensing agreement with Oxford Gene Technology (OGT) on behalf of the Hospital and the inventors at Department of Cancer Prevention, Guro E. Lind, Rolf I. Skotheim, Terje Ahlquist, Kim Andresen, Deeqa Ahmed, and Ragnhild A. Lothe. OGT will develop a non-invasive test for early detection of colorectal cancer based on biomarkers from two separate patent applications. It is years of research in the Lothe group with senior researcher Guro Elisabeth Lind leading the daily work that has led to this important milestone. Dr Lind and co-workers have validated the biomarkers in more than 500 patient samples and shown a high sensitivity and specificity for colorectal cancers as well as benign lesions.

Colorectal cancer is one of the most frequent cancer types in both men and women and more than 3600 new diagnoses are made annually in Norway alone. Less than 60% of the patients are still alive after 5 years. The

survival rate is highly dependent on how advanced the cancer is at the time of diagnosis. Detection at an early stage indicates curation by surgery alone.

The only non-invasive screening test shown to cause reduced mortality from colorectal cancer is the fecal occult blood test (FOBT), which is prone to miss positive cases (limited sensitivity) and to produce false positives (limited specificity). The new biomarkers have both sensitivity and specificity of more than 90% for colorectal cancer tissue samples. Dr Lind and co-workers received the Medinnova idea prize for the best idea with commercial potential in 2007, and since then, the lab has been working with validating the original findings in an independent clinical sample series as well as improving the methodology and optimizing the markers further with the aim of developing a non-invasive test based on fecal and/or blood samples.

The new early detection colorectal cancer biomarkers have sensitivity and specificity of more than 90% using tissue samples.



We thank everyone involved in CCB for 10 truly amazing years of high-level research combined with enthusiasm and a friendly and collegial environment.

2013

Highlights

New K.G. Jebsen Center for colorectal cancer research led by Ragnhild A. Lothe

Funding

We congratulate CCB co-director Ragnhild A. Lothe from the Department of Cancer Prevention at the Institute for Cancer Research with a new K.G. Jebsen Colorectal Cancer Research Centre that was appointed in December 2013 in strong competition with other outstanding scientific environments.

Colorectal cancer is the second most common cancer type in Europe and only half of the patients are alive five years after primary diagnosis.

The new Centre will focus on improving the methods for diagnosis and treatment of colorectal cancer and will receive 16 mill NOK + 6 mill NOK over a 4-year period (2014-2018) from the K.G. Jebsen Foundation and the South Eastern Regional Health Authorities, respectively.

Comment by CCB director Harald Stenmark:
The participation of several CCB members in the K.G. Jebsen Center for Colorectal Cancer entails an even stronger emphasis on this cancer disease and strengthens CCB's ties to clinical and epidemiological research environments. This is very good news not only for CCB but also for the future colorectal cancer patient, says Harald Stenmark.

“This is very good news not only for CCB but also for the future colorectal cancer patient”

– Harald Stenmark, CCB director

Kirsten Sandvig heads national nanoparticle project – A five year grant of 30 million NOK

Professor Kirsten Sandvig at the Centre for Cancer Biomedicine and Department of Biochemistry at The Institute for Cancer Research, Oslo University Hospital (OUS), has received a grant of 30 million NOK over a 5 year period for the project “Biodegradable Nanoparticles in Cancer Diagnosis and Therapy”.

This grant is part of an initiative of The Research Council of Norway to enhance the national knowledgebase of nanotechnology. A total of five projects were awarded such grants. The project headed by Sandvig is the only project within the field of biomedicine.

A main goal of the project is to build the necessary competence for developing safe and efficient nanoparticles for diagnosis and personalized therapy of cancer. Groups from academia, research institutes, university hospitals and pharmaceutical industry are involved with a focus on cross-functional collaborations. The project management group will consist of Sandvig and two senior scientists in her group: Dr. Tore-Geir Iversen will coordinate the in vitro activities and Dr. Tore Skotland will coordinate the in vivo activities.

Selected publications

CCB SCIENTISTS IDENTIFY NOVEL LIPID REGULATOR OF CELL MIGRATION

In EMBO Reports, CCB’s PhD student Angela Oppelt and her colleagues in Jørgen Wesche’s project group at the Institute for Cancer Research presented a novel regulator of cell migration.

Novel lipid regulator of cell migration:
Because metastasis involves migration of cancer cells, there is great interest in cancer biology to identify mechanisms that regulate cell migration. The novel regulator is a lipid, PI5P (phosphatidylinositol 5-phosphate), which is generated from the common phospholipid, phosphatidylinositol, through a 3-step reaction catalyzed by the consecutive actions of the enzymes VPS34, PIKfyve and MTMR3.

Interestingly, Oppelt and co-workers identified all these enzymes as regulators of cell migration, and when their function is impaired, cells migrate at a slower rate. Conversely, if cellular levels of PI5P are artificially enhanced, cell migration is speeded up. The authors also showed that fibroblast growth factor, which is known to stimulate cell migration, causes a significant increase in cellular PI5P levels.

What is the role of PI5P in cell migration? Oppelt and co-workers found evidence that this lipid controls (unknown) proteins that promote remodelling of actin filaments, a prerequisite for cell migration.

Number one in EMBO Reports ranking:
Given the interest for targeting cell migration in anti-metastatic therapy, the paper from Oppelt and co-workers has attracted considerable attention, and it is ranked as number one on the top-ten list of downloaded papers at EMBO Reports.

Oppelt A, Lobert VH, Haglund K, Mackey AM, Rameh LE, Liestøl K, Oliver Schink K, Marie Pedersen N, Wenzel EM, Haugsten EM, Brech A, Erik Rusten T, Stenmark H, Wesche J. (2013) Production of phosphatidylinositol 5-phosphate via PIKfyve and MTMR3 regulates cell migration EMBO Rep. 14(1):57-64.



Selected publications

Novel potential therapeutic target in follicular lymphoma

Immune cells are able to recognize cancer cells as foreign and eliminate them. However, immune cells infiltrating human cancers are often dysfunctional. Project leader June Myklebust and collaborators at Stanford University discovered that T cells in follicular lymphoma displayed highly reduced intracellular signaling in response to cytokines. The signaling defect was associated with high expression of the inhibitory receptor PD-1. Macrophages in the tumor microenvironment expressed the ligand PD-L1. Therefore, blocking PD-1/PD-L1 with monoclonal antibody which is now in clinical use, is expected to restore T-cell function and might benefit patients with this lymphoma type. The study was a collaboration with CCB's visiting professor Jan Delabie.

Myklebust JH, Irish JM, Brody J, Czerwinski DK, Houot R, Kohrt HE, Timmerman J, Said J, Green MR, Delabie J, Kolstad A, Alizadeh AA, Levy R. (2013) High PD-1 expression and suppressed cytokine signaling distinguish T cells infiltrating follicular lymphoma tumors from peripheral T cells Blood. 121(8):1367-76.

Fusion transcript detected in erythroleukemia

Project leader Francesca Micci and her colleagues in Sverre Heim's group have identified novel fusion genes every year in different types of neoplasia (lately using next generation sequencing methodology). The present example is of NFIA/CBFA2T3 which characterizes erythroleukemia (FAB M6) in a specific manner. This is the first fusion transcript to be identified in this type of leukemia.

Micci F, Thorsen J, Panagopoulos I, Nyquist KB, Zeller B, Tierens A, Heim S. (2013) High-throughput sequencing identifies an NFIA/CBFA2T3 fusion gene in acute erythroid leukemia with t(1;16)(p31;q24) Leukemia. 27(4):980-2.

Selected publications

New genes linked to testis cancer

Testis cancer is the most common cancer type in young men, and has had a markedly increase over the past half a century. An international collaboration was set up to identify novel genes which are associated with predisposition to this disease. CCB researchers in the Skotheim and Lothe groups have taken part in the study led by the US National Cancer Institute in Bethesda, Maryland. Two articles were published in 2013, and a new global testis cancer consortium was inaugurated, where CCB researchers are involved.

Chung CC, Kanetsky PA, Wang Z, Hildebrandt MA, Koster R, Skotheim RI, Kratz CP, Turnbull C, Cortessis VK, Bakken AC, Bishop DT, Cook MB, Erickson RL, Fosså SD, Jacobs KB, Korde LA, Kraggerud SM, Lothe RA, Loud JT, Rahman N, Skinner EC, Thomas DC, Wu X, Yeager M, Schumacher FR, Greene MH, Schwartz SM, McGlynn KA, Chanock SJ, Nathanson KL. (2013) Meta-analysis identifies four new loci associated with testicular germ cell tumor Nat Genet. 45(6):680-5.

Two-tiered control of epithelial growth and autophagy

Target of Rapamycin Complex1 (TORC1) is a central regulator of cell metabolism which integrates signals from the oncogenic and tumor suppressive PI3K-I and LKB1 pathways. Here O'Farrell et al. have shown that the Ret (stit in Drosophila) and Insulin Growth Factor Receptors cooperatively drive PI3K-I and TORC1. Tissues expressing Stit are thus protected from starvation and can grow, albeit at

a reduced rate, despite low Insulin signaling. This provides the first in-vivo evidence that multiple receptors can tune the activity level of TORC1 to match external stimuli and that the intracellular catabolic to anabolic shift is graded, rather than bi-stable.

O'Farrell F, Wang S, Katheder N, Rusten TE, Samakovlis C. (2013) Two-tiered control of epithelial growth and autophagy by the insulin receptor and the ret-like receptor, stitcher PLoS Biol. 11(7):e1001612.

Independent researcher grants to three CCB scientists

Three CCB scientists have been awarded the much sought-after 4 year independent researcher grant from the Norwegian Cancer Society. The grants amount to approx. 3.8 million NOK each and run for 4 years. We congratulate:

Alicia Llorente

Project leader, Senior scientist

Proposal title: Extracellular Vesicles and Prostate Cancer: In Search of Tumorigenesis Mechanisms and Biomarkers

Camilla Raiborg

Project leader, Senior scientist

Proposal title: ER-Endosome Contact: Implications for Tumour Suppressor Pathways, Cell Migration and Invasion

Edward Leithe

Project leader, Senior scientist

Proposal title: Role of ubiquitin and ubiquitin-like proteins in loss of tumor suppressor proteins during colorectal cancer development

This provides the first in-vivo evidence that multiple receptors can tune the activity level of TORC1 to match external stimuli.

Prizes / Awards

Three CCB researchers among the winners of OUS research awards
On the 26th of April nine research prizes were awarded to scientists from Oslo University Hospital. Three CCB researchers were among the prize winners. The prizes were presented by Bjørn Erikstein, managing director of Oslo University Hospital, at a ceremony taking place at Rikshospitalet.

We are happy to congratulate: CCB director Harald Stenmark with the Excellent Researcher Award of 300,000 NOK, Group leader Guro E. Lind with an Early Career Award of 150,000 NOK, Postdoc Anita Sveen with an Excellent Original Article Award of 50,000 NOK .



Polish-Norwegian Research Fund grant to CCB group leader Antoni Wiedlocha
Antoni Wiedlocha’s group was awarded a grant for the project ”Highly cytotoxic FGF2-conjugates in targeted therapy for FGFR-expressing cancer” from the Polish-Norwegian Research Fund for a period of 3 years. This project was a cooperation with Jacek Otlewski’s group at the University of Wroclaw, Poland. The total project funding amounted to 1,000,000 Euro.

Focused Research Area project to CCB Co-director Ragnhild A. Lothe
Five Focused Research Areas have been appointed for five years (2014-2018) at Oslo University Hospital. Colorectal cancer research in OUH becomes a focus area named “SMART colorectal cancer - screening, management, research and translation”, and the project is led by Ragnhild A. Lothe. Total financial support is 5 million NOK.

Prestigious research project grant to CCB’s lymphoma biology group
Principal investigator Erlend Smeland has been awarded a prestigious research project grant from the Research Council of Norway for the proposal “New diagnostic markers and targets for therapeutic intervention in B-cell lymphoma”. The grant amounts to 8 million NOK and runs for 4 years.

PhD student Åsmund Eikenes awarded “Hjernekraktpriisen 2013” - Popular science dissemination about cell division and fruit flies
We congratulate CCB’s PhD student Åsmund Husabø Eikenes with “Hjernekraktpriisen 2013” for his contribution “Begeistra grunnforskning” about cell division and fruit flies. The prize supports and promotes science dissemination, and is part of the campaign “Hjernekraktkverk” highlighting the societal importance of investing in research and development. The prize of 100,000 NOK is given by The Norwegian Association of Researchers and shared between three participants.

2014

Prizes / Awards

Congratulation to Professor Harald Stenmark with the King Olav V’s Cancer Research Award 2014
CCB director Harald Stenmark received King Olav V’s Cancer Research Award 2014 for his ground-breaking discoveries within cell biology. King Olav Vs Cancer Research foundation was established in 1992 by the Norwegian Cancer Society, and since then the Cancer Society has awarded this prestigious prize annually to Norway’s most outstanding cancer researchers.

Harald Stenmark is particularly known for his research on the development of normal cells into cancer cells. In particular, Stenmark’s group has contributed importantly to our understanding of how cellular growth factor signalling is regulated, and how its dysregulation may cause cancer. In an interview published by the Norwegian Cancer Society, Harald Stenmark emphasizes teamwork, collaboration, a talent for asking the right questions, a bit of luck, and a lot of hard work, as part of the success criteria for excellent research. The distinguished cancer research prize of 1 MNOK was handed over to Harald Stenmark by his Majesty King Harald V in a ceremony on the 2nd of June in the old ceremonial hall at the University of Oslo.

Professor Kirsten Sandvig receives the Fridtjof Nansen prize for excellent research 2014
The Fridtjof Nansen prize for excellent research in science and medicine 2014 was awarded to CCB’s Kirsten Sandvig for her groundbreaking work within the fields of biochemistry and cell biology. Sandvig is the first scientist in the field of cancer research to receive this prestigious prize. Prize winner Sandvig received a medal, a diploma, and 150,000 NOK at a ceremony on the 5th of May at the Norwegian Academy of Science and Letters. The esteemed prize was handed over by the Chairman of the Nansen Foundation, Øyvind Østerud. Kirsten Sandvig is Principal Investigator in CCB and Professor at the University of Oslo, Department of Biosciences.

Sandvig is the first scientist in the field of cancer research to receive the prestigious Fridtjof Nansen prize.

Selected publications

Novel role of G-protein coupled signaling in diffuse large cell B cell lymphoma
Germinal centre B-cell-like diffuse large B-cell lymphoma (GCB-DLBCL) is a common malignancy, yet the signalling pathways that are deregulated and the factors leading to its systemic dissemination are poorly defined. In this article by the LLMPP consortium, deep sequencing identified frequent function-disrupting mutations in the S1PR2–Ga13–ARHGEF1 signalling in GCB-DLBCL. Moreover, inactivation of this signalling pathway in mice allowed Akt activation and promoted dissemination of germinal centre B cells, consistent with a role in the systemic dissemination of large B-cell lymphoma. These findings identified a Ga13-dependent pathway that exerts dual actions in suppressing growth and blocking dissemination of germinal centre B cells that is frequently disrupted in germinal centre B-cell-derived lymphoma.

Muppidi JR, Schmitz R, Green JA, Xiao W, Larsen AB, Braun SE, An J, Xu Y, Rosenwald A, Ott G, Gascoyne RD, Rimsza LM, Campo E, Jaffe ES, Delabie J, Smeland EB, Brazil RM, Tubbs RR, Cook JR, Weisenburger DD, Chan WC, Vaidehi N, Staudt LM, Cyster JG. (2014) Loss of signalling via G 13 in germinal centre B-cell-derived lymphoma Nature. 516(7530):254-8.

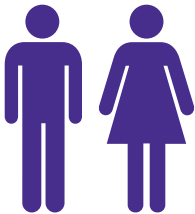
Predicting aggressive lymphoma
Each year, more than one thousand Norwegians develop lymphoma. A statistical genetic analysis can detect when the disease will be aggressive. Thereby, treatment can be initiated in time. Results from a collaboration study by CCB researchers, statisticians, and associated clinical researchers have been published in Blood, a top-of-the-line journal for haematologists. Professors Erlend Smeland and Harald Holte are among the country’s foremost specialists in B-cell lymphoma. This is the largest group of lymphomas, which affects more than 800 Norwegians each year. Together with Marianne Brodtkorb and Professor Ole Christian Lingjærde, the researchers have discovered a completely new method that can predict at an early stage of the disease, who will have a recurrence and when the recurrence will appear. The new statistical method will be able to determine who will need bone marrow transplantation and who can be spared the extreme burden that this excruciating treatment entails.

Novel gene signatures predict transformation in follicular lymphoma: Marianne Brodtkorb and colleagues performed a whole-genome study of DNA copy number and gene expression data in serial biopsies from follicular lymphoma. Among the genes with strong association between copy number and gene expression, a strong enrichment for the NFkB pathway was found. For 6 of the 14 NFkB-related genes thus identified, the subset of expression correlated downstream target genes were predictive of transformation, a disease state associated with rapid progression and death. This suggests that genes regulating B-cell survival and activation are involved in transformation, and that the potential to transform can be present long before transformation is observed.

Brodtkorb M, Lingjærde OC, Huse K, Trøen G, Hystad M, Hilden VI, Myklebust JH, Leich E, Rosenwald A, Delabie J, Holte H, Smeland EB. (2014) Whole-genome integrative analysis reveals expression signatures predicting transformation in follicular lymphoma Blood. 123(7):1051-4.

800

B-cell lymphoma is the largest group of lymphomas, which affects more than 800 Norwegians each year.



Prizes / Awards	Prestigious independent funding to CCB scientists We congratulate our two colleagues with their prestigious independent funding from 2015:
Proposal title	Guro E. Lind Professor, Group leader Methylation supernegative colorectal cancers - a key to unlocking the secrets of the DNA (de)methylation machinery. Young research talents grant from the Research Council of Norway. The grant amounts to NOK 7 million and runs for 4 years.
Proposal title	Tor Erik Rusten Project leader, Senior scientist Unveiling mechanisms of carcinogenesis using Drosophila melanogaster and human organoid models. Career grant from the South-Eastern Norway Regional Health Authority. The grant amounts to NOK 8 million and runs for 4 years.

Selected publications

Nature Cell Biology article from Sigrid B. Thoresen: ANCHR prevents aneuploidy
In an article in Nature Cell Biology, PhD student Sigrid B. Thoresen and her co-workers in Harald Stenmark's group at the Institute for Cancer Research and Centre for Cancer Biomedicine have uncovered a cellular mechanism that prevents completion of cell division if “lagging” chromosomes are detected in the bridge between the two forming daughter cells. This prevents occurrence of cells with abnormal numbers of chromosomes, aneuploidy. Since aneuploidy is strongly associated with cancer progression, these results open new possibilities for future cancer diagnosis and therapy.

Mechanism of cell division delay by the abscission checkpoint identified: The abscission checkpoint delays the final step of cell division in the presence of missegregating DNA to avoid cleavage furrow regression and cell binucleation, typical features of cancer cells. However, the mechanisms by which this occurs have been largely elusive. PhD student Sigrid B.

Thoresen and co-workers in Harald Stenmark’s group have identified a previously uncharacterized protein, ANCHR, which is essential for abscission checkpoint function. ANCHR cooperates with previously identified checkpoint factors to inhibit the action VPS4, an enzyme required for the final membrane scission step, until DNA bridges have been resolved. Importantly, this is the first identified mechanism by which the checkpoint can delay abscission.

Thoresen SB, Campsteijn C, Vietri M, Schink KO, Liestøl K, Andersen JS, Raiborg C, Stenmark H. (2014) ANCHR mediates Aurora-B-dependent abscission checkpoint control through retention of VPS4 Nat Cell Biol. 16(6):550-60.

Selected publications

Regulatory mechanism of fibroblast growth factor receptor signalling identified

Irregularities in FGFR1 (fibroblast growth factor receptor 1) signaling have been implicated in several pathological conditions, including human cancer. In order to discover novel regulators of FGFR1 signaling, postdoc Beata Nadratowska-Wesolowska and co-workers in Antoni Wiedlocha's group performed yeast two-hybrid screens and identified RSK2 (p90 ribosomal S6 kinase 2) as an FGFR1 interaction partner. RSK2 is a serine/threonine kinase and Nadratowska-Wesolowska et al., showed that activated RSK2 can directly phosphorylate FGFR1. Importantly, this phosphorylation was shown to be required for proper endocytosis and ubiquitination of FGFR1 and thus also termination of FGFR1 signaling. The data reveal a novel regulatory mechanism of FGFR1 signaling.

Nadratowska-Wesolowska B, Haugsten EM, Zakrzewska M, Jakimowicz P, Zhen Y, Pajdzik D, Wesche J, Wiedlocha A. (2014) RSK2 regulates endocytosis of FGF receptor 1 by phosphorylation on serine 789 *Oncogene*. 33(40):4823-36.

Prizes / Awards

CCB scientist Edward Leithe received Early Career Award

Edward Leithe has been recognized with the 2014 Early Career Award from Oslo University Hospital.

Prizes for outstanding research: The award was presented to Leithe for his contributions to the field of connexins and intercellular communication in cancer pathogenesis. The award, established in 2013, is given annually to two early career researchers at Oslo University Hospital and provides 150,000 NOK to support the recipients' research projects.

OUS excellent article award to CCB's Marianne B. Eide

In April six research prizes were awarded to scientists from Oslo University Hospital. CCB researcher Marianne Brodtkorb Eide was among the prize winners with her Blood article entitled Whole-genome integrative analysis reveals expression signatures predicting transformation in follicular lymphoma (*Blood*. 123(7):1051-4).

Prizes for excellent research articles: The prizes were presented by Tove Strand, vice managing director of Oslo University Hospital, at a ceremony taking place at Rikshospitalet. We are happy to congratulate Marianne Brodtkorb Eide with an Excellent Original Article Award of 50.000 NOK.

OUS excellent article award to CCB's Sigrid Thoresen

In November six research prizes were awarded to scientists from Oslo University Hospital. CCB postdoc Sigrid Thoresen was among the prize winners with her Nature Cell Biology article entitled ANCHR mediates Aurora-B-dependent abscission checkpoint control through retention of VPS4 (*Nat Cell Biol*. 16(6):550-60).

Prizes for excellent research articles: The prizes were presented by Bjørn Erikstein, managing director of Oslo University Hospital, at a ceremony taking place at Rikshospitalet on the 21st of November. We are happy to congratulate Sigrid Thoresen with an Excellent Original Article Award of 50.000 NOK.



2015

Selected publications

Nature article from Camilla Raiborg: Formation of cellular protrusions

In a paper in Nature, project leader Camilla Raiborg and her co-workers in Harald Stenmark’s group show an unexpected connection between endosomes (organelles involved in protein import into cells) and the endoplasmic reticulum (ER, organelle involved in protein export) in formation of cellular protrusions.

Formation of cellular protrusions: The authors find that a protein called Protrudin forms contact sites between ER and endosomes, and when such sites are formed, the endosomes are loaded with a motor that makes them migrate from the cell centre to the cell periphery. Here, they fuse with the cell membrane, and this induces formation of cellular protrusions.

If our hypothesis is correct, this could provide us with new targets for cancer therapy.

– Camilla Raiborg

- What is the importance of cellular protrusions?
In this paper we show that the mechanism we have identified promotes the outgrowth of neurites - precursors of nerve fibers - in nerve cells. This is interesting because mutations in Protrudin and its interacting proteins are associated with hereditary spastic paraplegias, a group of neurodegenerative diseases. Our findings could shed light on the causes of these enigmatic diseases.

- Is there any link to cancer? Cancer cells use protrusions called invadopodia to break through the extracellular matrix so that they can invade other tissues. It is plausible that Protrudin and its interactors play a role in invadopodia formation, and we are planning to investigate this. If our hypothesis is correct, this could provide us with new targets for cancer therapy.

- Are there other implications of the new findings?
In certain specialized cell types, fusion of endosome-like organelles with the cell membrane, have important physiological functions. An interesting example is cytotoxic T cells, which kill virus-infected cells and tumour cells. Protrudin is expressed at high level in such cells, so we would now like to investigate the possibility that the new mechanism we have identified might play a role in immunity.

The endoplasmic reticulum in regulation of endosome positioning and cellular protrusions:
The endoplasmic reticulum (ER) makes contact with various other cellular organelles including endosomes. Camilla Raiborg and co-workers now show that the ER protein Protrudin makes contact with the small GTPase RAB7 and phosphatidylinositol 3-phosphate on late endosomes (LEs). This allows transfer of the microtubule motor protein Kinesin-1 from Protrudin to the motor adaptor FYCO1 on LEs. Thus repeated ER-LE contacts promote microtubule-dependent translocation of LEs to the cell periphery and their subsequent fusion with the plasma membrane to induce outgrowth of cellular protrusions. These findings open up for further studies on cancer related processes that involves endosomal signalling and cell migration/invasion.

Commentary article: Krauß M, Haucke V. A grab to move on: ER-endosome contacts in membrane protrusion formation and neurite outgrowth EMBO J. 2015 Apr 9.

Raiborg C, Wenzel EM, Pedersen NM, Olsvik H, Schink KO, Schultz SW, Vietri M, Nisi V, Bucci C, Brech A, Johansen T, Stenmark H. (2015) Repeated ER-endosome contacts promote endosome translocation and neurite outgrowth Nature. 520(7546):234-8.

Prof. Kirsten Sandvig awarded INNO INDIGO grant for work with biodegradable nanoparticles
CCB’s principal investigator Prof. Kirsten Sandvig recently received a new grant for work with biodegradable nanoparticles through INNO INDIGO which is an innovation-driven initiative for the development and integration of Indian and European research.

New collaborations: The goal of the new project is to develop biodegradable nanoparticles for cancer therapy (breast and colorectal). The work in Oslo will include testing of the nanoparticles on cells and in animal models, in close collaboration with Gunhild Mælandsmo, Kjersti Flatmark and Tore Skotland. The nanoparticles will be produced by groups in India and Belgium; the group in Belgium will also perform in vivo studies.





Marina Vietri

Funding

Microscopy infrastructure funded by the Norwegian Research Council

The Norwegian Advanced Light Microscopy Imaging Network (NALMIN), coordinated by CCB director Harald Stenmark, has been funded by 49.5 MNOK by the Research Council of Norway. This is good news for Norwegian researchers who use light microscopy in their studies.

The vision of the Norwegian Advanced Light Microscopy Imaging Network is to provide Norwegian researchers with the most advanced light microscopy technology to image biologically and biomedically important molecules at high to ultra-high resolution in systems ranging from microorganisms and cell cultures through plants and small animals.

Selected publications

Nature article from Marina Vietri: Sealing holes in the nuclear envelope as a mechanism to protect the genome

In an article in Nature, published on-line 3rd June, PhD student Marina Vietri and her co-workers in Harald Stenmark's group at Centre for Cancer Biomedicine and Institute for Cancer Research have uncovered a new cellular mechanism that contributes to keep our genome intact.

During cell division, the nuclear envelope breaks down so that duplicated chromosomes can be separated by the microtubule-containing spindle apparatus. Upon completion of this process, in anaphase, new nuclear envelopes are formed around the two daughter nuclei,

and the mitotic spindle is disassembled by a mechanism that has not been known. Vietri and her co-workers noticed that certain subunits of a protein complex known as endosomal sorting complex required for transport (ESCRT) accumulate around the reforming daughter nuclei in anaphase. This observation made them uncover a mechanism whereby ESCRT proteins coordinate nuclear envelope sealing and mitotic spindle disassembly. The ESCRT proteins are recruited to points in the reforming nuclear envelope that are intersected by microtubules. Here, they recruit an enzyme, Spastin, which severs microtubules. The remaining holes in the nuclear envelope are then sealed by the membrane-healing activity of the ESCRT proteins.

Vietri and co-workers also addressed what happens if this process goes wrong. By interfering with normal ESCRT functions during anaphase, the researchers observed that DNA becomes damaged, so evidently the novel mechanism of spindle disassembly and nuclear envelope sealing is important for keeping our genome safe.

Because genome instability is strongly connected to cancer development, it will now be interesting to examine which roles the ESCRT machinery plays in preventing cancer.

This paper has been dedicated commentary articles in both of the world's most influential scientific journals, Nature and Science. This is very unusual for cell biological papers and illustrates the impact of the findings by the Norwegian research group.

Nature - News & Views: Cell biology: Nuclear dilemma resolved, Brian Burke, Nature. 2015 Jun 11;522(7555):159-60.

Perspective - Cell Biology: An ESCRT to seal the envelope, Wesley I. Sundquist, Katharine S. Ullman, Science. 2015 Jun 19;348(6241):1314-5.

Vietri M, Schink KO, Campsteijn C, Wegner CS, Schultz SW, Christ L, Thoresen SB, Brech A, Raiborg C, Stenmark H. (2015) Spastin and ESCRT-III coordinate mitotic spindle disassembly and nuclear envelope sealing Nature. 522(7555):231-5.

This paper has been dedicated commentary articles in both of the world's most influential scientific journals, Nature and Science.

Selected publications

Novel prognostic biomarker for colorectal cancer

Bruun and colleagues performed genetic analyses of cancer-critical mismatch-repair genes in independent patient series and found that a mutation in the cell cycle gene regulator of chromosome condensation 2, RCC2, can identify high-risk stage II patients with the microsatellite instability phenotype. This finding was explored and validated functionally. Furthermore, protein expression was shown to stratify clinically important patient groups in a large consecutive patient series. Hence, RCC2 risk stratification can potentially guide clinical decision making for a large number of colorectal cancer patients. Importantly, the mutation assay and the protein expression assessment can be done rapidly by cost-effective routine technologies.

Bruun J, Kolberg M, Ahlquist TC, Royrvik E, Nome T, Leithe E, Lind GE, Merok MA, Rognum TO, Bjorkoy G, Johansen T, Lindblom A, Sun XF, Svindland A, Liestol K, Nesbakken A, Skotheim RI, Lothe RA. (2015) Regulator of chromosome condensation 2 identifies high-risk patients within both major phenotypes of colorectal cancer Clin Cancer Res. 21(16):3759-70.

DNA methylation biomarkers detect cholangiocarcinoma

Up to 20% of patients with primary sclerosing cholangitis (PSC) develop the deadly disease cholangiocarcinoma, cancer of the bile ducts. Diagnosing this malignancy is particularly challenging. In a collaborative effort between CCBs group of Epigenetics and the Norwegian PSC Research Center, DNA methylation analyses of a large series of biliary brush samples identified a high performance biomarker panel with 85% sensitivity and 98% specificity. The molecular analyses outperformed conventional brush cytology, however, combining both modalities detected a high 94% with 96% specificity. These findings are promising for the development of a DNA methylation-based test for monitoring PSC patients for cholangiocarcinoma development.

Andresen K, Boberg KM, Vedeld HM, Honne H, Jebsen P, Hektoen M, Wadsworth CA, Clausen OP, Lundin KE, Paulsen V, Foss A, Mathisen Ø, Aabakken L, Schruppf E, Lothe RA, Lind GE. (2015) Four DNA methylation biomarkers in biliary brush samples accurately identify the presence of cholangiocarcinoma Hepatology. 61(5):1651-9.

Up to 20% of patients with primary sclerosing cholangitis develop the deadly disease cholangiocarcinoma, cancer of the bile ducts.



Two innovation projects in CCB funded by the Norwegian Cancer Society and the Research Council of Norway

Before Christmas the Norwegian Cancer Society and the Research Council of Norway distributed 56 million NOK to various innovation projects. Products that cancer patients are in need of will be developed by these projects. TTOs (Technology Transfer Offices) and Inven2 are project leaders for the majority of these projects.

Alicia Llorente's project: Urinary exosome test for improved prostate cancer management

This project's objective is to use new markers to develop a better diagnostic test for detecting prostate cancer from urine samples. The biomarkers will be adapted to an immunoassay format to provide a more specific, more sensitive first indication of prostate cancer than the currently used PSA test. Earlier detection of prostate cancer could save millions of lives worldwide, while an improved diagnostic test could substantially reduce the number of unnecessary biopsies and treatments.

Guro E. Lind's project: BladMetrix - a novel urine test for early detection and monitoring of bladder cancer

Bladder cancer is a common form of cancer and one of the most expensive cancers to treat. This project aims to find the best combination of biomarkers detectable in urine, and to confirm that the test is better than existing diagnostic methods. The result could be a new, non-invasive test to detect early stages of bladder cancer with high reliability, and which may also be used for post-treatment monitoring.



Selected publications

Aneuploidy as a prognostic marker in common cancers

Aneuploidy, an inevitable result of chromosome instability, is characterized by abnormal DNA content in tumor cells, which can be detected and quantified by using cytometric methods such as flow and image cytometry. In order to evaluate the usefulness of these economical and robust methods in the molecular era, Danielsen et al. reviewed the prognostic importance of ploidy analysis in common carcinomas (breast, endometrium, ovary, uterine cervix, oesophagus, colon and rectum, lung, prostate and bladder). The evidence supports that ploidy is an independent prognostic marker in patients with node-negative invasive breast, early stage endometrioid endometrial, early stage ovarian, prostate, and colorectal cancers.

Danielsen HE, Pradhan M, Novelli M. (2015) Revisiting tumour aneuploidy - the place of ploidy assessment in the molecular era Nat Rev Clin Oncol. 2016 May;13(5):291-304. Epub 2015 Nov 24.

Fusion genes in testicular cancer

Andreas Hoff and co-workers have by use of high-throughput RNA sequencing technology discovered the first fusion genes present in testicular germ cell tumors. The fusion genes *RCC1-HENMT1* and *RCC1-ABHD12B* and also a transcript variant of *ETV6* were highly expressed in poorly differentiated histological subtypes of testicular cancers. Absent expression in more differentiated subtypes of testicular cancers, as well as observations from an *in vitro* differentiation assay, demonstrated that the transcripts are markers of pluripotency in a malignant setting. The fusion genes are as such candidate biomarkers of malignant progression.

Hoff AM, Alagaratnam S, Zhao S, Bruun J, Andrews PW, Lothe RA, Skotheim RI. (2016) Identification of Novel Fusion Genes in Testicular Germ Cell Tumors Cancer Res.76(1):108-16. Epub 2015 Dec 9.

Prizes / Awards

H.M. the King's Gold Medal to Sigrid Bratlie Thoresen

Sigrid Bratlie Thoresen in Harald Stenmark's group at Institute for Cancer Research and Centre for Cancer Biomedicine has been awarded His Majesty the King's Gold Medal 2015 for the best PhD thesis at the Faculty of Medicine.

Sigrid's PhD thesis, entitled "Novel regulators of the cell division cycle", identifies and characterizes novel regulators of the cell cycle and discusses the importance of such regulators in preventing cancer. The main work in her PhD thesis, published in the prestigious journal Nature Cell Biology, concerns a novel protein called ANCHR, which is a key component of a cellular checkpoint that monitors that chromosomes are cleared from the bridge between two daughter cells before the two cells are finally separated through cleavage of the bridge. In the absence of ANCHR, this checkpoint does not work, which results in cells with abnormal chromosome numbers, a condition associated with carcinogenesis. This work has obtained considerable attention internationally.

The Medal was awarded at a Prize Ceremony at the Annual Celebration of the University of Oslo on 2nd September. Congratulations!

Sigrid Bratlie Thoresen has been awarded His Majesty the King's Gold Medal 2015 for the best PhD thesis at the Faculty of Medicine.

OUS awards to CCB's Marina Vietri and Camilla Raiborg for outstanding original scientific article

In December six research prizes were awarded to scientists from Oslo University Hospital. CCBs Marina Vietri and Camilla Raiborg were among the prize winners. Both Vietri and Raiborg are members of Harald Stenmark's group.

Prizes for excellent research articles: The prizes were presented by Bjørn Erikstein, managing director of Oslo University Hospital, at a ceremony taking place on the 11th of December. We are happy to congratulate both postdoc Marina Vietri and senior scientist Camilla Raiborg with Excellent Original Article Awards of 50.000 NOK each.

Vietri M, Schink KO, Campsteijn C, Wegner CS, Schultz SW, Christ L, Thoresen SB, Brech A, Raiborg C, Stenmark H. (2015) Spastin and ESCRT-III coordinate mitotic spindle disassembly and nuclear envelope sealing Nature. 522(7555):231-5.

Raiborg C, Wenzel EM, Pedersen NM, Olsvik H, Schink KO, Schultz SW, Vietri M, Nisi V, Bucci C, Brech A, Johansen T, Stenmark H. (2015) Repeated ER-endosome contacts promote endosome translocation and neurite outgrowth Nature. 520(7546):234-8.

2016

Funding

Håvard Danielsen’s project “DoMore!” receives Lighthouse project grant from the Norwegian Research Council

We congratulate CCB’s PI Håvard Danielsen, director of the Institute for Cancer Genetics and Informatics, Oslo University Hospital, with the prestigious Lighthouse Project grant for the DoMore! project focusing on heterogeneity in cancer. The funding is 60 million NOK over a five-year period.

About the DoMore! project: The Norwegian Research Council IKTPLUSS has selected the DoMore! project application as one of the 3 winners of the prestigious Lighthouse Project grant.

By largely digitalizing and automating diagnostics and prognostication of cancer, we can literally DoMore! and analyze a greater number of samples from the same tumor, leading to a more precise diagnosis for each patient. Safe storage, analysis and processing of the Big Data produced by the project, will also be handled by the project partners.

The DoMore! team is composed of experts within several fields, including digital imaging, processing, robotics, pathology, cell biology, surgery and oncology, both in Norway and abroad. Together, we will create solutions that will allow us to DoMore!, resulting in objective cancer diagnostics that can be made available to all patients.

Ragnhild A. Lothe substantially supported by Toppforsk grant from the Norwegian research Council

We congratulate CCB co-director Ragnhild A. Lothe with achieving the substantial NFR TOPPFORSK funding grant for the project “Modeling tumor heterogeneity in colorectal cancer management”.

The toppforsk is part of the FRIPRO - an open competitive arena for all research areas and disciplines, where there are no thematic guidelines and no requirements relating to the applicability or immediate utility of the research. The competition in FRIPRO is tough, and only the best researchers with particularly good projects and very well-written proposals have a chance at succeeding.

About the “modeling tumor heterogeneity” project: Heterogeneity implies that the tumor has several cell clones with unequal ability to spread to other organs and unequal ability to tolerate treatment, increasing the chance for continued tumor growth. This research project aims to model spatio-temporal tumor heterogeneity by multilevel genomic analyses of many samples from individual patients.

We hypothesize that patients with a high level of heterogeneity in their tumors have a poor disease outcome and commonly develop resistance to standard treatment of today. We anticipate that the new knowledge gained will contribute to identify the right treatment for the right patient at the right time.

Selected publications

Liliane Christ identified mechanism for regulation of daughter cell separation

In a February issue of Journal of Cell Biology, PhD student Liliane Christ from Harald Stenmark’s group provided new insight into how daughter cells are separated during the end of cell division. In the same issue, a “Biobytes” podcast with group leader Harald Stenmark and co-corresponding author Coen Campsteijn explained the importance of this work, as does a commentary article by two external experts in the field, Frankel and Audhya: Burning cellular bridges - Two pathways to the big breakup.

At the end of cell division, the two daughter cells are separated by the process known as cytokinesis, which culminates in the physical severing of the thin membrane bridge that joins the two cells. This scission is mediated by the so-called ESCRTs, a machinery of protein complexes originally identified for their role in endosomal protein sorting. A filamentous protein complex called ESCRT-III is thought to execute the scission step, but its recruitment to the intercellular membrane bridge has not been clarified.

Now, Christ and co-workers show that ESCRT-III is recruited to the intercellular

bridge by two parallel “arms”. One arm consists of the ESCRT-I and -II complexes, similar to what has been observed previously in endosomal sorting. The other arm consists of an ESCRT-binding protein called ALIX. Importantly, the authors also uncovered an additional function for ALIX, namely in recruitment of a component of the abscission checkpoint that delays abscission in the event of any lagging chromatin in the intercellular bridge. Depletion of ALIX leads to cytokinetic furrow regression in cells with chromatin bridges, resulting in cells with two nuclei, a known risk factor in carcinogenesis. These findings thus provide a novel link between the cytokinetic abscission machinery and the abscission checkpoint, with implications for our understanding of how ESCRT proteins may function as tumour suppressors.

Christ L, Wenzel EM, Liestøl K, Raiborg C, Campsteijn C, Stenmark H. (2016) ALIX and ESCRT-I/II function as parallel ESCRT-III recruiters in cytokinetic abscission J Cell Biol, 212 (5), 499-513.



Prizes / Awards

OUS award to CCB's Jarle Bruun for outstanding scientific article

On the 17th of June six research prizes were awarded to scientists from Oslo University Hospital. CCBs Jarle Bruun was among the prize winners. Jarle Bruun is a member of Ragnhild A. Lothe's group.

Prize for excellent research article: The prizes were presented at a ceremony at Rikshospitalet taking place in the month of June. We congratulate Postdoc Jarle Bruun with the Excellent Original Article Award of 50.000 NOK.

Bruun J, Kolberg M, Ahlquist TC, Røyrvik EC, Nome T, Leithe E, Lind GE, Merok MA, Rognum TO, Bjørkøy G, Johansen T, Lindblom A, Sun XF, Svindland A, Liestøl K, Nesbakken A, Skotheim RI, Lothe RA. (2016) **Regulator of Chromosome Condensation 2 Identifies High-Risk Patients within Both Major Phenotypes of Colorectal Cancer** Clin Cancer Res, 21 (16), 3759-70.

H.M. the King's Gold Medal to Marina Vietri

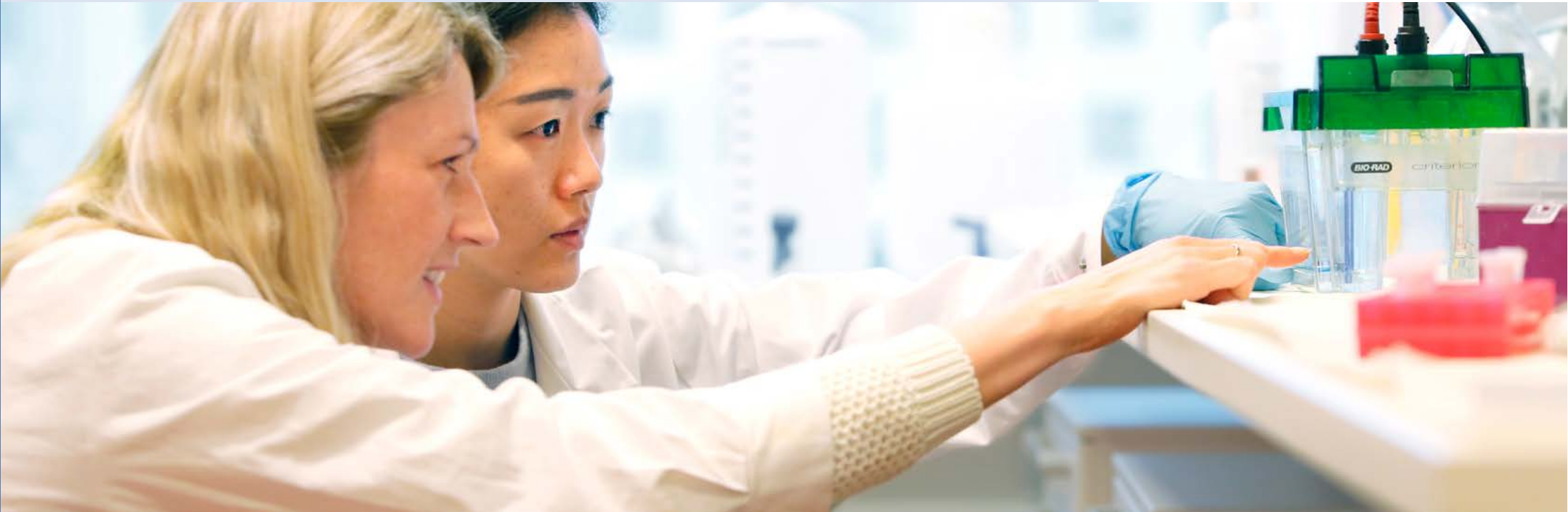
Marina Vietri from Harald Stenmark's group at Institute for Cancer Research and Centre for Cancer Biomedicine was awarded H.M. the King's Gold Medal 2016 for best thesis of the Faculty of Medicine.

Marina defended her PhD thesis "Closing the gap - ESCRT-III orchestrates nuclear envelope sealing" on 6th November 2015. It is interesting to note that this thesis, contrary to current practice, only contained a single published article. This article was published in the world-leading journal Nature with Marina as first author and gained worldwide attention as illustrated by the fact that it was dedicated commentary articles in both Nature and Science. The reason for this attention was that the article solved an enigma in cancer cell biology, namely how the newly formed nuclear envelope is sealed at the end of cell division. Marina showed that nuclear envelope sealing is mediated by a protein complex known as ESCRT, and that this is coordinated with disassembly of the mitotic spindle by the microtubule-severing enzyme Spastin. She found that cells with impaired ESCRT function have leaky nuclei and acquire DNA damage typical of cancer cells. Thus, this discovery provides new potential targets in cancer medicine.

Vietri received the medal at the annual celebration of the University of Oslo in the University Aula on the 2nd of September. Congratulations!



2017

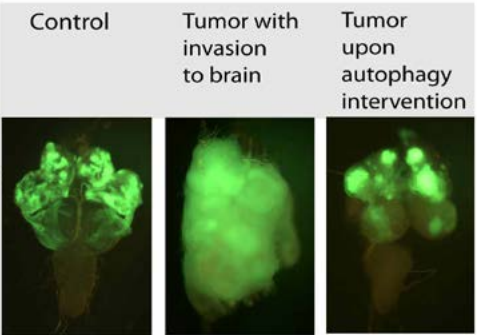
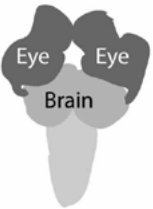
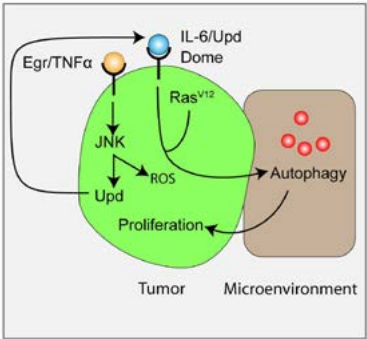


Selected publications

MICROENVIRONMENTAL AUTOPHAGY SUPPORTS TUMOR GROWTH. NATURE ARTICLE FROM NADJA KATHEDER

Nadja Katheder and collaborators in the lab of Tor Erik Rusten have published an article entitled “Microenvironmental autophagy supports tumor growth” in the journal Nature.

Friendly neighbors feed tumor cells (Left) Inflammatory and oncogenic signaling in the Cancer Cell (green) coerces neighboring cells of the microenvironment (brown) to produce amino acids by way of autophagy that may be taken up by tumors to support growth. (Right) Malignant tumors of the eye grow and invade the central nervous system killing the animal. Pharmacological or genetic inhibition of autophagy stalls tumor growth and invasion.



It is known that transformed tumor cells rewire growth and metabolism to support their own growth. How these changes occur in animals, however, are poorly understood. In the published study, Katheder and co-workers show how malignant tumors coerce neighboring microenvironmental cells to support their own growth.

Oncogenic and inflammatory cell signaling in transformed cells act together to reprogram tumor cells to elicit a stress-response, termed autophagy (self eating) in neighboring cells. Studies of autophagy was awarded the Nobel Prize in Physiology or Medicine earlier this year and is best known for shuttling cytoplasmic content to the lysosome for degradation and repurposing of recycled building blocks, like amino acids, nucleotides and fatty acids. In this study, researchers found that pharmacological or genetic inactivation of autophagy specifically in microenvironmental cells, or reducing amino acid import into tumor cells effectively blocked tumor growth and invasion.

The study, supported by Helse Sør Øst and the Norwegian Cancer Society, provides additional impetus to further elucidate the potential for pharmacological intervention of autophagy in cancer treatment. Phase I trials with experimental autophagy intervention is currently being carried out in numerous studies, but so far not in Norway.

Nadja S. Katheder, Rojyar Khezri, Fergal O’Farrell, Sebastian W. Schultz, Ashish Jain, Mohammed M. Rahman, Kay O. Schink, Theodossis A. Theodossiou, Terje Johansen, Gábor Juhász, David Bilder, Andreas Brech, Harald Stenmark & Tor Erik Rusten (2017) Microenvironmental autophagy promotes tumour growth Nature, 541 (7637), 417-420.



OUS Excellent Researcher Award to Prof. Kirsten Sandvig
On the 5th of May CCB Principal Investigator Kirsten Sandvig was awarded the Oslo University Hospital Excellent Researcher Award of 300,000 NOK.
Three scientists received the 2017 Excellent Research Awards for their outstanding research at a ceremony taking place at Oslo University Hospital. The major prize - the “Excellent Researcher Award” - went to professor Kirsten Sandvig. We congratulate Kirsten Sandvig with this prestigious and well-deserved award.

Clinically important genetic heterogeneity in colorectal cancers with microsatellite instability, a collaboration study between the Lothe and Skotheim groups
Microsatellite instability (MSI) defines a small subgroup of approximately 15% of colorectal cancers (CRC) which currently receives much attention due to its overall good response to immune-checkpoint inhibition. In the journal Genome Medicine, scientist Anita Sveen and colleagues published the largest multilevel genetic analysis of this tumor type reported to date, describing substantial inter- and intra-tumor heterogeneity. The clinical importance of these results, in particular with respect to the optimized use of immunotherapeutics for treatment of human cancers, was emphasized in a Research Highlight in the same issue of the journal.

The study is a collaboration between the Lothe and Skotheim groups, as part of the Norwegian Cancer Genomics Consortium. Exome sequencing revealed JAK1 as a new frequently mutated gene in MSI+ primary CRC, validated with a 20% mutation frequency in independent patient series. These truncating mutations were associated with gene expression-changes predicting a poor response to immune-checkpoint inhibition, consistent with a recent report of JAK1-associated treatment resistance in metastatic disease (Shin et al., Cancer Discov 2017;7:188-201). However, the mutations were also a marker of a good patient prognosis, predicting a low mutation frequency

in metastatic disease and highlighting the need to uncover additional resistance mechanisms.
The indication of immunotherapy in MSI+ tumors is a result of their large mutation burden and subsequent infiltration of cytotoxic lymphocytes. Sveen and colleagues describe that the mutation load is indeed associated with the predicted neoantigen load also specifically among these tumors, but is not proportional with the level of immune cell infiltration. Tumor immunity was more closely associated with the gene expression-based consensus molecular subtypes (CMS), identifying the immunogenic subgroup CMS1 as an independent marker of a good patient prognosis and reinforcing the potential also for prognostic stratification of MSI+ CRC.

Sveen A, Johannessen B, Tengs T, Danielsen SA, Eilertsen IA, Lind GE, Berg KCG, Leithe E, Meza-Zepeda LA, Domingo E, Myklebust O, Kerr D, Tomlinson I, Nesbakken A, Skotheim RI, Lothe RA. (2017) **Multilevel genomics of colorectal cancers with microsatellite instability-clinical impact of JAK1 mutations and consensus molecular subtype 1** Genome Med. 2017 May 24;9(1):46.

Research highlight article:
Dissecting microsatellite instability in colorectal cancer: one size does not fit all. Samstein RM, Chan TA., Genome Med. 2017 May 24;9(1):45.

OUS award to CCB’s June Myklebust for outstanding scientific article
On the 16th of June, six research prizes were awarded to scientists from Oslo University Hospital. CCBs June Myklebust was among the prize winners. June Myklebust is Co-PI of Erlend Smeland’s group at the Department of Immunology, Institute for Cancer Research, Oslo University Hospital.

Prize for excellent research article: The prizes were presented at a ceremony at Rikshospitalet on the 16th of June. We congratulate senior scientist June Myklebust with the Excellent Original Article Award of 50,000 NOK.

Myklebust JH, Brody J, Kohrt HE, Kolstad A, Czerwinski DK, Wälchli S, Green MR, Troen G, Liestøl K, Beiske K, Houot R, Delabie J, Alizadeh AA, Irish JM, Levy R (2016) **Distinct patterns of B-cell receptor signaling in non-Hodgkin lymphomas identified by single-cell profiling** Blood, 129 (6), 759-770.

CCB researchers uncover novel mechanism of cellular metabolic control
A protein kinase complex known as mTORC1 is known to control cell growth by upregulating anabolic processes and downregulating catabolism in response to growth factors and nutritional cues such as amino acids. Because mTORC1 signalling is an important driver of cancer development, we need to understand how this signalling is regulated.
mTORC1 signalling occurs from lysosome membranes and is regulated by the lipid kinase PIK3C3 and its catalytic product, phosphatidylinositol 3-phosphate (PI3P), but the mechanism has remained unknown. Now, postdoc Zhi Hong and her co-workers in Camilla Raiborg’s project group have discovered that PIK3C3 and PI3P control mTORC1 activation by regulating lysosome positioning. When cells are stimulated with amino acids, PIK3C3 is activated to produce PI3P, and two PI3P-binding proteins, Protrudin and FYCO1, cooperate to mediate transport of lysosomes along microtubules to the cell periphery. This brings mTORC1 in proximity to growth-signalling receptors at the plasma membrane, thus priming mTORC1 for activation. These results, which are published in the Journal of Cell Biology, are interesting since they open new avenues for pharmacological targeting of metabolic signalling in cancer.

Hong Z, Pedersen NM, Wang L, Torgersen ML, Stenmark H, Raiborg C (2017) **PtdIns3P controls mTORC1 signaling through lysosomal positioning** J Cell Biol. 2017 Oct 13. [Epub ahead of print]

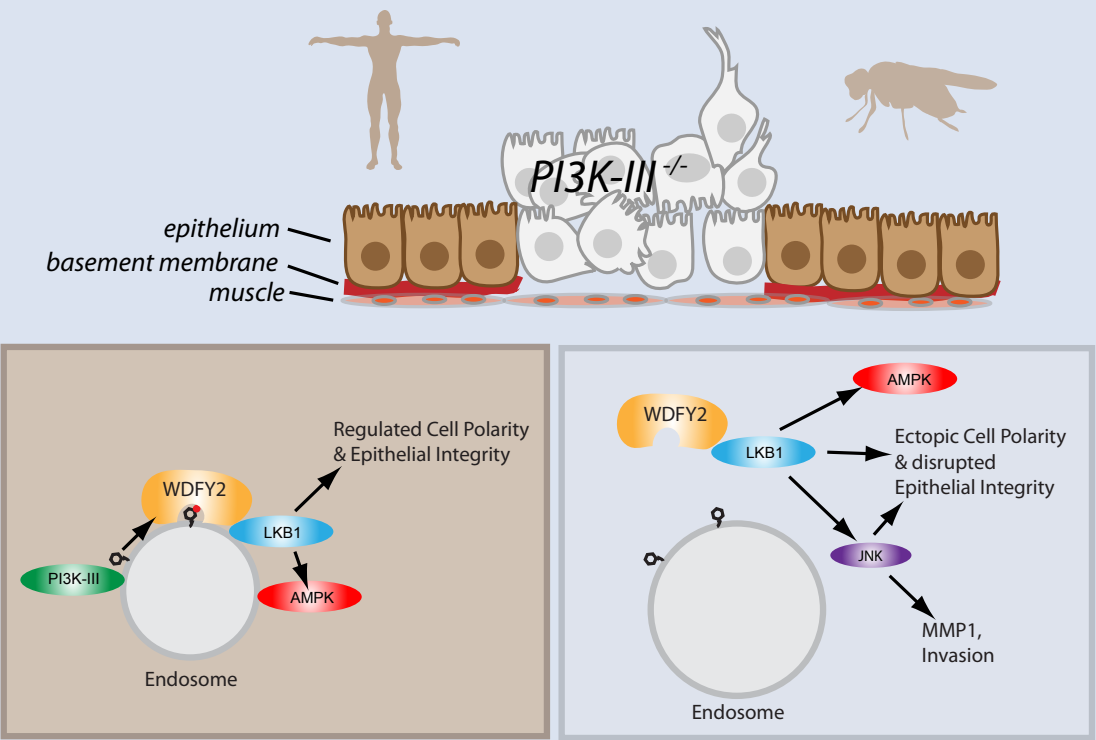
Selected publications

Fergal O’Farrell reports new insight into regulation of the Peutz-Jeghers Syndrome kinase, LKB1, in Nature Cell Biology

Scientist Fergal O’Farrell from the group of Tor Erik Rusten reports a new regulatory function of Liver Kinase B1, a well known tumor suppressor mutated in solid tumors and responsible for the Peutz- Jeghers human cancer syndrome. The work started as a close collaboration between Fergal O’Farrell and Viola Lobert in Harald Stenmark’s group, and has utilized both human organoid cell culture and *Drosophila* genetics to unravel a conserved cell biological mechanism that regulates LKB1 and prevents neoplasia-like epithelial growth in both species.

The project was initiated in an effort to understand why a lipid kinase, termed PI3K-class III, that controls endocytic and autophagic vesicle trafficking, acts as a tumor suppressor. O’Farrell and Lobert found that disrupting PI3K-class III led to neoplasia in fly and human epithelia. Disruption of the organized structure of epithelia is a common event in epithelial-derived cancers (carcinomas). LKB1 is anchored to the cytoplasmic leaflet of the plasma membrane where it is known to phosphorylate target proteins controlling cell polarity and metabolism. LKB1 was found to be endocytosed and directed to late endosomes where its signaling activity was attenuated. Mechanistically, the lipid phosphatidylinositol-3-phosphate (PI3P) generated by PI3K-class III on endosomes recruits the PI3P-binding protein, WDFY2, which acts in a complex with LKB1 to control its epithelial polarizing activity. Mutations in PI3K-class III cooperate with oncogenic RasV12 to drive tumor growth through LKB1 *in vivo*. In sum, these studies explains how PI3K-III acts as a tumor suppressor, and reveal that LKB1 can harbor contextual oncogene activity that cooperates with oncogenic Ras.

Fergal O’Farrell, Viola H  l  ne Lobert, Marte Sneeggen, Ashish Jain, Nadja Katheder, Eva Maria Wenzel, Sebastian Wolfgang Schultz, Kia Wee Tan, Andreas Brech, Harald Stenmark and Tor Erik Rusten Class III phosphatidylinositol 3-kinase controls epithelial integrity through endosomal LKB1 regulation Nat Cell Biol, in press, 2017.



Endosomal control of LKB1 restricts epithelial integrity disruption and invasion
Drosophila and human epithelial organoid models show loss of epithelial integrity and invasive behavior upon loss of PI3K-class III. Model (boxes) depicting the identified LKB1 endosomal signaling platform in normal (brown), and mutant (grey) cells. Endosomal phosphoinositide lipid modification by PI3K-class III recruits WDFY2 which associates with LKB1 and stabilizes its endosomal localization to regulate cell polarity and epithelial integrity through downstream targets. When PI3P production or PI3P-dependent endosomal recruitment of WDFY2 is perturbed, LKB1 signaling is elevated and delocalized, leading to ectopic cell polarization causing dysplasia-like epithelial disruption that cooperates with oncogenic Ras for tumor growth. This is in part through JNK signaling, which drives matrix metalloprotease 1 (MMP1) production and induces invasive cellular behavior.

In sum, these studies explain how PI3K-III acts as a tumor suppressor, and reveal that LKB1 can harbor contextual oncogene activity that cooperates with oncogenic Ras.

CELLULAR MEMBRANE DYNAMICS



The impact of CCB on our group

Through CCB the group has become involved in interdisciplinary cooperations that have increased the scientific quality of its work and have brought its research closer to clinical applications. CCB has also been important for developing the careers of the group’s young researchers, and four of its previous CCB group members - Anne Simonsen, Ioannis Nezis, Tor Erik Rusten and Coen Campsteijn - now run their own successful groups. Collaborations with these groups continue.

Achievements

The group was assigned a special role in studying the functional mechanisms of PIK3C3, a lipid kinase known to function as a tumour suppressor via its catalytic product, phosphatidylinositol 3-phosphate (PI3P). Two PI3P-binding proteins were identified as regulators of cytokinesis, the final stage of cell division, and their downregulation was shown to cause multinucleation, a condition that predisposes to tumourigenesis (Sagona

et al. *Nature Cell Biology*, 2010; Thoresen et al., *Nature Cell Biology*, 2014). Several other cancer-relevant regulators of cytokinesis were also identified (Haglund et al., *Current Biology* 2010; Lind et al., *Oncogene*, 2011; Christ et al., *Journal of Cell Biology*, 2016). Unexpectedly, the group also identified PI3P-binding proteins that mediate protrusion outgrowth and anabolic signalling, conditions that are upregulated in tumours (Raiborg et al., *Nature* 2015; Hong et al., *Journal of Cell Biology* 2017).

Studies of autophagy, the process of cellular “self-eating” was another of the group’s main tasks in CCB. An important finding was the identification of a mechanism by which autophagy can trigger cell death (Nezis et al., *Journal of Cell Biology*, 2010). Another finding, which received considerable attention, was the observation that tumours induce autophagy in the microenvironment in order to provide supply of amino acids that fuel their sustained growth. Indeed, pharmacological inhibition of autophagy was found to cause tumour shrinkage, a finding which is promising with

Overall the group has published 128 papers since it joined CCB, and 11 PhDs have been graduated.

respect to future cancer therapy (Katheder et al., *Nature*, 2017).

One of the group’s major interests has been to characterize the functional mechanisms of the endosomal sorting complex required for transport (ESCRT) machinery, known for its role in downregulation of oncogenic growth factor signaling (Raiborg and Stenmark, *Nature*, 2009). Importantly, this machinery was also found to control autophagy (Rusten et al., *Curr.Biol.* 2007), cell migration (Lobert et al., *Developmental Cell* 2010), and nuclear envelope reformation (Vietri et al., *Nature* 2015), all cancer relevant processes.

Most of the abovementioned papers have been collaborations with other CCB members, and, in particular, contributions with clinical data and statistical analyses from other CCB groups were crucial to the success of these studies.

Overall the group has published 128 papers since it joined CCB, and 11 PhDs have been graduated. In addition, the associated group of Antoni Wiedlocha, which has been specializing on fibroblast growth factor signalling, has published 31 papers and graduated 4 PhDs. Two of the PhDs in the Stenmark group, Sigrid Bratlie Thoresen (2015) and Marina Vietri (2016), were awarded H.M. the King’s gold medal for best PhD thesis of the Faculty of Medicine. The group has obtained substantial external funding, especially from the European Research Council, the Norwegian Cancer Society, the South-Eastern Norway Regional Health Authority, and the Research Council of Norway.

Our focus for the years to come

From 2018, the activities of the group will occur within the framework of a new Centre of Excellence, Centre for Cancer Cell Reprogramming (CanCell). A main focus of the group will be to identify cross-talk between cancer cell programmes, such as intersections between membrane dynamics and genome regulation. This will be performed together with other partners in CanCell, but the group will also continue some of its collaborations with CCB members.

CANCER GENETICS

The impact of CCB on our group

The inauguration and development of the Department of Molecular Oncology at the Institute for Cancer Research has paralleled the 10-year period of the CCB, and we have benefitted from being in a CoE in many ways. We have almost doubled the number of employees, and two previous postdocs, Rolf I. Skotheim and Guro E. Lind, now lead independent groups at the Department (since 2010 and 2012, respectively) and hold adjunct professorships at the University of Oslo. My research group has demonstrated successful interdisciplinary collaborations within the Centre and at both host institutions, the Oslo University Hospital and the University, and has gained from the advice and collaboration of the scientific advisory board and guest professors.

Achievements

In total, we have published 189 papers during the Centre period, of which two-thirds have group members as first and/or last authors. About half of the papers have been published with international partners, altogether 74 of the papers with other CCB partners, and 98 with clinical collaborators. We have established high-quality research biobanks with corresponding clinical records, as well as large series of well-characterized preclinical models, both of which are invaluable resources for basic and translational cancer research relevant for current clinical challenges. Our senior scientists have provided high-quality education and supervision for students at the University of Oslo, where we teach regularly at two faculties and three Institutes. In total, 49 academic degrees (21 PhDs and 28 MSc) have been completed during the Centre period.

During the Centre period we have identified high-performance biomarkers suitable for minimally invasive detection of colorectal



cancer (Lind et al., Gastroenterology 2007, Mol Cancer 2011), bladder cancer (Costa et al., Clin Cancer Res 2010) and cholangiocarcinoma (Andresen et al., Hepatology 2015), resulting in 13 patent applications and 4 granted biomarker patent-families.

Current adjuvant treatment guidelines for primary colorectal cancer have limited precision for the individual patient, frequently resulting in under- or over treatment. Identification of precise prognostic biomarkers to aid in treatment decisions is therefore a research area of world-wide interest, and we have contributed by developing prognostic gene expression signatures and biomarkers for stage II and III (Ågesen et al., GUT 2012; Sveen et al., Clin Cancer Res 2012; Merok et al., Ann Oncol 2013; Bruun et al., Clin Cancer Res 2015; Vedeld et al., Int J Cancer 2017), and identified genomic heterogeneity as an independent prognostic factor after partial liver resection in metastatic colorectal cancer (Sveen et al., PLoS Genetics 2016).

We have been central in the establishment of state-of-the-art genomic technologies essential for improved precision medicine

within the Centre and at the hospital, and we hold an active partnership in the Norwegian Cancer Genomics Consortium. Selected highlights in genomics research from the Centre period include development of a universal assay for fusion transcript detection (Skotheim et al., Mol Cancer 2009), identification of recurrent genomic aberrations with clinical impact in a sarcoma subgroup (Brekke et al., J Clin Oncol 2010), discovery of a novel pan-cancer phenotype termed transcriptome instability (Sveen et al., Genome Medicine, 2011), detection of fusion genes in germ cell tumors (Hoff et al., Cancer Res 2016), providing a multi-level genomics resource on preclinical colorectal cancer models (Berg et al., Mol Cancer 2017), discovery of JAK1 as a new target gene in a subgroup of colon cancers, prediction of response to immunotherapy by multi-level genomics (Sveen et al., Genome Med 2017), and validation of an exceptionally high degree of genomic heterogeneity in multifocal prostate cancer (Løvfi et al., in revision). Furthermore, we have established and applied molecular pathology protocols for patient risk-assessment in malignant peripheral nerve sheath tumors (Brekke et al., Neuro-Oncol 2009; Kolberg et al., Neuro-Oncol 2013; Danielsen et al., Neuro-Oncol 2015; Kolberg et al., Mol Oncol 2015), germ cell tumors (Hoei-Hansen et al., Mol Cancer 2007) and colorectal cancer (Sirnes et al., Int J Ca 2012; Bruun et al., Clin Cancer Res 2015).

Discoveries of novel targets and molecular mechanisms in cancer have been published during the Centre period: Regulator of chromosome condensation 2, RCC2, is functionally important in development of colorectal cancer (Bruun et al., Clin Cancer Res 2015), the Spartin protein acts as a regulator of cytokinesis (Lind et al., Oncogene 2011), novel functional miRNA targets in colon cancer were identified through a comprehensive screen (Cekaite et al., Neoplasia 2013), the NEDD4 ubiquitin ligase was found to promote colon cancer growth, independent of PI3K signaling, and loss of gap junctions in cancer (Eide et al., Cell Signal 2013; Totland et al., J Cell Sci 2017).

Finally, we have contributed to international multi-centre studies on testicular cancer (Chung et al Nature Genet 2013) and colorectal cancer (Matheu et al., Cancer Res., 2013; Domingo et al., Lancet Gastroenterol & Hepatology 2016; Dienstmann et al., Ann Oncol 2017).

Our focus for the years to come

The groups at the Department of Molecular Oncology will proceed with translational research on colorectal cancer and prostate cancer, with focus on tumor heterogeneity modeling and longitudinal pharmacogenomics, for improved and biology-based stratified treatment of these common malignancies. Major external and internal grants are secured for the first 5 years, including the K. G. Jebsen Colorectal Cancer Research Centre, “SMART-CRC” as one of five focus areas of Oslo University Hospital, “Toppforsk” from the University of Oslo and the Research Council of Norway, as well as grants from the Norwegian Cancer Society, the South-Eastern Regional Health Authorities, the Research Council of Norway and the European Union. We are grateful to and will maintain the collaborations with our clinical and international partners.

We have published 189 papers during the CCB period and 21 PhDs and 28 MSc have graduated.

Erlend Smeland /
June Myklebust group

LYMPHOMA BIOLOGY



The impact of CCB on our group

CCB has been of great importance for our group, and has facilitated new collaborations with other groups at the Centre and provided an important and stable basic financing of our research. Thus, the group has doubled in size during the 10-year period and has also received good external funding for the next 3-5 years. The Centre has also been instrumental in supporting young scientists, including financing of an academic position for June H. Myklebust.

Achievements

Our group has successfully collaborated with biostatisticians and lymphoma clinicians in the Centre to perform translational research in lymphoma. Use of a unique material of serial biopsies from follicular lymphoma patients enabled studies of clonal evolution and transformation in follicular lymphoma, and identified 12 upstream regulators of NF- κ B to be associated with transformation (Eide et al, Blood 2010 and Brodtkorb et al, Blood

2013). Furthermore, we collaborated with pathologists to show the negative influence of BCL2, MYC and Tp53 alterations for outcome of diffuse large B cell lymphoma patients (Fiskvik et al, Leuk Lymphoma 2015), and demonstrated that macrophages and T cell subset composition correlated with time to transformation in follicular lymphoma (Blaker et al, Br J Haematol 2016). In collaboration with the informatics group, we validated their image software program for automated scoring of immunohistochemical sections, using Ki67 expression in mantle cell lymphoma as a model system (Blaker et al, Histopathology 2015). Through our collaboration with the Molecular Oncology group in CCB, we identified genes that are frequently methylated in B cell lymphoma but not in normal B cells (Bethge et al, PloS One 2013, 2014 and Epigenetics 2014). The group has also run two large whole exome sequencing projects as part of the Norwegian Cancer Genomics Consortium. While one of the projects are still ongoing, the first project to identify the



Overall the group has published 68 papers since it joined CCB, and 7 PhDs have graduated.

mutational profile associated with relapsed and treatment refractory diffuse large B-cell lymphoma has been finalized, and identified increased mutational burden in the TP53 pathway (Wise et al, submitted).

We have continued our international collaboration with the lymphoma and leukemia molecular profiling project (LLMPP) (led by Louis M. Staudt at NCI, EB Smeland has been site-PI). This has led to a number of articles in top journals regarding molecular characterization of major lymphoma types and identification of prognostic gene expression signatures. In addition, three previously unrecognized, distinct subgroups of diffuse large B-cell lymphoma, the most frequent type of lymphoma, have been identified (several articles in N Eng J Med, Nature, Science and Cancer Cell during the Centre period). In addition, diagnostic tests, based on gene expression signatures for aggressive B cell lymphoma and mantle cell lymphoma, are under development for use on paraffin-embedded tissue.

We have also collaborated with the group of Ronald Levy at Stanford University. Important discoveries from this collaboration includes the identification of a lymphoma negative prognostic subset in follicular lymphoma, based on lack of B cell receptor signaling (Irish et al, PNAS 2010), and that BCR signaling strength was inversely correlated with the efficacy of BCR pathway inhibitors (Myklebust et al, Blood 2017). We have also identified dysfunctional T cells in the tumor microenvironment of FL, based on the expression of the checkpoint receptors PD-1 (Myklebust et al, Blood 2013) and TIGIT (Josefsson et al, in revision), and hence represent relevant targets for immunotherapy.

Overall the group has published 68 papers since it joined CCB, and 7 PhDs have graduated. The group has obtained substantial external funding, especially from the Norwegian Cancer Society, the South-Eastern Norway Regional Health Authority, NCI and the Research Council of Norway.

Our focus for the years to come

From 2018, the group continues with considerable external funding, especially from the Norwegian Cancer Society and the South-Eastern Norway Regional Health Authority. Our group is part of a K.G. Jebsen Centre application, which is in the final round (decision autumn 2017). We continue to focus on translational research to answer clinically important questions in the lymphoma field by utilizing state of the art technologies in sequencing, transcriptomics and proteomics.

INTRACELLULAR TRANSPORT

The impact of CCB on our group

CCB and the interaction with the other CCB groups have contributed to a change in the research focus of the group, which from the beginning of the CCB period was on basic research, but which throughout the period has changed to include translational research as well. CCB’s contribution concerning economical support has, although being minor compared to the total budget, been essential to ensure continuity and flexibility for several of the projects and the people involved.

Achievements

The group which throughout the period has consisted of 17-18 people including master students, started out studying various cellular transport pathways, partly by using protein toxins. As described below, both basic and translational research projects on exosomes and nanoparticles were started during the CCB period. During the 10 years with CCB the group has altogether published 105 original and review articles. Focus has also been on teaching and education, and during the CCB period, 9 Ph.D. students finished their degrees, and 15 students obtained their master degrees.

Concerning basic research we have investigated the different uptake mechanisms at the cell surface (reviews/comments by Sandvig and van Deurs, Nature, 2008; Sandvig et al.,

Curr.Opin.Cell Biol. 2011) as well as the role of cellular proteins (e.g. Wälcli et al., Mol.Biol. Cell 2008; Lingelem et al., Traffic 2012; Kvalvaag et al., Traffic 2013). New technology in mass spectrometry has allowed us to investigate the role of lipid species, of which there are several hundred in a cell. Changes in lipids have been correlated with changes in transport, thus providing new insight concerning cellular molecular mechanisms (e.g. Raa et al., Traffic 2009; Kavaliauskiene et al., Cell.Mol.Life Sci. 2014; Sandvig et al., Progr.Lipid Res. 2014; Bergan et al., Cell.Mol. Life Sci. 2014; Ailte et al., Sci.Rep. 2016; Kavaliauskiene et al., Oncotarget 2016; Ailte et al., Traffic 2017) . We have also developed methods to study turnover of lipids in cells (Skotland et al., J.Mol.Biol. 2016).

Due to a CCB fellowship awarded to Alicia Llorente, our research on exosomes was continued, starting out with studies on mechanisms of exosome release and composition (e.g. Sandvig and Llorente Mol.Cell Proteomics 2012; Llorente et al., BBA-Mol.Cell Biol.Lipids 2013; Phuyal et al., J.Biol.Chem. 2015; Skotland et al., Progr.Lipid Res. 2017) continuing with translation research on exosomes isolated from urine in prostate cancer patients and healthy individuals (Øverbye et al., Oncotarget 2015; Skotland et al., Eur.J.Cancer 2017). These studies have been very successful, and a number of DOFIs/patent applications have been obtained in collaboration with Inven2.



Our background in intracellular transport paved the way for new studies on cellular uptake of nanoparticles (Tekle et al., Nano Letters 2008; for review, see Iversen et al. Nano Today 2011, cited 472 times Sept. 2017; Øverbye et al., Oncotarget 2017), and we were successful in obtaining a large national competence building project from the Norwegian Research Council, “Biodegradable nanoparticles in cancer diagnosis and therapy”, a 5 year project involving 9 national and several international partners to build national competence in nanomedicine. In this project the Sandvig group is responsible for heading and coordinating all activities in addition to being in charge for in vitro cell studies. Particles showing promising results in in vivo tumor models have been developed (unpublished).

Throughout the CCB period we have been collaborating with other researchers from CCB, an example being the study of how the protein flotillin can function as a prognostic marker and serves to stabilize the presence of ErbB2 at the plasma membrane (Pust et al., Oncogene 2013).

Our focus for the years to come

During the years with CCB we have started several new activities which will be continued. This concerns our studies of prostate biomarkers for therapy and prognosis which have resulted in several DOFIs/patent applications, and our research on nanoparticles which involve both national and international collaborators. Not the least, we also continue our research on intracellular transport in general.

Our group of 17-18 people have during the CCB period published 105 articles, and 9 PhD students and 15 master students have been graduated.

LARGE SCALE GENOMIC INSTABILITY

The impact of CCB on our group

Through CCB the institute has been given access to valuable collaborations with the clinic and with a larger scientific community. Being a part of CCB for the last ten years undoubtedly helped put the institute in a position where it was able to expand, and thereby provided the possibility, among others, to perform patient analysis on a much larger scale. This in turn made the institute leading in its field.

Achievements

Cancer is a disease characterized by heterogeneity and genomic instability. The research group has been developing high throughput methods for detection and characterization of large-scale genomic instability (chromatin structure and DNA ploidy), based on high-resolution digital microscopy and advanced image analysis (Danielsen et al. Nature Reviews Clinical Oncology, 2016; Nielsen et al. Critical Reviews in Oncogenesis, 2008).

The group included an interdisciplinary team of members with background in medicine, biology, mathematics and computer science. We have been studying archival material from the time of diagnosis from cancer patients with proper clinical follow-up and known prognosis. Several methods such as IHC, FISH, DNA Ploidy, Tissue Micro Array, as well as original methods developed in the group (Nucleotyping, 3D-reconstruction, ImmunPath and MicroTracker) are used in an attempt to reveal and understand the 3-dimensional organisation of chromatin, and how this organisation controls gene expression (Nielsen et al. Cytometry, 2012; Nielsen et al. Annals of Cellular Pathology, 2012). The group has been engaged in the search for new diagnostic and prognostic markers among these methods and results, and have been running clinical validation studies on large series of colorectal (Hveem et al. British Journal of Cancer, 2014), oesophageal (Dunn et al. British Journal of Cancer, 2011), prostate (Cyll et al. British



Journal of Cancer, 2017; Hveem et al. British Journal of Cancer, 2016; Silva et al. Translational Oncology, 2016; Pretorious et al. Cellular Oncology, 2009) and gynaecological cancers (Hveem et al. Cancer Epidemiology, Biomarkers & Prevention, 2017; Nielsen et al. Cytometry, 2015; Micci et al. Genes, Chromosomes & Cancer, 2013; Pradhan et al. International Journal of Gynecological Pathology, 2010; Kildal et al. Annals of Oncology, 2009; Kildal et al. European Journal of Cancer, 2009; Micci et al. Virchows Archive, European Journal of Pathology, 2008) with a minimum of 5, and up to 20, years of clinical follow-up, with emphasis on disease-free survival.

The aim has all along been to improve cancer treatment by the identification of better prediction and prognosis of the outcome among these patients. Several of the above-mentioned papers have been collaborations with other CCB members, and contributions with biological knowledge, clinical data, and statistical analysis in particular, has been crucial to the success of these studies.

Our focus for the years to come

In 2016, the institute was awarded a large Lighthouse grant from the Norwegian Research Council for our DoMore! project. The DoMore! project will span 5 years (2016-2021) and the main focus will be to radically improve prognostication and hence treatment of cancer by introducing in silico pathology. We will continue our close collaborations with some of the CCB members in the DoMore! project.

In 2016, the institute was awarded a large Lighthouse grant from the Norwegian Research Council for our DoMore! project.

THE STATISTICAL ANALYSIS UNIT

The impact of CCB on our group

The interdisciplinary environment at CCB has provided our group with a unique base of interesting data and cases. Thereby the activity at CCB has brought our research closer to important biomedical and clinical applications, and pointed to particularly relevant topics on which the group could focus its development of methods and tools within biostatistics and informatics.

Achievements

The aim of the statistics and informatics group in CCB has been twofold:

- To support the activity of the biomedical CCB groups by providing data analysis, primarily through working on CCB projects.
- Developing methods and software for relevant biostatistical problems, typically motivated by problems originating from biomedical investigations at CCB.

In short, our group has aimed at optimizing the information obtained from the data sources at CCB. To fulfill this aim, our unit has

worked and published together with all other CCB groups, in total on projects resulting in about 45 co-authored papers.

Much of our work has focussed on analysis of data from high-throughput technologies. While rich in information, the complexity of these large data sets makes extraction of information a true challenge, requiring non-standard methods adapted a very high number of observations on each sample but a moderate number of samples.

Our ideal is initially to work on and solve a concrete problem at CCB and then address the problem in a more general setting and develop easy-to-use methods and software for the biomedical community. An example of this way of working in CCB was connected to copy number alterations. In short, traditional copy number estimation methods work on one sample/biopsy at a time. However, a shared subdivision of the chromosomes for all samples is necessary to be able to use regression analyses to pinpoint the areas where copy number alterations influence outcomes, including cancer progression. A method for



Our ideal is initially to work on and solve a concrete problem at CCB and then address the problem in a more general setting and develop easy-to-use methods and software for the biomedical community.

simultaneous analysis of several samples/tracks was developed and utilized on CCB-data for follicular lymphoma. Then the idea behind the method was generalized and used both for a widely used system for allele-specific copy number analysis and in a general Bioconductor system for copy number analysis.

Extensive work has also been done on developing methods for the analysis of siRNA screens, on adaption and evaluation of regression methods to handle high numbers of covariates, and on applications of survival analysis in translational studies and mixed factor models in cell biology.

Our focus for the years to come

Although the CoE-period ends in 2017, much of the long-term collaboration established during the CCB period will continue both with groups working within cell biology and in translational research. In particular, the collaboration within the DoMore lighthouse project should be mentioned, aiming at radically improving prognostication and hence treatment of cancer by using modern machine learning tools in digital pathology.

PHD DEGREES IN CCB

Research training was indeed a core activity in CCB, and the centre’s ambitious goal to graduate 50 PhD degrees during the 10-year Centre of Excellence period was reached in the spring of 2016 – one and a half year ahead of schedule. We would like to congratulate all 61 talented young scientists who have contributed to CCB’s research in such an excellent way.

2017	(to 31 August) Yngvild Nuvin Blaker Clinical and immunohistochemical studies in B-cell non-Hodgkin lymphoma Main supervisor: Erlend Smeland	Simona Kavaliauskiene Membrane dynamics in cancer cells Main supervisor: Kirsten Sandvig
	Nadja Sandra Katheder Nurturing tumor growth through autophagy Main supervisor: Tor Erik Rusten	Bjarne Johannessen Identification of novel DNA and RNA changes in solid tumors by high-throughput methodologies Main supervisor: Rolf I. Skotheim
	Liliane Florence Christ Protecting the genome during cytokinesis Main supervisor: Harald Stenmark	Thale Kristin Olsen The enigma of ependymal tumors: A journey in their genomic and transcriptomic landscapes Main supervisor: Petter Brandal
	Marianne Lislerud Smebye Transcriptomic consequences of chromosome 19 rearrangements in ovarian carcinomas Main supervisor: Francesca Micci	2015 Sigmund Brabrand Bilateral testicular germ cell cancer – Molecular and clinical aspects Main supervisor: Gustav Lehne
2016	Ieva Ailte Regulation of membrane trafficking in cancer cells Main supervisor: Kirsten Sandvig	Andreas Midbøe Hoff Identification of novel fusion genes and transcript variants in cancer Main supervisor: Rolf I. Skotheim
	Tarjei Sveinsgjerd Hveem Prognostic value of large scale genomic instability by image cytometry in selected malignancies and a premalignant condition Main supervisor: Håvard E. Danielsen	Marina Vietri Closing the gap – ESCRT-III orchestrates nuclear envelope sealing Main supervisor: Harald Stenmark
	Hege Marie Vedeld Epigenetic biomarkers for early detection and prognosis of colorectal cancer Main supervisor: Guro E. Lind	Audun Sverre Myrset Kvalvaag Shiga toxin: Uptake and transport in cancer cells Main supervisor: Kirsten Sandvig
	Tor Espen Thorvaldsen Dissecting the β-catenin destruction complex: Novel implications of tankyrase inhibitors Main supervisor: Harald Stenmark	Idun Fiskvik Prognostic tumor related factors in diffuse large B-cell lymphomas Main supervisor: Harald Jr. Holte
	Gro Nilsen Statistical learning in genomics: Uncovering patterns and groups in high dimensions Main supervisor: Ole Christian Lingjærde	

2014	Åsmund Husabø Eikenes Novel regulators of cytokinesis in vivo Main supervisor: Kaisa Haglund	Annette Bentsen Håvik Untangling the web of molecular changes in brain tumors: Molecular characterization of gliomas Main supervisor: Sverre Heim
	Santosh Phuyal Composition and cellular release of exosomes from cancer cells Main supervisor: Alicia Llorente	Naghm Theres Asp Regulation of ErbB2 and ErbB3 growth factor receptors in human breast cancer Main supervisor: Kirsten Sandvig
	Nicole Bethge DNA methylation alterations in B-cell lymphoma Main supervisor: Erlend Smeland	Torunn Sletten Role of intracellular FGF1 interaction partners, and HSP90 as a therapeutic target in FGFR1 driven malignancy Main supervisor: Antoni Wiedlocha
	Kaja Beate Nyquist Gene-level consequences of new cancer-specific chromosomal rearrangements Main supervisor: Francesca Micci	Sigrid Bratlie Thoresen Novel regulators of the cell division cycle Main supervisor: Harald Stenmark
	Marianne Aarstad Merok Genetic and clinical prognostic markers for colorectal cancer Main supervisor: Arild Nesbakken	

	Marianne Brodtkorb Eide Integrative genomic and clinical analysis of follicular lymphoma Main supervisor: Erlend Smeland	Maren Bakkebo Transforming growth factor super-family signaling and its role in B-cell lymphoma Main supervisor: Erlend Smeland	Helge Roar Brekke New insights into the biology of Malignant Peripheral Nerve Sheath Tumors identify biomarkers for disease outcome Main supervisor: Ragnhild A. Lothe
	Jarle Bruun Biomarkers with functional and clinical impact on colorectal cancer Main supervisor: Ragnhild A. Lothe	Anne Berit Dyve Lingelem Intracellular transport of Shiga toxin and ricin Main supervisor: Kirsten Sandvig	Wanja Kildal DNA ploidy as a prognostic marker in selected gynecological malignancies Main supervisor: Håvard E. Danielsen
	Marthe Løvf Detection of fusion genes and novel RNA variants in cancer Main supervisor: Rolf I. Skotheim	Manohar Pradhan DNA ploidy and DNA index in endometrial carcinoma Main supervisor: Bjørn Åke Risberg	Yan Zhen Intracellular trafficking and signaling of fibroblast growth factor 1 and its receptor Main supervisor: Antoni Wiedlocha
	2013 Torfinn Nome Novel RNA variants in colorectal cancer identified by deep sequencing Main supervisor: Rolf I. Skotheim	Antonia Sagona Regulation of cytokinesis and its consequences for human health Main supervisor: Harald Stenmark	2009 Ingrid Roxrud Endocytic trafficking of membrane proteins. Mechanisms in human disease Main supervisor: Harald Stenmark
	Catherine Sem Wegner Regulation of the endocytic pathway and receptor sorting by phosphoinositides and ESCRTs Main supervisor: Andreas Brech	Trude Holmeide Ågesen Genetics of colorectal cancer: new insights to early onset and to prognostication of disease Main supervisor: Ragnhild A. Lothe	Audrun Utskarpen Endocytosis and retrograde transport of Shiga toxin and ricin Main supervisor: Kirsten Sandvig
	Olav Erich Yri Germline genetic polymorphisms and morphological grading in malignant lymphomas: Impact on susceptibility and patient outcome Main supervisor: Harald Jr. Holte	Anita Sveen The transcriptome and prognosis in stage II and III colorectal cancer Main supervisor: Rolf I. Skotheim	Terje Cruickshank Ahlquist Novel genetic and epigenetic alterations in colorectal tumors and their potential as biomarkers Main supervisor: Ragnhild A. Lothe
	Jonas Bergan Investigation of membrane dynamics in cancer cells by following Shiga toxin Main supervisor: Kirsten Sandvig	Hanne-Sofie Spenning Dahlback Cytogenetic and molecular cytogenetic analyses of brain tumours Main supervisor: Sverre Heim	Ellen Margrethe Haugsten Endocytosis and intracellular transport of FGF1 and the FGF receptors Main supervisor: Sjur Olsnes
	Deeqa Ahmed Mohamed Ali DNA methylation alterations in colorectal cancer and their potential as biomarkers Main supervisor: Guro E. Lind	2011 Stine Aske Danielsen Molecular markers of colorectal cancer and their clinical potential Main supervisor: Ragnhild A. Lothe	Sigrid S. Skånland Mechanisms in intracellular transport of toxins Main supervisor: Kirsten Sandvig
	Kim Andresen Novel epi-markers in cholangiocarcinoma and their clinical potential Main supervisor: Guro E. Lind	Kanutte Huse The role of bone morphogenetic proteins in normal and malignant lymphocytes Main supervisor: Erlend Smeland	Susanne Stuffers The role of ESCRT proteins and phosphoinositides in MVE biogenesis, endocytic trafficking and disease Main supervisor: Andreas Brech
	Angela Oppelt Novel regulators of cell migration Main supervisor: Jørgen Wesche	Paula Paulo Fusion oncogenes involving the ETS family of transcription factors in prostate cancer: target genes and clinical applications Main supervisor: Manuel R. Teixeira	2008 None
	2012 Viola Hélène Lobert Identification of novel regulators of epithelial polarity and cell migration Main supervisor: Harald Stenmark	Lina Rodahl Regulators of endosome dynamics in cell signalling and disease Main supervisor: Harald Stenmark	(from 1 September) 2007 Karine Lindmo Regulation and function of autophagy in Drosophila melanogaster Main supervisor: Harald Stenmark
	Ane Hansen Kjenseth Posttranslational modification of the tumor suppressor protein connexin43 – implications for cell communication and cancer Main supervisor: Edgar Rivedal	Solveig Sirnes The connexin gene family in cell communication and cancer Main supervisor: Edgar Rivedal	
		2010 Marianne Berg Genomics of colorectal carcinomas from young and elderly patients Main supervisor: Ragnhild A. Lothe	

MASTER DEGREES IN CCB

We would like to congratulate all master students supervised in CCB with their degrees.

2017 Kristina Totland Carm
Investigation of DNA and RNA changes in multifocal prostate cancer - Identification of novel alterations and molecular subtyping of individual tumors
Main supervisor: Marthe Løv

Mariella Evelyn Güere
Identification of DNA methylation biomarkers for gastrointestinal cancer - Ubiquitin C-terminal hydro-lase L1 (UCHL1)
Main supervisor: Hege Marie Vedeld

Marthe Noreen Thorsen
Functional evaluation of polo like ki-nase 1 (PLK1), a potential drug target, in malignant peripheral nerve sheath tumor cells
Main supervisor: Matthias Kolberg

Shakiththiya Thiyagarajah
The role of diacylglycerol kinase “alfa” in retrograde transport
Main supervisor: Anne Berit Dyve Lingelem

2016 Hélène Spangenberg
PI(3)P-binding proteins in macropinocytosis
Main supervisor: Kay Oliver Schink

Stian Lågstad
Visualizing chimeric RNA
Main supervisor: Rolf I. Skotheim

Jonas Meier Strømme
Computational analyses of transcriptome instability in cancer
Main supervisor: Rolf I. Skotheim

Trym Vogt
Toxicology of cytostatic drug-loaded nanoparticles: The role of endocytosis
Main supervisor: Tore-Geir Iversen

Nikoline Rasmussen
The role of tumor necrosis factor α (TNFα) in regulation of connexin43 ubiquitination, endocytosis and degradation
Main supervisor: Edward Leithe

Dhaksshaginy Rajalingam
Regulation of exosome release by 2-hydroxyoleic acid and oleic acid
Main supervisor: Alicia Llorente

2015 Dorthea Gjørberg
The SW480 and SW620 cell lines as a model system for studying epitheli-al to mesenchymal transition (EMT) in colorectal cancer
Main supervisor: Edward Leithe

Christian Holst Bergsland
New insights into the regulation of the gap junction protein connexin43 by the E3 ubiquitin ligase Nedd4-1
Main supervisor: Edward Leithe

2014 Heidi Dietrichson Pharo
Quantitative methylation-specific PCR - optimization and application
Main supervisor: Guro E. Lind

Lars Mørland Knudsen
Role of the endolysosomal and autophagosomal pathways in deg-radation of the gap junction protein connexin 43
Main supervisor: Edward Leithe

Gro Kummeneje Presthus
DNA methylation super negatives - identification of a new subgroup of colorectal cancer
Main supervisor: Guro E. Lind

Ane Brenna
Identification of novel epigenetic masterkeys in cancer - with potential diagnostic value
Main supervisor: Guro E. Lind

Karin Svensson
The role of evectin-2 and its binding partner PS in toxin transport
Main supervisor: Kirsten Sandvig

Inger Oulie
Transport of biodegradable nanopar-ticles in cells: Uptake, intracellular transport, degradation and toxicity
Main supervisor: Tore Geir Iversen

Linn Kymre
Structure-function relationship of Shiga toxins; Role of the A-subunit in complex stability and endocytosis
Main supervisor: Kirsten Sandvig

Max Zachrisson Totland
Regulation of the gap junction protein connexin 43 by the E3 ubiquitin ligases Smurf1 and -2
Main supervisor: Edward Leithe

Marte Petersen-Øverleir
Tools for ESCRT protein studies - Visualising the invisible
Main supervisor: Camilla Raiborg

Ida Seim Jakobsen
Exosome release. Role of PIKfyve and ERM proteins
Main supervisor: Kirsten Sandvig

2013 Therese Pedersen
Differential effects of Bone Morphogenetic Proteins (BMPs) in human memory B cells
Main supervisor: June H. Myklebust

Chloé Beate Steen
ALix controls cytokinesis in vivo.
Main supervisor: Kaisa Haglund

Lise K. Bollum
Effects of Bone Morphogenetic Proteins (BMPs) in Human B Lymphocytes
Main supervisor: June H. Myklebust

Karolina Cyll
A new protocol for preparation of samples for image cytometry. An improved and reproducible Hedley’s method for preparation of monolayers from paraffin-embedded tissue for cytometric DNA ploidy analysis.
Main supervisor: Monica Jenstad

Anne Grete Gargul
In vitro studies of nanosized iron oxide particles
Main supervisor: Kirsten Sandvig

2012 Shiva Dahal-Koirala
Regulation of the gap junction protein connexin 43 during mitosis.
Main supervisor: Edward Leithe

Ane Hoel Høiset
Sorting Nexin 4 mediates chromosome congression
Main supervisor: Camilla Raiborg and Hilde Abrahamsen

Minna Kihlström
The effect of radixin on the retrograde transport of Shiga toxin and ricin
Main supervisor: Kirsten Sandvig

Ina Andrassy Eilertsen
New insights into the regulation of the tumor suppressor proteins PTEN and connexin 43 by post-translational modifications
Main supervisor: Edward Leithe

2011 Bjarne Johannessen
Identification of cancer-specific transcripts by computational analysis of genome-scale expression data at exon resolution
Main supervisor: Rolf I. Skotheim

Hege Marie Vedeld
DNA methylation biomarkers for colorectal cancer detection: CDO1, DCLK1, ZNF331 and ZSCAN18
Main supervisor: Guro E. Lind

Peter Eide
HECT E3 ubiquitin ligases in regula-tion of colon cancer cell growth and mitogenic signaling pathways
Main supervisor: Edward Leithe

Andreas Hoff
Transcript variation and protein expression in testicular germ cell tumours.
Main supervisor: Sharmini Alagaratnam

Carl-Martin Nymark
Cell context-dependent differences in interaction with Shiga toxin
Main supervisor: Kirsten Sandvig

Simona Lukoseviciute
The regulation of Gb3 biosynthesis in cancer cells: Implications for membrane dynamics
Main supervisor: Kirsten Sandvig

Audun Sverre Kvalvaag
The role of ERM proteins in binding and intracellular transport of Shiga toxin
Main supervisor: Kirsten Sandvig

2010 Santosh Phuyal
The role of lipids in the release of exosomes from the human prostate cancer PC-3 cell line
Main supervisor: Kirsten Sandvig

Maren Høland
Prognostic value of protein markers in malignant peripheral nerve sheath tumours
Main supervisor: Matthias Kolberg

Tone Aase Fykerud
Regulation of the gap junction pro-tein connexin43 by members of the Nedd4 E3 ubiquitin ligase family
Main supervisor: Edward Leithe

Ieva Ailte
The role of SNX8 in Retrograde Transport of Shiga Toxin2
Main supervisor: Kirsten Sandvig

Deeqa Ali
Identification of novel epigenetic biomarkers in colorectal cancer, GLDC and PPP1R14A
Main supervisor: Guro E. Lind

Marianne Guriby
New epigenetic biomarkers examined for added value in lymph node diagnostics of colon cancer
Main supervisor: Terje Ahlquist

2009 Anne Cathrine Bakken
Exon specific biomarkers in cancer: Experimental validation of exon microarray data from colorectal and testicular cancers
Main supervisor: Rolf I. Skotheim

Kristine Ingrid Sundet
The role of ERM proteins in endo-cytosis and intracellular transport of Shiga toxin and ricin
Main supervisor: Kirsten Sandvig

Gro Nilsen
A comparative study of existing and novel methods for estimating the number of clusters in a data set
Main supervisor: Ole Christian Lingjærde and Ørnulf Borgan

Daniel J. H. Nebdal
Presenting overrepresented words
Main supervisor: Einar Rødland

2008 Marthe Eken
Identification of cancer-specific tran-scripts: With emphasis on the hunt for fusion genes in colorectal cancer
Main supervisor: Rolf I. Skotheim

Jarle Bruun
Effect of Connexin 43 transfection on growth characteristics of the human colon adenocarcinoma cell line HT29
Main supervisor: Edgar Rivedal

Hilde Honne
Identification of novel epigenetic biomarkers in colorectal cancer
Main supervisor: Guro E. Lind

THE CCB ORGANISATION IN 2017

The PI group

Håvard Danielsen, Knut Liestøl, Kirsten Sandvig, Guro E. Lind (young PI), Ragnhild A. Lothe (Co-director), Harald Stenmark (Director), Erlend Smeland.

Associated groups

3 independent groups are associated with CCB: Genome biology group headed by *Rolf I. Skotheim* Cytogenetics group headed by *Francesca Micci* Protein internalization and signaling group headed by *Antoni Wiedlocha*

Leaders of the Clinical Research Programmes

Colorectal Cancer | *Arild Nesbakken*, Professor, MD, Senior Consultant, Department of Gastrointestinal Surgery, Oslo University Hospital

Lymphoma | *Harald Holte* MD, PhD, Senior Consultant, Department of Medical Oncology and Radiotherapy, Oslo University Hospital, Head of Lymphoma Treatment Programme and Lymphoma Research Group

Prostate Cancer | *Karol Axcrona*, MD, PhD, Head of Department of Urology, Akershus University Hospital, Lørenskog

Visiting Professors

Professor *Manuel Teixeira*, Portugese Oncology Institute, Porto, Portugal
Professor *Marco Novelli*, University College London Hospitals, UK
Professor *Jan Delabie*, University Health Network, Toronto, Canada

Management

The day-to-day management of CCB is performed by Director *Harald Stenmark*, Co-director *Ragnhild A. Lothe*, and Administrative coordinator *Anette Sørensen*. The Centre management reports to the CCB board.

The CCB Board

Karl-Erik Giercksky, Ole M. Sejersted, Hilde Irene Nebb (Chairperson), *Svein Stølen*.

Host institutions

University of Oslo, *Ivar P. Gladhaug*, Head of Institute of Clinical Medicine.

Oslo University Hospital, *Sigbjørn Smeland*, Head of Division of Cancer Medicine.

Scientific Advisory Board

Professor Manuel Sobrinho-Simões | Head of Department of Pathology, Medical Faculty of Porto & Director, Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP), Portugal

Professor Marja Jäätelä | Head of research unit Cell Death and Metabolism, Danish Cancer Society Research Center, Copenhagen, Denmark

Professor Olli Kallioniemi | Director, Institute for Molecular Medicine Finland (FIMM), Nordic EMBL Partnership for Molecular Medicine, University of Helsinki & Director, Academy of Finland Centre of Excellence in Translational Genome-Scale Biology, Helsinki, Finland.

Professor David J. Kerr | Professor of Cancer Medicine, Nuffield Department of Clinical and Laboratory Sciences, University of Oxford, UK.

The PI group

Håvard Danielsen, Knut Liestøl, Kirsten Sandvig, Guro E. Lind (young PI), Ragnhild A. Lothe (Co-director), Harald Stenmark (Director), Erlend Smeland.



The CCB Board

from left: *Karl-Erik Giercksky, Ole M. Sejersted, Hilde Irene Nebb* (Chairperson), *Svein Stølen*.



Leaders of the Clinical Research Programmes

from left: *Karol Axcrona, Harald Holte, Arild Nesbakken*

Host institutions

University of Oslo
Ivar P. Gladhaug
Head of Institute of Clinical Medicine

Oslo University Hospital
Sigbjørn Smeland
Head of Division of Cancer Medicine

