Centre for Cancer Biomedicine

2011

ANNUAL REPORT

MOVING CLOSER TO BEDSIDE

When Centre for Cancer Biomedicine started its activity in September 2007, a major long-term goal, and a part of the Centre's vision, was to provide "benefit to the cancer patient". Now, after some 4 ½ years of hectic research activity, CCB is moving closer to implementation of research results into the clinic. In particular the lymphoma research has shown clinically useable results, as presented elsewhere in this report. Several innovations have resulted from the interdisciplinary research in the centre, including development of novel biomarkers for diagnostics and prognostics, and recently a license agreement has been signed with Oxford Gene Technology for the rights of a biomarker panel suitable for early diagnostics of colorectal cancer. Several other CCB innovations for patient use are in the pipelines forwarded by the excellent collaboration we have with the representatives of the hospital's technology transfer office - Inven2. As we write this column, the message of a substantial funding to the National Cancer Genomic Consortium, led by Professor Ola Myklebost with key contributions from several senior CCB researchers, has reached us. This initiative, a national effort to test all cancer patients for actionable genes, for which drugs exist, using deep sequencing as the single tool, may find its way into the clinic in the near future.

During the first half of 2011, CCB underwent a mid-term review conducted by the Research Council of Norway, the outcome of which would be decisive for CCB´s future status as Centre of Excellence. We congratulate all CCB members with the highest obtainable evaluation score of "exceptionally good"! The positive outcome of the evaluation means that CCB will continue to receive Centre of Excellence funding from the Research Council until September 2017. Such a long-term funding is instrumental to the successful implementation of the ambitious research programmes that are in progress.

2011 was a successful year for CCB, also with respect to publication activity. CCB researchers published 71 papers in 2011, which is an increase of 13% from the previous all-time-high of 2010. As before, most CCB papers have CCB scientists as corresponding author, and a relatively large proportion of the papers are published in high-impact journals, including *Science* and *Nature*. The strong ties between basic and patient-oriented research in CCB is reflected by the fact that almost half of the CCB publications are collaborations with cancer clinicians and pathologists. Some of the scientific highlights from 2011 are presented in this report, and include significant progress in our understanding of how cancer develops, as well as identification of novel cellular and molecular traits of cancers that can be used diagnostically and prognostically.

Even though CCB´s progress has been faster than even the most optimistic among us had dared to hope for a few years ago, we are facing several scientific challenges that require special attention. In particular, we need to utilize the most cutting-edge technologies in order to maintain our position in the international forefront. The implementation of mass nucleotide sequencing in a national initiative for cancer genome sequencing (described elsewhere in this report) and the acquisition of a super-resolution microscope (due during the autumn of 2012) are examples of how CCB will be proactive in exploiting novel technologies to go significantly beyond the current state-of-the-art.

CCB is in the fortunate situation that we have unusually many advanced postdocs and project leaders with undisputed talent for top-notch cancer research. The potential problem is that almost all these scientists are on "soft" money, i.e., grant funding with strictly limited duration. As recommended by our Scientific Advisory Board, CCB will use substantial funds to secure the careers of our most talented young scientists, and we will also collaborate with our host institutions to promote permanent career paths for this future generation of Norway´s leading cancer scientists.

CCB scientists obtained several prizes and awards in 2011, and we would especially like to congratulate Professor Sverre Heim with the prestigious King Olav V´s prize for outstanding cancer research. He is a world-leading scientist in the field of cancer cytogenetics and has an impressive publication list and more than 10 000 total citations. Dr Heim´s excellent cancer research is a real inspiration to other members of CCB.

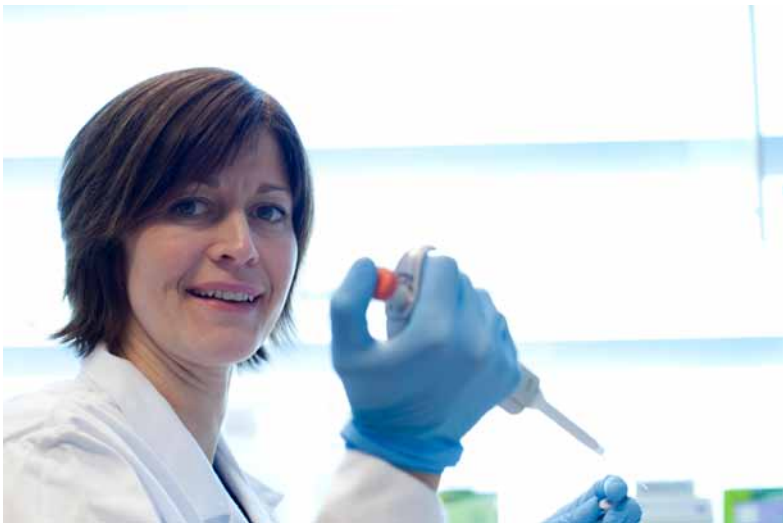
Director Harald Stenmark and Co-director Ragnhild A. Lothe | Photo: Linda Cartridge

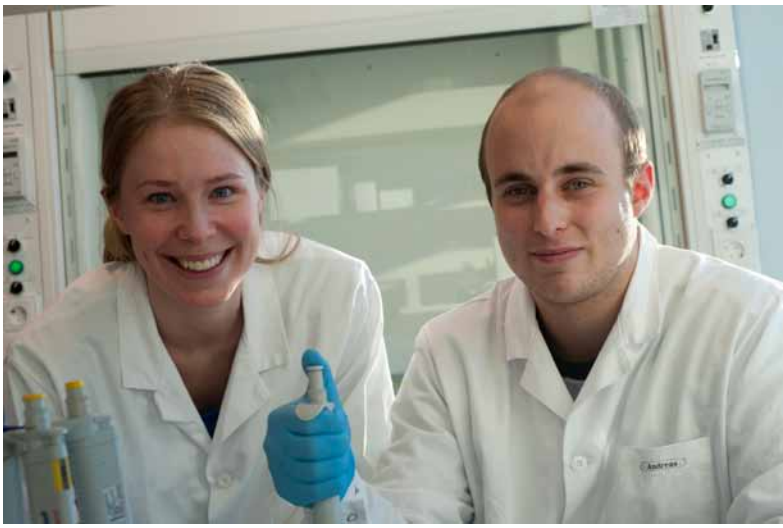
Even though the Centre of Excellence grant from the Research Council is essential to the very existence of CCB, the large majority of our funding comes from other sources, including Oslo University Hospital, the University of Oslo, the South-Eastern Norway Regional Health Authority, and international bodies such as the European Research Council, the European Science Foundation, the Polish-Norwegian Research Fund, and the National Institutes of Health. We thank these organizations for their continued support. Special thanks go to our long-standing sponsor and collaboration partner, the Norwegian Cancer Society (see page 61). This charity has generously sponsored the CCB groups through many years, and many of the currently most successful CCB scientists owe their training as PhD students, postdocs and scientists to grants sponsored by the Cancer Society. The policy of the Cancer Society, to support excellent cancer research within all disciplines, fits perfectly with the research strategy of the CCB, and we anticipate more fruitful cooperations in the near future.

Oslo, March 2012

Harald Stenmark

Ragnhild A. Lothe





Photos: Linda Cartridge

TABLE OF CONTENT

CCB Midterm Evaluation

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 is 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."

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 bio-banks 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."

CCB Research: Entering the Clinic

Marianne B. Eide
Photo: Per M. Didriksen

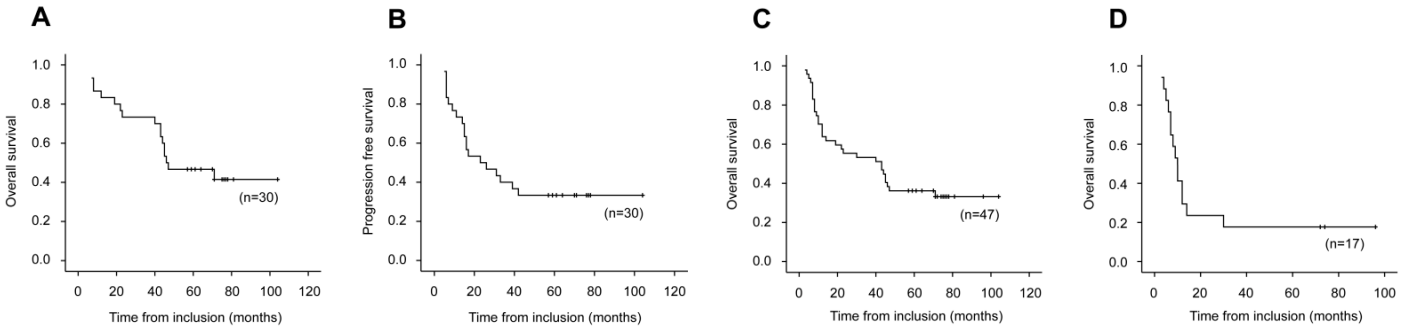
The lymphoma milieu in CCB is together with the rest of the lymphoma milieu at the hospital involved in extensive national and international collaboration. PhD student Marianne B. Eide and CCB associate clinician Harald Holte were first and senior authors on a national collaborative clinical phase II study examining the effects of high-dose therapy in transformed Follicular Lymphoma to Diffuse Large B-cell Lymphoma. This is the first prospective study in this group of patients, which traditionally have a dismal prognosis. The study indicates that a treatment programme including high dose therapy is beneficial for chemosensitive patients compared to previous reports of CHOP based treatment for transformed B-cell lymphomas. In spite of the intensified treatment, there was no treatment-related mortality. The study comprises a relatively large number of patients in a relatively rare condition, and the included patients represent a population-based and unselected patient cohort. Material collected through this study will be used for several follow-up studies of biological processes involved in histological transformation in collaboration with other CCB groups and Department of Pathology.

Eide MB, Lauritzsen GF, Kvalheim G, Kolstad A, Fagerli UM, Maisenhölder M, Østenstad B, Fluge Ø, Delabie J, Aarset H, Liestøl K, Holte H. (2011) **High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norwegian multi centre phase II study** Br J Haematol. 152(5):600-10.

Erlend Smeland
Photo: L. Cartridge

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-kB activation, and several mechanisms leading to NFkB 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 demonstrates 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.



Survival following high dose therapy, for the whole patient cohort and for patients not treated by high dose therapy. (A) Overall survival (OS) for HDT-treated patients, median 47 months (95% CI 43- ∞ months). (B) Progression free survival (PFS) for HDT-treated patients, median 26 months (95% CI 15- ∞ months). (C) OS for the whole cohort of patients with transformation of follicular lymphoma to DLBCL, median 43 months (95% CI 12-47 months). (D) OS for the patients that could not be treated by HDT, median 10 months (95% CI 7-14 months).

CCB Research: Identification of New Phenotype in CRC

From left: Trude H. Ågesen and Anita Sveen
Photo: Jarle Bruun

Colorectal cancer (CRC) is commonly characterized by inherent genomic instabilities such as chromosome instability and microsatellite instability. In a recent publication, 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.

Rolf Skotheim
Foto: L. Cartridge

By starting from genome-scale expression analyses of all exons in altogether 172 colorectal cancers, Anita Sveen, Trude Ågesen and co-workers discovered that the amount of aberrant alternative splicing was highly variable between different cancers. Based on this, the authors developed the concept of transcriptome instability as a novel phenotype in colorectal cancer. This molecular characteristic was strongly associated with splicing factor expression levels and associated with poor patient survival. “We were really surprised when discovering that the cancers with transcriptome instability also had reduced expression levels of a large fraction of all known splicing factors, which again also suggests a biological explanation for the new phenotype”, says Rolf Skotheim, senior author of the paper.

CCB Researchers join National Project on Personalized Cancer Medicine

CCB groups participate in Norwegian Cancer Genomics Consortium (NCGC)

Personalised cancer medicine was suggested by the Norwegian Council for quality improvements and priority setting in health care as the theme for a major grant announcement from the Norwegian Research Council in 2011. Professor Ola Myklebost (leader of NCGC) gathered a number of research groups, clinicians and expert core facilities and established the Norwegian Cancer Genomics Consortium. The three translational PI groups in CCB (E. Smeland, H.E. Danielsen and R.A. Lothe), together with the associated clinicians (K. Axcrona, H. Holte, A. Nesbakken) and the leader of the CCB deep sequencing platform Rolf I. Skotheim, all joined this initiative.

The Consortium suggests a national coordinated effort to introduce genome-based stratification of cancer treatment

The public kick-off of the Consortium was made on the 4th Cancer Cross links meeting.

The project is unique in the sense that it is a national project and includes in the first phase University hospitals from each health region. If funded, 4000 cancers including 9 diseases will be sequenced for actionable genes, for which drugs already exist, and for other cancer critical genes within a time frame of 2-3 years. In parallel, various inter-regional procedures will be established and the next phase of studies will be initiated aiming for clinical implementation.

Media attention to the suggested project:


THE LANCET

Home | Journals | Specialties | Clinical | Global Health | Audio | Conferences | Information for

The Lancet, Volume 379, Issue 9814, Page 386, 4 February 2012
doi:10.1016/S0140-6736(12)60170-6 Cite or Link Using DOI

« Previous Article | Next Article »

Genomic medicine and the NHS: it is possible

The advisory group noted that the UK must act quickly to avoid being left behind in this field—a point illustrated by the recent launch of the Norwegian Cancer Genomics Consortium, a national collaboration for genome-based diagnostics in cancer treatment. Responding to the report, Health Secretary Andrew Lansley announced plans for a new commissioning and funding structure for molecular testing in UK cancer care, to be complete by April, 2013. This is welcome news in the build up to Feb 4's World Cancer Day, for which this year's theme is "Together it is possible". This mantra might well be applied to the HGSG's recommendations. Large-scale adoption of genomic technology could revolutionise the health service—achieving it will require collaboration across many key groups, from policy makers to researchers, industry, and health-care workers.


nature International weekly journal of science

Home | News & Comment | Research | Careers & Jobs | Current Issue | Archive | Audio & Video

News & Comment > News > 2012 > March > Article

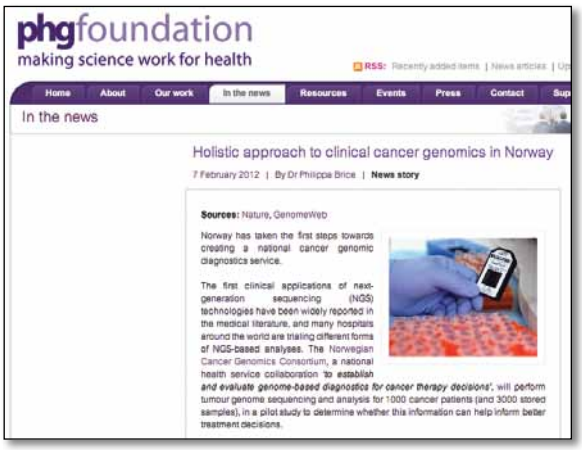
NATURE | NEWS

Norway to bring cancer-gene tests to the clinic

A pilot programme will use latest tumour-sequencing techniques to help guide cancer care.

Ewen Callaway

02 February 2012


phgfoundation
making science work for health

Home | About | Our work | In the news | Resources | Events | Press | Contact

In the news

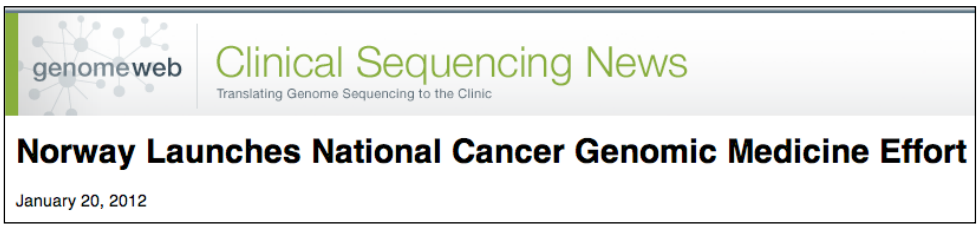
Holistic approach to clinical cancer genomics in Norway

7 February 2012 | By Dr Philippa Brice | News story

Sources: Nature, GenomeWeb

Norway has taken the first steps towards creating a national cancer genomic diagnostics service.

The first clinical applications of next-generation sequencing (NGS) technologies have been widely reported in the medical literature, and many hospitals around the world are trialing different forms of NGS-based analyses. The Norwegian Cancer Genomics Consortium, a national health service collaboration to establish *and evaluate genome-based diagnostics for cancer therapy decisions*', will perform tumour genome sequencing and analysis for 1000 cancer patients (and 3000 stored samples), in a pilot study to determine whether this information can help inform better treatment decisions.


genomeweb Clinical Sequencing News

Translating Genome Sequencing to the Clinic

Norway Launches National Cancer Genomic Medicine Effort

January 20, 2012

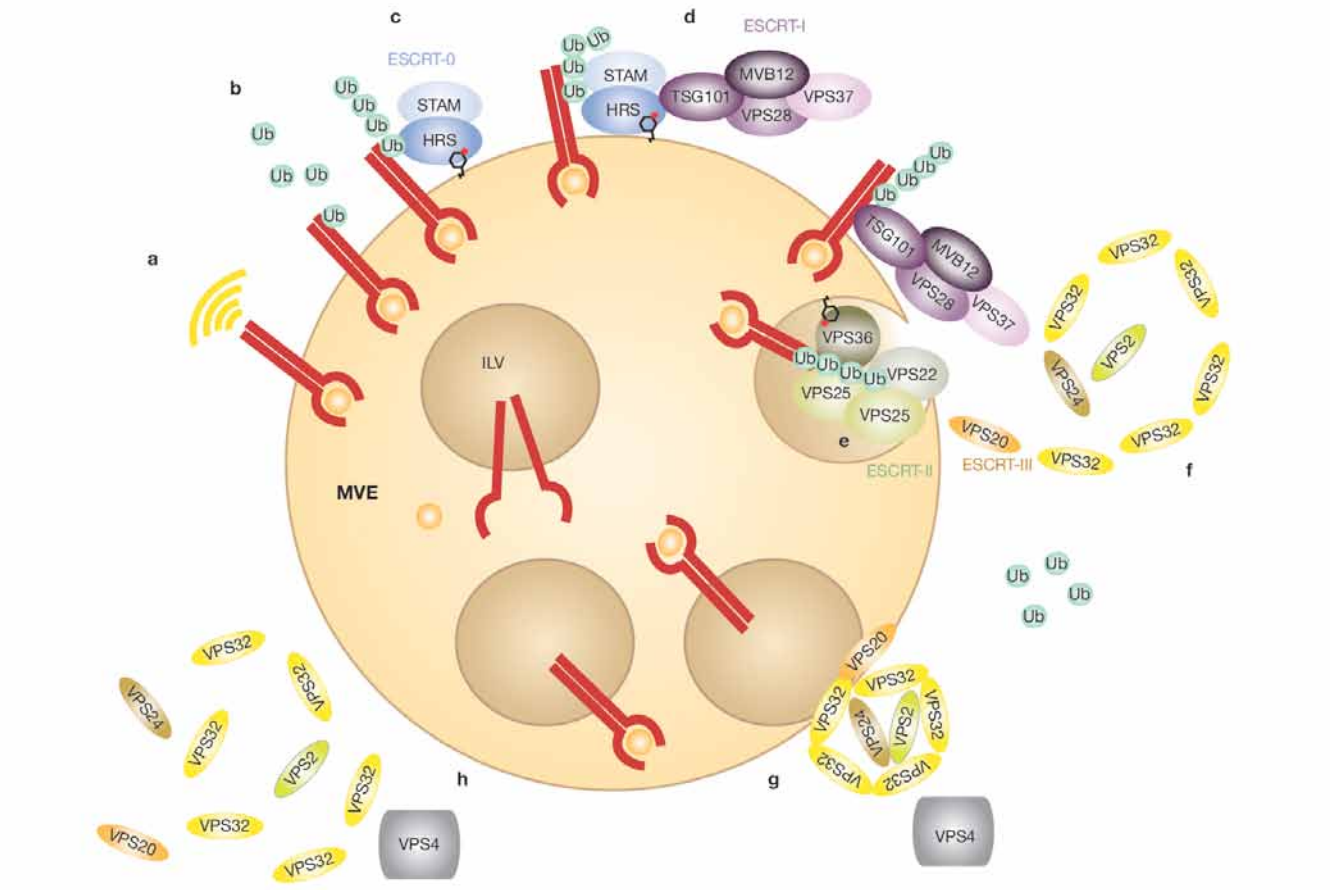
CCB Researchers: The Experts' Opinions

An ESCRT for signalling, development and cancer

One of the research programmes of CCB investigates mechanisms that control cell growth, proliferation, survival and migration. Central in such regulation are growth factors and their cognate receptors, and hyperactivation of growth factor signalling pathways is a well-known driver of tumourigenesis. Research in CCB and other centres has revealed that endocytosis (internalization) and degradation of growth factor receptors in response to growth factor binding provides a key mechanism for regulation of growth factor signalling, and CCB researchers have been central in identifying components of a molecular machinery that sorts endocytosed growth factor receptors to degradative lysosomes. This machinery is called ESCRT, for endosomal sorting complex required for transport, and was originally identified through studies of vacuolar protein sorting mutants of yeast. In two recent reviews, CCB researchers discuss different aspects of ESCRT proteins in cell signalling. The review by Wegner et al (*Traffic*, 2011) discusses how ESCRT proteins serve to control receptor signalling processes, and how perturbation of this regulation may result in diseases such as cancer. The review by Rusten et al. (*Nature Cell Biology*, 2011) highlights the involvement of ESCRT proteins in developmental processes and discusses the relationship between ESCRT functions in developmental processes and diseases.

Wegner CS, Rodahl LM, Stenmark H. (2011) **ESCRT proteins and cell signalling** Traffic. 12(10):1291-7.

Rusten TE, Vaccari T, Stenmark H. (2011) **Shaping development with ESCRTs.** Nat Cell Biol. 14(1):38-45.

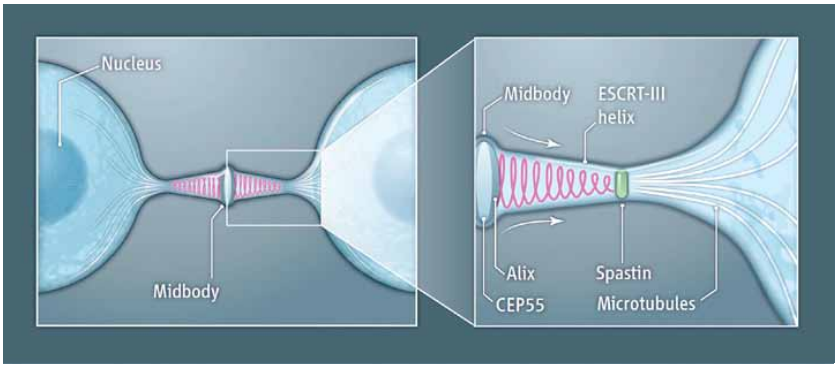


The ESCRT machinery in endosomal sorting of growth factor receptors. The illustration shows how a growth factor receptor (red colour) is initially able to transmit signals from the endosome membrane (a), and how ESCRT-0, -I, -II and -III function consecutively to mediate sorting of the receptor into an intraluminal vesicle (ILV) of the multivesicular endosome (MVE) (b-h), thereby terminating signalling.

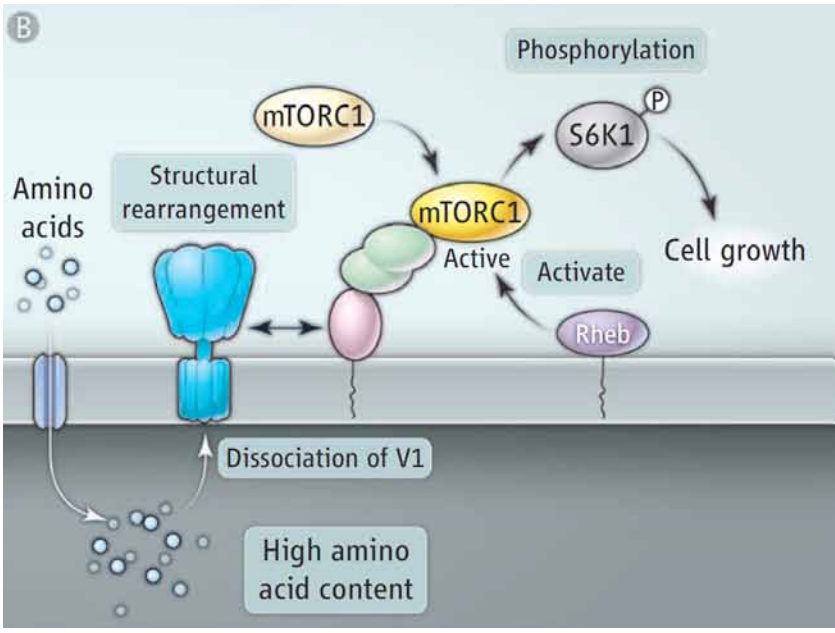
Science Perspectives on cell division and growth

Last year, CCB researchers contributed two Perspective articles in one of the most prestigious scientific journals, Science. One Perspective (Raiborg and Stenmark, Science, 2011) highlights recent progress on the mechanisms of abscission between two daugther cells during the final stage of cell division. Recent studies have suggested that ESCRT proteins are involved in this process, which results in complete separation of the two daugther cells. In the Science Perspective, the CCB researchers highlight evidence that a protein helix composed of ESCRT subunits constitutes a spring that accomplishes membrane scission during cytokinesis. In concert with this, Spastin, an ATPase which localizes to the end of the ESCRT helix, serves to mediate microtubule severing. The new data thus identify a molecular mechanism that explains membrane and microtubule severing during cytokinesis.

The other Perspective (Abrahamsen and Stenmark, *Science*, 2011), discusses recent findings that shed light on the way cells sense nutrition status. A fundamental property of the cells of our body is the ability to sense whether nutrients are scarce or abundant so that appropriate anabolic or catabolic programmes can be initiated. Such sensing is mediated by "mammalian TOR complex 1" (mTORC1), and major effort has been taken to delineate how various environmental inputs can regulate this central growth coordinator. In the *Science* Perspective, Abrahamsen and Stenmark discuss recent findings that amino acids are sensed inside the lumen of lysosomes. The sensing mechanism is an intriguing one: high amino acid levels within the lysosome alter the structural composition of a lysosomal proton pump, which mediates recruitment of mTORC1 to the cytoplasmic face of the lysosomal membrane to provide proximity between mTORC1 and its activator Rheb. This in turn causes activation of mTORC1. The central role of mTORC1 as a coordinator of nutrient responses is accompanied by a great interest in targeting mTORC1 pharmacologically. mTORC1 inhibitors are already being used clinically against certain cancers. The recent advance in our understanding of how mTORC1 is activated is therefore good news because it provides us with new strategies for targeting TOR signalling in cancer therapy.



Daughter cells that arise from cell division are separated by a thin membrane bridge that contains microtubule bundles. A helical filament, probably consisting of ESCRT III polymers, spans the bridge. Spastin is recruited to the narrowest part of the microtubule bundle (the constriction zone) to sever it. This causes the helix to constrict, which leads to membrane abscission at the same site.



(B) When amino acids are abundant, v-ATPase undergoes a structural rearrangement that alters the interaction surface between the v-ATPase dissociation and Ragulator. This changes the nucleotide loading of the Rag complex and results in recruitment of mTORC1. Rheb (in the lysosome membrane) activates mTORC1, which then phosphorylates growth-promoting targets such as S6 kinase.

Raiborg C, Stenmark H. (2011) **Cell biology. A helix for the final cut** Science. 331(6024):1533-4.

Abrahamsen H, Stenmark H. (2011) **Cell biology. Growth signaling from inside** Science. 334(6056):611-2.

Midbodies as cell fate determinants

During the final stage of cell division, newly formed daughter cells are connected by an intercellular bridge that contains bundled microtubules that overlap in the midzone. In the area of this overlap, an electron-dense structure, the midbody (also known as the 'Flemming body'), is formed. The precise role of the midbody is poorly understood, but one of its functions is to serve as an anchoring point for the machinery that mediates final abscission between the two daughter cells. During abscission, the microtubules connecting the two daughter cells are severed in constriction zones on one or both sides of the midbody, resulting in the formation of a midbody remnant. In a recent commentary article (Schink and Stenmark, *Current Biology,* 2011), CCB researchers discuss recent findings that describe a new role for the midbody remnant: One study finds that in stem cells the midbody remnant persists, whereas another study by Wieland Huttner and coworkers reports shedding of the midbody remnant from differentiating cells to the surrounding medium. The two papers converge on the view that midbody remnants contribute to cell-fate determination. Cancer cells are often poorly differentiated, and a popular hypothesis in cancer biology proposes that cancers arise from 'cancer stem cells'. It is therefore interesting that midbody remnants have been seen to accumulate in cancer cells, and that differentiation-resistant cancer cells fail to shed midbodies. The accumulation of midbody remnants in cancer cell lines might thus represent another facet of their stem-cell-like characteristics and an important factor for the undifferentiated state of cancer cells.

From left: Kay Oliver Schink and Harald Stenmark
Photos: Per M. Didriksen and Linda Cartridge

Schink KO, Stenmark H. (2011) **Cell differentiation: midbody remnants – junk or fate factors?** Curr Biol. 21(23):R958-60.

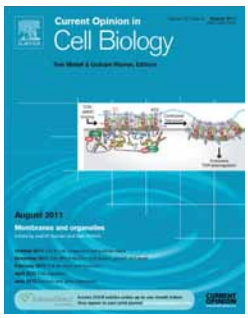
New high impact review article about nanoparticles

A review article about in vitro studies of nanoparticles was published by Tore-Geir Iversen, Tore Skotland and Kirsten Sandvig in Nano Today 6 (2011) 176-185 (journal impact factor 13.3). During recent years there has been much interest in the use of nanoparticles for *in vitro* studies as well as for delivery of drugs and contrast agents in animals and humans. In this review the authors describe the present knowledge and need for future studies in the field of endocytosis and intracellular transport. The possibilities, challenges and pitfalls in such studies are discussed.

From left: Tore-Geir Iversen, Tore Skotland and Kirsten Sandvig

Iversen TG, Skotland T, Sandvig K. (2011) **Endocytosis and intracellular transport of nanoparticles: Present knowledge and need for future studies** Nano Today. 6(2):176-185.

Two endocytosis reviews from CCB researchers in Current Opinion in Cell Biology



Norwegian research groups have a leading role in research on endocytosis, the internalisation of plasma membrane and extracellular molecules that is crucial for cellular functions. This is illustrated by the fact that in the 2011 "Membranes and Sorting" issue of Current Opinion in Cell Biology (journal impact factor 14.15), two groups from Centre for Cancer Biomedicine and Institute for Cancer Research contribute reviews about endocytosis. The first review is from Kirsten Sandvig's group and is entitled "Clathrin-independent endocytosis: mechanisms and function". Sandvig har for many years been studying different endocytic pathways and provided some of the first evidence for the existence of clathrin-independent uptake from the cell surface by investigating toxin uptake. The second review is from Harald Stenmark's group and is entitled "Endocytosis and signaling". This review highlights recent findings that demonstrate the importance of endocytosis and endocytic membrane trafficking in negative and positive modulation of receptor signalling.

Sandvig K, Pust S, Skotland T, van Deurs B. (2011) **Clathrin-independent endocytosis: Mechanisms and function** Curr. Opin. Cell Biol. 23(4):413-20.

Platta HW, Stenmark H. (2011) **Endocytosis and signaling** Curr Opin Cell Biol. 23(4):393-403.

Clonal evolution of tumours

Sverre Heim
Photo: L. Cartridge

A fundamental question in cancer biology is whether neoplasms stem from a single mother cell (monoclonality) or whether they hail from several transformed cells (polyclonality). Acquired chromosomal aberrations are markers of clonality and because they are so diverse, an in principle infinite number of clones can be detected. We have used cytogenetic analysis to assess clonality in various tumor types. Hematologic and mesenchymal cancer are almost invariably monoclonal, albeit sometimes with secondary polyclonality emerging because of genomic instability. Epithelial cancers, on the other hand, such as carcinomas of the breast and pancreas, often display unrelated chromosome aberrations indicating polyclonality. Studies of multiple lesions or samples drawn sequentially in time may demonstrate a reduction of karyotypic complexity indicative of altered selection pressure on the neoplastic cell population, for example when it penetrates the basal lamina to become infiltrative or when distant metastases are set up.

Teixeira MR, Heim S. (2011) **Cytogenetic analysis of tumor clonality** Adv Cancer Res. 112:127-49.

Fibroblast growth factor signalling in cancer

Jørgen Wesche

Fibroblast growth factors (FGF) and their receptors are emerging as important players in the progression of human cancer. They are found deregulated in many subsets of cancers and will, in the era of personalized medicine, be important targets in cancer therapy. An extensive review to document the different roles of these signaling molecules in different cancers were undertaken. Current efforts to invent new targeted drugs are also reviewed. It becomes clear that FGF receptor-targeted therapies warrant more research and development to be able to enter the clinic where the related EGFR-targeted therapies already play an important role.

Wesche J, Haglund K, Haugsten EM. (2011) **Fibroblast growth factors and their receptors in cancer** Biochem J. 437(2):199-213.

Innovation at CCB

During the first Centre period the researchers have given an increasing attention to innovation, which is documented in a number of patent applications/patents since 2007 ranging from ideas for soft ware development, technology platforms to cancer biomarkers. In 2011 we chose to be presented in an issue of the journal International Innovation, intended for a broad scope of readers including researchers, funders, policy makers and commercial partners. Last year we have also capitalised in the innovation field from the ongoing collaborative research between groups of the CCB. The groups of Lothe and Skotheim have in collaboration with the CCB guest professor Manuel Teixeira identified target genes of ETS fusions, which are present in more than half of all prostate cancers *. The Smeland and Lothe groups have filed a DOFI describing novel markers for early detection and monitoring of leukaemia and lymphoma**. The markers were found by using a stepwise approach initially described by Guro E. Lind (Lind et al., Cell. Oncol., 2006), and somewhat surprisingly the best biomarkers for the haematological diseases were partly overlapping with those best for early detection of colorectal cancer.

The latter are included in a biomarker panel for early detection of colorectal cancer which was licensed by Oxford Gene Techology early 2012. The directors of CCB foresee innovation as one of several exit strategies to continue CCB after the coming 5 year period during the discussion with the international expert panel that was responsible for the Mid-term evaluation of the Centre.

In 2011 the CCB also became a member of the Oslo Cancer Cluster. Although we have had good interactions with the staff of OCC during the whole Centre period, last year several of our members participated in many of their events which we consider very good meeting places for academics and company representatives. The co-director is currently a board member of OCC.

Showcase of CCB in “International Innovation 2011”

(www.researchmedia.eu)

CCB researchers with 4 patent applications and 3 disclosures of invention in 2011 as a result of collaborative work among the PIs, clinical associates and guest professor in the Centre:

- Håvard Danielsen: Audio visual camera support for operating theatre Submitted 2011. UK patent application no: 1118909.9

- Håvard Danielsen: Micrography Submitted 2011. UK patent application no: 1120681.0

- Lothe RA, Ahmed D, Andersen K, Skotheim RI, and Lind GE (2011). Methods and biomarkers for detection of gastrointestinal cancers. US provisional patent application filed 61/451,198, INVEN-31899/US-1/PRO.

- Ågesen TH, Sveen A, Lind GE, Nesbakken A, Skotheim RI, Lothe RA (2011). Prognostic signature for colorectal cancer stage II.

- *Paulo P, Teixeira MR, Lothe RA, Skotheim RI (2011). Specific and shared targets of ETS fusion genes in prostate cancer. DOFI

- Tore Skotland, Alicia Llorente og Kirsten Sandvig (2011) Prostate cancer markers and uses thereof. DOFI

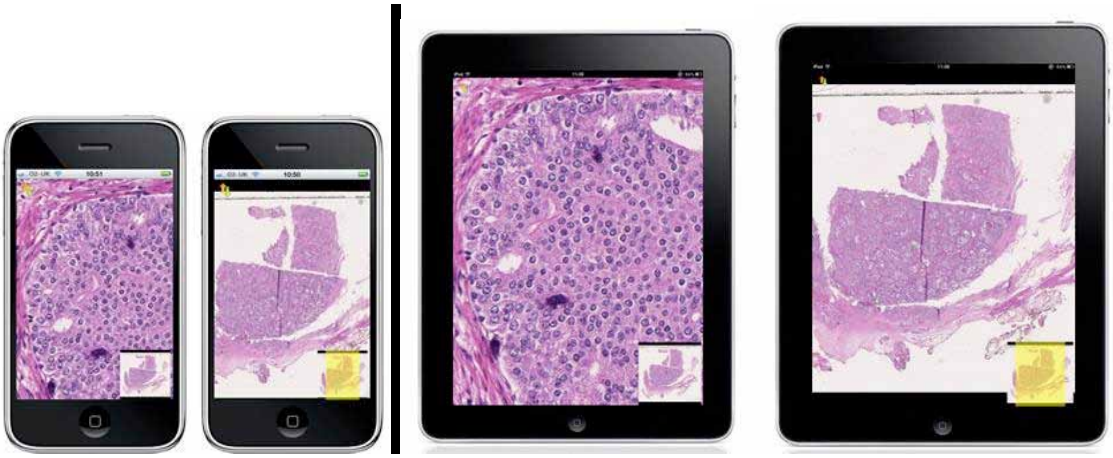
- **Smeland E, Bethge N, Myklebust JH, Delabie J, Holthe H, Lothe RA, Lind GE (2011). Markers for efficient early detection and monitoring of leukemia and lymphoma patients. DOFI

CCB researchers go iPad

Multiplatform virtual slide imaging system for diagnostic and research examination of tissue sections

Håvard Danielsen and his CCB colleagues have developed a virtual slide imaging system that can be used with PCs as well as with mobile devices such as iPhone and iPad. The whole slide (image) is stored on the server where different areas of the slide can be retrieved by the clients. Multiple client technologies can be used, accessing the server at the same time.

Danielsen H, Maddison JR. (2011) **A simple multiplatform virtual slide imaging system, supporting Mac, PC and mobile devices to enable widespread telepathology** In: iPhone & 4G mobile phones in telemedicine, Catai 2011, ISBN: 978-84-614-5997-1.



Early stage detection of colorectal cancer

License agreement signed with Oxford gene Technology early 2012. (http://www.ogt.co.uk/news)

Lind GE, Danielsen SA, Ahlquist T, Merok MA, Andresen K, Skotheim RI, Hektoen M, Rognum TO, Meling GI, Hoff G, Bretthauer M, Thiis-Evensen E, Nesbakken A, Lothe RA. **Identification of an epigenetic biomarker panel with high sensitivity and specificity for colorectal cancer and adenomas.** Mol Cancer, 10(1):85, 2011

CCB : new kid on the block - joins the Oslo Cancer Cluster Norwegian Centre of Expertise

March 2011, **OCC seminar - Personalized Medicine**:
Rolf I Skotheim: “Deep sequencing of colorectal cancer genomes and transcriptomes for personalized treatment and surveillance”

August 2011, **OCC seminar - New members**
Ragnhild A. Lothe: Presentation of Centre for Cancer Biomedicine

September 2011, **INNABIOSANTE - European Cancer Cluster Partnering, Toulouse**
Kirsten Sandvig: Drug delivery: Role of endocytosis and intracellular transport

October 2011, **OCC R&D seminar - Drug Delivery and Nanoparticles**
Tore-Geir Iversen: “Transport of nanoparticles into cells. Characterization and consequences”
Tore Skotland: “Challenges for clinical use of nanoparticles”

HARALD STENMARK GROUP

Intracellular communication

Harald Stenmark | Photo: Linda Cartridge

About

Harald Stenmark's group has 25 members from 8 nations and is divided into a main group and 4 project groups (led by Kaisa Haglund, Andreas Brech, Tor Erik Rusten and Camilla Raiborg/Hilde Abrahamsen). The major interest of the group is to understand how cellular membrane dynamics contribute to tumour suppression. In particular, the function of a specific membrane lipid, phosphatidylinositol 3-phosphate (PtdIns3P), in recruiting cytosolic protein complexes and thereby controlling membrane involution processes is being investigated. Recent evidence suggests that three PtdIns3P-dependent membrane involution processes - endosomal trafficking, autophagy and cytokinesis – all contribute to tumour suppression, and the group investigates the molecular mechanisms that connect Ptdins3P with these processes and tumour suppression. As model systems the group employs cultured cell lines derived from tumours and normal tissues, as well as the fruit fly Drosophila melanogaster as a genetically tractable multicellular organism. The group specializes in advanced microscopy, including confocal microscopy, live-cell microscopy and electron microscopy, and will soon be implementing super resolution microscopy. Regional core facilites in confocal microscopy and electron microscopy are run by the group.

Projects

- Endocytic control of receptor signalling (led by Harald Stenmark)
- PtdIns3P in regulation of autophagy (led by Harald Stenmark)
- Cytokinesis in development and carcinogenesis (led by Kaisa Haglund)
- Membrane-associated protein dynamics in cell division (led by Camilla Raiborg and Hilde Abrahamsen)
- Phosphatidyolinositol signalling & disease (led by Tor Erik Rusten)
- Unit of cellular electron microscopy (led by Andreas Brech)

Aims

The overall aim of the group's research is to understand how cellular membrane dynamics protect normal cells from becoming malignant. In collaboration with other CCB groups this information will be used for improved cancer diagnostics, prognostics and therapy.

Recent achievements

The scientific production of Stenmark's group in 2011 included 19 papers and one PhD degree (Lina Rodahl).

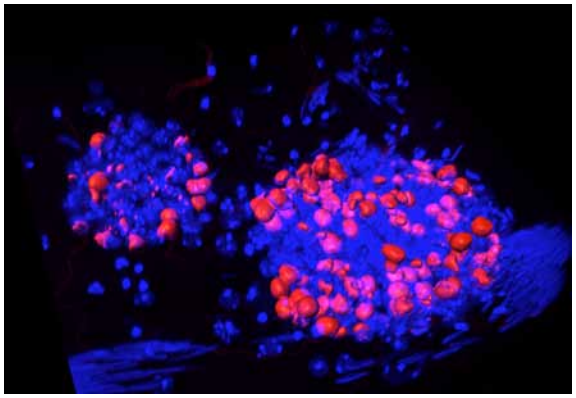
One of the key discoveries of the group is the finding that PtdIns3P localizes to endosomes, and we have uncovered a central role for the PtdIns3P-binding protein HRS in lysosomal downgregulation of growth factor receptors. HRS is a key subunit in the endosomal sorting complex required for transport (ESCRT), and the group has been investigating the functions of ESCRT proteins in receptor degradation and silencing. These studies recently led to the discovery of a novel mechanism of signal attenuation in response to growth factor stimulation of cells. It was previously known that growth factor stimulation leads to endocytosis and degradation of growth factor receptors, but we recently demonstrated that even a component of the ESCRT machinery, TSG101, is degraded in

The Stenmark group | Photo: Linda Cartridge

lysosomes in response to growth factor stimulation. This study, which was a close collaboration with CCB biostatistician Knut Liestøl, shows that the cell is equipped with multiple feedback regulatory mechanisms to finely tune the inputs and outputs from growth factors (Malerød et al., Traffic, 2011).

We recently discovered a novel role for PtdIns3P in membrane dynamics, namely in the regulation of the final stage of the cell division process, cytokinesis (Sagona et al., Nature Cell Biology, 2010). The PtdIns3P-binding protein FYVE-CENT, was identified as a regulator of cytokinesis, and we recently focused on the fact that a mutation in FYVE-CENT is associated with cancer. We established that FYVE-CENT interacts with a well-known tumour suppressor, Beclin 1, and that the cancer-associated FYVE-CENT mutation abolishes this interaction and interferes with normal cytokinesis. In collaboration with Rolf Skotheim's group in CCB we also observed that FYVE-CENT is downregulated in advanced breast cancers. Together, these observations suggest the possibility that FYVE-CENT, through interaction with Beclin 1, plays a role in cytokinesis regulation as well as in tumour suppression (Sagona et al., PLoS One, 2011).

Our recent experience with cytokinesis also came in handy for a collaborative project with cancer (epi) geneticists Guro E. Lind and Ragnhild A. Lothe in CCB. Their group identified a gene, SPG20, whose promoter becomes hypermethylated at a very early stage of colorectal cancer development and therefore is a very promising biomarker for early detection of colorectal cancer. When we studied the cellular function of the protein encoded by SPG20, Spartin, we noticed that the intercellular bridges between dividing cells had a strange shape. Upon closer investigation we discovered that Spartin is indeed a regulator of cytokinesis, and that reversal of SPG20 hypermethylation in cancer cells abolishes the cytokinesis defect. Since correct control of cytokinesis is thought to represent a mechanism for tumour suppression, it is tempting to speculate that SPG20 hypermethylation may not only be a diagnostic marker in colorectal cancer but could even represent a driver of oncogenesis (Lind et al., Oncogene, 2011).



An Imaris 3D-reconstruction of tumors in the male germline of Drosophila, where a labeled nucleotide (red) is incorporated in scattered nuclei (blue) within the two tumors, indicating loss of synchronous divsions. Image courtesy of Åsmund Eikenes

RAGNHILD A. LOTHE GROUP

Cancer genetics and epigenetics

Ragnhild A. Lothe | Photo: Linda Cartridge

About

Lothe group has 16 members, and includes one project group (n=5) led by Guro E. Lind. One PhD student is a 50% clinician.

The underlying biology of colorectal cancer and the many, yet unresolved, clinical challenges related to this disease are the crux of our translational research activities. We have a particular interest in a rare malignancy, MPNST, and we are active partners in molecular studies of urological cancers. Understanding molecular mechanisms underlying human tumour development is essential to improve the diagnosis and treatment of the cancer patient. Our group combines patient-oriented and detailed biology research using human biobanks and in vitro models. We apply a wide range of technologies in genetics, epigenetics, bioinformatics and cell biology and handle in-lab various microarray platforms and deep-sequencing.

Within CCB we collaborate with the groups of Axcrona, Danielsen, Heim, Liestøl, Lingjærde, Nesbakken, Rivedal, Smeland, Skotheim, Stenmark, and Teixeira.

Projects

- Genetics and molecular biology of cancer development (colorectal, prostate, malignant peripheral nerve sheath tumors, MPNST)
- Epigenetics of cancer (led by Guro E. Lind)
- Biomarkers for early detection of cancer (colorectal, bladder)
- Prognostic and predictive biomarkers for cancer (colorectal, prostate, MPNST).

Challenges

Colorectal cancer is the third most common type of cancer with a world wide annual incidence of 1.2 million and 3600 new cases in Norway alone. About 40% of the patients die within 5 years after diagnosis. There is a need for improved non-invasive screening tests to reduce the incidence and the mortality of this disease. Furthermore, the present clinical staging is crude and new more precise prognostic and predictive markers are asked for.

Prostate cancer is a common malignancy in men and about 4500 are diagnosed in Norway each year. The PSA testing is not suitable as a screening tool for detection of disease due to low sensitivity and specificity. Many cancers will not develop into clinically threatening disease and thus there is a strong need for understanding the molecular biology and heterogeneity of this disease in order to develop new diagnostic and therapeutic tools.

Bladder cancer has a very high risk of recurrence and it is expected 15-20 clinical follow up consultations per patient making the bladder cancer patient one of the most expensive in cancer care. A non- invasive molecular test with high performance both for early detection and recurrence is highly warranted.

Malignant peripheral nerve sheath tumours are rare and typically arise in young adults. The disease is highly aggressive and no standard treatment exists except for surgery. A European study including four Centres, led by Lothe, join their biobanks of this rare disease in order to develop new molecular prognostic and predictive tools.

Aims

The goals relevant for each disease are to elucidate the developmental biology and to identify, and validate new biomarkers for improved diagnostics and therapy of these malignancies.

Common goals across these malignancies are to identify the mutational events in known actionable genes, for which designer drugs exist. From the cancer exomes gain novel insights to the heterogeneity and treatment resistance mechanisms.

The Lothe group | Photo: Linda Cartridge

Recent achievements

The scientific production of the Lothe group in 2011 included 15 original papers, 1 review, 1 PhD (Stine A. Danielsen), 2MSc (Hege M. Vedeld, Andreas Hoff), 2 patent applications, 2 disclosures of invention.

Epigenetic biomarkers highly suitable for early detection of colorectal cancer were identified and validated in independent clinical series of benign and malignant colorectal tumours (Lind et al., Mol Cancer 2011). Each of the six markers had high sensitivity and specificity, but the combination of markers provides robustness to a future minimal non-invasive test. A patent application was filed in 2007 and together with additional unpublished markers (PA 2011) a license agreement between the Oslo University Hospital and Oxford Gene Technology was signed in February 2012.

In collaboration with Camilla Raiborg and Harald Stenmark a new cellular function, a regulator of cytokinesis, was shown for the Spartin protein encoded by one of the biomarkers, SPG20 (Lind et al., Oncogene 2011).

Very promising epigenetic biomarkers for detection of bladder cancer by analysis of DNA from urine samples was recently found in collaboration with the Teixeira group (Costa et al., CCR 2010; Costa et al., Epigenetics 2011). A joint PA between Oslo University Hospital and Portuguese Oncology Institute is filed and we are in progress with a collaborative validation study with a US biotech company.

Individuals with early onset of colorectal cancer may be genetically or epigenetically predisposed. We study germline and somatic differences between patient groups with 20 year difference in disease onset but otherwise matched for clinical variables. In a recent report of integrative analysis of genomic copy number changes and the transcriptome we show that overall the tumours from young and elderly patients were comparable, and a number of signalling pathways and cellular networks were significantly altered (Danielsen SA et al., PLoSone, 2011). However, immunity related genes were differentially expressed and a global immunity score was distinct between the age groups (Ågesen et al., Genes Immunity, 2011).

Based on the exon level microarray analyses of primary colorectal cancer we have recently identified prognostic signatures. A new phenotype was described for colorectal cancer, transcriptome instability –TIN, which was associated with prognosis for the patients (see highlight section) (Sveen et al., Genome Medicine, 2011).

The number of probes per gene (~40/gene) provides a robust average measurement for the average gene expression. By L1 (lasso) penalised Cox proportional hazards analyses a 13 gene classifier was developed specifically for stage II patients and another 7 gene classifier was particular suitable for stage III patients (Ågesen et al., GUT 2012 Jan; unpublished). These signatures were validated in independent clinical series from other countries. Currently, we are analysing the performance of the signatures in a prospective study design.

HÅVARD DANIELSEN GROUP

Large scale genomic instability

Håvard Danielsen | Photo: Linda Cartridge

About

Cancer arises from a single or a few transformed cells, and by the time a cancer is diagnosed, it comprises billions of cells carrying multiple, and mostly different, DNA- and chromatin abnormalities. Today's powerful technologies are enabling these changes to the genome to be catalogued in detail. If these billions of cells in a given tumour were carrying a specific aberration that initiated malignant proliferation of the single or few transformed cells, one would expect that the initiator would be easily detected. If indeed a given cancer type is characterised by one or a few specific aberrations, one would expect that such "true oncogenes" would also be easily detected. Evidence is instead accumulating indicating a close link between genomic instability and cancer initiation and progression. Neoplastic cells typically possess numerous genomic lesions, which may include sequence alterations and/or gross structural abnormalities in one or more chromosomes. Furthermore, karyotypic alterations, including whole chromosome loss or gain, ploidy changes (aneuploidy and polyploidy) and a variety of chromosome aberrations are common in tumour cells. The loss of genomic stability appears to be a key molecular and pathogenetic step that occurs early in tumorigenesis and serves to create a permissive environment for the occurrence of alterations in tumour suppressor genes and oncogenes.

The Danielsen group are developing high throughput methods for detection and characterisation of large-scale genomic instability (chromatin structure and ploidy), based on high-resolution digital microscopy and advanced image analysis. They are studying archival material at the time of diagnosis from patients with proper clinical follow-up and known prognosis, in large series of colorectal, breast, prostate and gynaecological cancers. In parallel, karyotyping, CGH and FISH are used to search for specific genomic changes in the same tumours, and attempts are made to establish the relationship between specific genomic changes and chromatin structure.

Specific aims

The main aims are to complete the methodology and system that detects and classifies large scale genomic instability in tumours by analysing nuclei in routine histological biopsies, and to use this to analyse the large series of common cancers and define more precise prognostic markers for these cancer types. Results from different cancer types, as well as from different methods of instability indicators (DNA ploidy, Nucleotyping, FISH, CGH, Karyotyping), are compared and analysed in an attempt to obtain new knowledge about the mechanistic and pathobiology of large scale genomic instability.

Detection and classification of genomic instability may be a key disease biomarker for cancer, and knowledge of the biochemical mechanisms behind it is likely to identify the next set of key therapeutic targets.

The Danielsen group | Photo: Linda Cartridge

Recent discoveries and achievements

Methods and systems for high throughput analysis of chromatin structure and DNA ploidy in nuclei from routine biopsies are developed, and DNA ploidy have been shown to have independent prognostic power in Gleason 7 prostate cancers (Pretorius et al, Cell Oncol.31(4):251-9,2009), in uterine sarcomas (Kildal et al, Ann Oncol, 20(6);1037-41,2009), in endometrial cancers (Pradhan et al, Ann Oncol, 2011) and most recently in cancers from colon and rectum (Danielsen et al, submitted). Our Nucleotyping method for characterizing chromatin structure has proven useful as a diagnostic tool in Barrett's oesophagus (Dunn et al, Bj J Cancer 105(8), 1218-23, 2011. Our high throughput method for analysing tissue micro arrays (TMA) based on virtual microscopy (Brekke et al, Neuro Oncol. 11(5):514-28,2009 and Arnoldussen et al, Cancer Res. 68(22):9255-64, 2008) is now complemented with new software for automatic quantification of expression (in prep). Microtracker, a new concept for cell-by-cell comparison of results from different methods has been patented (UK patent 2010). A new and enhanced version of the DNA Ploidy system has been finalised, and development of methods for high throughput automatic segmentation and classification of nuclei in histological sections have been completed (Nielsen et al, Cytometry 2012, in press and patents pending).

Current projects

- Nucleotyping as a prognostic marker in prostate cancer and colorectal cancers
- Heterogeneity of prostate cancers
- 2-D and 3-D analysis of chromatin structure
- Cell-by-cell comparison of FISH, IHC, ploidy and Nucleotyping in 3-D reconstructions of nuclei from routine histological biopsies (Microtracker)
- Visualization of textural features in chromatin

STATISTICAL ANALYSIS UNIT HEADED BY KNUT LIESTØL

Data analysis, Statistical methods development

Knut Liestøl | Photo: Linda Cartridge

About

The statistical analysis unit in CCB aims at

- Supporting the activity of the CCB groups by providing data analysis, primarily through working within projects at CCB. Additionally, the group addresses more specific statistical questions arising during the work of CCB scientists.

- Developing statistical methods and software for relevant biostatistical challenges, typically motivated by problems originating from concrete biomedical investigations at CCB.

The statistical analysis unit is part of the Biomedical research group (Bio) at the Department of Informatics, located at the main campus of the University of Oslo. The research activity in the Bio group is directed towards methods development and applications of biostatistics, bioinformatics and computational science in the medical areas, and with special emphasis on medical genomics and sequence analysis.

Challenges

The statistical analysis group has a focus on the analysis of data from high throughput technologies in genomics and molecular biology. While rich in information, the complexity of these large data sets makes extraction of information a true challenge. As opposed to the typical situation in classical statistics, high throughput technologies require methods adapted to (relatively) few samples and high numbers of observations on each sample.

The group's philosophy is to work in close interaction with the biomedical research groups and to achieve own competence in central biomedical application areas for CCB. Typically, projects in the group initially focus on a concrete biomedical problem; we then try to solve the arising statistical challenges in a broader context and finally develop adapted software tools. On the methodological side, our focus has been on problems from survival/event history analysis and in nonparametric/ nonlinear statistical modelling, with special emphasis on the challenges from high dimensional data analysis.

The Liestøl group | Photo: Linda Cartridge

Recent achievements

One main area in recent years has been the analysis of copy number alterations. This includes both biomedical applications together with other CCB groups and development of methods and software. A software system (named copynumber) written in R and adapted to the Bioconductor requirements has been further developed. In 2011, methods for analysing SNP genotype data (data including both total copy number and B allele frequency) has been included to the system, and improved methods for particularly long data sequences has been added.

Another main activity in 2011 has been the analysis of survival data. This includes work on genetic risk factors in lymphoma (together with the Smeland group), ploidy as risk factor in colon cancer (Danielsen group), and flotillins as risk factor in breast cancer (Sandvig group).

Moreover, together with Lothe's group, we have worked on identifying smaller sets of genes that may be used for predicting the outcome for patients with colorectal cancer or malignant peripheral nerve sheath tumors.

Another continued activity has been analysis based on siRNA screens, with data mainly arising from work in the Stenmark group. This work has now moved on to the "verification" phase, where candidates from the initial screens are further tested for biological activity; the statistics is then focused on efficient hypothesis testing.

Additionally, we have in 2011 contributed to several projects using modern regression methods on RNA expression data, mainly in collaboration with the groups of Lothe and Smeland.

KIRSTEN SANDVIG GROUP

Intracellular transport

Kirsten Sandvig | Photo: Linda Cartridge

About

Sandvig's group is interested in the mechanisms of endocytosis, intracellular transport and secretion. Uptake of receptors and ligands and correct intracellular sorting of endocytosed molecules are crucial for maintenance of a normal differentiated phenotype. In some of our studies we are using protein toxins which are well established as markers for studies of membrane traffic, and which can be used as agents in cancer diagnosis and therapy. Our expertice is also applied to investigate uptake of nanoparticles and to characterize release of exosomes from prostate cancer cells with the goal of detecting lipid and protein biomarkers.

These projects aim at increasing our knowledge about intracellular transport and biomarkers in order to provide a rational basis for diagnosis, treatment and prevention of disease.

Challenges

Cancer is associated with errors in trafficking and signaling, and differences in expression of surface molecules and transport/signaling between normal and cancer cells can be exploited to detect and kill tumor cells. The Shiga toxin receptor is expressed by a number of human tumors, and Shiga toxin can be used for in vivo tumor targeting and imaging. A number of the protein toxins are of interest also in connection with targeted drug delivery of toxin conjugates. To construct active toxin conjugates, one needs to know which part of the toxin molecule to include, and whether targeting to a specific intracellular compartment is required. For this purpose, knowledge about the relationship between toxin structure and function and the mechanisms of intracellular sorting is essential. Importantly, the toxins have proven valuable to reveal and characterize pathways in cells. More recently we have started to study the interaction of nanoparticles with cells since there are large expectation for such particles in medicine. Such particles can change endocytic pathways as well as intracellular sorting, and characterization is required for each particle type. Another new project concerns release of exosomes from prostate cancer cells. Surprisingly little is known about the mechanism of formation and release of these vesicles in spite of their importance in cancer biology. We are characterizing the impact of protein complexes, kinases and specific membrane lipids on intracellular sorting. Several international collaborations, as well as colloborations with other members of CCB, are ongoing to increase the impact of our projects.

By using a combination of morphological, biochemical and molecular biological approaches, we are investigating the various aspects of intracellular transport, and we are characterizing nanoparticles and biomarkers that can be used in cancer diagnosis and therapy.

Projects

- **Characterization of intracellular transport**
  We have a main focus on characterization of endocytic mechanisms and intracellular transport. In some of our studies we use protein toxins to discover and characterize intracellular pathways. A main focus is to investigate cellular transport mechanisms in normal and cancer cells to provide a scientific basis for cancer diagnosis and therapy.

- **Entry of nanoparticles into cells**
  This project aims at gaining more knowledge about endocytic mechanisms and intracellular pathways induced and followed by various nanoparticles in cells, and the role of size and composition of nanoparticles for the compartments reached and for their clearance from cells. Such knowledge is essential for exploiting nanoparticles in medicine.

The Sandvig group | Photo: Linda Cartridge

- **Membrane transport in prostate cancer cells: Release of microvesicles**
  One principal objective of this project is to obtain knowledge on vesicular transport in prostate cancer cells. This will increase our understanding of prostate carcinogenesis. Both proteomics and lipidomics of exosomes are run with the goal of obtaining biomarkers.

Recent achievements

Some recent findings/articles published by our group in 2011-:

Cancer cells, in contrast to normal cells, often express the neutral glycosphingolipid Gb3 which can bind Shiga toxin. This toxin is being tested for use in diagnosis and therapy, and we have published a review on the use of Shiga toxin in targeted cancer therapy and imaging: Engedal et al. Microbial. Biotechnol. 4 (2011) 32-46. More detailed knowledge about the interaction of Shiga toxin with cancer cells is warranted, and we have investigated the importance of Toll-like receptor 4 in Shiga binding (Torgersen et al. FEMS Immunol. & Med. Microbiol. 61 (2011) 63-75). Recently, we have by studying Shiga toxin found a new role for the proton-pump in endosomes. Remarkably, it has a role in sorting that is not directly related to its effect on intravesicular pH (Lingelem et al. Traffic 13 (2012) 443-454). Clearly different lipids are involved in sorting, and we found that phospholipase A2 is involved in retrograde sorting to the ER (Klokk et al. Toxins 3 (2011) 1203-12019). The complexity of intracellular sorting is also evident from a study of derlins, proteins known to be in the ER, but now found to play a role also in retrograde transport (Dang et al. Traffic 12 (2011) 1417-1431). Minor mutations in a ligand are sufficient to change the sorting (Sokolowska et al. Biochem. J. 436 (2011) 371-385). A collaborative project with another CCB-group on the endocytic mechanism used by FGFR3 (a fibroblast receptor) was published in 2011 (Haugsten et al. PloS ONE 6 (2011)e21708). Side-projects in collaboration with other groups resulted in one article about protein C (Tjeldhorn et al. PloS ONE 6 (2011) e24009), and one about a toxin (Cordara et al. Biochem.Biophys.Res.Commun. 408 (2011) 405-410). Reviews published during the year, on endocytosis, toxins and nanoparticles include: Iversen et al. Nano Today 6 (2011) 176-185; Sandvig et al. Curr.Opin.Cell Biol. 23 (2011) 413-420.

ERLEND SMELAND GROUP

Translational research in malignant lymphoma

Erlend Smeland | Photo: Linda Cartridge

About

Smeland group has 11 members, of which 2 are PhD students with a 50% clinical position. The main focus of the group is to study B-cell lymphoma biology. Our research projects have a strong translational focus and we have a close collaboration with the lymphoma program in the Hospital. Several projects are connected to ongoing clinical trials, and we analyze primary patient samples using a broad spectrum of methods which involves molecular characterization as well as functional studies. Selected lymphoma-specific genetic aberrations are followed up by basic cell biology research, using B-cell lymphoma cell lines as models. Central techniques include studies of signalling pathways by Western blot analysis and multi-color flow cytometry, confocal microscopy, tissue micro array (TMA), array comparative genomic hybridization (aCGH), and gene expression profiling. The group has ongoing collaboration with the groups of Ragnhild Lothe, Knut Liestøl and Håvard Danielsen within CCB, and extensive international collaboration with Stanford and NCI, USA. We are also actively participating as one of four European groups in a large international collaborative project regarding molecular profiling of B-cell lymphomas (LLMPP, headed by Dr. Louis Staudt at NCI; Smeland is site-PI for this project).

Projects

- Molecular characterization and studies of gene expression.
- Epigenetic mechanisms in the development of malignant lymphoma
- TGF-β/BMP-induced signaling and functional effects in normal and malignant B-cells
- High-throughput profiling of signaling pathways in B-cell lymphoma by Phospho-Flow cytometry
- Lymphoma/Leukemia Molecular Profiling Project (LLMPP)

Challenges

Lymphomas are cancers derived from cells of the immune system, most frequently from B-cells in the lymph nodes. B-cell lymphoma is a very heterogeneous group of diseases, consisting of many subgroups. Some of these are challenging to diagnose correctly with current methods. Correct diagnosis is critical since different subgroups require different treatment regimes to achieve best possible outcome. Many patients still experience relapse. A large number of targeted therapies has recently entered clinical trials (monoclonal antibodies, kinase inhibitors, proteasome inhibitors, epigenetic drugs, and immune modulating agents), but how efficient they are in the various B-cell lymphoma subgroups, and their exact mechanism of action still needs to be determined.

Aims

We use high throughput analysis of gene expression and genomic and epigenetic alterations in lymphoma samples, with the aim to elucidate oncogenic mechanisms in lymphoma development. The overall goal is to develop new diagnostic tools, new prognostic biomarkers and to identify new targets for therapeutic intervention in this group of malignancy.

Recent achievements

The scientific production of 2011 included 8 peer review papers and one PhD degree (Kanutte Huse) from our laboratory.

The activated B cell subtype of diffuse large B cell lymphoma (ABC DLBCL) has constitutive active NF-

The Smeland group | Photo: Linda Cartridge

κB pathway. It has recently been discovered that this is due to activating mutations in central components of the B cell receptor (BCR) signaling pathway. Ten percent of ABC DLBCL patients have mutations in the adaptor protein CARD11 (Lenz et al, Science 2008), whereas 30% of the patients have mutations in the BCR associated molecules CD79a and b (Davis R et al, Nature, 2010). This implicates BCR signalling in the pathogenesis of ABC DLBCL and suggests that antigenic stimulation participates during disease development. In a collaborative study conducted at Stanford University, we found that BCR signaling responses was associated with patient outcome and response to chemotherapy (Irish et al, P.N.A.S 2010). Recently, we also discovered oncogenic mutations in MYD88 in ABC DLBCL tumours (Ngo VN et al., Nature 2011). MYD88 is an adaptor protein that mediates Toll and Interleukin (IL)-1 receptor signalling. RNA interference screening revealed that MYD88 and the associated kinases IRAK1 and IRAK4 are essential for ABC DLBCL survival. The MYD88 mutation found in 29% of ABC DLBCL, was rare or absent in other DLBCL subtypes and Burkitt's lymphoma (Ngo VN et al., Nature 2011).

Resistance to negative regulators, including TGF-β family members, can further influence the pathogenesis of B cell lymphoma. Whereas TGF-β is well established as one of the most prominent suppressor of normal immune cells, little is known about other TGF-β family members. Bone morphogenetic proteins (BMPs) are members of the TGF-β superfamily, and we discovered that various BMP members efficiently suppressed plasma cell differentiation and antibody production from naive and memory B cells, purified from healthy blood donors (Huse et al., Eur J Immunol, 2011). We also observed a striking difference in functional effects between the structurally similar BMP-6 and BMP-7, as BMP-6 inhibited plasmablast differentiation, and BMP-7 induced apoptosis. We also observed that B-cell lymphoma cells can escape the negative influence of BMPs, and that upregulation of the inhibitory protein Smad7 is sufficient to become BMP resistant (Huse et al., submitted).

The monoclonal antibody rituximab (anti-CD20) is widely used in treatment of non-Hodgkin lymphoma. This results in a prolonged depletion of normal B cells, which might impair the production of protective antibodies. We investigated whether lymphoma patients undergoing rituximab-treatment were able to mount protective antibody responses to the influenza A(H1N1) 2009 virus vaccine Pandemrix during the 2009 "swine flu" pandemic. We found that none of the 67 patients investigated achieved protective antibody titers, in contrast to the healthy control group, where 82% responded adequately to the vaccine (Yri OE et al, Blood 2011). These results suggest that lymphoma patients receiving rituximab-containing regimens might not benefit from prophylactic vaccines in general.

Protein internalization and signaling group headed by Antoni Wiedlocha

Associated with the Stenmark group

The Wiedlocha group | Photo: Linda Cartridge

About

The FGFs-FGFRs signaling system exerts a powerful combination of biological effects including during development and in maintaining a malignant phenotype. FGF signaling is strongly oncogenic once the tight regulation on its physiological function is lost; it is enabled to be a central driver of tumor progression. The growth factors as well as their receptors are frequently and abundantly expressed in various cancers and recognized as mediators of the epithelial-mesenchymal transition, tumor cell survival, migration/metastasing and neoangiogenesis, and also stress-induced agents causing rescue of tumor tissues.

Challenges

In addition to the kinase domain, FGFR contain a serine rich C-terminal tail of unknown function. Recently we revealed that upon FGFR1 activation the receptor is directly phosphorylated on a C-terminally located serine by activated MAP kinases Erk1 and 2 resulting in decreased tyrosine kinase activity of the receptor, as well as cell proliferation and migration. This serine phosphorylation provides a novel downregulation mechanism of FGF-FGFR signaling.

Since signalling from FGF receptors are crucial for the motility of many cancer cells we believe that a deeper understanding of the process of cell migration may lead to new therapeutic strategies for the inhibition of tumour cell invasion.

FGF1 and 2 may, in addition, be translocated into the cytosol and nucleus of cells. We want to understand the molecular mechanism of the intracrine signalling of the growth factors by identification of new intracellular FGF1 and 2 binding protein partners. Furthermore we want to know how the translocation process of the growth factors occurs and is regulated.

Projects

- Activation and termination of FGF-FGFR induced signaling
- Endocytosis, sorting and intracellular transport of FGF1 and FGFRs
- Mechanisms of FGF-induced cancer cell migration
- Identification of intracellular proteins interacting with FGF1 and 2

Achievements

- Clathrin–mediated endocytosis is required for efficient internalization and downregulation of FGFR1 while FGFR3 is internalized by both clathrin-dependent and clathrin-independent mechanism (Haugsten et al. Plos One, 6, 2011).

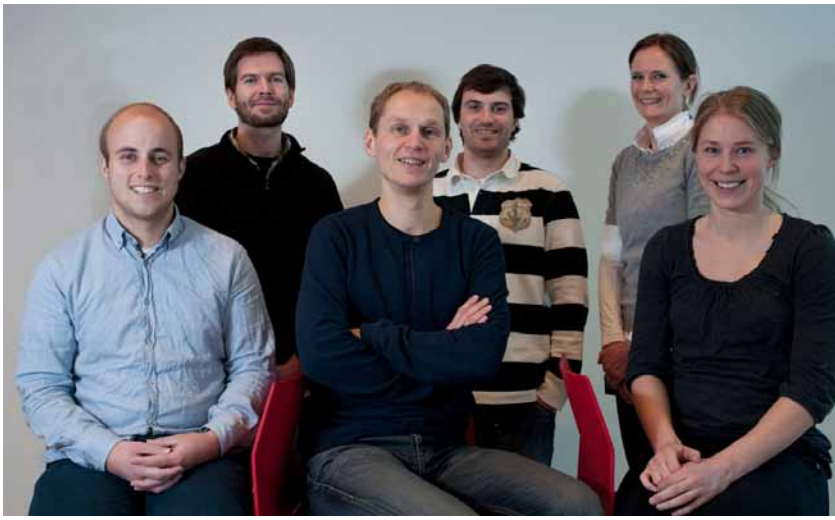
- The stability of the oncogenic fusion protein FOP2-FGFR1 in KG-1a human leukemic cells depends on activity and elevated expression level of HSP90 and the presence of its co-chaperone CDC37 (Jin et al. Cell. Signal. 2011, 23, 2011).

- FGF-FGFR1 complex constitutes a signaling module that independently of the receptor tyrosine kinase can convey a signal that initiates a strictly timed and periodic release of endocytosed FGF1 into the cytosol/nucleus (Zakrzewska et al. Exp. Cell Res., 17, 2011).

- The ER membrane anchored LRRC59 protein facilitates transport of cytosolic FGF1 through the nuclear pores by interaction with importinκ and importinκ, and movement of LRRC59 along the membrane of the ER and the nuclear envelope (Zhen et al. submitted).

Genome biology group headed by Rolf Skotheim

Associated with the Lothe group



The Skotheim group | Photo: Linda Cartridge

About

The Genome Biology group investigates cancer genomes and transcriptomes by integrated computational and laboratory based approaches. The projects are mainly focused on testicular, prostate and colorectal cancers.

The main aim is to identify and characterise critical genes involved in the cancer development. Such genes may serve as diagnostic or prognostic biomarkers and also as targets for future molecularly tailored therapy. Particularly, we use high-throughput sequencing and various microarray technologies to do in-depth studies of clinical biobank material and in vitro models. To facilitate insightful data analysis pipelines, we have personnel from informatics, biology and medicine working together in our projects. Promising results are followed up by experimental validation and further exploration by wet-lab analyses.

Projects

- **Fusion genes and other cancer-specific transcript variants**
  We search for cancer specific transcripts resulting from gene fusions, alternative promoters and aberrant splicing. Transcripts only expressed in malignant cells represent a valuable resource in development of biomarkers and drug targets. Initially, novel transcripts are identified from RNA-sequencing data. Their prevalence in cancerous and healthy tissues is explored within larger biobanks, for example by integration with large datasets obtained by exon microarrays.

- **Transcriptome instability in cancer**
  We study aberrantpre-mRNA splicing in cancer, and recently, we described transcriptome instability as a novel phenotype in colorectal cancer. We seek to develop this concept further, and also investigate whether this phenomenon can be seen for other types of cancer.

Recent achievements

The group has previously developed a novel microarray design for universal detection of all known fusion genes, covering all chimeric exon-exon breakpoints. In 2011, a second generation Fusion gene microarray was published enabling simultaneous assessment of 548 fusion genes (Løvf et al., Genes Chromosomes and Cancer 2011). Analyses of samples representing a wide-range of cancer types supported that although several genes are commonly present as fusion partners across multiple cancer types, the particular pair of genes are generally cancer-type specific.

Genome-scale studies of aberrant mRNA splicing in colorectal cancer pointed towards *SLC39A14* as having mutually exclusive variants of exon 4 between colorectal cancer and normal colonic mucosa. The biomarker potential was further explored by surveying RNA from a multitude of different sources, demonstrating that the exon-level biomarker has organ confined cancer specificity in colorectal cancer (Sveen et al., International Journal of Cancer 2011). On a more genome-wide scale, the amount of aberrant splicing was determined, and transcriptome instability was identified as a novel phenotype of colorectal cancer, which again was associated with both expression levels of splicing factors and poor patient survival (Sveen et al., Genome Medicine 2011).

Molecular cell biology group headed by Edgar Rivedal

Associated with the Lothe group

The Rivedal group | Photo: Linda Cartridge

About

Our research group studies molecular mechanisms involved in cancer development, with emphasis on intercellular communication and colorectal cancer. We combine various molecular cell biology methods, and use cell lines derived from normal tissue and tumours as model systems, as well as relevant human biobank material.

Main interests

Multicellular organisms have multiple mechanisms for the exchange of information between cells. We are studying a family of 20 proteins called connexins, which form intercellular channels between adjacent cells. These channels are assembled in specialized plasma membrane domains called gap junctions, and enable cells to exchange ions, metabolites and signaling molecules. Intercellular communication via gap junctions is usually lost during cancer development. Connexins, some of which have been shown to act as tumor suppressors, are potential biomarkers and targets in chemoprevention and -therapy. We are focusing on the mechanisms involved in down-regulation of connexins during cancer development, and the molecular basis underlying their role as tumor suppressors. Additional areas of interest are mechanisms involved in dysregulation of the MAPK and PI3K pathways during colorectal cancer progression. The latter includes a better understanding of the post-translational mechanisms involved in downregulation of the tumor suppressor protein PTEN.

Projects

- Elucidate the role of intercellular communication in cell growth control and differentiation, and the molecular mechanisms by which connexins act as tumor suppressors.

- Investigate post-translational mechanisms involved in downregulation of connexin43 and PTEN during colorectal cancer development, with emphasis on the role of ubiquitin and ubiquitin-like proteins.

Recent discoveries

- Connexin43 is a colorectal cancer tumor suppressor protein and prognostic marker (Sirnes and Bruun et al, Int J Cancer 2011).

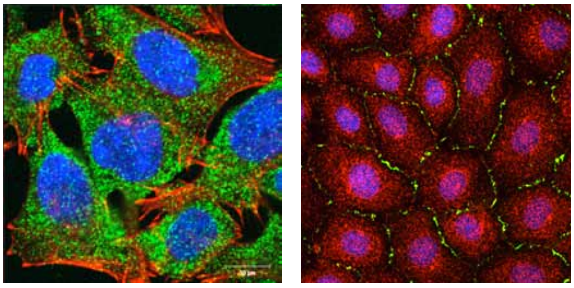
- GJC1, encoding connexin45, is silenced in colorectal cancers as a result of promoter methylation (Sirnes et al, Epigenetics 2011).

- SUMOylation of connexin43 as a novel mechanism for regulation of intercellular communication (Kjenseth et al, J Biol Chem in press 2012).

- The pesticide and endocrine disruptor Ioxynil is a potent inhibitor of intercellular communication via gap junctions (Leithe et al, Toxicol Appl Pharmacol 2010).

- The tumor promoter TPA induces endocytosis and trafficking of connexin43 to early endosomes and lysosomes in a process mediated by Hrs and Tsg101 (Leithe et al, J Cell Sci 2009).

- Smad ubiquitination regulatory factor-2 controls gap junction intercellular communication by modulating endocytosis and degradation of connexin43 (Fykerud et al, submitted).



Immunofluorescence confocal microscopy images showing PTEN (green) and β-actin (red) in HCT15 colon cancer cells (left panel), and connexin43 (green) and the E3 ubiquitin ligase Smurf2 (red) in IAR20 liver epithelial cells (right panel).

Cancer cytogenetics group headed by Sverre Heim

Associated with the Danielsen group

Sverre Heim | Photo: Linda Cartridge

The Heim group | Photo: Linda Cartridge

About

This is the research part of the Section for Cancer Cytogenetics which does both clinical and scientific analyses of the acquired chromosome aberrations of neoplastic cells. First we karyotype cultured tumor cells establishing their genomic aberration pattern at the chromosomal level, then we examine changes of particular interest at higher resolution using those molecular techniques that are best suited to the task. We strive for diagnostic and prognostic information based on the karyotypic patterns, information about different tumors' clonal composition, but first and foremost pathogenetic information: Which molecular rearrangements do the cancer-specific chromosomal aberrations correspond to?

Projects

Most of our research takes place within three main projects: 1. Molecular cytogenetic analyses of brain tumors (headed by Heim and Petter Brandal, two PhD-students work with this project). 2. Molecular cytogenetic analyses of gynecologic tumors (headed by Heim and Francesca Micci, one PhD-student works with this project). Most efforts are directed towards the analysis of genomic changes of ovarian carcinomas, especially the chromosome 11- and 19-aberrations that we were first to show characterized these tumors. 3. Detection of new fusion genes caused by novel cancer-specific chromosomal translocations (headed by Heim and Micci, one PhD-student works with this project).

Aims

Ours is a long-term research strategy that has proved fruitful over the years (see list of publications). We intend to stick to our plans, combining the initial use of investigative techniques that provide us with a bird's eye view of the whole genome, with the later use of molecular techniques that allow us a more detailed examination at ever higher resolution levels of those changes that are the most likely to be pathogenetically crucial. An ultimate goal is that the type of new knowledge we generate can eventually be used to generate new specific medications useful for patients suffering from genomically selected subsets of cancer

Sverre Heim
Photo: Marianne Otterdahl-Jensen

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, Institute for Medical Informatics, Section for Cancer Cytogenetics.

Sverre Heim is one of the world's leading experts within cancer cytogenetics with 30 years' experience within this field. He is 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.

The following article was published on the Norwegian Cancer Society's web on the 14th of June, in Norwegian only:

Sverre Heim mottok 14. juni Kong Olav Vs kreftforskningspris 2011. På bildet ser vi Anne Lise Ryel (t.v), H.M Kong Harald, Sverre Heim og Paul Hellandsvik.
Foto: Tobias Barvik.

Kreftforskningsprisen 2011

Professor og overlege Sverre Heim ble i dag tildelt Kong Olav Vs kreftforskningspris. Heim er en av verdens ledende eksperter på kromosomavvik i kreftceller.

Sverre Heim ble tildelt prisen på bakgrunn av sin snart 30 år lange forskning på kromosommønstre i kreftceller. Ved å studere avvik i kromosomer får man ny kunnskap om hvordan ulike kreftformer oppstår. Det gir grunnlag for å utvikle medisiner som virker direkte inn på mekanismene for hvordan sykdommene oppstår. Heim er i dag leder for Seksjon for kreftcytogenetikk ved Oslo Universitetssykehus.

– Heim har vært med på å etablere fagfeltet i Norge, og har utmerket seg på sitt område. Han gjør en stor innsats som forsker, og forskningen hans på kromosomer er banebrytende, sa Paul Hellandsvik, styreleder i Kreftforeningen i sin begrunnelse for hvorfor Heim ble tildelt årets pris.

Prisen ble overrakt Heim av Hans Majestet Kong Harald V. Prisvinneren mottok et beløp på 750 000 kroner, samt et bilde av Tone Dietrichson.

– Jeg er glad og stolt over å motta denne prisen. Jeg setter den svært høyt og det er en ære for meg å få denne utmerkelsen, sa Heim.

Hedrer forskerne for 20. gang

Kong Olav Vs kreftforskningspris deles hvert år ut til en kreftforsker som har bidratt til å fremme den norske kreftforskningens kvalitet og omfang. I år er det 20. gang prisen deles ut. Den har høy prestisje i det norske forskningsmiljøet, og går til det ypperste av det ypperste innen hele spekteret av norsk kreftforskning.

– Vi ønsker å hedre forskerne. Det er derfor vi deler ut denne prisen hvert år. Det er en utmerkelse som betyr at de har gjort en fremragende innsats både i Norge og internasjonalt, sa Anne Lise Ryel, generalsekretær i Kreftforeningen

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. The ceremony took place on Friday, November 11th in the Research Building at The Norwegian Radium Hospital. Raiborg is currently a project leader in Harald Stenmark´s group at the Institute for Cancer Research and Centre for Cancer Biomedicine.

Harald Stenmark and Camilla Raiborg
Photo: Peter Wiedswang

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).

From left: Carl Rieber-Mohn, chairman of the board of the Ragnar Mørk legacy, Harald Stenmark, Camilla Raiborg and Sjur Olsnes
Photo: Peter Wiedswang

Kaisa Haglund | Photo: Øystein Horgmo

Kaisa Haglund awarded prestigious career grant

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 amounts to NOK 2 million per year and runs from April 2012 to March 2016.

CCB director Harald Stenmark elected fellow of European Academy of Cancer Sciences

Harald Stenmark | Photo: Øystein Horgmo

CCB director Harald Stenmark has been elected Fellow of The European Academy of Cancer Sciences in September 2011.

Stenmark is the third scientist from Norway to be included. Hosted under the auspices of ECCO (European CanCer Organisation), the Academy strives for excellence, independence, leadership, diversity and flexibility.

The Academy is a "virtual" body, grouping together representatives with outstanding scientific and academic backgrounds from all cancer disciplines to provide knowledgeable and unbiased advice on matters of policy and priorities at the national, European and global level.

Guro Lind receives Young Researcher award 2011

Guro E. Lind
Photo: Jarle Bruun

CCB congratulates Guro Lind with the Oncological Forum Young Researcher award 2011. The prize was awarded to Guro Lind at the Oncological Forum annual meeting held at Holmenkollen Park Hotel in Oslo in November.

After receiving the prize, Lind presented a plenary lecture about the research that has led to the award. Lind and her colleagues have identified altogether 12 novel epigenetic biomarkers for early detection of colorectal cancer.

Ragnhild A. Lothe
Photo: L. Cartridge

Ragnhild A. Lothe elected to the EACR Council

Co-director Ragnhild A. Lothe was elected to the EACR Council as the National Network Representative for Norway. The term of office as 'National Network' representative is four years.






Photos: Linda Cartridge and Øystein Horgmo

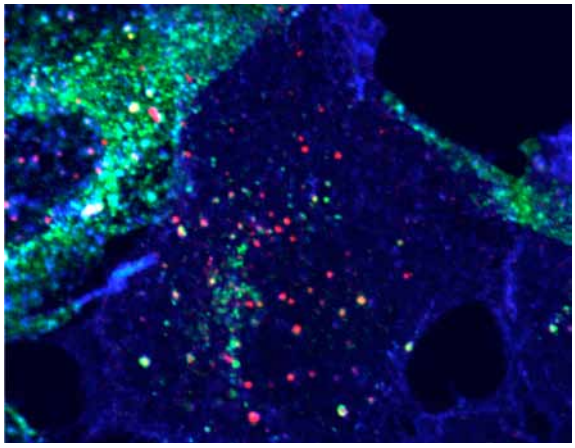
Fibroblast growth factor receptors go their own ways

FGF receptors (FGFRs) are attractive drug targets in many types of cancers and it is important to understand in detail their mechanisms of action. In particular, it is important to elucidate how their proliferative signalling is down-regulated.

Researchers from several CCB groups teamed up to study the precise endocytic internalization mechanisms of FGFRs. The internalization of FGFRs leads to degradation of the receptors and termination of their signalling. Investigators from Wiedlocha's group (Ellen M. Haugsten, Malgorzata Zakrzewska, Sjur Olsnes and Jørgen Wesche) collaborated with Sascha Pust and Kirsten Sandvig (from the Sandvig-group), who contributed with expertise on clathrin-independent endocytosis. Andreas Brech (Stenmark-group) added his knowledge on ultrastructural investigations.

The main result from the study is that while FGFR1 is taken up by classical clathrin-mediated endocytosis, another FGF receptor, FGFR3, is internalized by a new previously uncharacterised pathway. Notably, clathrin, dynamin and several other molecules involved in endocytosis did not block FGFR3 internalization. This might have consequences for how to target the different FGFRs for therapy.

Haugsten EM, Zakrzewska M, Brech A, Pust S, Olsnes S, Sandvig K, Wesche J. (2011) **Clathrin- and dynamin-independent endocytosis of FGFR3-implications for signalling** PLoS One. 6(7):e21708.

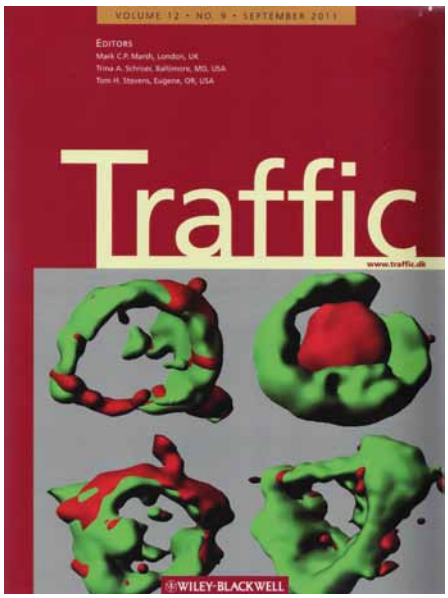


In cells where clathrin (in green) is depleted, Transferrin (in blue), which is dependent on clathrin for internalization is seen on the cell-surface. FGFR3/FGF1 (red dots), however, is detected intracellularly showing that they are endocytosed even when clathrin is not present.

Cover story in Traffic: ESCRT degradation in control of cell signalling

The endosomal sorting complex required for transport (ESCRT) machinery is well known for its role in ligand-dependent degradation of growth factor receptors, as studied extensively by CCB researchers. Now, CCB researchers have joined forces to unravel an unexpected twist in ESCRT regulation of receptor signalling. Cell biologists in Harald Stenmark's group (Lene Malerød, Nina Marie Pedersen, Catherine Sem Wegner, Viola Lobert and Andreas Brech) performed light and electron microscopic studies of epidermal growth factor (EGF) receptors that were endocytosed and degraded in cells in response to EGF. Edward Leithe in Edgar Rivedal's group contributed with his expertise on another membrane protein, the gap junction protein Connexin43, and biostatistician Knut Liestøl helped analyzing the complex imaging data. Together, the CCB scientists discovered that engagement of the ESCRT machinery leads to lysosomal degradation of a component of this machinery, and that EGF stimulation not only causes degradation of EGF receptors but at the same time prevents degradation of Connexin43 (and vice versa). This novel mechanism of negative feedback was dedicated the cover of *Traffic*.

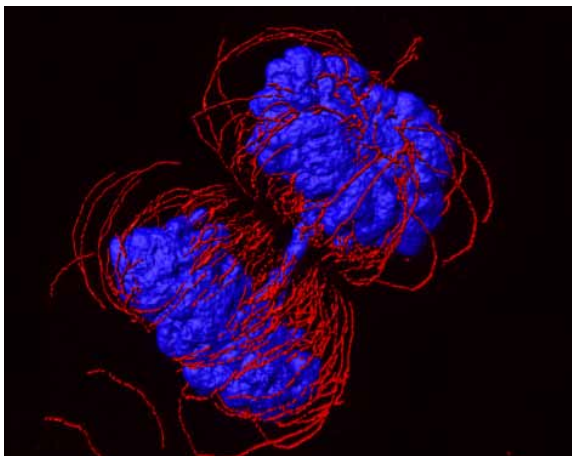
Malerød L, Pedersen NM, Sem Wegner CE, Hélène Lobert V, Leithe E, Brech A, Rivedal E, Liestøl K, Stenmark H. (2011) **Cargo-Dependent Degradation of ESCRT-I as a Feedback Mechanism to Modulate Endosomal Sorting** Traffic. 12(9):1211-26.



It takes FYVE-CENT to suppress tumours

As a continuation of a previous CCB collaboration, cell biologists and translational cancer scientists in CCB have proceeded to develop the concept that correct control of cytokinesis (the final stage of the cell division process) is important in order to prevent tumourigenesis. Antonia Sagona, Ioannis Nezis, Kristi Bache and Kaisa Haglund in Harald Stenmark's lab found that the cytokinesis regulator, FYVE-CENT, interacts with a well-known tumour suppressor, Beclin 1, and that a cancer-associated mutation in FYVE-CENT prevents this interaction. Anne-Cathrine Bakken in Rolf Skotheim's group used DNA sequencing to show that a cell line derived from breast cancer, HCC-1954, contains almost exclusively the mutant form of FYVE-CENT, and the cell biologists demonstrated that this cell line has impaired cytokinesis and a predominant binuclear phenotype. Rolf Skotheim analyzed expression data from breast cancers and found that FYVE-CENT and its associated proteins are downregulated in high versus low-grade breast cancers, which is consistent with the possibility that FYVE-CENT is a tumour suppressor. Collectively, these data suggest that FYVE-CENT and Beclin 1 function together to mediate correct cytokinesis, and that disturbing this function may promote tumourigenesis.

Sagona AP, Nezis IP, Bache KG, Haglund K, Bakken AC, Skotheim RI, Stenmark H. (2011) **A tumor-associated mutation of FYVE-CENT prevents its interaction with Beclin 1 and interferes with cytokinesis** PLoS One. 6(3):e17086.



Two daughter cells resulting from cell division, as imaged by super-resolution microscopy. DNA is stained in blue and microtubules in red. Image courtesy of Ellen Skarpen and Kay Schink.

Clinical study raises new hope for patients with rare lymphoma

The lymphoma milieu in CCB is together with the rest of the lymphoma milieu at the hospital involved in extensive national and international collaboration. Researchers from CCB (Marianne B. Eide, Knut Liestøl and CCB associate clinician Harald Holte collaborated with several other persons from the lymphoma milieu at Oslo University Hospital (J. Delabie, G. Lauritzen, G. Kvalheim, A. Kolstad and B. Østenstad) and other national collaborators in a national collaborative clinical phase II study examining the effects of high-dose therapy in transformed Follicular Lymphoma to Diffuse Large B-cell Lymphoma. This is the first prospective study in this group of patients, which traditionally have a dismal prognosis. The study indicates that a treatment programme including high dose therapy is beneficial for chemosensitive patients compared to previous reports of CHOP based treatment for transformed B-cell lymphomas. In spite of the intensified treatment, there was no treatment-related mortality. The study comprises a relatively large number of patients in a relatively rare condition, and the included patients represent a population-based and unselected patient cohort. Material collected through this study will be used for several follow-up studies of biological processes involved in histological transformation in collaboration with other CCB groups and the Department of Pathology.

Eide MB, Lauritzsen GF, Kvalheim G, Kolstad A, Fagerli UM, Maisenhölder M, Østenstad B, Fluge Ø, Delabie J, Aarset H, Liestøl K, Holte H. (2011) **High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norwegian multi centre phase II study** Br J Haematol. 152(5):600-10.

CLINICAL ASSOCIATES VALUE COLLABORATION WITH CCB

Harald Holte

Harald Holte MD, PhD, Senior Consultant, Department of Medical Oncology and Radiotherapy, Oslo University Hospital

Although cancer pathogenesis and - biology is complicated, the knowledge is expanding rapidly and medical treatment with increased efficacy and less side effects is evolving. Understanding mechanisms of proliferation, apoptosis and cell signaling in cancer cells is challenging for a clinician. At the same time it is becoming increasingly important as treatment today and for the future take advantage of knowledge learned from molecular biology studies during the last 20 years. One aim for clinical units at our University Hospital is to deliver treatment at a high international level. Collaboration with CCB at our Institute for Cancer Research is of high importance to reach this goal.

The Lymphoma Program has for more than 30 years a fruitful collaboration with the Institute for Cancer Research, most of all Department of Immunology. From that time, and in collaboration with Department of Pathology, we have developed a tumor biobank with frozen tissue, tumor cell suspensions and paraffin embedded tissue. In addition, we have built up a clinical database with detailed clinical information of great value for translational research. The clinical Lymphoma Program has today collaboration with several groups at CCB, hopefully of value not only from a clinical point of view, but also for CCB.

Karol Axcrona

Karol Axcrona, MD, PhD, Consultant, Department of Urology, The Norwegian Radium Hospital, Oslo University Hospital

Urologic cancer accounts for 25% of all new cancer diagnosed each year. Prostate cancer is the most diagnosed cancer in Norway accounting for more than 4.400 new cases in 2008. A substantial proportion of patients with prostate cancer never develop clinical threatening disease - while radical treatment has side effects. The diagnosis of prostate cancer also imposes the patients and their families an uncertainty and anxiety being diagnosed with prostate cancer. Radical treatment gives side effects, which the patients have to live with for many years and affecting their quality of life.

We believe that molecular biological approaches will be necessary to deepen understanding of biological behavior and development of prostate cancer. Those studies - especially the composition of genes, and their expression, will be giving answers on which cancers are indolent, not giving rise to life threatening disease, and thus will not be necessary to treat but to observe. On the other hand, we believe that deepened molecular biological understanding of prostate cancer will give us ideas of how tailored cancer treatment can be delivered to the patients in need. Past and present collaboration with the Department of Pathology, and Ragnhild Lothe, Håvard Danielsen and Rolf Skotheim at the CCB is crucial to reach the above-mentioned goals.

Arild Nesbakken

Arild Nesbakken, Professor, MD, Senior Consultant, Department of Gastrointestinal Surgery, Oslo University Hospital

In 1993 we started a clinical research program on colorectal cancer and all (consecutive) patients from a defined catchment area were included. Comprehensive data sets were registered prospectively, including perioperative diagnostics, treatment, short term outcome and histopathology results, and long term outcome was registered during five year follow-up. The focus was mainly on prognostic factors for recurrence and death of cancer, but many other aspects have been studied.

Some 10 years later we gradually realized that molecular biology was important in the understanding of colorectal cancer, and that biomarkers could become essential in diagnostics and treatment of the disease. Clinicians therefore needed to build competence in this field. We also recognized that our large patient series with good clinical data were ideal for translational research. In 2005 a fruitful cooperation with Ragnhild A. Lothe and Håvard Danielsen groups started, and our biobank now contains TMA from 1500+ patients, fresh frozen tumor tissue from 500+ patients, and lately blood and stool has also been sampled.

The cooperation with CCB has been excellent and is expanding, and very promising and clinically important scientific results have been achieved regarding diagnostics, prognostication and prediction of response to therapy. The true translational aspects are demonstrated, and through close collaboration, fruitful discussions and exchange of knowledge, the biology researchers show impressive understanding of the clinical aspects of the disease, and the clinicians gradually build competence in molecular biology for the benefit of patients.

CCB Seminars 2011

January 27:

Poster Seminar – Presentation of ongoing CCB projects
During this event CCB gave a broad presentation of its ongoing research projects by showing 66 posters grouped in 4 categories: Biomarkers in cancer, Cell signaling in cancer, Genomics, epigenomics and proteomics, and Bioinformatics and imaging tools for cancer research.

CCB had the pleasure to invite colleagues from the Institute for Cancer Research and from the Division of Surgery and Cancer Medicine at the Norwegian Radium Hospital to join in for scientific discussions followed by social gathering, tapas and wine.

June 14:

Transcriptome instability in colorectal cancer identified by exon microarray analyses
Anita Sveen, PhD student – CCB and Department of Cancer Prevention, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital.

ZFYVE9/SARA has a role in EGF receptor trafficking, but is not essential in TGF-βsignaling
Morten Oksvold, Postdoc, PhD – CCB and Department of Immunology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital.

June 29:

Signaling via receptors for PDGF and TGF-beta – possible targets in tumor therapy
Professor Carl-Henrik Heldin - Director and Professor in Molecular Cell Biology, Ludwig Institute for Cancer Research, and Vice-President in the European Research Council.

September 1-2:

The annual CCB seminar 2011
Again this year, the annual seminar in CCB was arranged at Hotel Leangkollen in Asker. More than hundred CCB members participated in this two day event where scientific presentations and discussions as well as social gathering were the focus of attention. This year's seminar was opened with a celebration speech by Harald Stenmark to highlight the excellent results of CCB's Midterm Evaluation. The annual get-together is certainly of great importance, and it is the perfect way to boost the common CCB spirit.

September 12:

Discovery of Endophagy, an Early Endosomal Protein-Associated Mode of Mitochondrial Clearance Operating during Apoptosis
Dr. Nathan Brady - German Cancer Research Center, Heidelberg.

October 25:

Malignancy in pluripotency: Transcriptional studies in embryonal carcinomas and embryonic stem cells
Sharmini Alagaratnam, Postdoc, PhD – CCB and Department of Cancer Prevention, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital.

November 24:

Integrin trafficking and cancer invasion
Professor Jim C. Norman - Beatson Institute for Cancer Research, Glasgow, Scotland.

December 13:

Production of phosphatidylinositol 5-phosphate via PIKfyve and MTMR3 regulates cell migration
Angela Oppelt, PhD student – CCB and Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital.

Tracking of phosphoinositide dynamics during cell division
Kay Oliver Schink, Postdoc, PhD – Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital.

All CCB seminars are open to the Institute for Cancer Research and the Division of Cancer Medicine, Surgery and Transplantation, and to all other colleagues within our fields of research at the Oslo University Hospital and the University of Oslo.

DEGREES

PhD degrees 2011

Stine Aske Danielsen, PhD – Molecular markers of colorectal cancer and their clinical potential
Faculty of Medicine, University of Oslo, November 2011

Kanutte Huse, PhD – The role of bone morphogenetic proteins in normal and malignant lymphocytes
Faculty of Medicine, University of Oslo, June 2011

Lina Rodahl, PhD – Regulators of endosome dynamics in cell signalling and disease
Faculty of Medicine, University of Oslo, June 2011

Solveig Sirnes, PhD – The connexin gene family in cell communication and cancer
Faculty of Medicine, University of Oslo, April 2011

Master degrees 2011

Bjarne Johannessen, M.Sc. in Molecular Biosciences - Identification of cancer-specific transcripts by computational analysis of genome scale expression data at exon resolution
Faculty of Mathematics and Natural Sciences, University of Oslo, December 2011

Hege Marie Vedeld, M.Sc. in Molecular Biosciences - DNA methylation biomarkers for colorectal cancer detection: CDO1, DCLK1, ZNF331 and ZSCAN18
Faculty of Mathematics and Natural Sciences, University of Oslo, December 2011

Andreas Kleppe, M.Sc. in Informatics, Image analysis - Prognostics from adaptive spatial entropy in early ovarian cancer cell nuclei
Faculty of Mathematics and Natural Sciences, University of Oslo, June 2011

Peter Eide, M.Sc. in Molecular Biosciences – HECT E3 ubiquituin ligases in regulation of colon cancer cell growth and mitogenic signaling pathways
Faculty of Mathematics and Natural Sciences, University of Oslo, June 2011

Andreas Hoff, M.Sc. in Molecular Biosciences – Transcript variation and protein expression in testicular germ cell tumours
Faculty of Mathematics and Natural Sciences, University of Oslo, June 2011

Carl-Martin Nymark, M.Sc. in Molecular Biosciences – Cell context-dependent differences in interaction with Shiga toxin
Faculty of Mathematics and Natural Sciences, University of Oslo, June 2011

Simona Lukoseviciute, M.Sc. in Molecular Biosciences – The regulation of Gb3 biosynthesis in cancer cells: Implications for membrane dynamics
Faculty of Mathematics and Natural Sciences, University of Oslo, June 2011

Audun Sverre Kvalvaag, M.Sc. in Molecular Biosciences – The role of ERM proteins in binding and intracellular transport of Shiga toxin
Faculty of Mathematics and Natural Sciences, University of Oslo, February 2011

VISITORS TO CCB

Visitors to CCB in 2011:

Hosted at Ragnhild A. Lothe's lab:

Ricardo Celestino, PhD student from the University of Porto, Portugal
October 2011 (1 month)

Diogo Silva, PhD student from the Portuguese Oncology Institute, Portugal
From August to October 2011 (1,5 months)

Hosted at Kirsten Sandvig's lab:

Minna Kihlstrøm, Master student from the University of Oulu, Finland
From June to December 2011 (6,5 months)

Hosted at Harald Stenmark's lab:

Anders Sundan, Professor, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway
From February to December 2011 (total of 1 month)

Katarzyna Pielaszkiewicz, Master student from the University of Poznan, ERASMUS, Poland
From January to June 2011 (5,5 months)

Hosted at Antoni Wiedlocha's lab:

Michal Kostas, PhD student from the University of Wroclaw, Poland
December 2011 (3 weeks)

EDUCATIONAL ACTIVITIES

Courses:

MBV3020: Molecular Genetics and Developmental Biology
Faculty of Mathematics and Natural Sciences, University of Oslo, Autumn 2011.
Course responsible: Fahri Saatcioglu
Section responsible - Cancer Biology and Cell Cycle: Ragnhild A. Lothe
Lecturers from CCB: Ragnhild A. Lothe, Edward Leithe, Guro E. Lind, Edgar Rivedal, Rolf Skotheim

MBV 4320: Advanced Physiology and Cell Biology
Faculty of Mathematics and Natural Sciences, University of Oslo, Spring 2011.
Lecturer from CCB: Kirsten Sandvig

MBV 4150: Molecular Biology of Microbes-Host Interactions
Faculty of Mathematics and Natural Sciences, University of Oslo, Spring 2011.
Lecturer from CCB: Kirsten Sandvig

MBV4240/9240: Biochemical Mechanisms in Intracellular Transport
Faculty of Mathematics and Natural Sciences, University of Oslo, Autumn 2011.
Course responsible: Kirsten Sandvig
Lecturers from CCB: Kirsten Sandvig, Antoni Wiedlocha, Harald Stenmark

MBV9100 BTS: PhD school, Molecular Biology Research Course
Biotechnology Centre of Oslo, University of Oslo, Autumn 2011.
Lecturer from CCB: June H. Myklebust, Rolf Skotheim

MF9170: Flow Cytometry in Medical Research and Diagnostics
Faculty of Medicine, University of Oslo, Spring and Autumn 2011.
Lecturer from CCB: June H. Myklebust

MF9410: Principles of Stem Cell Biology
Faculty of Medicine, University of Oslo, Autumn 2011.
Lecturer from CCB: Rolf Skotheim

MOL8006: Receptor Signalling and Trafficking
Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Spring 2011.
Course responsible: Harald Stenmark
Lecturers from CCB: Harald Stenmark, Hilde Abrahamsen, Jørgen Wesche, Tor Erik Rusten

INF4350: Basic Course in Bioinformatics
Faculty of Mathematics and Natural Sciences, University of Oslo, Autumn 2011.
Lecturer from CCB: Ole Christian Lingjærde

BIO4530: Regulatory Toxicology
Faculty of Mathematics and Natural Sciences, University of Oslo, Spring 2011.
Lecturer from CCB: Edgar Rivedal

BM0730: Flow Cytometry for Intracellular Targets - Hands on Phosphoflow Workshop
University of Bergen and CANGENIN/COST Action, Autumn 2011.
Lecturer from CCB: June H. Myklebust

Advanced Flow Cytometry Course
Oslo University Hospital, Autumn 2011.
Course responsible: June H. Myklebust
Lecturer from CCB: June H. Myklebust

PBL Course, 9th term, Gynecology, Obstetrics, and Pediatrics
Faculty of Medicine, University of Oslo, Spring and Autumn 2011.
Lecturer from CCB: Sverre Heim

Inter-Facultary CCB Course in Advanced Cancer Biology

MBV4160/9160: Advanced Cancer Biology
Department of Molecular Biosciences, Faculty of Mathematics and Natural Sciences, University of Oslo, Spring 2011.
Course responsible: Guro E. Lind (leader, ass. prof.) and Ragnhild A. Lothe (prof II)

Spring 2011 a CCB associated course in advanced cancer biology was offered to master and PhD students at the Department of Molecular Biosciences (IMBV), the Faculty of Mathematics and Natural Sciences, and to PhD students at the Medical Faculty. The course is initiated and designed by Guro E. Lind and Ragnhild A. Lothe and provides the students with a comprehensive insight into the molecular biology of cancer and awareness of the complexity in cancer-biology and -medicine.

The vast majority of lectures in the course were provided by Lind and other CCB members, Edgar Rivedal, Matthias Kolberg, Sharmini Alagaratnam, Edward Leithe, Hilde Abrahamsen, Trude Ågesen, June Myklebust, Alicia Llorente, Karol Axcrona, Ole-Christian Lingjærde, Gard O. Thomassen, Anita Sveen, Kay Schink, Nina Marie Pedersen, Tor Erik Rusten, Annette B. Håvik, Morten Oksvold, Tore Geir Iversen and Rolf Skotheim. Additional contributors were: Ian Mills, Alexander Fosså, Beata Grallert, Pål Selbo, and Randi Syljuåsen.

The students acquired an in depth understanding of the underlying biology and clinical challenges of selected diseases studied at the centre, and were also invited for a two-day site visit. The CCB members demonstrated advanced instruments and methodologies such as high throughput sequencing and discussed the technological challenges and opportunities for cancer biomedicine with the students. In addition to the lectures and site visits, Lind gave the students an opportunity to improve their ability to obtain, process and present essential scientific literature through an oral presentation and a short written essay, both rewarded with personal feed back.

17 master and 5 PhD students completed the course in 2011, including Bjarne Johannssen, Ina A. Eilertsen, Chloé B. Steen, and Jonas Bergan from CCB.

Bjarne Johannessen
PhD student:
“Great class. Informative and well organized.”

Ina A. Eilertsen
Master student:
“The course has inspired me in my work as a graduate student and to continue research in the field of cancer”

Photo: Jarle Bruun

CCB Stand at Oslo Science Fair

On Friday the 23rd and Saturday the 24th of September 2011, CCB presented the stand "New knowledge about Cancer" at the annual Oslo Science Fair. The fair had altogether 15 stands and was located on Karl Johan's street in downtown Oslo.

The stand was an initiative from the CCB co-director Ragnhild A. Lothe and was organized by Guro E. Lind.

More than 20 dedicated members of the CCB participated in planning and setting up the stand as well as in meeting the public.

Colorectal cancer, which is one of the focus areas of the CCB, was used as a theme throughout the stand. The public was offered insight into how CCB research and technological advances can benefit patients not only by allowing earlier detection of cancer, which results in higher rates of survival, but also by ensuring that patients get better optimized treatment. To bring this message across, a series of informative posters were presented, describing a patient's experience of colorectal cancer as it is today, as it would be tomorrow and finally as it may be in the future, with tailor-made, personalized treatment options for each individual. Visitors could also find posters with a "Did you know…" series of facts about colorectal cancer as well as a collection of press cuttings about the CCB from 2009 and 2010.

In addition to the posters a number of hands-on activities were available to the public, including using iPads to zoom in on high resolution images of tumour cells, and looking into the microscope to observe cancer cells in culture. Videos of an operation on a cancer patient, a colonoscopy and cell division in normal and cancerous cells were shown on a widescreen. Eager visitors could also participate in a pipetting competition, which turned out to be very popular. Participants were awarded apples and plastic test tubes with CCB stickers in them. When leaving the stand visitors could bring with them a pamphlet with background information on colorectal cancer and the research carried out at the CCB. The stand was visited by all age groups, and attracted interest from both school kids and the general public.

Photos: Jarle Bruun

Total number of CCB publications in 2011: ..... 71 publications

Number of publications in high impact journals (impact factor > 9): ..... 12 publications (17%)

Number of publications with CCB scientists as corresponding author: ..... 44 publications (62%)

Number of collaboration publications with clinicians and pathologists: ..... 34 publications (48%)

Number of publications with international partners: ..... 22 publications (31%)

Publications 2011:

Abrahamsen H, Stenmark H. (2011) **Cell biology. Growth signaling from inside** Science. 334(6056):611-2.

Ahmed D, Lothe RA, Rivedal E, Lind GE. (2011) **Quantitative validation of GJC1 promoter hypermethylation in benign and malignant colorectal tumours** Endocr Relat Cancer. 18(6):C31-4.

Alagaratnam S, Lind GE, Kraggerud SM, Lothe RA, Skotheim RI. (2011) **The testicular germ cell tumour transcriptome** Int J Androl. 34(4 Pt 2):e133-50; discussion e150-1.

Alizadeh AA, Gentles AJ, Alencar AJ, Liu CL, Kohrt HE, Houot R, Goldstein MJ, Zhao S, Natkunam Y, Advani RH, Gascoyne RD, Briones J, Tibshirani RJ, Myklebust JH, Plevritis SK, Lossos IS, Levy R. (2011) **Prediction of survival in diffuse large B-cell lymphoma based on the expression of 2 genes reflecting tumor and microenvironment** Blood. 118(5):1350-8.

Andersen MK, Autio K, Barbany G, Borgström G, Cavelier L, Golovleva I, Heim S, Heinonen K, Hovland R, Johannsson JH, Johansson B, Kjeldsen E, Nordgren A, Palmqvist L, Forestier E. (2011) **Paediatric B-cell precursor acute lymphoblastic leukaemia with t(1;19)(q23;p13): clinical and cytogenetic characteristics of 47 cases from the Nordic countries treated according to NOPHO protocols** Br J Haematol. 155(2):235-43.

Bartlett BJ, Isakson P, Lewerenz J, Sanchez H, Kotzebue RW, Cumming RC, Harris GL, Nezis IP, Schubert DR, Simonsen A, Finley KD. (2011) **p62, Ref(2)P and ubiquitinated proteins are conserved markers of neuronal aging, aggregate formation and progressive autophagic defects** Autophagy. 7(6):572-83.

Berge G, Costea DE, Berg M, Rasmussen H, Grotterød I, Lothe RA, Mælandsmo GM, Flatmark K. (2011) **Coexpression and nuclear colocalization of metastasis-promoting protein S100A4 and p53 without mutual regulation in colorectal carcinoma** Amino Acids 41(4):875-84.

Boberg KM, Lind GE. (2011) **Primary sclerosing cholangitis and malignancy** Best Pract Res Clin Gastroenterol. 25(6):753-64.

Cordara G, Egge-Jacobsen W, Winter HC, Goldstein IJ, Sandvig K, Krengel U. (2011) **Marasmius oreades agglutinin (MOA) is a chimerolectin with proteolytic activity** Biochem Biophys Res Commun. 408(3):405-10.

Costa VL, Henrique R, Danielsen SA, Eknaes M, Patrício P, Morais A, Oliveira J, Lothe RA, Teixeira MR, Lind GE, Jerónimo C. (2011) **TCF21 and PCDH17 methylation: An innovative panel of biomarkers for a simultaneous detection of urological cancers** Epigenetics. 6(9).

Dahlback HS, Brandal P, Gorunova L, Widing E, Meling TR, Krossnes BK, Heim S. (2011) **Genomic aberrations in pediatric gliomas and embryonal tumors** Genes Chromosomes Cancer. 50(10):788-99.

Dahlback HS, Brandal P, Krossnes BK, Fric R, Meling TR, Meza-Zepeda LA, Danielsen HE, Heim S. (2011) **Multiple chromosomal monosomies are characteristic of giant cell ependymoma** Hum Pathol. 42(12):2042-6.

Dahlback HS, Gorunova L, Brandal P, Scheie D, Helseth E, Meling TR, Heim S. (2011) **Genomic aberrations in diffuse low-grade gliomas** Genes Chromosomes Cancer. 50(6):409-20.

Dahlback HS, Gorunova L, Micci F, Scheie D, Brandal P, Meling TR, Heim S. (2011) **Molecular cytogenetic analysis of a gliosarcoma with osseous metaplasia** Cytogenet Genome Res. 134(2):88-95.

Dang H, Klokk TI, Schaheen B, McLaughlin BM, Thomas AJ, Durns TA, Bitler BG, Sandvig K, Fares H. (2011) **Derlin-dependent retrograde transport from endosomes to the Golgi apparatus** Traffic. 12(10):1417-1431.

Danielsen H, Maddison JR. (2011) **A simple multiplatform virtual slide imaging system, supporting Mac, PC and mobile devices to enable widespread telepathology** In: iPhone & 4G mobile phones in telemedicine, Catai 2011, ISBN: 978-84-614-5997-1.

Danielsen SA, Cekaite L, Ågesen TH, Sveen A, Nesbakken A, Thiis-Evensen E, Skotheim RI, Lind GE, Lothe RA. (2011) **Phospholipase C isozymes are deregulated in colorectal cancer - insights gained from gene set enrichment analysis of the transcriptome** PLoS One. 6(9):e24419.

Dunn JM, Hveem T, Pretorius M, Oukrif D, Nielsen B, Albregtsen F, Lovat LB, Novelli MR, Danielsen HE. (2011) **Comparison of nuclear texture analysis and image cytometric DNA analysis for the assessment of dysplasia in Barrett's oesophagus** Br J Cancer. 105(8):1218-23.

Eide MB, Lauritzsen GF, Kvalheim G, Kolstad A, Fagerli UM, Maisenhölder M, Østenstad B, Fluge Ø, Delabie J, Aarset H, Liestøl K, Holte H. (2011) **High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norwegian multi centre phase II study** Br J Haematol. 152(5):600-10.

Engedal N, Skotland T, Torgersen ML, Sandvig K. (2011) **Shiga toxin and its use in targeted cancer therapy and imaging** Microb Biotechnol. 4(1):32-46.

Gorunova L, Bjerkehagen B, Heim S. (2011) **Paratesticular leiomyoma with a der(14)t(12;14)(q15;q24)** Cancer Genet. 204(8):465-8.

Haglund K, Nezis IP, Stenmark H. (2011) **Structure and functions of stable intercellular bridges formed by incomplete cytokinesis during development** Commun Integr Biol. 4(1):1-9.

Haugsten EM, Zakrzewska M, Brech A, Pust S, Olsnes S, Sandvig K, Wesche J. (2011) **Clathrin- and dynamin-independent endocytosis of FGFR3-implications for signalling** PLoS One. 6(7):e21708.

Huse K, Bakkebø M, Oksvold MP, Forfang L, Hilden VI, Stokke T, Smeland EB, Myklebust JH. (2011) **Bone morphogenetic proteins inhibit CD40L/IL-21-induced Ig production in human B cells: differential effects of BMP-6 and BMP-7** Eur J Immunol. 41(11):3135-45.

Haakensen VD, Lingjaerde OC, Lüders T, Riis M, Prat A, Troester MA, Holmen MM, Frantzen JO, Romundstad L, Navjord D, Bukholm IK, Johannesen TB, Perou CM, Ursin G, Kristensen VN, Børresen-Dale AL, Helland A. (2011) **Gene expression profiles of breast biopsies from healthy women identify a group with claudin-low features** BMC Med Genomics. 4:77.

Hurley JH, Stenmark H. (2011) **Molecular mechanisms of ubiquitin-dependent membrane traffic** Annu Rev Biophys. 40:119-42.

Iversen TG, Skotland T, Sandvig K. (2011) **Endocytosis and intracellular transport of nanoparticles: Present knowledge and need for future studies** Nano Today. 6(2):176-185.

Jin Y, Zhen Y, Haugsten EM, Wiedlocha A. (2011) **The driver of malignancy in KG-1a leukemic cells, FGFR1OP2-FGFR1, encodes an HSP90 addicted oncoprotein** Cell Signal. 23(11):1758-66.

Josefsen D, Forfang L, Dyrhaug M, Blystad AK, Stokke T, Smeland EB, Kvalheim G. (2011) **Side population cells in highly enriched CD34-positive cells from peripheral blood progenitor cells identify an immature subtype of hematopoietic progenitor cells but do not predict time to engraftment in patients treated with high-dose therapy** Eur J Haematol. 87(6):494-502.

Klokk TI, Lingelem AB, Myrann AG, Sandvig K. (2011) **Role of phospholipase a(2) in retrograde transport of ricin** Toxins. 3(9):1203-19.

Kyriazoglou AI, Dimitriadis E, Arnogiannaki N, Brandal P, Heim S, Pandis N. (2011) **Similar cytogenetic findings in two synchronous secondary peripheral chondrosarcomas in a patient with multiple osteochondromas** Cancer Genet. 204(12):677-81.

Lind GE, Danielsen SA, Ahlquist T, Merok MA, Andresen K, Skotheim RI, Hektoen M, Rognum TO, Meling GI, Hoff G, Bretthauer M, Thiis-Evensen E, Nesbakken A, Lothe RA. (2011) **Identification of an epigenetic biomarker panel with high sensitivity and specificity for colorectal cancer and adenomas** Mol Cancer. 10:85.

Lind GE, Raiborg C, Danielsen SA, Rognum TO, Thiis-Evensen E, Hoff G, Nesbakken A, Stenmark H, Lothe RA. (2011) **SPG20, a novel biomarker for early detection of colorectal cancer, encodes a regulator of cytokinesis** Oncogene. 30(37):3967-78.

Lobert VH, Stenmark H. (2011) **Cell polarity and migration: emerging role for the endosomal sorting machinery** Physiology (Bethesda). 26(3):171-80. Review.

Løvf M, Thomassen GO, Bakken AC, Celestino R, Fioretos T, Lind GE, Lothe RA, Skotheim RI. (2011) **Fusion gene microarray reveals cancer type-specificity among fusion genes** Genes Chromosomes Cancer. 50(5):348-57.

Malerød L, Pedersen NM, Sem Wegner CE, Hélène Lobert V, Leithe E, Brech A, Rivedal E, Liestøl K, Stenmark H. (2011) **Cargo-Dependent Degradation of ESCRT-I as a Feedback Mechanism to Modulate Endosomal Sorting** Traffic. 12(9):1211-26.

Malumbres R, Fresquet V, Roman-Gomez J, Bobadilla M, Robles EF, Altobelli GG, Calasanz MJ, Smeland EB, Aznar MA, Agirre X, Martin-Palanco V, Prosper F, Lossos IS, Martinez-Climent JA. (2011) **LMO2 expression reflects the different stages of blast maturation and genetic features in B-cell acute lymphoblastic leukemia and predicts clinical outcome** Haematologica. 96(7):980-6.

Micci F, Thorsen J, Haugom L, Zeller B, Tierens A, Heim S. (2011) **Translocation t(1;16)(p31;q24) rearranging CBFA2T3 is specific for acute erythroid leukemia** Leukemia. 25(9):1510-2.

Mollerup S, Hofgaard JP, Braunstein TH, Kjenseth A, Leithe E, Rivedal E, Holstein-Rathlou NH, Nielsen MS. (2011) **Norepinephrine inhibits intercellular coupling in rat cardiomyocytes by ubiquitination of connexin43 gap junctions** Cell Commun Adhes. 18(4):57-65.

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.

Nyquist KB, Thorsen J, Zeller B, Haaland A, Trøen G, Heim S, Micci F. (2011) **Identification of the TAF15-ZNF384 fusion gene in two new cases of acute lymphoblastic leukemia with a t(12;17)(p13;q12)** Cancer Genet. 204(3):147-52.

Ohnstad HO, Paulsen EB, Noordhuis P, Berg M, Lothe RA, Vassilev LT, Myklebost O. (2011) **MDM2 antagonist Nutlin-3a potentiates antitumour activity of cytotoxic drugs in sarcoma cell lines** BMC Cancer. 11:211:1-11.

Platta HW, Stenmark H. (2011) **Endocytosis and signaling** Curr Opin Cell Biol. 23(4):393-403.

Raiborg C, Stenmark H. (2011) **Cell biology. A helix for the final cut** Science. 331(6024):1533-4.

Randen U, Yri OE, Tierens A, Heim S, Beiske K, Delabie J. (2011) **Mantle cell lymphoma with features of marginal-zone lymphoma** J Hematopathol. 4:7–11.

Rønning SB, Pedersen NM, Madshus IH, Stang E. (2011) **CIN85 regulates ubiquitination and degradative endosomal sorting of the EGF receptor** Exp Cell Res. 317(13):1804-16.

Ribeiro FR, Paulo P, Costa VL, Barros-Silva JD, Ramalho-Carvalho J, Jerónimo C, Henrique R, Lind GE, Skotheim RI, Lothe RA, Teixeira MR. (2011) **Cysteine-Rich Secretory Protein-3 (CRISP3) is strongly up-regulated in prostate carcinomas with the TMPRSS2-ERG fusion gene** PLoS One. 6(7):e22317.

Rusten TE, Vaccari T, Stenmark H. (2011) **Shaping development with ESCRTs.** Nat Cell Biol. 14(1):38-45.

Sagona AP, Nezis IP, Bache KG, Haglund K, Bakken AC, Skotheim RI, Stenmark H. (2011) **A tumor-associated mutation of FYVE-CENT prevents its interaction with Beclin 1 and interferes with cytokinesis** PLoS One. 6(3):e17086.

Sandve GK, Gundersen S, Rydbeck H, Glad IK, Holden L, Holden M, Liestøl K, Clancy T, Drabløs F, Ferkingstad E, Johansen M, Nygaard V, Tøstesen E, Frigessi A, Hovig E. (2011) **The differential disease regulome** BMC Genomics. 12:353.

Sandvig K, Pust S, Skotland T, van Deurs B. (2011) **Clathrin-independent endocytosis: Mechanisms and function** Curr. Opin. Cell Biol. 23(4):413-20.

Schink KO, Stenmark H. (2011) **Cell differentiation: midbody remnants – junk or fate factors?** Curr Biol. 21(23):R958-60.

Shahzidi S, Cunderlíková B, Wiкdłocha A, Zhen Y, Vasovik V, Nesland JM, Peng Q. (2011) **Simultaneously targeting mitochondria and endoplasmic reticulum by photodynamic therapy induces apoptosis in human lymphoma cells** Photochem Photobiol Sci. 10(11):1773-82.

Sirnes S, Honne H, Ahmed D, Danielsen SA, Rognum TO, Meling GI, Leithe E, Rivedal E, Lothe RA, Lind GE. (2011) **DNA methylation analyses of the connexin gene family reveal silencing of GJC1 (Connexin45) by promoter hypermethylation in colorectal cancer** Epigenetics. 6(5):602-9.

Sjo OH, Berg M, Merok MA, Kolberg M, Svindland A, Lothe RA, Nesbakken A. (2011) **Peritoneal carcinomatosis of colon cancer origin: Highest incidence in women and in patients with right-sided tumors** J Surg Oncol. 104(7):792-7.

Skotland T, Iversen TG, Sandvig K. (2011) **Comment on "short ligands affect modes of QD uptake and elimination in human cells"** ACS Nano. 5(10):7690; author reply 7691-2.

Sokołowska I, Wälchli S, Wegrzyn G, Sandvig K, Słomiкska-Wojewódzka M. (2011) **A single point mutation in ricin A-chain increases toxin degradation and inhibits EDEM1-dependent ER retrotranslocation** Biochem J. 436(2):371-85.

Stenmark H. (2011) **Harald Stenmark: hands on FYVE-fingers**. Interview by Caitlin Sedwick J Cell Biol. 192(4):544-5.

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.

Teixeira MR, Heim S. (2011) **Cytogenetic analysis of tumor clonality** Adv Cancer Res. 112:127-49.

Thorsen J, Micci F, Heim S. (2011) **Identification of chromosomal breakpoints of cancer-specific translocations by rolling circle amplification and long-distance inverse PCR** Cancer Genet. 204(8):458-61.

Tjeldhorn L, Iversen N, Sandvig K, Bergan J, Sandset PM, Skretting G. (2011) **Protein C mutation (A267T) results in ER retention and unfolded protein response activation** PLoS One. 6(8):e24009.

Tkacz-Stachowska K, Lund-Andersen C, Velissarou A, Myklebust JH, Stokke T, Syljuåsen RG. (2011) **The amount of DNA damage needed to activate the radiation-induced G2 checkpoint varies between single cells** Radiother Oncol. 101(1):24-7.

Torgersen ML, Engedal N, Pedersen AM, Husebye H, Espevik T, Sandvig K. (2011) **Toll-like receptor 4 facilitates binding of Shiga toxin to colon carcinoma and umbilical vein endothelial cells** FEMS Immunol. Med. Microbiol. 61(1):63-75.

Warsame AA, Aasheim HC, Nustad K, Trøen G, Tierens A, Wang V, Randen U, Dong HP, Heim S, Brech A, Delabie J. (2011) **Splenic marginal zone lymphoma with VH1-02 gene rearrangement expresses poly- and self-reactive antibodies with similar reactivity** Blood. 118(12):3331-9.

Wegner CS, Rodahl LM, Stenmark H. (2011) **ESCRT proteins and cell signalling** Traffic. 12(10):1291-7.

Wesche J, Haglund K, Haugsten EM. (2011) **Fibroblast growth factors and their receptors in cancer** Biochem J. 437(2):199-213.

Yri OE, Torfoss D, Hungnes O, Tierens A, Waalen K, Nordøy T, Dudman S, Kilander A, Wader KF, Ostenstad B, Ekanger R, Meyer P, Kolstad A. (2011) **Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment** Blood. 118(26):6769-71.

Zakrzewska M, Sørensen V, Jin Y, Wiedlocha A, Olsnes S. (2011) **Translocation of exogenous FGF1 into cytosol and nucleus is a periodic event independent of receptor kinase activity** Exp Cell Res. 317(7):1005-15.

Zhao X, Rødland EA, Sørlie T, Naume B, Langerød A, Frigessi A, Kristensen VN, Børresen-Dale AL, Lingjærde OC. (2011) **Combining gene signatures improves prediction of breast cancer survival** PLoS One. 6(3):e17845.

Ågesen TH, Berg M, Clancy T, Thiis-Evensen E, Cekaite L, Lind GE, Nesland JM, Bakka A, Mala T, Hauss HJ, Fetveit T, Vatn MH, Hovig E, Nesbakken A, Lothe RA, Skotheim RI. (2011) **CLC and IFNAR1 are differentially expressed and a global immunity score is distinct between early- and late-onset colorectal cancer** Genes Immun. 12(8):653-62.

Publications 2012:

Dyve Lingelem AB, Bergan J, Sandvig K. (2012) **Inhibitors of intravesicular acidification protect against shiga toxin in a pH-independent manner** Traffic. 13(3):443-54.

Hausott B, Vallant N, Hochfilzer M, Mangger S, Irschick R, Haugsten EM, Klimaschewski L. (2012) **Leupeptin enhances cell surface localization of fibroblast growth factor receptor 1 in adult sensory neurons by increased recycling** Eur J Cell Biol. 91(2):129-38.

Horgmo ØH, Danielsen H. (2012) **A Camera Support for Operating Theatre Videography** J Vis Commun Med. 35(1):20-4.

Kildal W, Micci F, Risberg B, Abeler VM, Kristensen GB, Heim S, Danielsen HE. (2012) **Genomic imbalances in endometrial adenocarcinomas – Comparison of DNA ploidy, karyotyping and comparative genomic hybridization** Mol Oncol. 6(1):98-107.

Lobert VH, Stenmark H. (2012) **The ESCRT machinery mediates polarization of fibroblasts through regulation of myosin light chain** J Cell Sci. 125(Pt 1):29-36.

Matheu A, Collado M, Wise C, Manterola L, Cekaite L, Tye AJ, Canamero M, Bujanda L, Schedl A, Cheah KS, Skotheim RI, Lothe RA, Lopez de Munain A, Briscoe J, Serrano M, Lovell-Badge R. (2012) **Oncogenicity of the developmental transcription factor Sox9** Cancer Res. 72(5):1301-1315.

Paulo P, Barros-Silva JD, Ribeiro FR, Ramalho-Carvalho J, Jerónimo C, Henrique R, Lind GE, Skotheim RI, Lothe RA, Teixeira MR. (2012) **FLI1 is a novel ETS transcription factor involved in gene fusions in prostate cancer** Genes Chromosomes Cancer. 51(3):240-9.

Platta HW, Abrahamsen H, Thoresen SB, Stenmark H. (2012) **Nedd4-dependent lysine-11-linked polyubiquitination of the tumour suppressor Beclin 1** Biochem J. 441(1):399-406.

Skotland T. (2012) **Molecular imaging: challenges of bringing imaging of intracellular targets into common clinical use** Contrast Media Mol. Imaging. 7:1-6.

Van Loo P, Nilsen G, Nordgard SH, Vollan HK, Børresen-Dale AL, Kristensen VN, Lingjærde OC. (2012) **Analyzing cancer samples with SNP arrays** Methods Mol Biol. 802:57-72.

Wahlin BE, Yri OE, Kimby E, Holte H, Delabie J, Smeland EB, Sundström C, Christensson B, Sander B. (2012) **Clinical significance of the WHO grades of follicular lymphoma in a population-based cohort of 505 patients with long follow-up times** Br J Haematol. 156(2):225-33.

Publications in press:

Gualtieri M, Skuland T, Iversen TG, Låg M, Schwarze P, Bilaniková D, Pojana G, Refsnes M. (2011) **Importance of agglomeration state and exposure conditions for uptake and pro-inflammatory responses to amorphous silica nanoparticles in bronchial epithelial cells** Nanotoxicology. 2011 Jul 28. [Epub ahead of print].

Håvik AB, Brandal P, Honne H, Dahlback H-SS, Scheie D, Hektoen M, Meling TR, Helseth E, Heim S, Lothe RA, Lind GE. (2012) **Assessment by pyrosequencing and quantitative methylation-specific PCR of MGMT promoter methylation status in gliomas** J Translational Medicine. In press.

Leithe E, Sirnes S, Fykerud T, Kjenseth A, Rivedal E. (2011) **Endocytosis and post-endocytic sorting of connexins** Biochim Biophys Acta. 2011 Oct 4. [Epub ahead of print].

Mathiesen RR, Fjelldal R, Liestøl K, Due EU, Geigl JB, Riethdorf S, Borgen E, Rye IH, Schneider IJ, Obenauf AC, Mauermann O, Nilsen G, Christian Lingjaerde O, Børresen-Dale AL, Pantel K, Speicher MR, Naume B, Baumbusch LO. (2011) **High-resolution analyses of copy number changes in disseminated tumor cells of patients with breast cancer** Int J Cancer. 2011 Sep 20. [Epub ahead of print].

Nezis IP, Stenmark H. (2012) **p62 at the Interface of Autophagy, Oxidative Stress Signaling, and Cancer** Antioxid Redox Signal. 2012 Jan 11. [Epub ahead of print].

Nyquist KB, Panagopoulos I, Thorsen J, Roberto R, Wik HS, Tierens A, Heim S, Micci F. (2012) **t(12;13)(q14;q31) leading to HMGA2 deregulation in acute myeloid leukaemia** Br H Haematol. 2012 Mar 7. [Epub ahead of print].

Pradhan M, Abeler VM, Danielsen HE, Sandstad B, Tropé CG, Kristensen GB, Risberg BA. (2011) **Prognostic importance of DNA ploidy and DNA index in stage I and II endometrioid adenocarcinoma of the endometrium** Ann Oncol. 2011 Sep 30. [Epub ahead of print].

Sirnes S, Bruun J, Kolberg M, Kjenseth A, Lind GE, Svindland A, Brech A, Nesbakken A, Lothe RA, Leithe E, Rivedal E. (2011) **Connexin43 acts as a colorectal cancer tumor suppressor and predicts disease outcome** Int J Cancer. 2011 Aug 22. [Epub ahead of print].

Sveen A, Bakken AC, Ågesen TH, Lind GE, Nesbakken A, Nordgård O, Brackmann S, Rognum TO, Lothe RA, Skotheim RI. (2011) **The exon-level biomarker SLC39A14 has organ-confined cancer-specificity in colorectal cancer** Int J Cancer. 2011 Dec 15. [Epub ahead of print].

Zhen Y, Sørensen V, Skjerpen CS, Haugsten EM, Jin Y, Wälchli S, Olsnes S, Wiedlocha A. (2012) **Nuclear import of exogenous FGF1 requires the ER-protein LRRC59 and the importins Kpnβ1 and Kpnβ1** Traffic. 2012 Feb 9. [Epub ahead of print].

Ågesen 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. 2012 Jan 2. [Epub ahead of print].

Invited Lectures/Selected Presentations:

Lind GE.: "Translational research in colorectal cancer", Oncological Forum, November 18, 2011, Oslo, Norway.

Lothe RA.: "Epigenetic biomarkers for early detection of cancer". Invited speaker at "Horizons in Molecular Life Science", The Royal Swedish Academy of Sciences, September 29-30, 2011, Stockholm, Sweden.

Lothe RA.: "Biomarkers for early detection and prognostics of colorectal cancer". Invited guest speaker at 13th Bergen Conference on Cancer Research, BCCR, Solstrand April 27-28, 2011, Bergen, Norway.

Sandvig K.: "Roles of annexin A1 and A2 in retrograde transport of Shiga toxin", International Conference on Annexins, August 2011, Barcelona, Spain.

Sandvig K.: "Drug delivery: Role of endocytosis and intracellular transport", Workshop NBI Tech 2 Life, INNABIOSANTE (European Cancer Cluster Partnership), September 2011, Toulouse, France.

Skotheim RI.: "Deep sequencing of colorectal cancer genomes and transcriptomes for personalized treatment and surveillance", Oslo Cancer Cluster, R & D network meeting on Personalized Medicine, March 31, 2011, Oslo, Norway.

Skotheim RI.: "Porto-Oslo, a long term successful biotech research programme on gastrointestinal- and urological cancer diseases", Health Cluster Portugal's mission to Scandinavia, March 30, 2011, Oslo, Norway.

Skotheim RI.: "Transcript variant based biomarkers for cancer". Invited lecturer to Biomedicum Health Seminar, February 14, 2011, Helsinki, Finland.

Stenmark H.: "Class III PI 3-kinase in cell division". Invited speaker at the NordForsk cilia/centrosome meeting, March 25-27, 2011, Lyngby, Denmark.

Stenmark H.: "Multivesicular endosomes as regulators of receptor signalling and cell migration". Invited lecturer at the DFG graduate school on "Quantitative Analysis of Dynamic Processes in Membrane Transport and Translocation", June 5-7, 2011, Heidelberg, Germany.

Stenmark H.: "Studies of a lipid kinase reveal the role of membrane dynamics in tumour suppression". Invited speaker at the Norwegian Cancer Symposium, September 5-9, 2011, Oslo, Norway.

Stenmark H.: "Endosomes and cell division". Invited speaker at the EMBO Conference on "Dynamic Endosomes", September 24-30, 2011, Chania, Greece.

Stenmark H.: "Function of the tumour suppressor, class III PI 3-kinase, in membrane dynamics". Guest lecturer at the Physiological Laboratory, University of Liverpool, November 7, 2011, Liverpool, UK.

Stenmark H.: "Class III phosphatidylinositol 3-kinase as tumour suppressor". Invited speaker at the NCRI Cancer Congress, November 8-9, 2011, Liverpool, UK.

Wiedlocha A.: "Activation and termination of Fibroblast Growth Factor (FGF) induced cellular signaling". Invited speaker at University in Brno, Institute of Biophysics, May 12, 2011, Brno, Czech Republic.

Yri OE.: "Genetic polymorphisms influence the risk of Hodgkin's lymphoma", 11th International Conference on Malignant Lymphoma, June 15-18, 2011, Lugano, Switzerland.

Yri OE.: "Lymphoma patients treated with Rituximab-containing regimens do not achieve protective serological responses to H1N1 influenza virus after vaccination", 11th International Conference on Malignant Lymphoma, June 15-18, 2011, Lugano, Switzerland.

National collaboration:

Dr. Vera Abeler, MD, PhD, Department of Pathology, Oslo University Hospital, The Norwegian Radium Hospital

Prof. Fritz Albregtsen, Faculty of Mathematics and Natural Sciences, Department of Informatics, University of Oslo

Dr. Bodil Bjerkehagen, MD, Department of Pathology, Oslo University Hospital, The Norwegian Radium Hospital

Egil Blix, Department of Oncology, University Hospital North Norway, Tromsø and Department of Immunology, University of Tromsø, Tromsø

Prof. Michael Bretthauer, Department of Health Management and Health Economy, University of Oslo and Department of Transplantation Medicine, Gastroenterology, Oslo University Hospital, Rikshospitalet

Prof. Ben Davidson, Department of Pathology, Oslo University Hospital, The Norwegian Radium Hospital

Prof. Jan Delabie, Division of Pathology, Oslo University Hospital, The Norwegian Radium Hospital

Prof. Terje Espevik, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim

Dr. Espen Thiis Evensen, Department of Medicine, Oslo University Hospital, Rikshospitalet

Prof. Donald Gullberg, Department of Biomedicine, University of Bergen

Erik Haug, MD, PhD, Department of Urology, Vestfold Hospital, Tønsberg

Prof. Terje Johansen, Institute of Medical Biology, University of Tromsø

Arne Kolstad, MD, PhD, Division of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital, The Norwegian Radium Hospital

Prof. Ute Krengel, Faculty of Mathematics and Natural Sciences, Department of Chemistry, University of Oslo

Prof. Stein Kvaløy, Division of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital, The Norwegian Radium Hospital

Dr. Kathrine Lie, Department of Pathology, Oslo University Hospital, The Norwegian Radium Hospital

Dr. Torstein R Meling, MD, PhD, Department of Neurosurgery, Oslo University Hospital, Rikshospitalet, Oslo, Norway

Ludvig Munthe, MD, PhD, Institute of Immunology, Oslo University Hospital, Rikshospitalet

Prof. Ola Myklebost, Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, The Norwegian Radium Hospital

Prof. Gunhild Mælandsmo, Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, The Norwegian Radium Hospital

Prof. Fahri Saatcioglu, Faculty of Mathematics and Natural Sciences, Department of Molecular Biosciences, University of Oslo

Prof. Erik Schrumpf, Department of Medicine, Oslo University Hospital, Rikshospitalet

Associate Prof. Anne Simonsen, Faculty of Medicine, Institute of Basic Medical Sciences, University of Oslo

Dr. Grethe Skretting, Department of Hematology, Oslo University Hospital, Ullevål

Prof. Sigbjørn Smeland, Head of Division of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital

Kirsten Sundby Hall, MD, PhD, Head of Sarcoma Programme, Oslo University Hospital, The Norwegian Radium Hospital

Prof. Aud Svindland, Department of Pathology, Oslo University Hospital, Aker and The Norwegian Radium Hospital

Prof. Claes Trope, MD, PhD, Department of Gynecology, Oslo University Hospital, The Norwegian Radium Hospital

Prof. Kjell Tveit, Department of Oncology, Oslo University Hospital and Institute for Clinical Medicine, University of Oslo

International collaboration:

Ash A. Alizadeh, MD, PhD, Stanford University, USA

Prof. Peter Andrews, University of Sheffield, England

Prof. David Bilder, University of California, Berkeley, USA

Joshua Brody, Director, Lymphoma Immunotherapy Program, Mount Sinai School of Medicine, USA

Prof. Stephen Chanock, NIH, National Cancer Institute, USA

Prof. Bo van Deurs, University of Copenhagen, Denmark

Prof. Ivan Dikic, Goethe University, Frankfurt, Germany

Dr. Kim Ekroos, Finland

Prof. Hanna Fares, The University of Arizona, USA

Dr. Jude Fitzgibbon, Institute of Cancer, Queen Mary School of Medicine and Dentistry, London, UK

Prof. V. Gerke, University of Münster, Germany

Associate Prof. Jonathan M. Irish, Vanderbilt University, Department of Cancer Biology, USA

Prof. Olli Kallioniemi, Finnish Institute for molecular medicine, Helsinki, Finland

Dr. Pavel Krejci, Medical Genetics Institute, Cedars-Sinai Medical Center, LA, USA

Prof. Ron Levy, MD, Stanford University, USA

Prof. Robin Lovell-Badge, Division of Stem Cell Biology and Developmental Genetics, MRC National Institute for Medical Research, London, UK

Dr. Nicholas J. Mantis, Div. Infect. Diseases, Wadsworth Center, NY, USA

Dr. Adriano Marchese, Stritch School of Medicine, Loyola University, Chicago

Prof. Katherine McGlynn, NIH, National Cancer Institute, USA

Prof. Fredrik Mertens, Dept Clinical Genetics, University of Lund, Sweden

Dr. Jim Norman, The Beatson Institute for Cancer Research, Glasgow, UK

Prof. Marco Novelli, University College London, England

Prof. Yasufumi Omori, Department of Pathology, University of Akita, Japan

Prof. Jacek Otlewski, University of Wroclaw, Inst. Mol. Biol. and Biochem, Poland

Prof. Nikos Pandis, PhD, Saint Savas Oncological Hospital, Athens, Greece

Prof., Director Piero Picci, Lab Experimental Oncology, Rizzoli Ortopedic Institute, Bologna, Italy

Dr. Ewa Rajpert-De-Meyts, University Dept Growth and reproduction, The National hospital, Copenhagen, Denmark

Lucia E. Rameh, PhD, Boston Biomedical Research Institute, USA

Prof. Christos Samakovlis, The Wenner-Gren Institute, Stockholm University

Dr. Monika Slominska-Wojewodzka, Department of Molecular Biology, University of Gdansk, Poland

Prof. Louis M Staudt, MD, PhD, Head of The Leukemia and Lymphoma Molecular Profiling Project (LLMPP), National Cancer Institute, USA

Prof. Torsten Steinmetzer, University of Marburg, Germany

Prof. Manuel Teixeira, Portuguese Oncology Institute, Porto, Portugal

Associate Prof. John Timmerman, University of California, Los Angeles Medical Center, Division of Hematology & Oncology, USA

Prof. Ian Tomlinson, Nuffield Department of Clinical Medicine, University of Oxford, UK

RADIO

Interview with Kirsten Sandvig in NRK-P1 - EKKO

The 15th ETOX Meeting – European Workshop on Bacterial Protein Toxins.

18th – 22nd June 2011.
Soria-Moria Conference Centre
Oslo, Norway.

Kirsten Sandvig was interviewed by Guro Tarjem in NRK-P1, the program EKKO, 23 June 2011, about the use of Shiga toxin in cancer diagnosis and therapy. The interview was made in connection with the international meeting ETOX15, which was arranged at Soria Moria, June 18th-22nd, 2011. The meeting was coorganized by Sandvig.

NEWSPAPERS

Interview with CCB's Rolf Skotheim in VG cover story about cancer treatment

30 September 2011 (in Norwegian only)


VG

Nr. 270
Fredag
30. september
2011
Uke 39
Kr. 17,00

Revolusjon på norsk sykehus:

FINNER SKJULT KREFT i rekord-fart

PROSTATA: Med den nye metoden oppdager legene svulsten med en gang.

● SIDE 20, 21 og 22

URINTEST KAN AVSLØRE KREFT

Av INGUNN SALTBONES, ERIC B. UTHEIM og INGUNN VIKEN

I løpet av de siste fem årene har forskere oppdaget 25 genforandringer som kan avsløre prostatakreft.

Forskere over hele verden jobber nå med å finne sikkalte fusjonsgener.

– Disse genene oppstår bare når en person har kreft. Blant de vanligste kreftformene er det foreløpig funnet fleet fusjonsgener i prostatakreft, sier forsker Rolf I. Skotheim, ved Avdeling for kreftforebygging, Oslo universitetssykehus, Radiumhospitalet.

Ny viten

Fusjonsgener oppstår ved at cellene brytar ned gener for så å sette dem feil sammen igjen. Disse fusjonsgenene er deretter med på å forårsake kreft.

– Dette er et forskningsfelt som er i en rivende utvikling. For fem år siden var ingen fusjonsgener kjent for noen av de mest vanlige kreftformene, sier Skotheim.

Denne typen genforandringer oppstår i halvparten av prostatakreftcellene og det er påvist at disse fusjonsgenene skilles ut med urinen.

– Det betyr at man har håp om å oppdage halvparten av prostatakreftfallene ved en enkel rutinetest på legekontoret, sier Skotheim.

Flere kreftformer

Sjansen er da stor for at man hos mange kan påvise kreften langt tidligere enn i dag.

Det er allerede firmaer som jobber med å kommersialisere enkle urinetester for påvisning av prostatakreft.

– Jeg tror vi har slike rutinetester for flere kreftformer i løpet av fem til ti år, men for prostatakreft kan det komme tidligere, sier Skotheim.

Skotheims gruppe på Radiumhospitalet, forsker moderne genteknologi for å finne fusjonsgener som kan påvise blant annet tykktarmskreft.

– Vi er på sporet av noen gener nå, sier han optimistisk.

Epost: ingunn.saltbones@gmail

"Book a Cancer Researcher" during the National Science Week

CCB's Rolf Skotheim gave a lecture on genome studies in cancer research for three high school classes at Bjørnholt videregående skole in September.

The National Science Week in Norway (Forskningsdagene) is a nationwide event held every year to make science and research available to the public. Research and knowledge institutions throughout Norway have an opportunity to participate and provide the general public with new insight into what they do.

The newspaper VG published a supplement on behalf of the Research Council of Norway on the National Science Week. Interview with Rolf Skotheim, in Norwegian only:

Forhåpentligvis vil foredragene motivere ungdommer til å gå videre innen realfag – og gjerne kreftforskning. Flere fag trengs i moderne kreftforskning. Både biologer, medisinere og informatikere arbeider i Skotheims gruppe.

– Genteknologi er foreløpig noe vi holder mest på med i forskningslaboratoriene. Men teknologien blir nå i større grad også brukt på pasientprøver. Når dette blir brukt rutinemessig vil det bety svært mye for kreftbehandlingen, sier Skotheim.

Mange tester er nå under utvikling. Prostatakreft er ett eksempel på en kreftform der mange pasienter får genforandringer som kan oppdages med en urinprøve. Finner man genforandringer, er det svært sannsynlig at det dreier seg om kreft. Selv jobber Skotheim først og fremst med tykktarmskreft. Dette er en snikende sykdom, med få symptomer. Derfor er det mange som går for lenge før kreften oppdages.

– Vi benytter genteknologi i utviklingen av en test som vil kunne oppdage denne kreften langt tidligere, slik at pasienten kan bli operert før kreften sprer seg, sier en optimistisk kreftforsker.

The Norwegian newspaper Dagens Næringsliv interviews CCB researcher Skotheim in a highlight on financing of research driven innovation in August

(in Norwegian only)

Gruppeleder Rolf Skotheim ved Avdeling for kreftforebygging ved Institutt for kreftforskning ved Radiumhospitalet utvikler blant annet en test for å kunne påvise tykktarmskreft gjennom DNA-prøver, noe som vil være langt mer behagelig for pasientene enn dagens metode.

INSTITUTT FOR KREFTFORSKNING

- Avdeling for kreftforebygging er en del av Institutt for Kreftforskning, Radiumhospitalet, Oslo Universitetssykehus. Avdelingen har 38 ansatte og ledes av professor Ragnhild A. Lothe.
- Får innovasjonsstøtte fra Oslo Universitetssykeus og Universitetet i Oslo gjennom kommersialiseringsaktøren Inven2.
- Får finansiering til innovasjon fra Forskningsrådets Forny-program og fra Helse Sør-øst.

Ledende kreftforsker Rolf Skotheim (i midten) veileder assistent Anne Cathrine Bakken (til høyre) og ingeniør Zere Yohannes. – Å forske på kreft i Norge gir bedre effekt enn i land hvor det er større gen- og livsstilsforskjeller i befolkninger, sier Skotheim. Foto: Ketil Blom Haugstulen

MAGAZINES AND INTERNET

Hands on FYVE-fingers - Interview with Harald Stenmark in Journal of Cell Biology

The Journal of Cell Biology (impact factor 9.6) brought an interview with Harald Stenmark in the February 21st issue.

Harald Stenmark | Photo: Øystein Horgmo, UiO

The prestigious journal has dedicated two full pages to the interview, which is entitled “Harald Stenmark: Hands on FYVE-fingers” and is published in their “People & Ideas” section. Here, Stenmark goes through important steps in his successful career so far, and talks about how FYVE-finger proteins control cellular membrane dynamics.

Research by Kirsten Sandvig highlighted in Lab Times, a European communication platform for scientists

Kirsten Sandvig

The work performed in the Sandvig group is highlighted in an article in Lab Times, issue 2-2011. The article describes ongoing research in Sandvig’s group, as well as some of the major earlier contributions from Sandvig to our present knowledge of endocytosis and intracellular transport. Lab Times has established itself as one of the most popular Life Science journals in Europe and is recognised as a grassroots magazine produced by scientists for scientists.

Endocytosis and intracellular transport of toxins have been the passion of Kirsten Sandvig and her colleagues at the Norwegian Radium Hospital in Oslo for years. Her persistence in clarifying the underlying basic cellular processes may soon pay off, as toxins face promising applications in cancer treatment and molecular imaging.

Tor Erik Rusten's research highlighted by the Norwegian Cancer Society

The Norwegian Cancer Society highlights one research project each month, and in September 2011 the project obtaining attention is directed by CCB's senior researcher Tor Erik Rusten.

Rusten heads the project group "Phosphatidylinositol signalling & disease", and makes extensive use of the fruit fly Drosophila melanogaster as model organism.

Bananfluen viser vei i kreftforskning

(in Norwegian only)

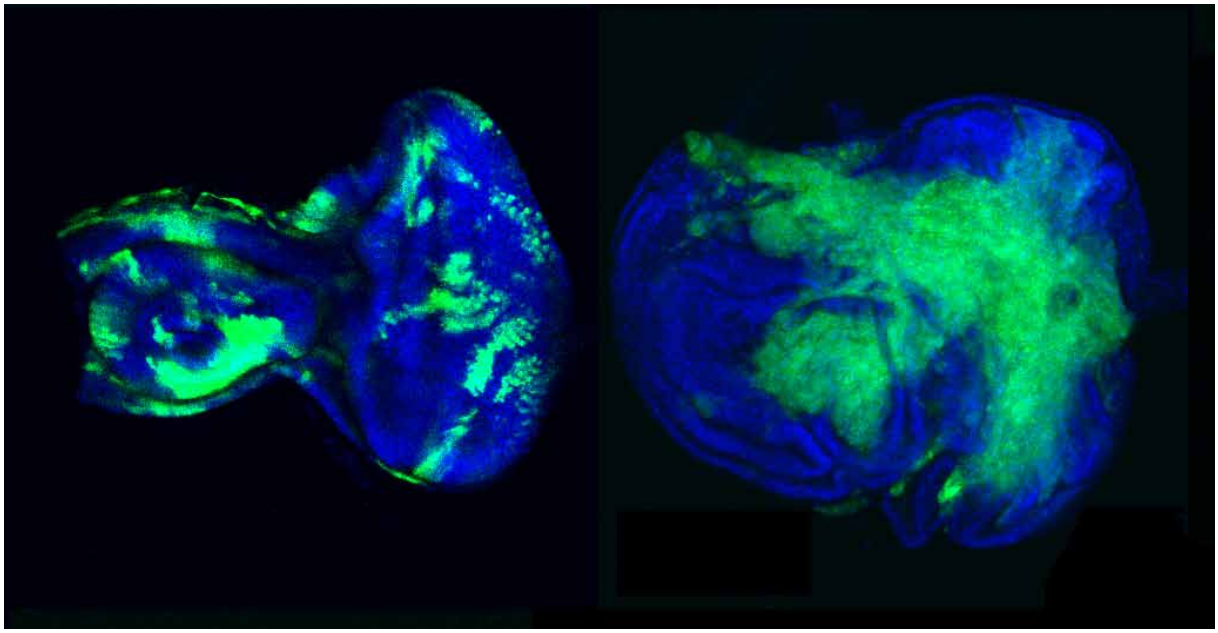
Drosophila melanogaster, hann til venstre og hunn til høyre.

De små irriterende fluene som surrer rundt på kjøkkenet vårt er i andre sammenhenger svært viktige. De er nemlig ideelle modellorganismer for å studere genfeil i kreftsvulster i mennesker.

Gjennom slike studier kan man finne ut hva som forårsaker fremveksten av kreftsvulster hos mennesket. Samtidig kan man finne feil i prosesser som man vet er viktig i kreftutvikling, slik som kontroll av celledeling og celledød, og dermed sjekke om denne feilen i fluen også finnes i kreftsvulster i mennesket.

- Ved å gå frem og tilbake mellom mennesket og modeller som mus og fluer oppnår man hurtigere en bedre viten, nye diagnosemetoder eller behandling som ikke ellers ville vært mulig, sier forsker Tor Erik Rusten ved Oslo Universitetssykehus, Radiumhospitalet.

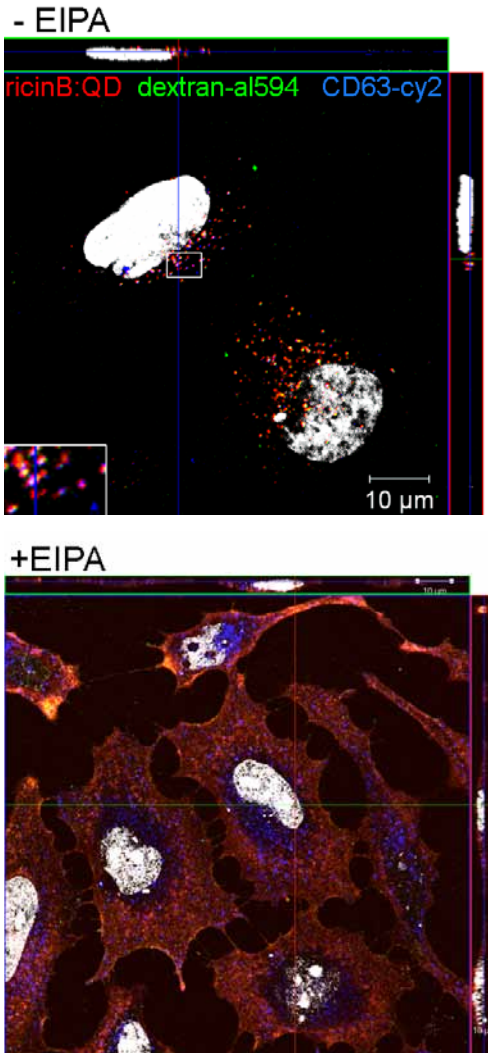
Rusten har brukt bananfluer (Drosophila melanogaster) som modellsystem i over 10 år og kan nok sies å være Norges ekspert på dette området. Modellorganismen brukes også som et viktig verktøy ved de beste kreftforskningsinstitusjonene i verden for å oppnå ny viten om kreft.



I øyeorganet fører samtidig fjerning av to tumor-suppressor gener til kraftig tumorvekst (høyre, grønne celler), mens tilsvarende vekst av normale utransformerte celler (grønne celler) er vist til venstre.

Successful nanoparticle research attracts attention

The research on nanoparticles and their cellular interactions performed by Tore-Geir Iversen and his colleagues at the Centre for Cancer Biomedicine has gained considerable international attention after an interview with Iversen entitled “Nanoparticles can hinder intracellular transport” was published on the web pages for the Norwegian Research Council in October 2011. The story has been picked up by Web Portals such as Science Daily, Health Canal, Medical News and Nanowerk.



Internalization of ricin:QD nanoparticle conjugates by a macropinocytosis-like mechanism. Uptake of the ricinB:QDs was inhibited by the amiloride-derivative EIPA, an inhibitor of macropinocytosis.

Senior researcher Tore-Geir Iversen interviewed about nanoparticles on www.forskning.no

Tore-Geir Iversen

The popular Norwegian research web site “forskning.no” has interviewed CCB’s Tore-Geir Iversen about his work on nanoparticles in February 2011, in Norwegian only.

Nanopartikler skaper trafikkork

Cellene er ikke i stand til å behandle nanopartikler på samme måte som andre forbindelser. Dermed hoper partiklene seg opp og kan potensielt være skadelige for cellene.

Nanopartikler kan hjelpe til med mer målrettet levering av medikamenter til spesifikke celler og vev. Nanopartikler kan også brukes som markører for å gjøre det lettere å se kreftsvulster i forbindelse med scanning eller operasjon. Men dersom nanopartikler av for eksempel tungmetaller ikke blir skilt ut av kroppen etter bruk, kan det gi skadelige effekter.

- Tidligere toksikologiske studier har vist at nanopartikler kan forårsake oksidativt stress i celler, og skade DNA og cellevegg, sier Tore-Geir Iversen, seniorforsker ved Senter for Kreftbiomedisin ved Radiumhospitalet.

Nå har han sammen med medarbeidere vist at nanopartikler også kan være skadelige ved at de forstyrrer transporten av molekyler inne i celler.

Facts 2011

Centre for Cancer Biomedicine

CCB was established in September 2007 as a Centre of Excellence appointed by the Research Council of Norway with the University of Oslo as host institution. The majority of our Centre is located at Oslo University Hospital, the Norwegian Radium Hospital. A consortium agreement regulates cooperation between the University of Oslo and Oslo University Hospital with the intention to make conditions favourable for fulfilling the scientific aims and strategic plans of CCB.

The Research Groups

Six research groups and four associated groups embracing an average of 130 people in 2011 constitute CCB.

The six research groups are headed by Prof. Harald Stenmark, Prof. Ragnhild A. Lothe, Prof. Kirsten Sandvig, Prof. Erlend Smeland, Prof. Håvard Danielsen, and Prof. Knut Liestøl.

Four independent groups are associated with CCB. These are Antoni Wiedlocha's group (associated with the Stenmark group), Edgar Rivedal's group (associated with the Lothe group), Rolf Skotheim's group (associated with the Lothe group), and Prof. Sverre Heim's group (associated with the Danielsen group).

Management

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

From left: Ragnhild A. Lothe, Anette Sørensen and Harald Stenmark | Photo: Linda Cartridge

The Board

The Centre management reports to the CCB board having two members from the University of Oslo as well as two members from Oslo University Hospital. Board meetings are held twice a year. In 2011 we welcomed two new board members.

The board members are:
Prof. Hilde Irene Nebb - Chairperson of the board, Dean of Research, Faculty of Medicine, University of Oslo (new board member from 2011)

Prof. Anders Elverhøi, Dean of Research, Faculty of Mathematics and Natural Sciences, University of Oslo

Prof. Karl-Erik Giercksky, Head of section for Surgical Oncology, Division of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital

Prof. Ole M. Sejersted, Head of Institute for Experimental Medical Research, Oslo University Hospital (new board member from 2011).

Scientific Advisory Board

The Scientific Advisory Board of CCB has five members:

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

Professor Lena Claesson-Welsh, Head of Department of Genetics and Pathology, Uppsala University, Sweden

Professor David J. Kerr, Professor of Cancer Medicine, University of Oxford, UK

Professor Marja Jäättelä, Head of the Department, Institute of Cancer Biology, Danish Cancer Society, Copenhagen, Denmark

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

The Scientific Advisory Board supports our Centre with valuable input on strategy and science which helps us to achieve our goal of becoming one of Europe's leading centres for cancer research. SAB's fourth visit to CCB is planned for 13-14 June 2012.

Visiting Professors

CCB has three professors associated to the Centre.

Professor Bo van Deurs
The Panum Institute, University of Copenhagen

Professor Manuel Teixeira
Portugese Oncology Institute, Porto

Professor Marco Novelli (new visiting professor from January 2011)
University College London Hospitals

Clinical Associates

CCB has three clinicians associated to the Centre. We are pleased that Karol Axcrona joined CCB in 2011. Read more about their work elsewhere in this annual report.

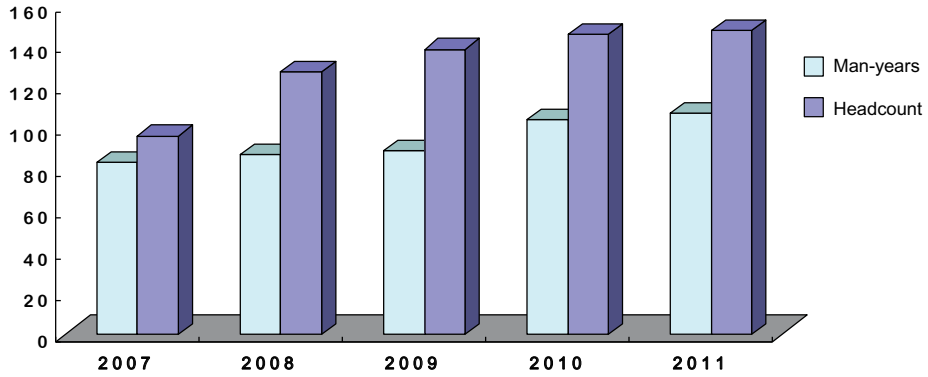
Harald Holte, Dr. med.
Oslo University Hospital, The Norwegian Radium Hospital

Prof. Arild Nesbakken,
Oslo University Hospital, Aker

Karol Axcrona, MD PhD
Oslo University Hospital, The Norwegian Radium Hospital

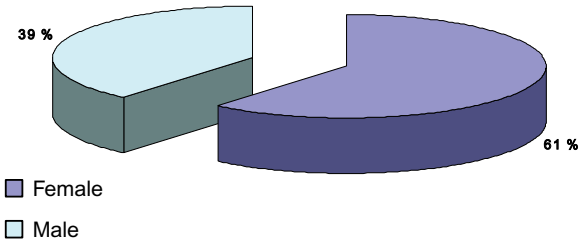
Figures 2011

CCB staff – Development in man-years/headcount



Since CCB's inauguration in 2007, the number of man-years has increased with approx. 25%. Our current infrastructure restricts further expansion of the centre, and we therefore plan only a modest expansion during the years to come. The total number of people registered in the centre in 2011 is 147, corresponding to 107 man-years. CCB currently houses 21 different nationalities.

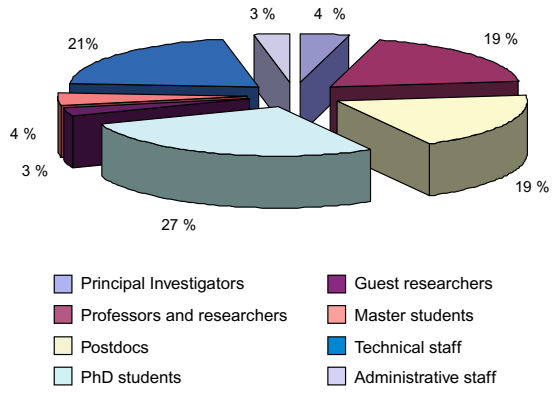
Gender distribution in %



In 2011 we have seen a minor reduction in the number of female employees in our centre. This year the number is 61% as opposed to 65% in 2010. Recruitment of female scientists at PhD student and postdoc level is not considered a major obstacle in CCB. Nevertheless, the real challenge still lies in ensuring that the leaky pipeline of women through the academic hierarchy is stopped. CCB actively supports the promotion of talented female scientists through various means where the overall strategy is to create predictability and continuity, and thereby motivating women to stay in their current career path.

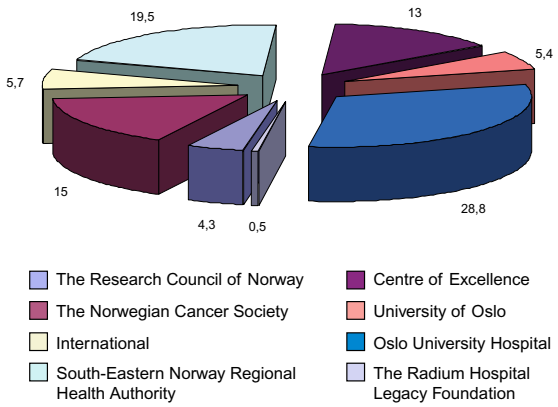
Based on the fact that 61% of CCB members are female, an analysis of the representation of female scientists in CCB was conducted by CCB´s committee for gender equality again this year. Earlier, we have identified one problem area, namely the promotion of women to the highest scientific category, the project leader/senior scientist level. Again this year we are happy to report that major progress has been made in this category: The female representation at the project leader/senior scientist level has increased to 45% in 2011. Previous figures are 13 % in 2007 and 32 % in 2010.

CCB staff categorized by position in %



We have counted 147 CCB members in 2011, corresponding to 107 man-years. The pie chart shows the categorization of our staff by position.

Funding in MNOK (excluding in-kind contributions from our two host institutions)



The funding situation for CCB is good in the sense that the centre has been obtaining sufficient financial resources to implement all its planned activities. The total funding for 2011 is 92.2 MNOK excluding in-kind contributions.

Particularly the funding from the South-Eastern Norway Regional Health Authority has increased dramatically in 2011, from 9.5 MNOK in 2010 to 19.5 MNOK in 2011.

The overall funding for CCB has increased with 5 MNOK from 2010 to 2011.

THE NORWEGIAN CANCER SOCIETY

- a main contributor to CCB funding

”The Cancer Society supports excellent basic and clinical research, and has therefore, for many years, supported the researchers of the Centre of Excellence in Cancer Biomedicine. We appreciate their high quality science which is required for the development of novel and improved diagnostics and better personalised treatment of cancer patients”,

says Anne Lise Ryel, the Secretary-General of the Norwegian Cancer Society.

Anne Lise Ryel
Photo: Marianne Otterdahl-Jensen

CCB researchers funded by the Cancer Society portrayed in Norwegian newspapers:

CCB research highlighted on www.kreftforskning.no:

Ny genbasert prognostisk test for kreft i tykk- og endetarm
Forskere ved Oslo universitetssykehus har utviklet en test som forutsier sykdomsforløpet for pasienter med tykk- og endetarmskreft, stadium II. Testen måler aktiviteten til 13 gener i svulsten, og hvert gen bidrar med prognostisk informasjon.

From left: Anita Sveen and Trude H. Ågesen | Photo: Per Marius Didriksen

Våpenet må fininnstilles bedre mot blinken
Det finnes i dag medisiner som dirigeres primært til kreftceller og sparer normalt vev. Ny forskning viser at målet for behandlingen ikke bare er kreftcellen, men også riktig sted i cellen.

Prof. Kirsten Sandvig | Photo: Linda Cartridge

Bananfluen viser vei i kreftforskning
De små irriterende fluene som surrer rundt på kjøkkenet vårt er i andre sammenhenger svært viktige. De er nemlig ideelle modellorganismer for å studere genfeil i kreftsvulster i mennesker.

Tor Erik Rusten | Photo: Øystein Horgmo

CCB STAFF AND STUDENTS 2011

Name	Position	Group	Nationality	Employer	Academic title
Abrahamsen, Hilde	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Ailte, Ieva	PhD student	Sandvig	Latvia	University of Oslo	MSc
Alagaratnam, Sharmini	Postdoc	Lothe	Malaysia	Oslo University Hospital	PhD
Ali, Deeqa Ahmed Mohammed	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Andresen, Kim	PhD student	Lothe	Norway	University of Oslo	MSc
Askevold, Kaja	PhD student	Wiedlocha	Norway	Oslo University Hospital	MSc
Bakkebø, Maren	PhD student	Smeland	Norway	Oslo University Hospital	MSc
Bakken, Anne Cathrine	Research fellow	Lothe	Norway	Oslo University Hospital	MSc
Bassols, Jose Maria	Computer specialist	Stenmark	Spain	Oslo University Hospital	
Bergan, Jonas	PhD student	Sandvig	Norway	Oslo University Hospital	MSc
Bergersen, Anne Gro	Technician	Stenmark	Norway	Oslo University Hospital	
Bethge, Nicole	PhD student	Smeland	Germany	Oslo University Hospital	MSc
Brabrand, Sigmund	PhD student	Lothe	Norway	Oslo University Hospital	MD
Brandal, Petter	Scientist	Danielsen	Norway	Oslo University Hospital	PhD
Brech, Andreas	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Bredahl, May Kristin Lyamouri	Senior scientist	Smeland	Norway	Oslo University Hospital	PhD
Bruun, Jarle	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Campsteijn, Coen	Postdoc	Stenmark	Holland	Oslo University Hospital	PhD
Cekaite, Lina	Postdoc	Lothe	Lithuania	Oslo University Hospital	PhD
Celestino, Ricardo	Guest PhD student	Lothe	Portugal	University of Porto	MSc
Cordara, Gabriele	PhD student	Sandvig	Italy	University of Oslo	MSc
Dahlback, Hanne-Sofie Spenning	PhD student	Danielsen	Norway	University of Oslo	MSc
Danielsen, Håvard	PI., professor	Danielsen	Norway	Oslo University Hospital	PhD
Danielsen, Stine Aske	PhD student/Postdoc	Lothe	Norway	Oslo University Hospital	PhD
Eide, Marianne Brodtkorb	PhD student	Smeland	Norway	Oslo University Hospital	MD
Eide, Peter Andreas Wold	Master student/Research fellow	Lothe	Norway	Oslo University Hospital	MSc
Eikenes, Åsmund Husabø	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Eilertsen, Ina Andrassy	Master student	Lothe	Norway	Oslo University Hospital	
Eknæs, Mette	Technician	Lothe	Norway	Oslo University Hospital	
Engen, Anne	Technician	Stenmark	Norway	Oslo University Hospital	
Ersvær, Elin	Research fellow	Danielsen	Norway	Oslo University Hospital	MSc
Forfang, Lise	Technician	Smeland	Norway	Oslo University Hospital	MSc
Fykerud, Tone	Research fellow	Lothe	Norway	Oslo University Hospital	MSc
Gorunova, Ludmila	Scientist	Danielsen	Russia	Oslo University Hospital	PhD
Guriby, Marianne	Research fellow	Lothe	Norway	Oslo University Hospital	MSc
Haglund, Kaisa	Project leader, Senior scientist	Stenmark	Sweden	Oslo University Hospital	PhD
Haugom, Lisbeth	Research fellow	Danielsen	Norway	Oslo University Hospital	
Haugsten, Ellen M.	Postdoc	Wiedlocha	Norway	Oslo University Hospital	PhD
Heim, Sverre	Group leader, Senior scientist	Danielsen	Norway	Oslo University Hospital	PhD
Hektoen, Merete	Technician	Lothe	Norway	Oslo University Hospital	MSc
Hessvik, Nina Pettersen	Postdoc	Sandvig	Norway	Oslo University Hospital	PhD

Name	Position	Group	Nationality	Employer	Academic title
Hilden, Vera Irene	Technician	Smeland	Norway	Oslo University Hospital	MSc
Hoff, Andreas Midbøe	Master student/Research fellow	Lothe	Norway	Oslo University Hospital	MSc
Honne, Hilde	Research fellow	Lothe	Norway	Inven2	MSc
Huse, Kanutte	PhD student/Postdoc	Smeland	Norway	Oslo University Hospital	PhD
Hveem, Tarjei Sveinsgjerd	PhD student	Danielsen	Norway	Oslo University Hospital	MSc
Høimyr, Helene	Research fellow	Danielsen	Norway	Oslo University Hospital	MSc
Høiseth, Ane Hoel	Master student	Stenmark	Norway	Oslo University Hospital	
Høland, Maren	PhD student	Lothe	Norway	University of Oslo	MSc
Håvik, Annette Bentsen	PhD student	Danielsen	Norway	Oslo University Hospital	MSc
Iversen, Tore-Geir	Project leader, Senior scientist	Sandvig	Norway	Oslo University Hospital	PhD
Jenstad, Monica	Postdoc	Danielsen	Norway	Oslo University Hospital	PhD
Johannessen, May Elisabeth	Secretary		Norway	Oslo University Hospital	
Karerwa, Jeanne D'Arc	Technician	Danielsen	Norway	Oslo University Hospital	
Katheder, Nadja Sandra	PhD student	Stenmark	Switzerland	Oslo University Hospital	MSc
Kavaliauskiene, Simona	Master student/PhD student	Sandvig	Lithuania	Oslo University Hospital	MSc
Kihlstrøm, Minna	Master student	Stenmark	Finland	Oslo University Hospital	
Kildal, Wanja	Postdoc	Danielsen	Norway	Oslo University Hospital	PhD
Kjenseth, Ane Hansen	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Kjæreng, Marna Lill	Technician	Danielsen	Norway	Oslo University Hospital	
Klokk, Tove Irene	Postdoc	Sandvig	Norway	Oslo University Hospital	PhD
Kolberg, Matthias	Scientist	Lothe	Norway	Oslo University Hospital	PhD
Kostas, Michal	Guest PhD student	Wiedlocha	Poland	University of Wroclaw	MSc
Kraggerud, Sigrid M.	Scientist	Lothe	Norway	Oslo University Hospital	Dr. Philos
Kvalvaag, Audun Sverre	Master student/Research fellow	Sandvig	Norway	Oslo University Hospital	MSc
Kvamme, Linko Sigrid Izumi	Laboratory assistant	Stenmark	Norway	Oslo University Hospital	
Leithe, Edward	Project leader, Senior scientist	Lothe	Norway	Oslo University Hospital	Dr. Philos
Liestøl, Knut	P.I., professor	Liestøl	Norway	University of Oslo	Dr. Philos
Lind, Guro Elisabeth	Project leader, Senior scientist	Lothe	Norway	Oslo University Hospital	Dr. Philos
Lingelem, Anne Berit Dyve	PhD student	Sandvig	Norway	Oslo University Hospital	MSc
Lingjærde, Ole Christian	Associate professor	Liestøl	Norway	University of Oslo	PhD
Llorente Alicia	Project leader, Senior scientist	Sandvig	Spain	Oslo University Hospital	Dr. Philos
Lobert, Viola	PhD student	Stenmark	France	Oslo University Hospital	MSc
Lothe, Ragnhild A.	P.I., professor	Lothe	Norway	Oslo University Hospital	Dr. Philos
Løvf, Marthe	PhD student	Lothe	Norway	University of Oslo	MSc
Martinsen, Janne	Laboratory assistant	Stenmark	Norway	Oslo University Hospital	
Merok, Marianne Aarstad	PhD student	Lothe	Norway	Oslo University Hospital	MD
Micci, Francesca	Scientist	Danielsen	Italy	Oslo University Hospital	PhD
Mjøen, Linda Uv	Advisor		Norway	Oslo University Hospital	
Musa, Nagham	PhD student	Sandvig	Sweden	Oslo University Hospital	MSc
Myklebust, June Helen	Project leader, Senior scientist	Smeland	Norway	Oslo University Hospital	PhD
Myrann, Anne Grethe	Technician	Sandvig	Norway	Oslo University Hospital	

Name	Position	Group	Nationality	Employer	Academic title
Nadratowska-Wesolowska, Beata	Postdoc	Wiedlocha	Poland	Oslo University Hospital	PhD
Nesheim, John Arne	Head of developement	Danielsen	Norway	Oslo University Hospital	MSc
Nezis, Ioannis	Postdoc	Stenmark	Greece	Oslo University Hospital	PhD
Nielsen, Birgitte	Postdoc	Danielsen	Norway	Oslo University Hospital	PhD
Nilsen, Gro	PhD student	Liestøl	Norway	University of Oslo	MSc
Nome, Torfinn	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Norgren, Axel	Medical student	Stenmark	Norway	Oslo University Hospital	
Nymark, Carl-Martin	Master student/Technician	Sandvig	Norway	Oslo University Hospital	MSc
Nyqvist, Kaja Beate	PhD student	Danielsen	Norway	Oslo University Hospital	MSc
O'Farrell, Fergal	Postdoc	Stenmark	Ireland	Oslo University Hospital	PhD
Oksvold, Morten	Postdoc	Smeland	Norway	Oslo University Hospital	PhD
Olsnes, Sjur	Professor emeritus	Wiedlocha	Norway	Oslo University Hospital	MD, PhD
Oppelt, Angela	PhD student	Wiedlocha	Germany	Oslo University Hospital	MSc
Panagopoulos Ioannis	Senior scientist	Danielsen	Hellas	Oslo University Hospital	PhD
Pedersen, Anne-Mari Gjestvang	Technician	Sandvig	Norway	Oslo University Hospital	MSc
Pedersen, Nina Marie	Postdoc	Stenmark	Norway	Oslo University Hospital	PhD
Phuyal, Santosh	Research fellow	Sandvig	Nepal	Oslo University Hospital	MSc
Pielaszkiewicz, Katarzyna	Guest master student	Stenmark	Poland	University of Poznan, ERASMUS	
Platta, Harald	Postdoc	Stenmark	Germany	EMBO	PhD
Pradhan, Manohar	PhD student	Danielsen	Nepal	Oslo University Hospital	MD
Pretorius, Maria	Administrative head	Danielsen	Norway	Oslo University Hospital	MSc
Pust, Sascha	Postdoc	Sandvig	Germany	Oslo University Hospital	PhD
Raiborg, Camilla	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Rivedal, Edgar	Group leader, Senior scientist	Lothe	Norway	Oslo University Hospital	Dr. Philos
Rodahl, Lina W.	PhD student/Postdoc	Stenmark	Norway	Oslo University Hospital	PhD
Rusten, Tor Erik	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Rødland, Einar	Scientist	Liestøl	Norway	University of Oslo	PhD
Rønning, Eva	Head technician	Stenmark	Norway	Oslo University Hospital	
Sagona, Antonia	PhD student	Stenmark	Greece	Oslo University Hospital	MSc
Sandvig, Kirsten	P.I., professor	Sandvig	Norway	Oslo University Hospital	Dr. Philos
Schink, Kay Oliver	Postdoc	Stenmark	Germany	Oslo University Hospital	PhD
Sem Wegner, Catherine E.	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Sheikh, Danial	Software developer	Danielsen	Norway	Oslo University Hospital	MSc
Silihagen, Mette	Research fellow	Danielsen	Norway	Oslo University Hospital	MSc
Silva, Diogo	Guest PhD student	Lothe	Portugal	Portuguese Oncology Institute	MSc
Simm, Roger	Lab. manager	Sandvig	Sweden	Oslo University Hospital	PhD
Sirnes, Solveig	PhD student/Postdoc	Lothe	Norway	Oslo University Hospital	PhD
Skarpen, Ellen	Scientist	Stenmark	Norway	Oslo University Hospital	PhD
Skotheim, Rolf I.	Group leader, Senior scientist	Lothe	Norway	Oslo University Hospital	Dr. Philos

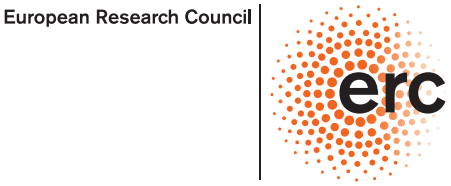
Name	Position	Group	Nationality	Employer	Academic title
Skotland, Tore	Guest scientist	Sandvig	Norway	Oslo University Hospital	Dr. Philos
Sletten, Torunn	PhD student	Wiedlocha	Norway	Oslo University Hospital	MSc
Smedbye, Marianne Lislerud	PhD student	Danielsen	Norway	Oslo University Hospital	MD
Smeland, Erlend Bremertun	P.I., professor	Smeland	Norway	Oslo University Hospital	MD, PhD
Smestad, Marianne	Technician	Stenmark	Norway	Oslo University Hospital	
Steen, Chloe B.	Master student	Stenmark	Norway	Oslo University Hospital	
Stenmark, Harald	P.I., professor	Stenmark	Norway	Oslo Univ. Hosp./ University of Oslo	Dr. Philos
Sundan, Anders	Guest professor	Stenmark	Norway	NTNU	Dr. Philos
Sveen, Anita	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Syvertsen, Rolf Anders	Software developer	Danielsen	Norway	Oslo University Hospital	MSc
Sørensen, Anette	Administrative coordinator		Denmark	University of Oslo	
Sørensen, Vigdis	Postdoc	Wiedlocha	Norway	Oslo University Hospital	PhD
Tcatchoff, Lionel	Postdoc	Sandvig	France	Oslo University Hospital	PhD
Thomassen, Gard O. Sundby	Postdoc	Lothe	Norway	Oslo University Hospital	PhD
Thoresen, Sigrid Bratlie	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Thorsen, Jim	Postdoc	Danielsen	Norway	Oslo University Hospital	PhD
Vedeld, Hege Marie	Master student	Lothe	Norway	Oslo University Hospital	
Vietri, Marina	PhD student	Stenmark	Italy	Oslo University Hospital	MSc
Wenzel, Eva	Postdoc	Stenmark	Germany	Oslo University Hospital	PhD
Wesche, Jørgen	Project leader, Senior scientist	Wiedlocha	Norway	Oslo University Hospital	Dr. Philos
Wiedlocha, Antoni	Group leader, Senior scientist	Wiedlocha	Poland	Oslo University Hospital	Dr. Philos
Wæhre, Håkon	Medical consultant	Danielsen	Norway	Oslo University Hospital	MD, PhD
Yohannes, Zeremariam	Technician	Lothe	Norway	Oslo University Hospital	
Yri, Olav Erich	Phd student	Smeland	Norway	Oslo University Hospital	MD
Zhen, Yan	Postdoc	Wiedlocha	China	Oslo University Hospital	PhD
Ågesen, Trude Holmeide	PhD student	Lothe	Norway	Oslo University Hospital	MSc

The Norwegian Radium Hospital area in front and a fantastic view of the Oslo fjord | Photo: Per Marius Didriksen

The Norwegian Radium Hospital area with the Research Building to the right. | Photo: Per Marius Didriksen

SPONSORS 2011

CCB would like to thank the following funding organizations and sponsors for their valuable financial commitment and support:



ANNUAL REPORT 2011

CCB
Centre for Cancer Biomedicine
Oslo University Hospital
The Norwegian Radium Hospital
Montebello
N-0379 Oslo
Norway

Phone: +47 22 78 18 27

post@ccb.uio.no
www.uio.no/ccb

Established by the Research Council of Norway

Norwegian Centre of Excellence

Oslo University Hospital

UiO : University of Oslo

design | essenz.no

Photos by:
Linda Cartridge
Øystein H. Horgmo, Foto- og videotjenesten, UiO/OUS
Per M. Didriksen, Foto & Grafisk, Radiumhospitalet