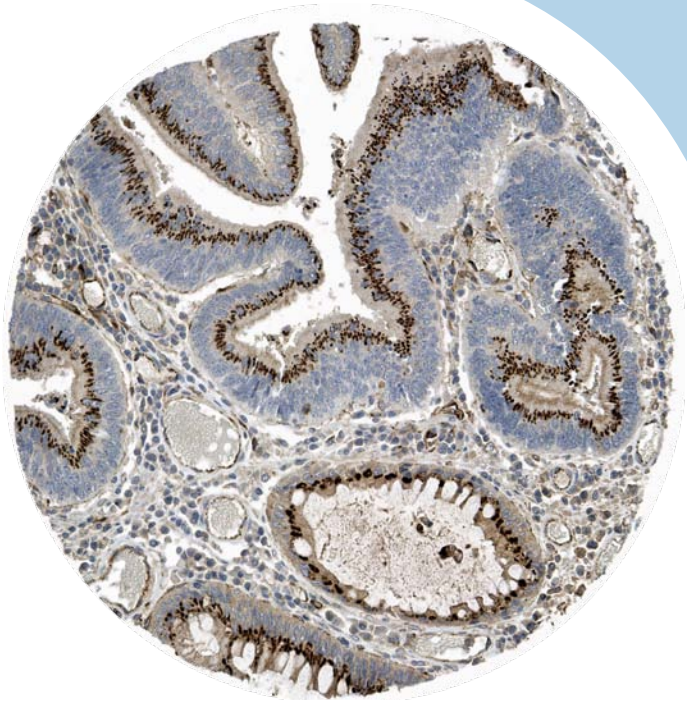


Centre for Cancer Biomedicine

2009

ANNUAL REPORT

CENTRE FOR CANCER BIOMEDICINE MAKES A MOVE

Since its inauguration in September 2007, CCB has made major transformations in order to fulfil its vision, the unification of basic and translational research for the benefit of the cancer patient. The interdisciplinary collaborations within the Centre got a real boost last summer by the move of most of the Centre's scientists into the 3.-6. floors of the West wing in the new research building at the Norwegian Radium Hospital. An increasing number of projects that involve two or more CCB groups have been initiated, and several joint papers have already been published. Furthermore, CCB has implemented state-of-the-art technology platforms that form hubs for collaborations between Centre groups. CCB's ties to the clinic have been strengthened by the appointments of two prominent cancer clinicians, professor Arild Nesbakken and Dr. Harald Holte, as Clinical Associates. The Centre's scientific activity in 2009 has been high, as demonstrated by the publication of 47 scientific papers, 6 PhD and 4 MSc degrees.

A timely example of a successful interdisciplinary CCB collaboration is a project that started with basic cell biological studies of phosphatidylinositol 3-phosphate (PtdIns3P), a lipid known to regulate cellular functions such as membrane traffic and cell signalling. PhD student Antonia Sagona in the Stenmark lab noticed that this lipid accumulates at the midbody, the membrane bridge that separates two dividing cells. Antonia and her co-workers went on to show that the lipid kinase that produces PtdIns3P is required for cytokinesis, the final stage of cell division, and that depletion of this enzyme leads to an increased number of multinucleated cells. These findings were recently published in *Nature Cell Biology* (Sagona et al.). Translational scientists within CCB found this interesting, since the lipid kinase is a known tumour suppressor, and since multinucleation may develop into chromosomal instability, a hallmark of many cancers. A PtdIns3P-binding protein, FYVE-CENT, which turned out to regulate cytokinesis, is indeed frequently mutated in cancer, and ongoing interdisciplinary research in the Centre will resolve whether the PtdIns3P-FYVE-CENT axis can be exploited in cancer diagnostics.

That large-scale genomic instability, measured as tumour chromosomal DNA content (ploidy), can be used as a prognostic tool is illustrated by two recent CCB studies from the Danielsen lab. In a study of prostate cancer, DNA ploidy was shown as an independent predictor of disease recurrence and, importantly, the only significant predictor among a group of patients with advanced disease (Pretorius et al., *Cellular Oncology*). Likewise, ploidy was established as a prognostic marker in patients with uterine cancers (Kildal et al., *Annals of Oncology*).

Another interdisciplinary study involving several CCB groups has identified the well-known tumour suppressor p53 as a strong predictor of survival in patients with malignant peripheral nerve sheath tumour (MPNST), a highly aggressive cancer (Brekke et al., *Neuro-Oncology*). In a multi-centre study led by Ragnhild Lothe, PhD student Helge Brekke and co-workers recently published striking findings in *Journal of Clinical Oncology*. Genomic aberrations at three defined chromosomal positions identify a high risk patient group with only 11% 10-year survival versus 74% for patients without these changes in their tumours.

A universal assay for cancer diagnostics and research has been developed by CCB scientist Rolf Skotheim and co-workers in the Lothe lab (Skotheim et al., *Molecular Cancer*). The ability to detect either of all known fusion genes by one single assay opens for many applications in the clinic as well as in cancer research. A patent application has been filed, and Skotheim and his colleagues are currently working with blinded diagnostic samples from two European laboratories to evaluate the sensitivity and specificity of the second generation array.

A central idea of CCB is to characterize cellular signalling pathways in order to understand carcinogenic mechanisms. Such knowledge can then be exploited for clinical use. A successful example has been provided by a multi-centre international collaboration that involved Erlend Smeland´s group. These scientists used RNA interference screening to establish chronic active B-cell receptor signalling as a new pathogenic mechanism in a subtype of diffuse large B-cell lymphoma, which is of great importance for the choice of therapeutic strategies (Davis et al., *Nature*).

Other signalling pathways of great importance in carcinogenesis are those mediated by growth factors that bind to receptor tyrosine kinases on target cells. Here, CCB scientists have contributed to a new concept by elucidating fibroblast growth factor (FGF) signalling. Postdoc Malgorzata Zakrzewska and her co-workers in the Olsnes lab used protein engineering to show that binding of FGF1 to proteoglycans serves to stabilize the FGF1 molecule and is not critical for its ability to transmit signals through cell-surface receptors (Zakrzewska et al., *Journal of Biological Chemistry*). This contrasts with textbook models for FGF signalling and has therapeutic relevance.

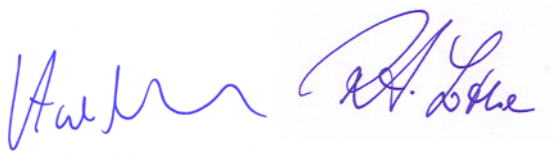
One of the strengths of the cell biological research at CCB lies in studies of intracellular trafficking. Internalization and lysosomal degradation of growth factor receptors serves as an important attenuation of growth factor signalling and plays a role in tumour suppression, as discussed by CCB scientists in recent high-profile commentaries and reviews (Malerød and Stenmark, *Cell*; Raiborg and Stenmark, *Nature*). Work by the Sandvig lab has revealed several novel regulators of endocytic membrane trafficking, including sorting nexins 4 and 8 (Skånland et al. *PLoS One*; Dyve et al., *Biochemical and Biophysical Research Communications*), flotillin and glycosphingolipids (Pust et al., *PLoS One*; Raa et al., *Traffic*). Moreover, cell biologists in the Stenmark lab have characterized the endosomal sorting complex required for transport (ESCRT) machinery in downregulation of growth factor receptors, and showed the role of these protein complexes in tumour suppression in a fly model (Stuffers et al., *Traffic*; Rodahl et al, *PLoS One*). It will now be interesting to extend these basic studies into translational research by examining the possible mutations or aberrant expression of ESCRT components in cancers.

In conclusion, CCB has already made significant progress in understanding basic mechanisms of oncogenesis and tumour suppression as well as identifying molecular and chromosomal traits of potential diagnostic and prognostic value. However, there is no reason to be complacent as the Centre faces great challenges ahead. CCB had its first meeting with its Scientific Advisory Board (SAB) in May 2009, and it was extremely useful to receive advice from these top international cancer researchers (Lena Claesson-Welsh, Marja Jäättelä, Olli Kallioniemi, David J. Kerr and Manuel Sobrinho-Simões). Even though the SAB acknowledged the high-level cancer research at CCB, it had several suggestions for further improvement, including an even stronger emphasis on translational research, more involvement of young scientists, and tighter collaborations between CCB groups. CCB has responded to these suggestions in several ways. In order to strengthen the Centre´s leadership of translational research, Ragnhild A. Lothe has been appointed as co-director, and two Clinical Associates have been appointed. In order to increase the inclusion and visibility of young scientists, CCB has established a scientific leadership forum that includes young project leaders.

A new technological advance is likely to form a core for new collaborations within CCB. The nucleic acid sequencing technology has now advanced to a level where we are able to sequence billions of bases per week with a single machine. In collaboration with the Microarray Core Facility of the Institute for Cancer Research, and with generous sponsorship from the Norwegian Radium Hospital Foundation, CCB has recently acquired an Illumina Genome Analyzer platform for “deep” sequencing. From CCB, wet lab handling is carried out by personnel from the Lothe lab, and this lab together with Liestøl’s group will also take care of the bioinformatics. The first data sets are under analysis, and the preliminary results look very encouraging. In 2008, CCB implemented the Affymetrix microarray technology, and a few hundred colorectal and prostate cancers have been run on exon-level microarrays. These datasets are currently being analysed and we already have exciting new findings both at the global and single-gene level that will be published later this year.

CCB’s commitment to equal opportunities for scientists at all levels has resulted in the first senior scientist hired directly by the CCB, Dr. Alicia Llorente employed as a project leader in the Sandvig lab, and in promotion of several other female scientists as project leaders.

The significant progress in cancer research obtained by the Centre members during the reporting period would not have been possible without extensive collaborations both within the Centre and with national and international partners. We would also like to acknowledge our host institutions, the University of Oslo and Oslo University Hospital, and the Research Council of Norway for supporting our activities in 2009. Finally, we thank our external funding bodies, especially the Norwegian Cancer Society, for continuing to provide vital support to our research.



Harald Stenmark *Ragnhild A. Lothe*

TABLE OF CONTENTS

VISION AND AIMS

Cancer is a highly complex invasive cell disease, unique to small patient groups or even to single patients. Improvement of prognostics, diagnostics and therapy requires an integrated approach based on tumour parameters and patient specific properties. In Centre for Cancer Biomedicine more than 100 scientists from different disciplines share the common focus of disease understanding and development of affordable tools for early detection and tailored treatment of cancer.

Vision

The overall vision is to unite basic and translational research for the benefit of the cancer patient.

The efforts of the centre are aimed towards a better understanding of the complex dynamics of cancer evolution, a more accurate prediction of cancer prognosis and response to treatment and more powerful molecular based treatment.

Scientific aims

- Identify genetic, epigenetic and morphological characteristics of cancer cells
- Develop and implement bioinformatic and biostatistical tools for handling complex data sets from canceromics and image analyses
- Identify and characterize molecular and cellular mechanisms for regulation of cell growth, proliferation, survival, differentiation and motility – and link these to potential cancer biomarkers
- Identify potential biomarkers for cancer, and validate their clinical utility

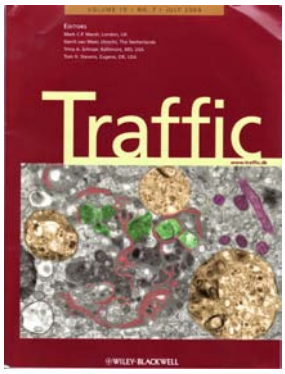
Three cover stories

Joint CCB review presented on the cover of Molecular Oncology

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

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

Article from CCB group on the cover of Traffic



An article from Andreas Brech's project group, with Sanne Stuffers as first author, is the cover story of the July issue of Traffic.

The article is entitled "Multivesicular Endosome Biogenesis in the Absence of ESCRTs". In this article Stuffers and co-workers have used electron microscopy to study the importance of endosomal sorting complex required for transport (ESCRT) proteins in growth factor receptor trafficking.

Figure from Camilla Raiborg paper on the cover of the 2009 edition of Experimental Cell Research

A figure from the paper "Differential functions of Hrs and ESCRT proteins in endocytic membrane trafficking" by Camilla Raiborg and co-workers in Harald Stenmark's group at the Department of Biochemistry (Institute for Cancer Research), published in March 2008, has been selected for the cover of the whole 2009 edition (24 issues) of Experimental Cell Research. In the article the authors characterize the functions and sites of actions of the so-called "endosomal sorting complexes required for transport (ESCRTs) in endocytic membrane trafficking.

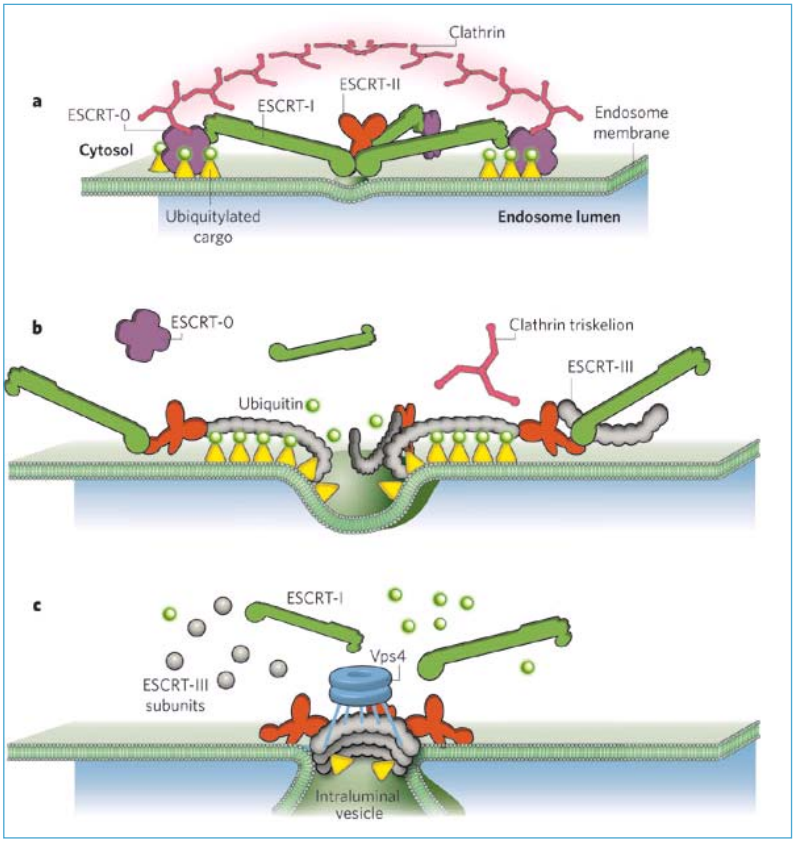
The figure shows two HeLa cells in which a subunit of ESCRT-III has been depleted. Such depletion causes a dispersion of the Golgi apparatus (green). Nuclei are stained in blue and actin in red.

Review and commentary in Nature and Cell

CCB Scientists with Review in Nature

In the March 26 issue of Nature, Camilla Raiborg and Harald Stenmark have published a review about the functions of endosomal sorting complex required for transport (ESCRT) proteins in endosomal sorting of ubiquitylated membrane proteins.

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



The ESCRT machinery in endosomal sorting of ubiquitinated membrane proteins. a) Cargo sorting into clathrin-coated microdomains. Initial recognition of ubiquitinated cargo (ubiquitin shown in red) is mediated by ESCRT-0, which is concentrated in microdomains through interaction with a clathrin coat (violet). ESCRT-0 also serves to recruit ESCRT-I. The elongated ESCRT-I recruits ESCRT-II and possibly contributes to membrane involution (indicated by black shadow). b) Membrane deformation. ESCRT-III is recruited by binding to the two Vps25 subunits of ESCRT-II and forms spiral-shaped filaments that gate cargo into invaginations that are caused by the ESCRT-III filaments. During this process, cargo is deubiquitinated by proteases that are recruited by ESCRT-III, but the diffusion of cargo is strictly limited by the ESCRT-III filaments. c) membrane abscission. As ESCRT-III filaments assemble into circular arrays, the membrane continues to invaginate. Vps4 enters into the invagination to disassemble ESCRT-III filaments, ensuring that filaments only assemble at the neck of the forming ILV. Vps4 may also serve to remove subunits of the neck filaments, thereby contributing to construction of the neck which ultimately causes membrane abscission.

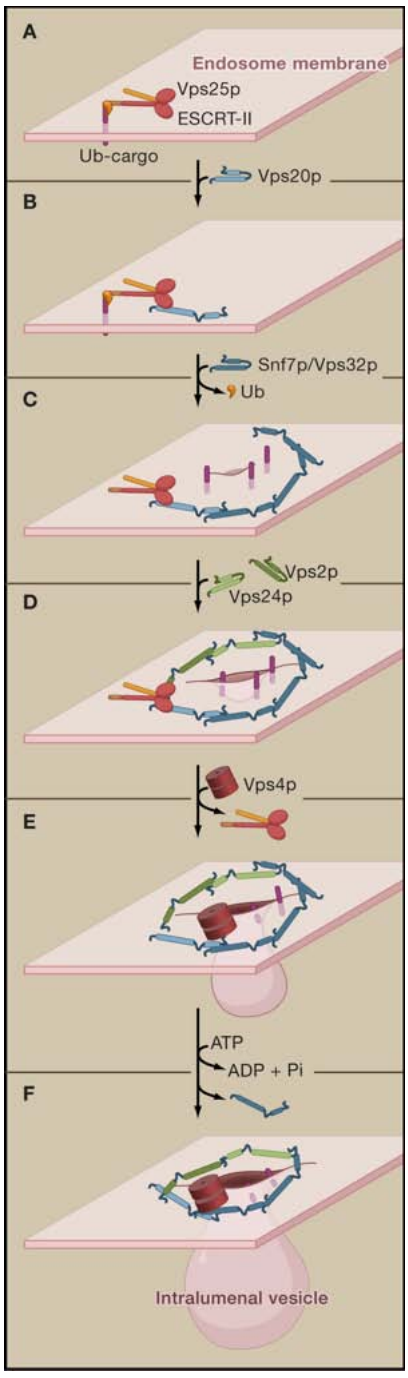
Centre for Cancer Biomedicine researchers with comment in Cell

The ESCRT-III complex mediates membrane budding away from the cytosol in endosome biogenesis, cytokinesis, and viral budding.

In the January 9 issue of Cell, Lene Malerød and Harald Stenmark highlight recent research that defines the sequential activation, recruitment, and disassembly of ESCRT-III subunits during membrane involution in vitro.

Assembly starts with recruitment of the ESCRT-III subunit Vps20p by the ESCRT-II subunit Vps25p on endosomes (A), which causes activation of Vps20p through release of an autoinhibitory interaction (B). The activated Vps20p in turn binds Snf7p/Vps32p and nucleates Snf7p monomers to oligomerize into circular filaments that mediate cargo entrapment and membrane invagination©. Upon binding of Vps24p-Vps2p, oligomerization terminates (D) and Vps4 is recruited (E) and facilitates disassembly of ESCRT-III by releasing Snf7p molecules (F).

The Vps4p-mediated removal of Snf7p monomers at the end of the filament might cause its constriction, ultimately leading to membrane abscission. Each individual interaction facilitates specific conformational changes opening up and closing protein structures allowing only specific partners to interact. Cumulatively, these changes in protein conformations lead to the recruitment of a specific sequence of factors, thereby driving and controlling each step along the pathway for cargo sorting and membrane deformation. ESCRT-III-mediated membrane deformation in cytokinesis and viral budding is likely to be equivalent to that proposed for the biogenesis of intralumenal vesicles, with the exception that the initial recruitment and activation of Vps20 is mediated by other components.



Ordered assembly and disassembly of the ESCRT-III complex to mediate cargo sorting and invagination of endosome membranes.

Selected collaborative studies

Interdisciplinary CCB collaboration on p53

"Identification of p53 as a strong predictor of survival for patients with malignant peripheral nerve sheath tumors" is published from Lothe lab with PhD student Helge Brekke as first author.

Malignant peripheral nerve sheath tumor (MPNST) is a highly aggressive malignancy for which no consensus therapy exists besides surgery. In a Scandinavian interdisciplinary study including several of the CCB groups we have assessed in situ expression of multiple cell-cycle-regulating proteins in MPNST patients. We here developed a new software application for evaluation and logistics for tissue microarray images. p53 was shown to be the best independent predictor of survival among the analysed proteins. Patients without remission, with tumor size larger than 8 cm, and with positive p53 expression had a 60 times greater risk of dying within the first 5 years compared with the remaining patients ($p = 0.000002$). Patients in complete remission with a primary p53-positive MPNST diagnosis may be considered in a high-risk subgroup and candidates for adjuvant treatment.

Reference: Neuro Oncol. 2009 Oct;11(5):514-28. PMID: 19182148

CCB collaboration study on gap junction proteins

"Ubiquitylation of the gap junction protein connexin-43 signals its trafficking from early endosomes to lysosomes in a process mediated by Hrs and Tsg101". CCB project leader Edward Leithe is first author.

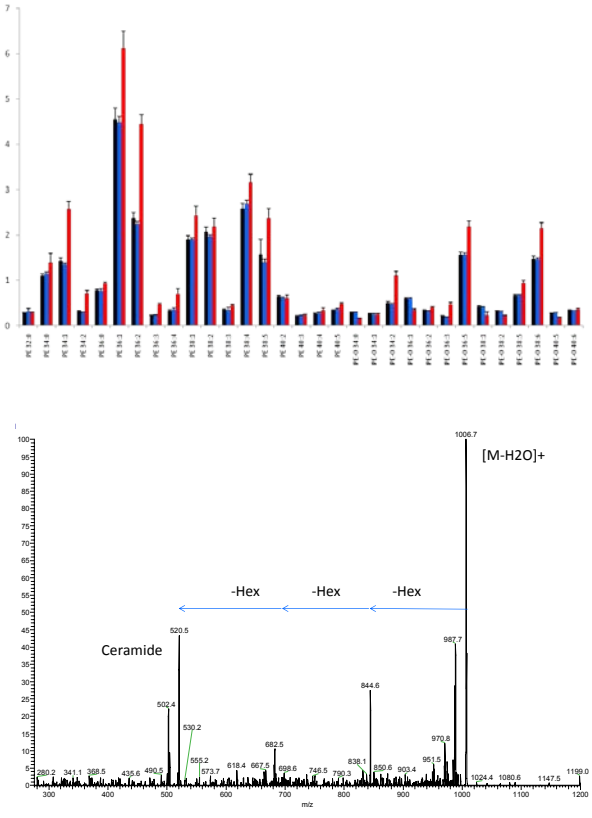
Gap junctions are dynamic plasma membrane domains, and their protein constituents, the connexins, have a high turnover rate in most tissue types. However, the molecular mechanisms involved in degradation of gap junctions have remained largely unknown. Here, we show that ubiquitin is strongly relocalized to connexin-43 (Cx43; also known as Gja1) gap junction plaques in response to activation of protein kinase C. Cx43 remained ubiquitylated during its transition to a Triton X-100-soluble state and along its trafficking to early endosomes. Following internalization, Cx43 partly colocalized with the ubiquitin-binding proteins Hrs (hepatocyte growth factor-regulated tyrosine kinase substrate; also known as Hgs) and Tsg101 (tumor susceptibility gene 101). Depletion of Hrs or Tsg101 by small interfering RNA abrogated trafficking of Cx43 from early endosomes to lysosomes. Under these conditions, Cx43 was able to undergo dephosphorylation and deubiquitylation, locate to the plasma membrane and form functional gap junctions. Simultaneous depletion of Hrs and Tsg101 caused accumulation of a phosphorylated and ubiquitylated subpopulation of Cx43 in early endosomes and in hybrid organelles between partly degraded annular gap junctions and endosomes. Collectively, these data reveal a central role of early endosomes in sorting of ubiquitylated Cx43, and identify Hrs and Tsg101 as crucial regulators of trafficking of Cx43 to lysosomes.

Reference: J Cell Sci. 2009 Nov 1;122(Pt 21):3883-93. PMID: 19808888

Emerging topics in cancer research

Lipids in intracellular transport – an emerging field

Changes in membrane lipids have been found to be associated with growth and metastasis of cancer cells. However, lipids have been partly ignored due to the difficulties in analyzing them. A collaborative study where the planning as well as the cell biology and biochemical work were performed by Sandvig's group and the lipid analysis (mass spectrometry of whole cell extracts) was carried out at Max Planck Institute in Dresden resulted in an article correlating changes in transport with changes in lipids and localization of proteins involved in sorting (Raa et al., Traffic 2009). More than 250 lipids were analyzed, and the data show that lipids clearly deserve more attention than received so far when studying intracellular transport.



Lipid analysis

A novel microarray design

Molecular Cancer paper entitled "A universal assay for detection of oncogenic fusion transcripts by oligo microarray analysis" published by project leader Rolf I. Skotheim from Lothe's group.

The ability to detect neoplasia-specific fusion genes is important in clinical settings to ensure that correct diagnosis is made and the optimal treatment is chosen. However, the available methodologies to detect such fusions all have their distinct short-comings. Skotheim and colleagues published in 2009 a novel oligonucleotide microarray strategy whereby one can screen for all known oncogenic fusion transcripts in a single experiment. This first generation of this new array contained 68,861 oligonucleotide probes that includes oligos covering all combinations of chimeric exon-exon junctions from 275 pairs of fusion genes, as well as sets of oligos internal to all the exons of the fusion partners. The proof of principle was demonstrated by detection of known fusion genes in all six positive controls consisting of leukemia cell lines and prostate cancer biopsies. This new method bears promise of an important complement to currently used diagnostic and research tools for the detection of fusion genes in neoplastic diseases.

A second generation tool is already developed and the sensitivity and specificity of this tool is currently being explored by blinded analyses of diagnostic samples of sarcomas and leukemias from two European laboratories.

Reference: Mol Cancer. 2009 Jan 19;8:5. PMID: 19152679

Radio

Harald Stenmark was invited as Lunch guest to speak about *Cancer* in NRK Østlandssendingen, 30 December 2009.

Newspapers/Magazines

CCB group leader Ragnhild A. Lothe, interviewed in Dagens Næringsliv

On 6 March 2009 the Norwegian economic newspaper *Dagens Næringsliv* published a supplement covering biotechnology subjects. Ragnhild A. Lothe gave an interview about her research projects. The article, in Norwegian only, holds the title *Tidlig diagnostikk – et mulighetens vindu.*

- Det er fortrinnsvis innenfor de fire store kreftformene at innsatsen har vært konsentrert, nemlig bryst, prostata, lunge og tykk- og endetarmskreft. Spesielt gjelder det tykk- og endetarmskreft. Her er dødeligheten høyest, samtidig som et langt forstadie gjør det mulig å oppdage og behandle kreften tidlig, før den blir ondartet og før det oppstår spredning til andre organer, sier Ragnhild A. Lothe, professor og forskningssjef på avdeling for kreftforebygging ved Radiumhospitalet.

Tidlig oppdagelse av tykktarmskreft

Interview with Guro Elisabeth Lind, APOLLON No. 2/2009, in Norwegian only: Oppdager tykktarmskreft før den blir dødelig

Interview with Guro Elisabeth Lind, Aftenposten, 3 June 2009, in Norwegian only: Tykktarmskreft kan oppdages tidlig

Guro Elisabeth Lind (Foto: Ola Sæther)

- Hvert år får 3500 norske kvinner og menn kreft i tykktarmen. Mange lever med kreften uten å vite om den – helt til den blir dødelig. Nå har en ung forsker funnet fram til en metode som oppdager kreften mens den ennå kan kureres.

En vinner i norsk forskning

Interview with Harald Stenmark, Morgenbladet, 2 October 2009, in Norwegian only.

- CCB driver med både grunnforskning i cellebiologi og med anvendt forskning i samarbeid med leger som behandler kreftpasienter. Kreft er det samme som ukontrollert cellevekst, forklarer Stenmark. Hans forskere studerer hvordan cellevekst starter, og hvordan den kan stoppes.

- Senteret er attraktivt for utenlandske forskere, de ansatte blir hyppig invitert til konferanser verden rundt, og publiseringstakten er høy. CCB ser ut til å lykkes med å være blant de beste.

– SFF-statusen gjør det mulig å samhandle innen flere disipliner og å satse stort, sier Stenmark.

Cancer cell migration and metastasis

The Norwegian Cancer society awarded support to Jørgen Wesche's project "Cancer cell migration and metastasis" in 2009. In addition, Jørgen Wesche and the project were selected to be presented in advertisements in major Norwegian newspapers, autumn 2009.

Jørgen Wesche: Forsker ved Radiumhospitalet

– Jeg arbeider med å finne en metode som kan hindre at kreftceller sprer seg. Forskningspengene jeg har fått fra Kreftforeningen gjør det mulig å få gode resultater enda raskere.

Har funnet nye fraktruter i cellene

Interview with Audrun Utskarpen, www.forskning.no, 10 December 2009, in Norwegian only.

Cellene våre består av mange små rom, og nærings- og signalstoffer blir transportert mellom rommene ved at de fester seg på ulike fraktmolekyler. Ny forskning har kartlagt flere fraktruter, noe som bidrar sterkt til blant annet kreftforskning.

Audrun Utskarpen
(Foto: Kristin Storbæk)

- Rommene i cellene våre kalles organeller, og alle har hver sin funksjon. Det er derfor viktig at det som skjer i en celle foregår i riktig rekkefølge.

- Dersom transportrutene ikke fungerer, kommer ikke nærings- og signalstoffene dit de skal. Dette er skadelig for cellene og kan føre til at blant annet kreftceller ikke får beskjed om å slutte å dele seg, forklarer Audrun Utskarpen.

I sin ferske doktorgrad i bioteknologi ved Universitetet i Oslo har Utskarpen i samarbeid med Radiumhospitalet funnet nye baner som transporterer giftstoffer (toksiner) fra rom til rom i cellene våre.

Dette kan bidra til å forstå hvordan kreft oppstår og hvordan den kan bekjempes.

Growth factor signalling and cancer

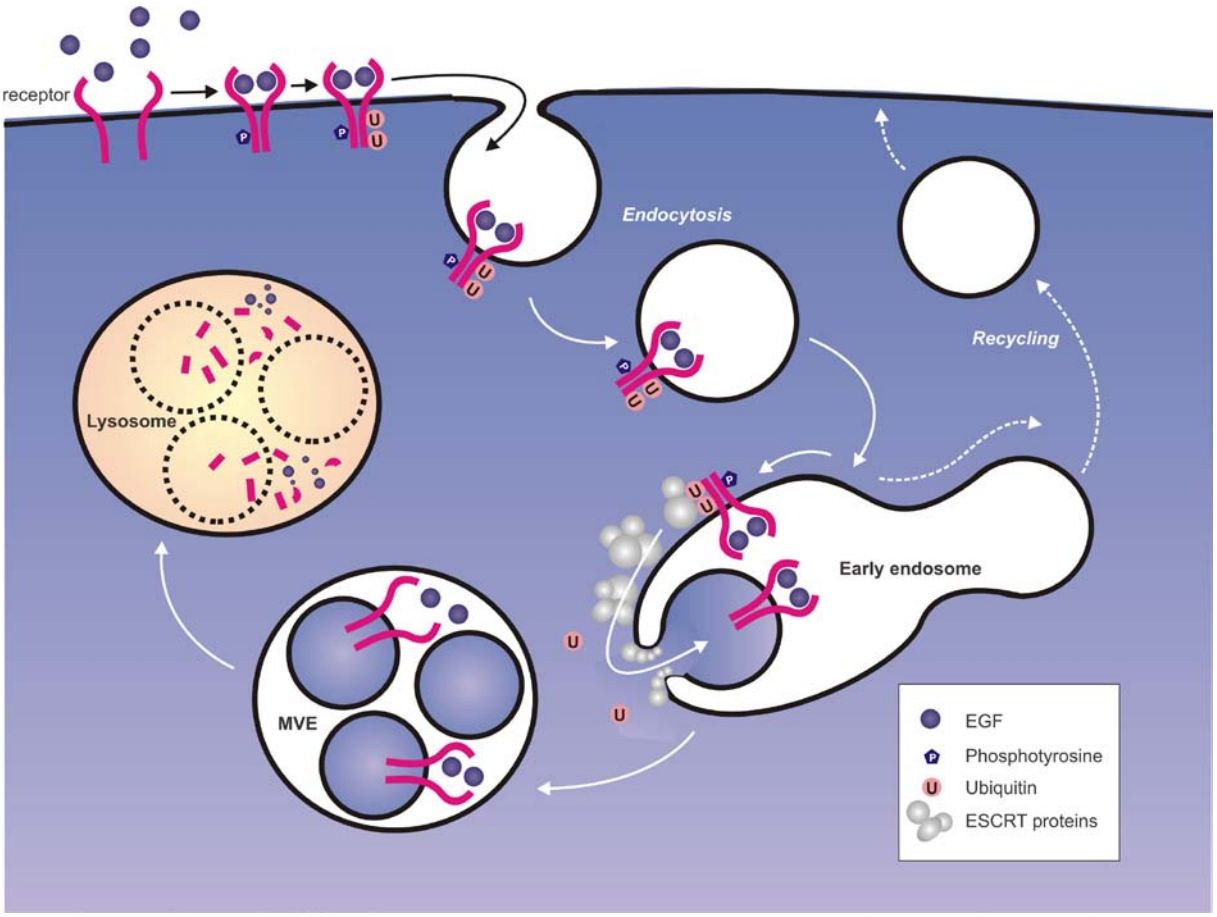
Hyperactive growth factor signalling is a hallmark of many cancers. One of the joint activities in CCB is to characterize a mechanism that serves to attenuate growth factor signalling in normal cells, and to establish how this mechanism is disrupted in cancer cells.

A key mechanism in cancer development is that certain cells change their intrinsic properties and become unresponsive to their surroundings, thereby neglecting normal signals that restrict cell survival and proliferation. Such signals are provided by chemical compounds that are secreted by some cells and received by other cells. Among the variety of chemical compounds that function in signalling between cells, **growth factors** play a key role in cancer. Growth factors are small proteins that bind to **receptors** on target cells and thereby provide instructions for the behaviour of these cells. Cancer cells often contain elevated numbers of growth factor receptors, which make them more sensitive to proliferation and survival signals, thereby promoting their growth and aggressiveness. One of the strategies of CCB in cancer biomedicine is therefore to identify and characterize molecular mechanisms that lead to elevated levels of growth factor receptors, in the hope that disruption of such mechanisms can be turned against the cancer cells.

One of the mechanisms that regulate the numbers of growth factor receptors is the internalisation and degradation of the receptors in response to growth factor binding. This is particularly well documented in the case of epidermal growth factor (EGF) and its receptor (EGFR). Binding of EGF to EGFR causes the receptor to dimerise. Because the intracellular domain of the receptor is an enzyme that is capable of phosphorylating protein tyrosine residues, EGF-induced dimerisation causes autophosphorylation of the receptor. The phosphotyrosine groups are recognized by various signalling molecules that serve to transmit signals to the nucleus, the “brain” of the cell. However, activation of the EGFR not only initiates signalling cascades but also triggers internalization of the receptor from the cell surface by a membrane involution process known as **endocytosis** (see Figure). Endocytosis results in the inclusion of the EGFR within the membrane of an endocytic vesicle, which delivers its cargo to an **early endosome**. Here, the receptor is still able to transmit signals, but it is on a road to destruction.

Among the molecules that bind to tyrosine-phosphorylated EGFR is an enzyme that catalyzes the attachment of a small protein, **ubiquitin**, to the intracellular part of the receptor. Ubiquitin essentially functions as an address tag for the EGFR, instructing its delivery to the **lysosome**, an organelle filled with degradative enzymes. The ubiquitinated EGFR becomes recognized by a molecular machinery in the endosome membrane, endosomal sorting complex required for transport (ESCRT). This machinery mediates the invagination of the endosome membrane, the sorting of activated EGFRs into these invaginations, and their abscission to form **intraluminal vesicles** (ILVs) that contain the receptors (reviewed by Raiborg and Stenmark, *Nature* 458, 445-452, 2009). Since EGFRs are unable to transmit signals when trapped within ILVs, this sorting process is an efficient way of shutting off receptor signalling. Moreover, when the endosomes that contain ILVs, often referred to as **multivesicular endosomes** (MVEs), fuse with lysosomes, the ILVs and their content are degraded, thereby requiring synthesis of new EGFRs for further signalling to occur.

The fact that the ESCRT pathway mediates downregulation of growth factor receptors and attenuates their signalling has raised the possibility that this pathway functions in tumour suppression. Indeed, one of the human ESCRT subunits identified by CCB scientists, VPS37A, is a putative suppressor of hepatocellular carcinoma. Moreover, a protein found to CCB scientists to interact with VPS37A, TSG101, was originally identified as a suppressor



of breast cancer in mice. In collaboration with David Bilder´s group at the University of California, Berkeley, project leader Tor Erik Rusten and his co-workers in Harald Stenmark´s CCB lab have established multiple ESCRT subunits as tumour suppressors in fruit flies, and these studies have shown that several signalling pathways are hyperactive in fly tissues with improper ESCRT functions. The collective data thus point to a role for ESCRTs in receptor downregulation, signal attenuation and tumour suppression.

In spite of the data obtained in flies and mice, there is no definitive evidence that ESCRTs are genuine tumour suppressors in humans. Interdisciplinary collaborations within CCB aim at resolving this issue. For this purpose, the expression levels and mutation status of ESCRT subunits are being studied in tumour biopsies. Should the hypothesis be confirmed, that ESCRTs are tumour suppressors in humans, these molecules will be excellent candidates for biomarkers in cancer. Such biomarkers may potentially be used for cancer diagnostics and prognostics, thereby forming a basis for improved therapy.

”Talking up translation”

This title refers to *Nature* news January 2010, which presented Alan Ashworth, his speed in moving **from basic science to the patient** and his strong dedication to an **integrated approach** for translational medicine. The **CCB vision** shares this philosophy, and through the first two years we have been able to initiate a number of collaborative projects that integrate basic biology with clinical challenges (see project list). The integrated approach requires **interdisciplinary work** that includes cell biologists, biostatisticians, translational cancer researchers and dedicated pathologists and clinicians.

The lymphoma research in CCB, led by **Erlend B. Smeland**, has enjoyed international success by this approach, as demonstrated by several publications in the world's leading journals (*New England Journal of Medicine*, *Science*, and *Nature*) that go hand in hand with the improved diagnostics and treatment of lymphoma patients. Smeland leads a group of basic scientists who explore new hypotheses through new projects initiated within CCB. This group has broadened the use of advanced technologies in their own lab and applies new and integrated approaches with other CCB groups. In January 2010, Smeland once again co-authored a *Nature* paper on lymphoma research.

Erlend B. Smeland

The success of CCB will be obtained through frontier science also for the other malignancies being studied (including colorectal and prostate cancer) and transfer of knowledge into clinical use. For a rare cancer, malignant peripheral nerve sheath tumour, we run a strong **European multicentre study** that has resulted in several recent publications (Brekke et al., *J Clin Oncol* 2010; Brekke et al., *Neuro Oncology* 2009). This project depends on an on-site oncology ortopedic expert clinic and reference pathologists, a setup that works smoothly in the current project.

Lessons learnt from hereditary diseases with cancer phenotypes have been clearly documented and may be applicable to the biology and clinical management of more common diseases. This type of knowledge is also used in designing new projects and hypotheses. One of the new projects involves the LKB1 gene, which predisposes to Peutz-Jeghers syndrome. LKB1, which encodes a protein kinase, was cloned after chromosome comparative genomic hybridisation studies of tumours from Peutz-Jeghers syndrome patients and showed copy number aberrations in a specific chromosomal position. Kinases in general are known to be of great importance in cancer, and represent attractive therapeutic targets. Two of the **young project leaders** of CCB, **Rolf I. Skotheim** and **Tor Erik Rusten** take advantage of this knowledge in their ongoing novel approaches: Rolf is developing a novel microarray tool that can test all known fusion genes in one assay (proof-of-principle shown in Skotheim et al., *Mol. Cancer* 2009), and Tor Erik is studying the importance of LKB1 and similar kinases in an in vivo model system. Both of these project leaders have recently received the Ragnar Mørk legacy prize.

Rolf I. Skotheim

Tor Erik Rusten

June Myklebust

Alicia Llorente Martinez

The CCB promotes **equal opportunities**, and young female scientists are now taking centre stage in CCB´s research. **June Myklebust** is currently a project leader in the Smeland group and has published twice in *Blood* last year after a successful guest visit at Stanford University. **Alicia Llorente Martinez** has been recruited by CCB for a project leader position to work with basic prostate cancer research. An initiative was taken by the directors of CCB and the guest professor Manuel R. Teixeira to join an Innovative Medicines Initiative (IMI) grant application on biomarkers to strengthen international collaborations on colorectal cancer and prostate cancer. Our “expression of interest” was in March 2010 evaluated as number two out of 27 applications.

CCB has established several advanced technologies in its own laboratories, and initially the **new generation equipment** of microarrays and deep-sequencing platforms are being used for colorectal cancer projects. The implementation of the new technology has already proven successful, and the first manuscripts using this technology are currently in preparation. With CCB’s many top scientists, our integrated approach and our aim of improving the life for cancer patients, we enthusiastically move forward translational cancer medicine. We are grateful for the possibilities offered through the Medinnova/Birkeland technology transfer office and the Oslo Cancer Cluster initiative with regard to reaching the final translational step into commercial development.

RESEARCH GROUPS

Stenmark's group

About

Stenmark's group studies mechanisms that control the proliferation, growth and motility of cells, and how dysregulation of these processes may cause cancer. Cellular pathways of particular interest to the group include endocytosis and degradation of growth factor receptors, autophagy, and cytokinesis. All these processes are known to contribute to tumour suppression, and the group is trying to elucidate the underlying molecular mechanisms in the hope that these may reveal pathways that may be exploited diagnostically or therapeutically. The translation of this research into applications that benefit cancer patients occurs in close collaboration with biostatisticians and translational cancer researchers in CCB. The model systems employed by the group include fruit flies and cultured cancer cell lines, and a range of biochemical, molecular biological, genetic and cell biological methods are employed. In particular, confocal and electron microscopy is central to the group's work, and the CCB biostatisticians contribute with quantitative analyses of imaging data.

Challenges

- To identify molecular mechanisms responsible for the regulation of growth factor receptor signalling, autophagy and cytokinesis.
- To clarify the contribution of such mechanisms to tumour suppression or promotion.

Projects

- Endocytic downregulation of growth factor receptors and its role in tumour suppression
- Integrin trafficking and cancer
- Cytokinesis and cancer

Recent discoveries

The lab has been characterizing the cellular functions of class III phosphoinositide 3-kinase (PI3K-III), a known tumour suppressor, in cell regulation. A central discovery was the identification of the FYVE zinc finger domain, and the demonstration that this domain binds specifically to the PI 3-kinase product, phosphatidylinositol 3-phosphate (PI3P) (Gaullier et al., *Nature*, 1998). Using a tandem FYVE domain (2xFYVE) as a probe, the lab demonstrated the enrichment of PI3P on endosomal membranes (Gillooly et al., EMBO J., 2000). The lab has identified several PI3P effectors in endocytic membrane trafficking, including EEA1 as an effector of Rab5 and PI3P in endosome fusion (Simonsen et al., Nature, 1998), and Hrs and the downstream ESCRT machinery in sorting of ubiquitinated membrane proteins (including activated growth factor receptors) from endosomes to lysosomes (Raiborg et al., *Nat.Cell Biol.* 2002; Bache et al., *J. Cell Biol.* 2004; reviewed in Raiborg and Stenmark, *Nature* 2009). Autophagy, a process that involves the sequestration and degradation of portions of cytoplasm, plays a role in both tumour suppression and promotion (reviewed in Brech et al., *Mol. Oncol*. 2009). Stenmark´s lab was the first to identify a mammalian PI3P effector in autophagy, Alfy (Simonsen et al., *J.Cell Sci.* 2004), and has identified important crosstalk between endocytic trafficking and autophagy (Rusten et al., *Curr.Biol*. 2007). While PI3K-III promotes autophagy, the lab also discovered that another enzyme, PI3K-I, is downregulated in order to trigger developmentally-induced autophagy in the fruit fly Drosophila. The downregulation of PI3K-I is mediated by a steroid hormone, ecdysone (Rusten et al., *Dev. Cell* 2004). One of the most recent accomplishments of Stenmark´s lab is the discovery that PI3K-III and PI3P control cytokinesis, the final stage of the cell division process. Using siRNA screening, the PI3P-binding FYVE-CENT protein was identified as a key PI3P effector in cytokinesis, and a functional mechanism for this protein in cytokinesis has been elaborated (Sagona et al. *Nat.Cell Biol.* 2010). Because FYVE-CENT is frequently mutated in cancer, and because faulty cytokinesis has been implicated in carcinogenesis, this cellular process is one of the current focus areas of the lab.

Sandvig's group

About

Our group is interested in the mechanisms of endocytosis and intracellular transport. Uptake of receptors and ligands and correct intracellular sorting of endocytosed molecules are crucial for maintenance of a normal differentiated phenotype. Protein toxins are now well established as markers for studies of membrane traffic, as tools in molecular cell biology, and they are used in cancer diagnosis and therapy. This project aims at increasing our knowledge about transport and signaling both in normal and tumor cells in order to provide a rational basis for treatment and prevention of disease.

Challenges

Errors in trafficking and signaling are associated with cancer, and the differences in expression of surface molecules and transport/signaling between normal and cancer cells can be exploited to detect and kill tumor cells using drugs based on protein toxins. The Shiga toxin receptor is overexpressed by a number of human tumors, and Shiga toxin or its binding subunit can be used for *in vivo* tumor targeting and imaging. Importantly, a number of the protein toxins, such as ricin, diphtheria toxin and Shiga toxin are of interest also in connection with targeted drug delivery of toxin conjugates. To construct active toxin conjugates, it is important to know which part of the toxin molecule to include, and whether the construct needs targeting to a specific intracellular compartment. For this purpose, knowledge about the relationship between toxin structure and function and the mechanisms involved in intracellular sorting is essential. By using a combination of morphological, biochemical and molecular biological approaches, we are investigating the various aspects of intracellular transport, and we are characterizing the impact of protein complexes, kinases and specific membrane lipids on intracellular sorting. Several international collaborations are ongoing to increase the impact of our projects.

Projects

1) Protein toxins: Probes for intracellular transport and tools in medicine. Toxins are used to discover and characterize intracellular pathways. A main focus of the group is to investigate these mechanisms to provide the scientific basis for cancer diagnosis and therapy. **2) Entry of nanoparticles into cells.** This project aims at gaining more knowledge about the endocytic mechanisms and intracellular pathways followed by various nanoparticles in cells, and the role of size and composition of nanoparticles for the compartments reached and for clearance from the cells is studied. Very little is known about these topics, although such knowledge is essential for exploiting nanoparticles in medicine. **3) Membrane transport in prostate cancer cells: Release of microvesicles.** The principal objective of this project is to obtain knowledge on vesicular transport in prostate cancer cells. This will increase our understanding of prostate carcinogenesis.

Recent discoveries

We were the first to publish that a molecule can be transported all the way from the cell surface, through endosomes, to the Golgi apparatus and then retrogradely to the endoplasmic reticulum (Sandvig et al., Nature 358 (1992) 510-512). Since then, we and others have been unraveling the complex machinery involved in intracellular sorting, and toxins have proven useful to investigate the complexity of endocytic mechanisms, the pathways between endosomes and the Golgi apparatus, as well as transport to the ER. Some recent findings on proteins involved in transport published by our group in 2009: Shiga toxin induces Syk-clathrin interactions (Wälchli et al., Cell.Signalling 21 (2009) 1161-1168); A role for SNX4 in Golgi transport (Skånland et al., PLoS ONE 4 (2009) e5935); A role for β-arrestins in Golgi transport (Skånland et al., Cell. Microbiol. 11 (2009) 796-807); The first description of localization and role of SNX8 (Dyve et al., Biochem. Biophys. Res. Commun. 390 (2009) 109-114). Importantly, new technologies in mass spectrometry of lipids have revealed the importance of performing cell lipidomics when studying intracellular transport; this is exemplified with our study of the influence of glycosphingolipid species on Golgi transport (Raa et al., Traffic 10 (2009) 868-882).

RESEARCH GROUPS

Smeland's group

About

Our group studies B-cell lymphoma, which is a solid cancer of lymphocytes of the immune system, and often originates in lymph nodes. B-cell lymphomas represent a heterogeneous group of diseases consisting of many subgroups that can be separated on the basis of tumor's molecular signature and hallmark translocations. The different subgroups differ highly in clinical course. New therapeutic approaches, in particular treatment with monoclonal antibodies (Rituximab, targeting CD20), in combination with chemotherapy, has highly improved the outcome. However, many patients still experience relapse. To address various aspects of B-cell lymphoma biology, the group has a translational focus, using primary patient samples and the patients clinical data, in order to identify changes of importance for response to therapy and overall survival. Second, the clinical important changes are followed up by basic cell biology research, using B cell lymphoma cell lines as models. Central techniques includes studies of signalling pathways by Westen blot analysis and multicolour flow cytometry, confocal microscopy, tissue micro array (TMA), array copy number genetic changes (aCGH), and gene expression profiling. The group has significant international collaboration and has established collaboration with other groups in CCB, including Department of cancer prevention as well as the biostatisticians and imaging people, in order to handle the complex patient sample data sets, and to obtain automatic scoring of TMAs.

Challenges

In B-cell lymphoma, most patients initially respond to therapy. However, in certain subgroups which include follicular lymphoma, many patients experience relapse and their tumours become therapy resistant. Thus, there is a need to develop methods which, at time of diagnosis, can predict who will respond and who will not. There is also a need to identify therapeutic targets. Furthermore, in the era of Rituximab treatment, most of the pre-existing biomarkers have lost their predictive power. Hence, new reliable biomarkers are needed.

Our aims are to:

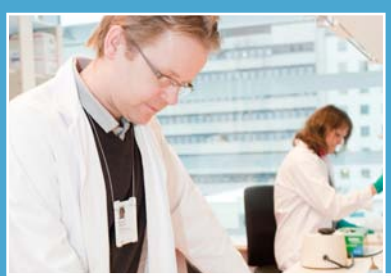
- Identify new biomarkers
- Identify genetic, epigenetic or proteomic changes associated with adverse prognosis in various lymphoma subgroups
- Identify candidate genes/proteins that can be therapeutically targeted

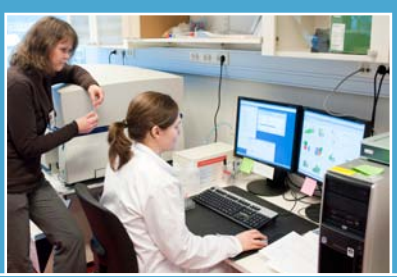
Projects

- Characterization of signaling pathways in B-cell lymphoma at the single cell level
- The impact of BMP/TGF-β signaling pathways in B cell lymphomas
- CGH array and expression profiling of serial biopsies of follicular lymphoma
- Immunohistochemical analysis of signaling pathways and infiltrating cells during progression and transformation of follicular lymphoma using TMAs
- Epigenetic mechanisms in the development of malignant lymphoma
- Interaction of TGF-beta and PI3-kinase signaling pathways in B cell lymphoma
- Studies of SNPs in immune response genes and genes involved in drug metabolism – correlation to clinical parameters in malignant lymphoma

Recent discoveries

June Myklebust worked in the laboratory of Ronald Levy, Stanford University, 2008–2009. Together with Jonathan Irish, she used flow cytometry to study antigen receptor and cytokine induced signaling at the single cell level in primary lymphoma patient samples, to identify signalling profiles that could predict patient's response to therapy and overall survival. In follicular lymphoma, they identified a negative prognostic subpopulation of lymphoma cells, characterized by being insensitive to antigen receptor signaling (Irish et al, submitted). This technology which is very powerful to discover tumor cell heterogeneity is now established in the Smeland laboratory and can be used for any biopsy where single cell suspension can be made.





Olsnes' group

About

Different types of imbalances in FGFs signaling cause a wide spectrum of pathological conditions in human including many developmental disorders as well as different types of cancer. Nuclear FGF1 and FGF2 have been reported to be involved in regulating DNA and rRNA synthesis and cell growth as well as in tumor metastasis formation process. Intracellular FGF2 accumulates in the nucleus during hypoxia, in a positive feedback loop with hypoxia-induced factor 1α. Direct involvement of FGFs/FGFRs in carcinogenesis of human cancer has been proved for prostate, bladder and urothelial tumor as well as in some hematologic malignances. A large body of evidence also implicated FGFs as mediator of tumor angiogenesis and stress-induced agents able to rescue the tumor tissue. Importantly, FGFs are the growth factors used to expand stem cells, including human embryonic stem cells and several tissue-specific stem cells. Moreover, it has recently been recognized that FGFs are useful for culturing cancer stem cells derived from various types of human tumor tissue, though the molecular mechanisms underlying the control of stemness by FGFs still remains elusive.

Challenges

Since FGF-induced inappropriate signaling often led to tumor initiation as well as to development of malignant/metastatic phenotype in many types of human cancer, this project aims to understanding in details the fundamental mechanism of the growth factor action including (i) FGF1 and FGF2 translocation into the cytosol and nucleus, (ii) identification of new intracellular FGF1 and FGF2 binding partners, (iii) endocytosis, sorting and down-regulation of activated FGFRs – what would be beneficial for finding new molecular targets for anti-cancer therapy.

Projects

1) Vesicular transport and translocation to the cytosol and nucleus of FGF1 and 2. In this project we are studying the mechanism for translocation of FGF1 and FGF2 into cells and we are trying to elucidate which cellular responses are elicited by the translocated growth factors. **2) Identification of intracellular proteins interacting with FGF1.** This project aims to identify new intracellular proteins able to interact with translocated FGF1. **3) Cancer cell migration and metastasis.** The project will lead to new insight into the process of cancer cell migration that may pave the way for new drug-targets in metastatic cancers.

Recent discoveries

Identification of a functional and transferable FGF1 nuclear export sequence (NES). The FGF1 NES was found to be situated along a β-strand, which has not been reported before. Demonstration that FGF1 binds to exportin1 and RanGTP, (to form the nuclear export complex), and that the binding is FGF1 phosphorylation dependent (Nilsen T., et al., J. Biol. Chem., 2007, 287, 26245-26256). Demonstration that translocation of FGF1 to the cytosol and nucleus requires active p38 MAPK. The requirement for p38 MAPK activity is due to the requirement for p38 MAPK-mediated phosphorylation of FGFR1 at Ser777, demonstrating for the first time a specific role for serine phosphorylation of FGFR1 (Sorensen V., et al., Mol. Cell. Biol., 2008, 28, 4129-4141). Demonstration that ubiquitination is important for sorting FGFR1 and FGFR4 but not for their endocytosis (Hausten et al., Mol. Biol. Cell., 2008, 19, 3390-3403). Demonstration that FGF1 can deliver heterologous polypeptides into the cytosol and nucleus of mammalian cells (Zakrzewska M. et al., Biochemistry, 2009, 48, 7209-7218). Demonstration that main role of heparin/heparans is to protect FGF1 against heat and proteases under physiological conditions and that it is not required to form functional FGF/FGFR complex (Zakrzewska M. et al., J.Biol. Chem., 2009, 284, 25388-25403). Discovery that while FGFR1 are mainly internalized via a clathrin- and dynamin-dependent pathway, internalization of FGFR3 occurs also by an alternative mechanism that involves neither clathrin nor dynamin. Depletion of cells for clathrin prolonged FGFR1 signalling whereas FGFR3 signalling was hardly affected (Haugsten E., et al., manuscript submitted).

RESEARCH GROUPS

Statistical analysis unit

by Knut Liestøl

About

The statistical analysis unit is part of the Biomedical research group (BioMed) at the Department of Informatics, University of Oslo. The research activity in the BioMed group is directed towards methods development and applications of biostatistics, bioinformatics and computational science in the medical sciences, and in particular in medical genomics.

Aims

The statistical analysis unit in CCB aims at

- Supporting the activity of the CCB groups by providing data analysis, primarily through working within CCB projects but additionally by adressing more specific statistical questions arising in CCB.
- Developing methods and software for relevant biostatistical problems, typically motivated by problems originating from concrete biomedical investigations.

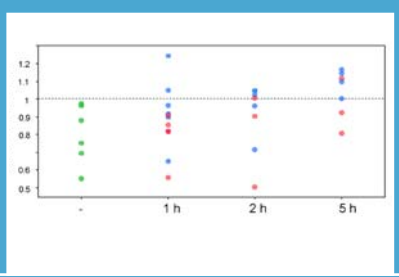
Challenges

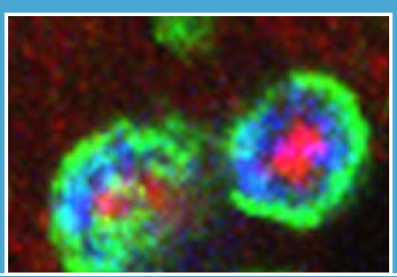
The statistical analysis group has its main activity within analysis of data from high throughput technologies in genetics and molecular biology. While rich in information, the complexity of these large data sets makes extraction of information a true challenge. As opposed to the typical situation in 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 biomedical research groups and also to obtain own competence in the application areas. Typically, projects in the group initially focus on a concrete biomedical problem; we then try to solve the statistical challenges in a broader context and finally develop adapted software tools. On the methodological side, our focus has been on problems from survival analysis, nonparametric/nonlinear statistical modeling, and how to handle many covariates in regression.

Recent work

One main area of work has been the analysis of copy number alterations, including further development of the CGHexplorer system (Bioinformatics 2005, 21, 821-822) and the release of a new R-based program system. The latter includes tools for simultanous estimation from several samples, partly developed to solve problems arising when analysing lymphoma data within CCB. Another main effort has been the analysis of siRNA screens. Additionally, we address other statistical problems arising in CCB, including problems related to biomarkers and in translational research.





Danielsen's group

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 the tumorigenesis process and serves to create a permissive environment for the occurrence of alterations in tumour suppressor genes and oncogenes.

Danielsens group are developing high throughput methods for detection and characterisation of large-scale genomic instability, 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 prostate, colorectal, breast, oesophagus and gynaecological cancers.

Challenges

The first aim is to complete the methodology and develop a 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, CGH, Karyotyping), will be 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.

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, Cellular Oncology, 2009), in uterine sarcomas (Kildal et al, Annals of Oncology, 2009) and colon adenocarcinomas (Bondi et al, APMIS, 2009). A new high throughput method for analysing tissue micro arrays (TMA) based on virtual microscopy has also been completed (Brekke et al, Neuro Oncol. 2009, and Arnoldussen et al, Cancer Res., 2008). The use of texture analysis to analyse nuclear chromatin in cancers have been reviewed (Nielsen et al, Reviews in Oncogenesis 2009), and development of methods for automatic segmentation and classification of nuclei in histological sections have been completed and patented. An application for measuring cell movement has also been completed recently.

RESEARCH GROUPS

Lothe's group

About

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. The researchers at department of Cancer Prevention study secondary and tertiary cancer prevention, aiming to identify, develop and validate new biomarkers with high sensitivity and specificity for use in improved early diagnostics, prediction of disease course and treatment response, and as novel targets for therapy.

Understanding molecular mechanisms underlying human tumour development is essential to improve the diagnosis and treatment of the cancer patient. To gain knowledge of the complex dynamics of these abnormal processes our department combines large-scale and detailed biology research using *in vitro* models and human samples. Technologies in genetics, epigenetics, bioinformatics and cell biology are employed in our laboratory, and in particular, various microarray platforms, including an in-lab designed universal fusion gene array, deep-sequencing, and confocal microscopy.

The researchers of the department are also involved in studies of other solid tumours, with an increasing activity on urological cancers, and we have initiated and/or contribute in several collaborative projects within the CCB.

Challenges

Colorectal cancer is the second most frequent cause for cancer deaths in the Western world and the incidence in Norway alone is more than 3500 per year. The golden standard for early detection is colonoscopy; the invasiveness of the method and costs show the need for improved non-invasive tests for discovery of precursor lesions and of early cancer stages. Furthermore, the present clinical staging is crude and more precise molecular tools are asked for to better select those that will benefit from adjuvant treatment with the intention to cure and leave those who will be cured by surgery alone. There is an urgent need for biomarkers with predictive power and to identify those that can be used for targeted therapy.

Several initiatives have been taken during 2009 to increase and improve the research on prostate cancer. Of particular importance are our collaborative studies, including exchange of personnel, with Professor Manuel R. Teixeira (guest professor at CCB) and with Håvard Danielsen's group in CCB. But also initiative from CCB towards our own clinic has been forwarded and is currently being evaluated.

Projects

- biomarkers for early detection of colorectal cancer and development of non-invasive tests
- identification of predictive and prognostic markers of CRC
- epigenetic key markers across gastrointestinal cancers
- genetics of young at onset colorectal cancer
- cancer specific transcripts for diagnostics and targeted therapy
- disease mechanisms: protein degradation and intercellular communication in interplay with cell signaling
- genetic risk, tumour etiology and long-term treatment effects after germ cell tumour
- disease mechanisms and biomarkers for malignancies in patients with and without the hereditary disease neurofibromatosis type 1

Recent discoveries

The scientific production dated 2009 included 11 peer review papers, one patent application, and two academic degrees, Terje Ahlquist and Anne-Cathrine Bakken, from our laboratory. In addition, a couple of papers were published ahead of print.

In the following some of the scientific activity of 2009 is commented.

Malignant peripheral nerve sheath tumour (MPNST) is a highly aggressive malignancy for which no consensus therapy exists besides surgery. In a Scandinavian interdisciplinary study including several of the CCB groups we have shown P53 to be the best independent predictor of survival among the 14 analysed proteins, and patients in complete remission with a primary p53-positive MPNST diagnosis may be considered in a high-risk subgroup and candidates for adjuvant treatment (Brekke et al., Neuro Oncol. 2009 11:514-28). Three recent studies on MPNST are summarized in the thesis of Helge R. Brekke who will defend his PhD degree in 2010. The last paper was recently published in Journal of Clinical Oncology (Brekke et al., JCO 28: 1573-1582), which shows that specific genomic aberrations carry striking prognostic information. In 2009 another European laboratory of experimental oncology (Prof Picci), Bologna, Italy has accepted to join this collaboration, and more than 50 new MPNST patients are currently added to this multicenter study.

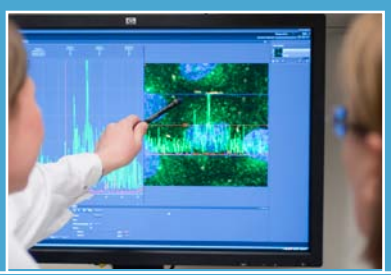
In 2009 we published associations among polymorphisms of glutathione S-transferases and primary and post-chemotherapy in a series of about 700 testicular cancer survivors (Kraggerud et al., Pharmacogenet Genomics 2009, 19:751-759). The search for risk associated SNPs and for long term effect associated SNPs is an international effort and we joined a NIH/NCI run GWAS study in 2009 and are currently validating specific SNPs in the Norwegian cohort.

In a CCB collaborative study we have shown that the two ubiquitin-binding proteins Hrs and Tsg101 play a central role in regulation of connexin43 trafficking and degradation (Leithe et al., J Cell Sci. 2009 122:3883-93). Connexins, constituents of gap junctions, have a high turnover rate in most tissue types, are deregulated in colorectal cancer and recent results suggest cross-talk with proteins central in development of this disease(unpublished).

During the last year, getting a new deep-sequencing platform up and running has been a task for our lab within the CCB. Furthermore, a new confocal microscope has been taken into use in the lab and the second generation of the fusion gene microarray has been developed. The latter is currently being tested for sensitivity and specificity for previously diagnosed samples obtained blinded from European diagnostics laboratories.

Furthermore, we have in 2009 analysed more than 220 primary colorectal cancer samples on exon-microarrays, a CCB platform established in 2008. The patient series are stratified according to survival and adjuvant treatment (historic series), and global instability as well as predictive and prognostic markers are currently being analysed and experimentally validated.

Integrated genome and transcriptome studies of colorectal cancers from an additional 50 patients with a 20 year age difference in disease onset, and whom are not carriers of hereditary syndromes, show differences in tumour development and novel candidate susceptibility loci are found. These data are part of a Marianne Berg's thesis to be submitted spring 2010.



COLLABORATIVE PROJECTS WITHIN CCB

Cell cycle regulation and cancer

Cytokinesis regulation as a mechanism in tumour suppression - collaboration between Stenmark, Liestøl and Skotheim (Lothe) labs. First paper recently published in *Nature Cell Biology*.

CIN85 as a regulator of cytokinesis - collaboration between Stenmark, Wesche (Olsnes) and Liestøl groups. Submitted for publication.

Expression of cell cycle components in MPNST and relevance for clinical end-points - collaboration between Lothe, Danielsen and Liestøl groups. First paper published in *Neuro Oncology* in 2009.

Intra- and intercellular communication and transport

Endosomal sorting of growth factor receptors and gap junction proteins - collaboration between Stenmark, Liestøl and Rivedal (Lothe) labs. First paper published in *Journal of Cell Science* in 2009. Second manuscript in preparation.

Endocytic mechanisms involved in FGF (fibroblast growth factor) receptor internalization - Collaboration between Olsnes, Sandvig and Stenmark labs. Submitted for publication.

SNX4 in complex with clathrin and dynein: implications for endosome movement - collaboration between Sandvig and Brech (Stenmark) labs. Published in *PLoS One* in 2009.

Degradation of integrins as a mechanism in cell migration - collaboration between Stenmark and Wesche (Olsnes) labs. Submitted for publication.

Colorectal cancer

Biomarkers for early detection of colorectal cancer - Lothe and Stenmark labs. First manuscript in preparation.

Epigenetic mechanisms in colorectal cancer - Lothe, Smeland and Stenmark labs. Ongoing.

Predictive and Prognostic markers in colorectal cancer - Lothe and Danielsen labs. First manuscript in preparation.

Integrated –omics and clinical end-points in colorectal cancer - Lothe and Liestøl groups. Ongoing.

Autophagy in colorectal cancer - collaboration between Stenmark and Lothe labs. Brech et al Molecular Oncology 2009 review; First original manuscript in revision.

Transcript variants in colorectal cancer - Lothe, Stenmark, Olsnes and Smeland labs. Work in progress.

MAPK and PIP signalling in colorectal cancer - Wesche (Olsnes), Stenmark, Lothe labs. Work in progress.

Lymphomas

Genomic alterations in follicular lymphoma - collaboration between Liestøl and Smeland labs. First manuscript submitted for publication.

Epigenetic mechanisms in lymphomas - collaboration between Smeland and Lothe labs. First manuscript in preparation.

In situ expression of signalling components in longitudinal follicular lymphomas samples. Development of automatic scoring system - Collaboration between Smeland and Danielsen labs. Ongoing.

Prostate cancer

Secretion of prostasomes - Ongoing collaboration between Sandvig and Stenmark labs.

Prognostic markers in prostate cancer - Ongoing collaboration between Danielsen, Teixeira and Lothe labs.

Genomics and transcriptomics of prostate cancer - collaboration betweeen Lothe, Teixeira and Danielsen labs. Manuscripts in preparation.

Advanced technologies shared by CCB scientists

Joint efforts for establishment, handling, analyses and project collaborations:

Microarray platforms
Deep nucleic acid sequencing
Confocal microscopy
Electron microscopy
Live-cell microscopy and tracking software development
High-throughput microscopy and siRNA screening
Tissue microarrays – own software and automated scoring development

INTERACTION ACTIVITIES

The annual CCB seminar 2009

The second annual seminar in CCB history was arranged at Losby Gods on 26-27 October 2009. Ninety CCB members participated in this two day event in the pleasant atmosphere and beautiful surroundings of Losby Gods.

The scientific programme covered project presentations by CCB group leaders and project leaders, and again this year the CCB awards were given to three papers carefully selected by the group leaders. The three papers were proudly presented by the prize winners and first authors:

Hilde Raa - Glycosphingolipid Requirements for Endosome-to-Golgi Transport of Shiga Toxin (Kirsten Sandvig presented the paper on behalf of Hilde)

Lina M. Rodahl - Disruption of Vps4 and JNK Function in Drosophila Causes Tumour Growth

Rolf I. Skotheim - A universal assay for detection of oncogenic fusion transcripts by oligo microarray analysis.

Our programme also included a poster session where 21 posters were presented. Fruitful discussions filled the room and this year's poster prize went to:

Jarle Bruun with his poster "Role of the connexin protein family in colorectal cancer".

Popular science dissemination was on our programme as well, and much attention was dedicated to this important topic. Group work with the aim to produce a short film about cancer demanded plenty of effort from the participants, most of whom are unaccustomed to exploring this particular angle of their creativity.

Beside the scientific benefits from this get-together another important gain is the opportunity to strengthen interaction between the CCB members. Being together for two days immersed in scientific as well as social activities is a great boost for the common CCB spirit.

Group work with enthusiastic participants

Prize winner Lina Rodahl

CCB seminars 2009

A new regulator of cytokinesis, and its involvement in cancer
Speaker: Harald Stenmark
Date: 6 January 2009

CCB goals and strategy
Speaker: Harald Stenmark and Ragnhild Lothe (Centre Management)
Date: 3 February 2009

Development of cancer in the peripheral nerves. New biological insight with clinical impact.
Speaker: Ragnhild Lothe and Matthias Kolberg (Lothe group)
Date: 3 March 2009

A status report, and a presentation of Microtracker – a new research tool
Speaker: Håvard Danielsens group
Date: 24 April 2009

The annual CCB seminar at Losby Gods
Speaker: See separate article
Date: 26 – 27 October 2009

Multidrug resistance of cancer cells and expression of the Shiga toxin receptor Gb3: An exploitable link?
Speaker: Nicolai Engedal (Sandvig group)
Date: 17 November 2009

Genetic alterations in the relapse and progression of Follicular Lymphoma
Speaker: Marianne Brodtkorb Eide (Smeland group)
Date: 15 December 2009

DEGREES

PhD degrees 2009:

Susanne Stuffers PhD – The role of ESCRT proteins and phosphoinositides in MVE biogenesis, endocytic trafficking and disease. Faculty of Medicine, University of Oslo, January 2009

Sigrid S. Skånland PhD – Mechanisms in intracellular transport of toxins. Faculty of Mathematics and Natural Sciences, University of Oslo, January 2009

Ellen Margrethe Haugsten PhD – Endocytosis and intracellular transport of FGF1 and the FGF receptors. Faculty of Medicine, University of Oslo, April 2009

Terje Cruickshank Ahlquist PhD – Novel genetic and epigenetic alterations in colorectal tumors and their potential as biomarkers. Faculty of Medicine, University of Oslo, May 2009

Audrun Utskarpen PhD – Endocytosis and retrograde transport of Shiga toxin and ricin. Faculty of Mathematics and Natural Sciences, University of Oslo, June 2009

Ingrid Roxrud PhD – Endocytic trafficking of membrane proteins. Mechanisms in human disease. Faculty of Medicine, University of Oslo, November 2009

Master degrees 2009:

Daniel J. H. Nebdal, M.Sc. in Informatics – Presenting overrepresented words. Faculty of Mathematics and Natural Sciences, University of Oslo, January 2009

Gro Nilsen, M.Sc. in Data Analysis and Modelling – A comparative study of existing and novel methods for estimating the number of clusters in a data set. Faculty of Mathematics and Natural Sciences, University of Oslo, March 2009

Kristine Ingrid Sundet, M.Sc. in Biomedicine – The role of ERM proteins in endocytosis and intracellular transport of Shiga toxin and ricin. Faculty of Health Sciences, Oslo University College, May 2009

Anne Cathrine Bakken, M.Sc. in Molecular Biosciences – Exon specific biomarkers in cancer: Experimental validation of exon microarray data from colorectal and testicular cancers. Faculty of Mathematics and Natural Sciences, University of Oslo, December 2009

FORUMS

PhD forum

The PhD board consisting of one member from each of the CCB groups, arranged six meetings during 2009, taking turns in hosting the meetings and giving short presentations of their groups. At the first meeting in February, two invited speakers covered the following topics: “Cancer epidemiology in Norway and the world” (by Bjørn Møller, the Norwegian Cancer Registry) and “The evolutionary logics of cancer” (by Jarle Breivik, The Faculty of Medicine, UiO). Next we had Daniel Fryer from Oslo University College and Harald Stenmark to teach us the main principles of “Scientific writing”. The third meeting was arranged in collaboration with the Postdoc forum. The actress Mina Saunte from Ergo;Ego was hired to demonstrate techniques for oral presentation. Next we had Mariann Seiergren from Håvard Danielsen’s group who lectured about the design of figures and posters. The two next meetings focused on career possibilities after the PhD. Three Postdocs from CCB (June Myklebust, Kristi Grønvold Bache and Camilla Skiple Skjerpen) talked about their experiences from working in labs in the USA and Japan. Tore Skotland and Thomas Slagsvold spoke about their experiences from working in a pharmaceutical company (Nycomed/Amersham/GE) and in the Norwegian Research Council.

The attendance at each meeting varied. The general comments from the students were that they felt the topics were relevant and interesting. We in the board felt that we obtained valuable experience in arranging meetings, and that the forum contributed to establishing contacts between PhD students within the CCB.

A new forum for all PhD students at the Norwegian Radium Hospital has been initiated by the Faculty of Medicine, UiO, and the PhD students in CCB will enter this new, joint PhD forum as from 2010.

Marianne Brodtkorb Eide, Chairperson

Postdoc forum

The CCB Postdoc forum was established in January 2009. The overall aim of this forum is to provide an arena for facilitating discussions and collaborations between the postdoctoral fellows and scientists at CCB. A particularly important objective of the forum is to stimulate translational research by bridging the basic cell biology research projects and the clinically based research projects within the CCB. As of January 2010, there were approximately 40 postdoctoral fellows and scientists associated with the CCB. A committee consisting of one representative from each group within CCB is responsible for organizing the Postdoc forum meetings.

In 2009, four Postdoc forum meetings were organized. An important objective of these meetings was to share knowledge on the various state-of-the-art technologies within CCB in order to facilitate future collaborative projects between the various research groups. Among the topics that were covered in these meetings were genome analysis, confocal and electron microscopy, high-throughput microscopy and microarray technologies. In addition, a meeting focusing on presentation techniques was organized together with the CCB PhD forum.

In 2010, we aim to continue to stimulate interaction between the postdoctoral fellows and scientists within CCB by organizing meetings on subjects of joint interest. We will also invite scientists from other institutions within the Oslo region that we believe might contribute with new technologies and skills important for the ongoing research projects within CCB. In particular, we will invite representatives from the various technology core facilities at the University of Oslo. We also plan to invite clinicians at the Oslo University Hospital to attend the CCB Postdoc forum meetings in order to facilitate future collaborations between CCB and the cancer clinic at the hospital.

Edward Leithe, Chairman

Advanced Grant from the European Research Council to CCB director Harald Stenmark

Harald Stenmark from the Department of Biochemistry at the Institute for Cancer Research has been awarded an Advanced Grant from the European Research Council (ERC) in 2009, amounting to 2.27 mill Euro over a period of 5 years for running the project "The PI3K-III complex: Function in cell regulation and tumour suppression".

The ERC Advanced Investigator Grants, known as Advanced Grants, aim to encourage and support excellent, innovative investigator-initiated research projects by leading advanced investigators across the EU Member States and Associated Countries. This funding stream complements the Starting Grant scheme by targeting the population of researchers who have already established themselves as being independent research leaders in their own right. ERC Advanced Grants provide an opportunity to established scientists and scholars to pursue frontier research of their choice. Applicants for Advanced Grants are expected to be active researchers who have a track record of significant research achievements in the last 10 years.

About the project: The PI3K-III complex: Function in cell regulation and tumour suppression. Interactions between proteins and cellular membranes are essential for most physiological processes, but we still know little about how the functions of cytosolic protein complexes are coordinated with membrane rearrangements.

In this project, the functions of a cytosolic lipid kinase complex (PI3K-III) and its membrane-bound reaction product will be characterized in-depth in order to understand how these molecules function in membrane dynamics and tumour suppression.

The project involves thorough biochemical characterisations of the lipid kinase complex, in situ imaging of its reaction product using novel assays, detailed cell biological studies of relevant trafficking and signalling pathways, and novel Drosophila models for oncogenesis.

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

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

The overall objective of the Polish-Norwegian Research Fund is to establish and strengthen a fruitful and long-term co-operation between Polish and Norwegian researchers focusing primarily on environmental and health research, and between Norway and Poland in general.

About the project: "Translocation of fibroblast growth factor 1 (FGF1) and 2 (FGF2) from the cell exterior to the cytosol and nucleus is a new principle for these growth factors signalling. However so far, we do not know details about the mechanism of translocation", Wiedlocha explains. "We are using our knowledge from the protein toxin work in attempts to elucidate the mechanism. We also intend to study the mechanism by which the translocated exogenous growth factor signals. We also plan to test if other growth factors have an intracellular mode of action in addition to their ability to signal through a transmembrane receptor".

CCB project leader Rolf I. Skotheim receives Dr. Ragnar Mørk's prize 2009

The Ragnar Mørk's legacy award for 2009 went to Rolf Skotheim, working at the Department of Cancer Prevention at the Institute for Cancer Research. This award is distributed annually to a scientist who has achieved important results. Skotheim is involved in research where DNA and RNA from various cancers types are analysed by integrated computational and laboratory based approaches. The award is personal, and amounts to NOK 200.000.

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

Ingrid Roxrud receives prize for best poster at the Contact Meeting of the Norwegian Biochemical Society

PhD student Ingrid Roxrud in Harald Stenmark's group at Centre for Cancer Biomedicine, Institute for Cancer Research, received the prize for best poster at the 45th Contact Meeting of the Norwegian Biochemical Society at Røros in January 2009. Roxrud's poster was entitled "Multiple degradation mechanisms ensure disposal of an Angelman-syndrome associated NHE6 deletion protein".

The prize of NOK 5 000 was awarded to the best poster among 92 competing posters, based on the criteria of scientific content, clarity and layout.

Stine Aske Danielsen receives prize for best poster at the 30th Scandinavian Sarcoma Annual Meeting

PhD student Stine Aske Danielsen in Ragnhild Lothe's group at Centre for Cancer Biomedicine and Institute for Cancer Research received the prize for best poster at the 30th Annual Meeting of the Scandinavian Sarcoma Group in Oslo in May 2009. Danielsen's poster was entitled "Methylation of *RASSF1A* – a Prognostic Biomarker in NF1-patients with Malignant Peripheral Nerve Sheath Tumors".

The prize was awarded to the best poster based on the criteria of scientific content and layout.

EACR Cancer Researcher Award to CCB project leader Rolf I. Skotheim

Rolf I. Skotheim received the EACR Cancer Researcher Award 2009 - Highly Commended, at the European Association of Cancer Research meeting "ECCO 15 - 34 ESMO" in Berlin, 20-24 September 2009.

VISITORS

Scientists visiting CCB in 2009:

Hosted at Kirsten Sandvig's lab:
Josefine Betz, PhD student from the University of Münster, Germany
From September to Desember 2009 (3 months).

Hosted at Harald Stenmark's lab:
Dr. Björn Stork, University Clinic Tübingen, Germany
From June to November 2009 (6 months).

Hosted at Ragnhild Lothe's lab:
Franclim Ribeiro, Postdoc, Portuguese Oncology Institute, Portugal
From November to December 2009 (6 weeks).
Diogo Silva, PhD student, Portuguese Oncology Institute, Portugal
From November to December 2009 (5 weeks).
Barbara Mesquita, PhD student, Portuguese Oncology Institute, Portugal
October 2009 (2 weeks).
Paula Paulo, PhD student, Portuguese Oncology Institute, Portugal
From September to October (6 weeks).
Vera Costa, PhD student, Portuguese Oncology Institute, Portugal
From August to September (6 weeks).

EDUCATIONAL ACTIVITIES

Courses:

MOL8006 "Receptor Signalling and Trafficking", Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, 25 March-3 April 2009, Course responsible: Harald Stenmark.

MBV4240/9240 "Biochemical Mechanisms in Intracellular Transport", Faculty of Mathematics and Natural Sciences, University of Oslo, Autumn 2009, Course responsible: Kirsten Sandvig, Lecturers from CCB: Kirsten Sandvig, Antoni Wiedlocha, Harald Stenmark.

BIO4530 Regulatorisk toksikologi - Toksikologisk risikovurdering med noe risikohåndtering, "Risikovurdering av plantevernmidler", Faculty of Mathematics and Natural Sciences, University of Oslo, May 2009, Lecturer: Edgar Rivedal.

MBV9100BTS Molecular Biology Research Course, "Genome Biology of Cancer", Faculty of Mathematics and Natural Sciences, University of Oslo, October 2009, Lecturer: Rolf I. Skotheim.

MBV3020 Molecular genetics and developmental biology, Faculty of Mathematics and Natural Sciences, University of Oslo, November 2009, Responsible for "Cancer Biology session": Ragnhild A. Lothe, Lecturers from CCB: Ragnhild A. Lothe, Edgar Rivedal, Edward Leithe, Matthias Kolberg, Marthe Løvf.

PUBLICATIONS AND PRESENTATIONS

Publications 2009

Abeler VM, Røyne O, Thoresen S, Danielsen HE, Nesland JM, Kristensen GB (2009) **Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients** Histopathology 54:355-64.

Alagaratnam S, Hardy JR, Lothe RA, Skotheim RI, Byrne JA (2009) **TPD52, a candidate gene from genomic studies, is overexpressed in testicular germ cell tumours** Mol Cell Endocrinol. 306:75-80.

Bjørkøy G, Lamark T, Pankiv S, Øvervatn A, Brech A, Johansen T (2009) **Monitoring autophagic degradation of p62/SQSTM1** Methods Enzymol. 452:181-97.

Bondi J, Pretorius M, Bukholm I, Danielsen H (2009) **Large-scale genomic instability in colon adenocarcinomas and correlation with patient outcome** APMIS 117:730-6.

Bottillo I, Ahlquist T, Brekke HR, Danielsen SA, van den Berg E, Mertens F, Lothe RA, Dallapiccola B (2009) **Germline and somatic NF1 mutations in sporadic and NF1-associated malignant peripheral nerve sheath tumors** J Pathol 217:693-701.

Brech A, Ahlquist T, Lothe RA, Stenmark H (2009) **Autophagy in tumour suppression and promotion** Mol. Oncol. 3:366-375.

Brekke H, Kolberg M, Skotheim RI, Hall KS, Bjerkehagen B, Risberg B, Domanski HA, Mandahl N, Liestøl K, Smeland S, Danielsen HE, Mertens F, Lothe RA (2009) **Identification of p53 as a strong predictor of survival for patients with malignant peripheral nerve sheath tumors** Neuro Oncol. 11:514-28.

Danielsen SA, Lind GE, Biornslett M, Meling GI, Rognum TO, Heim S, Lothe RA (2009) **Novel Mutations of the Suppressor Gene PTEN in Colorectal Carcinomas Stratified by Microsatellite Instability- and TP53 Mutation** Hum. Mutat. 30:1023.

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Døving KB, Sandvig K, Kasumyan A (2009) **Ligand-specific induction of endocytosis in taste receptor cells** J. Exp. Biol. 212:42-49.

Godmann M, Gashaw I, Eildermann K, Schweyer S, Bergmann M, Skotheim RI, Behr R (2009) **The pluripotency transcription factor Krüppel-like factor 4 is strongly expressed in intratubular germ cell neoplasia unclassified and seminoma** Mol Hum Reprod. 15:479-488.

Haugsten EM (2009) **Endocytosis and intracellular transport of FGF1 and the FGF receptors** Norsk Farmaceutisk Tidsskrift 6:21-22 (in Norwegian).

Holte H, Kvaløy S, Delabie J, Trøen G, Smeland EB (2009) **[Molecular diagnosis of malignant lymphomas]** Tidsskr Nor Laegeforen. 129:2352-6.

Iversen TG, Frerker N, Sandvig K (2009) **Quantum dot bioconjugates: Uptake into cells and induction of changes in normal cellular transport** Progr. Biomed. Optics and imaging 7189:1-9.

Kildal W, Abeler VM, Kristensen GB, Jenstad M, Thoresen SØ, Danielsen HE (2009) **The prognostic value of DNA ploidy in a total population of uterine sarcomas** Ann Oncol. 20:1037-41.

Kildal W, Pradhan M, Abeler VM, Kristensen GB, Danielsen HE (2009) **Beta-catenin expression in uterine sarcomas and its relation to clinicopathological parameters** Eur J Cancer 45:2412-7.

Kraggerud SM, Oldenburg J, Berg M, Alnæs GIG, Kristensen VN, Fosså SD, Lothe RA (2009) **Functional glutathione S-transferase (GST) genotypes among testicular germ cell tumor (TGCT) survivors - associations with primary and post-chemotherapy tumor histology** Pharmacogenetics and Genomics 19:751-759.

Leithe E, Kjenseth AH, Sirnes S, Stenmark H, Brech A, Rivedal E (2009) **Ubiquitination of the gap junction protein Connexin43 signals its trafficking from early endosomes to lysosomes: Distinct roles of Hrs and Tsg101** J. Cell Sci. 122:3883-3893.

Lo A, Chiu YY, Rodland EA, Lyu PC, Sung TY, Hsu WL (2009) **Predicting helix-helix interactions from residue contacts in membrane proteins** Bioinformatics 25:996-1003.

Malerød L, Stenmark H (2009) **ESCRTing membrane deformation** Cell 136:5-17.

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Nezis IP, Lamark T, Velentzas AD, Rusten TE, Bjørkøy G, Johansen T, Papassideri IS, Stravopodis DJ, Margaritis LH, Stenmark H, Brech A (2009) **Cell death during Drosophila melanogaster early oogenesis is mediated through autophagy** Autophagy 5:298-302.

Nielsen B, Albregtsen F, Danielsen HE (2009) **Statistical nuclear texture analysis in cancer research: a review of methods and applications** Crit Rev Oncog. 2008; 14:89-164. Published in 2009.

O'Riain C, O'Shea DM, Yang Y, Le Dieu R, Gribben JG, Summers K, Yeboah-Afari J, Bhaw-Rosun L, Fleischmann C, Mein CA, Crook T, Smith P, Kelly G, Rosenwald A, Ott G, Campo E, Rimsza LM, Smeland EB, Chan WC, Johnson N, Gascoyne RD, Reimer S, Braziel RM, Wright GW, Staudt LM, Lister TA, Fitzgibbon J (2009) **Array-based DNA methylation profiling in follicular lymphoma** Leukemia 23:1858-66.

Pradhan M, Davidson B, Tropé CG, Danielsen HE, Abeler VM, Risberg B (2009) **Gross genomic alterations differ between serous borderline tumors and serous adenocarcinomas – an image cytometric DNA ploidy analysis of 307 cases with histogenetic implications** Virchows Arch. 454:677-83.

Pretorius ME, Waehre H, Abeler VM, Davidson B, Vlatkovic L, Lothe RA, Giercksky KE, Danielsen HE (2009) **Large Scale Genomic Instability as an additive prognostic marker in early prostate cancer** Cell Oncol. 31:251-259.

Raa H, Grimmer S, Schwudke D, Skotland T, Shevchenko A, Sandvig K (2009) **Glycosphingolipid requirements for endosome-to-Golgi transport of Shiga toxin** Traffic 10:868-882.

Raiborg C, Stenmark H (2009) **The ESCRT machinery in endosomal sorting of ubiquitylated membrane proteins** Nature 458:445-452.

Rodahl LM, Haglund K, Sem-Jacobsen C, Wendler F, Vincent JP, Lindmo K, Rusten TE, Stenmark H (2009) **Disruption of Vps4 and JNK function in Drosophila causes tumour growth** PLoS One 4:e4354.

Rodahl LM, Stuffers S, Lobert VH, Stenmark H (2009) **The role of ESCRT proteins in attenuation of cell signalling** Biochem. Soc. Trans. 37:137-142.

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Sirnes S, Kjenseth A, Leithe E, Rivedal E (2009) **Interplay between PKC and the MAP kinase pathways in connexin43 phosphorylation and inhibition of gap junction intercellular communication** Biochem. Biophys. Res. Commun. 382:41-45.

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Groves B, Abrahamsen H, Clingan H, Frantz M, Mavor L, Bailey J, Ma D (2010) **An inhibitory role of the G-protein regulator AGS3 in mTOR-dependent macroautophagy** PLoS One 5:e8877.

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Brekke HR, Ribeiro FR, Kolberg M, Agesen TH, Lind GE, Eknæs M, Hall KS, Bjerkehagen B, van den Berg E, Teixeira MR, Mandahl N, Smeland S, Mertens F, Skotheim RI, Lothe RA (2010) **Genomic Changes in Chromosomes 10, 16, and X in Malignant Peripheral Nerve Sheath Tumors Identify a High-Risk Patient Group** J. Clin. Oncol. **(**Epub ahead of print 16 Feb 2010).

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Rivedal E, Witz G, Leithe E (2010) **Gap junction intercellular communication and benzene toxicity** Chem Biol Interact. (Epub ahead of print).

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Sandvig K, Bergan J, Dyve AB, Skotland T, Torgersen ML (2009) **Endocytosis and retrograde transport of Shiga toxin** Toxicon (Epub ahead of print).

Invited lectures/Selected presentations:

Iversen, Tore-Geir: Invited lecture at SPIE congress "Colloidal Quantum Dots for Biomedical Applications IV" in San Jose, California, USA, 24-26 January 2009.

Kolberg, Matthias: Invited speaker at the 34th meeting of the Scandinavian Sarcoma Group, Title: "Novel druggable targets identified for malignant peripheral nerve sheath tumors", Oslo, Norway, May 2009.

Lind, Guro E.: Invited speaker at the 2nd Oncology Biomarkers Conference, Title: "Novel diagnostic biomarkers for early detection of colorectal tumors", Miami FL, USA, January 2009.

Lind, Guro E.: Invited speaker at IPATIMUP, University of Porto, Title: "Epigenetics and intestinal carcinogenesis", Porto, Portugal, June 2009.

Lothe, Ragnhild A.: Invited speaker at Oslo Cancer Cluster seminar for biotech companies, Title: "Identification of novel biomarkers for early diagnosis of colorectal cancer", Oslo, Norway, July 2009.

Lothe, Ragnhild A.: Invited speaker at the European Cancer Cluster partnering, Title: "Molecular biomarkers in colorectal cancer and prostate cancer", Toulouse, France, September 2009.

Myklebust, June: Invited lecture at American Society of Hematology Annual meeting, Title: "A subpopulation of follicular lymphoma tumor infiltrating T cells shows suppressed common gamma chain cytokine signaling", New Orleans, USA: 4-8 December 2009.

Olsnes, Sjur: Invited by Institute of Molecular Biology, Russian Academy of Sciences, Title: "Translocation of FGF1 into cells", Moscow, Russia, October 2009.

Rivedal, Edgar: Invited speaker at Benzene International Symposium, Title: “Gap junction intercellular communication and benzene toxicity”, Munich, Germany, September 2009.

Sandvig, Kirsten: Invited lecture at “XVI World congress of the International Society of Toxicology. X Congresso da Sociedade Brasileira de Toxinologia, Biodiversity in Toxins: Tools for Biological Research and Drug Development, Recife, Brazil, 15-20 March 2009.

Sandvig, Kirsten: University of Münster, Germany, 29 April 2009.

Sandvig, Kirsten: Invited lecture at 109th General Meeting of the American Society for Microbiology in Philadelphia, USA, 17-21 May 2009.

Sandvig, Kirsten: EMBO Lecture at the ETOX14-meeting, Obernai, France, 27 June -2 July 2009.

Sandvig, Kirsten: 46th Congress of the European Societies of Toxicology, Dresden, Germany, 13-16 September 2009.

Sandvig, Kirsten: Endocytosis-meeting at Crete, Greece, 3-8 October 2009.

Skotheim, Rolf I.: Lund University hospital, Title: ”Fusion gene microarray”, Lund, Sweden, February 2009.

Skotheim, Rolf I.: Invited speaker at pHealth, Title: “A new microarray design used as a universal cancer diagnostic tool for detection of fusion genes”, Oslo, Norway, June 2009.

Skotheim, Rolf I.: Invited speaker at Jornadas de Oncologia [Oncology congress], Title: “Integrative genome-scale biology for cancer biomarker discovery”, Porto, Portugal, July 2009.

Skotheim Rolf I.: Invited speaker at VTT Medical Biotechnology, Title: “Cancer Biomarker Discovery: focus on colorectal and prostate cancers”, Turku, Finland, October 2009.

Skotheim, Rolf I.: Ragnar Mørk’s legacy prize lecture for 2009, Oslo, Norway, November 2009.

Stenmark, Harald: Invited speaker at the international workshop “The Endocytotic Pathway in Health and Disease”, Seminar title: “Endosomes, cytokinesis and cancer”, Fleischer Hotel, Voss, Norway, 19-21 March 2009.

Stenmark, Harald: Guest lecturer at the Pasteur Institute, Host: Chiara Zurzolo, Seminar title: ”Endocytic downregulation of growth factor receptors”, Paris, France, 15 June 2009.

Stenmark, Harald: Invited speaker at the EMBO Conference on ”Autophagy”, Seminar title: ”Caspase-dependent cell death triggered by selective autophagy of an apoptosis inhibitor”, Monte Verita, Switzerland, 18-23 October 2009.

Stenmark, Harald: Invited speaker at the ICMM Cluster Meeting, Seminar title: ”How a lipid functions as a tumour suppressor”, Helsingør, Denmark, 2-3 November 2009.

Stenmark, Harald: Invited speaker at the course “The Yin and Yang of endocytosis: health, development and disease”, Seminar title: “Endocytosis and cancer”, Dept. of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden, 14 November 2009.

Stenmark, Harald: Guest lecturer at the CNRS-CGM, Host: Renaud Legouis, Seminar title: ”Endosomal sorting and its role in tumour suppression”, Gif-sur-Yvette, France, 27 November 2009.

Wiedlocha, Antoni: Invited by University of Wroclaw, Faculty of Biotechnology, Title: ”Role of p38 MAPK in translocation of FGF1 into cells”, Wroclaw, Poland, June 2009.

COLLABORATION

National collaboration:

Prof. Oddmund Bakke, Faculty of Mathematics and Natural Sciences, Department of Molecular Biosciences, University of Oslo

Prof. Heidi Kiil Blomhoff, Institute of Basic Medical Sciences, Department of Biochemistry, University of Oslo

Prof. Bjarne Bogen, Institute of Immunology, Oslo University Hospital, Rikshospitalet

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

Prof. Kjell Bjarne Døving, Faculty of Mathematics and Natural Sciences, Department of Molecular Biosciences, University of Oslo

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

Prof. Sophie D. Fosså, Clinic for cancer and surgery, Oslo University Hospital, Norwegian Radium Hospital

Dr. med. Harald Holte, Clinic for cancer and surgery, Oslo University Hospital, Norwegian Radium Hospital

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

Arne Kolstad, MD, PhD, Clinic for cancer and surgery, Oslo University Hospital, Norwegian Radium Hospital

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

Prof. Stein Kvaløy, Clinic for cancer surgery, Oslo University Hospital, Norwegian Radium Hospital

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

Prof. Arild Nesbakken, Department of Gastrointestinal surgery, Oslo University Hospital, Aker

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

Dr. Sigbjørn Smeland, Head of Clinic for cancer and surgery, Oslo University Hospital

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

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

Ph.D. student Lena Tjeldhorn, Department of Hematology, Oslo University Hospital, Ullevål

International collaboration:

Prof. Peter Andrews, University of Sheffield, England

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

Prof. Dallapiccola, University of Rome, Italy

Prof. Bo van Deurs, University of Copenhagen, Denmark

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

Prof. V. Gerke, University of Münster, Germany

Jonathan Irish, PhD, Stanford University, USA

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

Prof. Tom Kirchhausen, Harvard University, Boston, USA

Ron Levy, MD, Stanford University, USA

Raquel Malumbres, PhD, Departamento de Oncología, CIMA, Pamplona, Spain

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

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

Prof. A. Schevchenko, Max Planck Institute, Dresden, Germany

Dr. Dominik Schwudke, Max Planck Institute, Dresden, Germany

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

Prof. Manuel Sobrinho-Simoes, IPATIMUP, Porto, Portugal

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

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

Dr. Jean-Paul Vincent, National Institute for Medical Research, London, UK

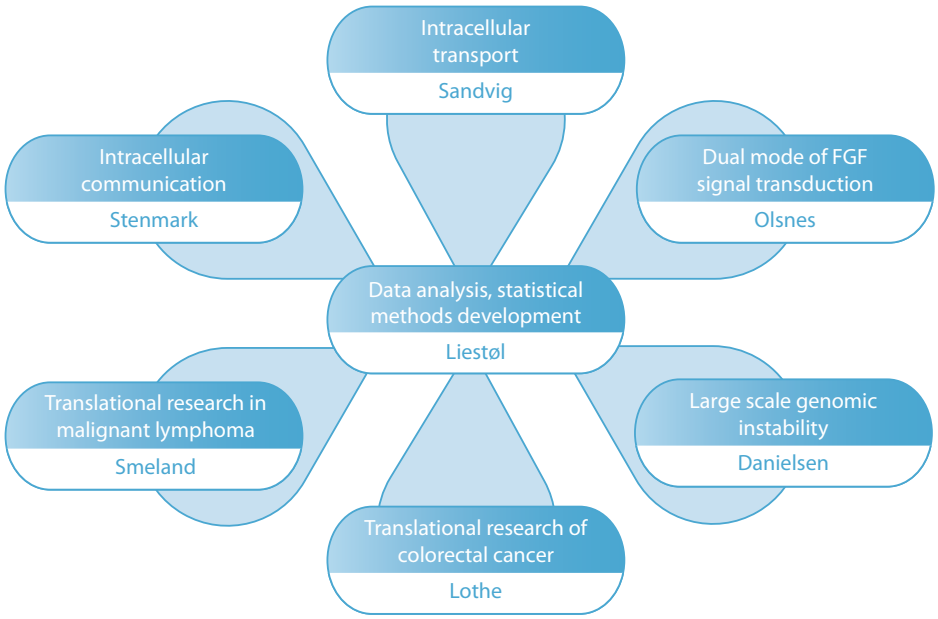
Centre for Cancer Biomedicine

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, in the brand new research building which was inaugurated in August 2009. 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

Seven research groups embracing an average of 125 people in 2009 constitute CCB. These seven groups are headed by Prof. Harald Stenmark, Prof. Ragnhild A. Lothe, Prof. Kirsten Sandvig, Prof. Erlend Smeland, Prof. Håvard Danielsen, Prof. Knut Liestøl, and Prof. Sjur Olsnes (due to the retirement of Prof. Olsnes, Antoni Wiedlocha will lead this group as from 2010). The group leaders meet once a month for scientific and strategic discussions.

BASIC CELL BIOLOGY



TRANSLATIONAL CANCER RESEARCH

Management

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

The Board

The Centre management reports to the CCB board which has two members from the University of Oslo as well as two members from Oslo University Hospital. Board meetings are held two to three times a year.

The board members are:

Prof. Sigbjørn Fossum - Chairman of the board, Dean of Research, Faculty of Medicine, University of Oslo

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, the Cancer Clinic, Oslo University Hospital

Prof. Erlend Smeland, Director of Research and Development, Oslo University Hospital.

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), Porto, 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 & Chief Research Advisor, Sidra Medical & Research Center, Qatar Foundation, Doha, Qatar

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.

The Scientific Advisory Board performed its first visit to CCB from 11-12 May 2009. They support 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. The second visit is planned for 18-19 May 2010.

Visiting professors

CCB has three professors associated to the Centre.

Professor Zena Werb
Department of Anatomy,
University of California,
San Francisco

Professor Bo van Deurs
The Panum Institute, University of Copenhagen

Professor Manuel Teixeira
Portugese Oncology Institute, Porto

Clinical Associates

In 2009 two clinical associates joined CCB:

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

Prof. Arild Nesbakken, Oslo University Hospital, Aker

Administrative support

Since 1 June 2009 Anette Sørensen has been responsible for the administration of CCB. Her main tasks include financial management, reporting, administrative research service as well as web pages, to mention a few. When it comes to other administrative services, e.g. personnel administration, accounting and IT support, CCB benefits from existing administrative support environments at both our host institutions.

Committee for Equality

Diversity with respect to gender representation, age and educational background is a plus for any working environment devoted to innovative work.

Recruitment of female scientists at PhD student and postdoc level is not considered a major obstacle in CCB. The real challenge lies in ensuring that the most talented female scientists are promoted at project leader as well as group leader level. CCB will actively support 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. It is an aim for the centre that at least 50% of the new project leader and group leader positions are offered to women.

CCB's Committee for Equality meets once a year. Of course the management and group leaders in CCB realize that equal opportunities is a matter which demands continuous attention.

Starting in 2009 the Centre will fund one project leader for three years as part of its program for equal opportunities in science. Support will also be provided for leadership training and courses in lab management. Three female scientists attended laboratory management courses in 2009 and another four female scientists will be participating in 2010.

In 2009 CCB certainly took action when it comes to increasing the number of women in leading positions. Out of 12 project leader positions 5 were held by women. In 2008 only 1 out of 7 project leader positions was held by a woman. In percentage these figures represent an increase from 14% in 2008 to 42% in 2009 for the share of female project leaders in the Centre.

FINANCING

Funding

In 2009 the total funding of CCB was 102 mill NOK. The overall funding has increased also in 2009, compared to the figures from the original funding plans for the Centre. The indirect cost of infrastructure at our host institutions amounts to a total of 29 mill NOK. This cost is reflected as an indirect personnel cost in the table below. Similarly this amount, almost in full, is included as funding from Oslo University Hospital where the majority of our staff is located.

Expenditures

The total expenditures in 2009 add up to 97 mill NOK. This leaves CCB with a surplus of 5 mill NOK which will be transferred to 2010 for future salary obligations and planned research activities.

Funding (in 1000 NOK)	2009
University of Oslo (UiO) funding 1)	6 651
Research Council of Norway - CoE 2)	11 088
Oslo University Hospital (OUS) funding 3)	51 019
International funding	575
Other public funding 4)	16 219
Other private funding 5)	16 868
Sum funding	**102 420**

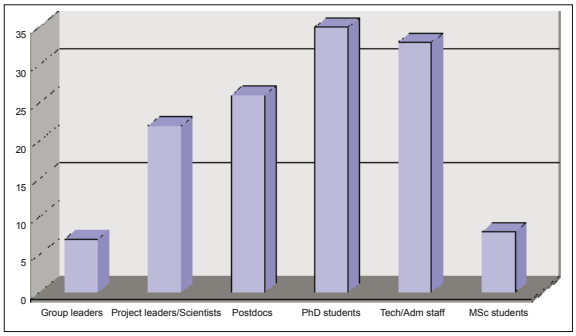
Expenditures (in 1000 NOK)	2009
Personnel UiO (incl. indirect costs)	6 063
Personnel OUS (incl. indirect costs)	67 584
Equipment	2 484
Other operating expenses	20 974
Sum expenditures	**97 105**

1) Including indirect cost of infrastructure of 900 KNOK
2) Including equal opportunities grant of 166 KNOK
3) Including indirect cost of infrastructure of 28 065 KNOK
4) Including other grants from the Research Council of Norway
5) Including grants from the Norwegian Cancer Society

PEOPLE

For 2009 we counted 131 CCB members. Some of them were not present during the whole year and furthermore a few hold part-time positions. This results in a total of 89 man-labour years in CCB in 2009 which represents a slight increase compared to 2008. The column chart shows the number of people categorized by position.

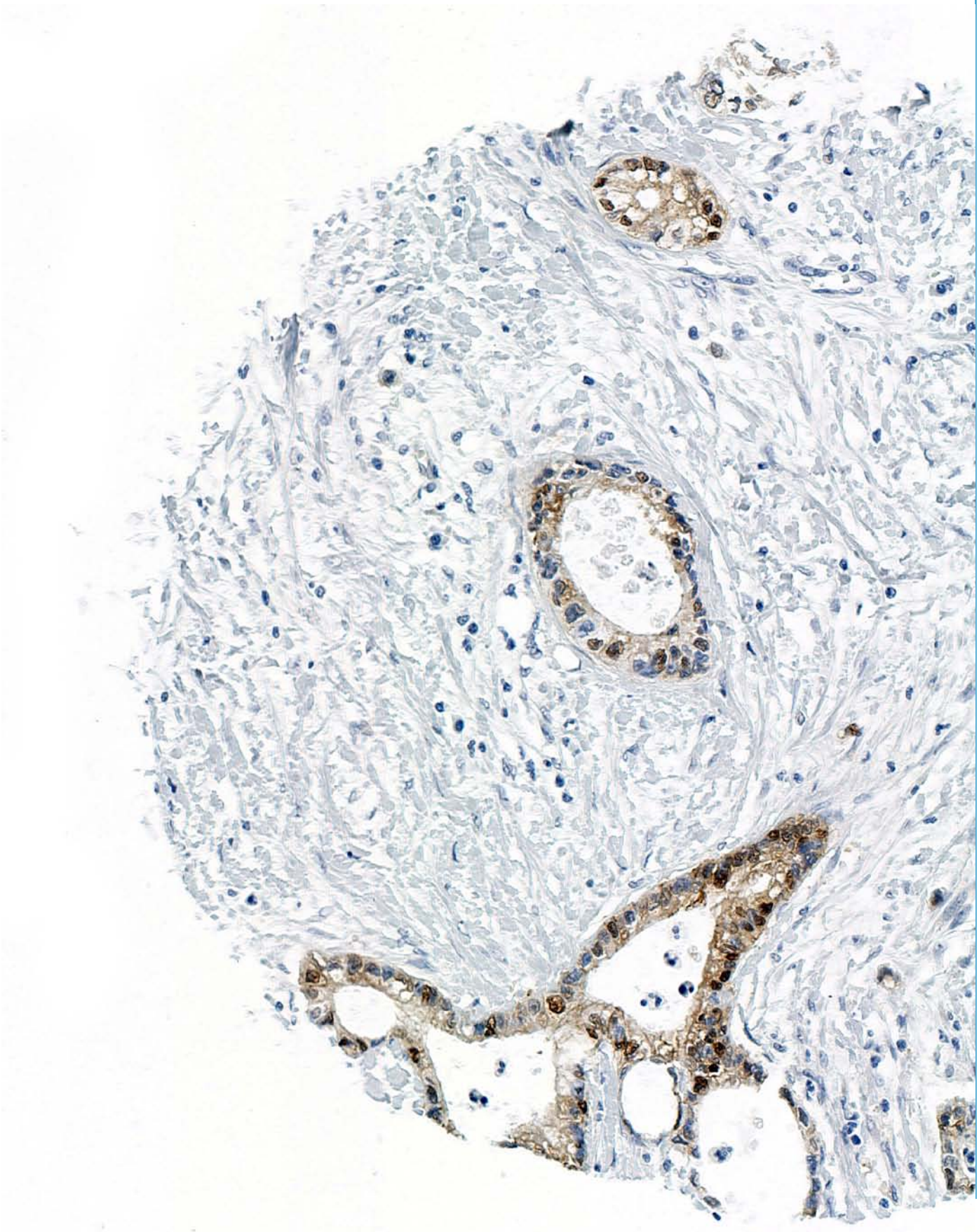
15 different nationalities are represented amongst our employees. 88 (67%) of our members are women and 43 (33%) are men.

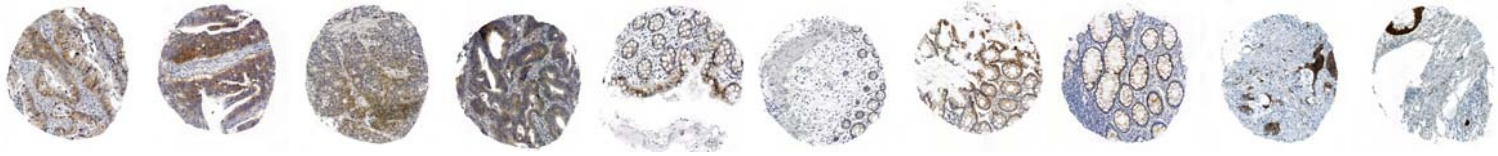


Name	Position	Group	Nationality	Employer	Academic title
Abrahamsen, Hilde	Postdoc	Stenmark	Norway	Oslo University Hospital	PhD
Ahlquist, Terje	PhD student/Postdoc	Lothe	Norway	Oslo University Hospital	MSc, PhD
Ailte, Ieva	Master student	Sandvig	Latvia	Oslo University Hospital	
Alagaratnam, Sharmini	Postdoc	Lothe	Malaysia	Oslo University Hospital	PhD
Albregtsen, Fritz	Senior scientist	Danielsen	Norway	Oslo University Hospital	PhD
Ali, Deeqa A.M.	Master student	Lothe	Norway	Oslo University Hospital	
Andersson, Sofia	Postdoc	Sandvig	Sweden	Oslo University Hospital	PhD
Andresen, Kim	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Bache, Kristi Grønvold	Postdoc	Stenmark	Norway	Oslo University Hospital	PhD
Bakkebø, Maren	PhD student	Smeland	Norway	Oslo University Hospital	MSc
Bakken, Anne Cathrine	Master student	Lothe	Norway	Oslo University Hospital	
Bassols, Jose Maria	Computer specialist	Olsnes	Spain	Oslo University Hospital	
Bentsen, Annette	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Berg, Marianne	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Bergan, Jonas	PhD student	Sandvig	Norway	Oslo University Hospital	MSc
Bergersen, Anne Gro	Technician	Olsnes	Norway	Oslo University Hospital	
Bethge, Nicole	PhD student	Smeland	Germany	Oslo University Hospital	MSc
Betz, Josefine	Guest PhD student	Sandvig	Germany	University of Münster	MSc
Brech, Andreas	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Bredahl, May Kristin L.	Senior scientist	Smeland	Norway	Oslo University Hospital	PhD
Brekke, Helge	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Bruun, Jarle	Research fellow	Lothe	Norway	Oslo University Hospital	MSc
Cekaite, Lina	Postdoc	Lothe	Lithuania	Medinnova AS	PhD
Christensen, Lene	Laboratory assistant	Olsnes	Norway	Oslo University Hospital	
Cordara, Gabriele	PhD student	Sandvig	Italy	University of Oslo	MSc
Costa, Vera	Guest PhD student	Lothe	Portugal	Portuguese Oncology Institute	MSc
Danielsen, Håvard	Group leader, professor	Danielsen	Norway	Oslo University Hospital	PhD
Danielsen, Stine Aske	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Dyve, Anne Berit	PhD student	Sandvig	Norway	Oslo University Hospital	MSc
Eide, Marianne B.	PhD student	Smeland	Norway	UiO/ Oslo University Hospital	MD
Eiken, Hans Geir	Senior scientist	Lothe	Norway	Oslo University Hospital	PhD
Eknæs, Mette	Technician	Lothe	Norway	Oslo University Hospital	
Engedal, Kim Nikolai	Postdoc	Sandvig	Norway	Oslo University Hospital	PhD
Engen, Anne	Technician	Olsnes	Norway	Oslo University Hospital	
Ersvær, Elin	Research fellow	Danielsen	Norway	Oslo University Hospital	
Forfang, Lise	Technician	Smeland	Norway	Oslo University Hospital	MSc
Frerker, Nadine	Postdoc	Sandvig	Germany	Oslo University Hospital	PhD
Fykerud, Tone	Master student	Lothe	Norway	Oslo University Hospital	
Gedde, Ida	Laboratory assistant	Stenmark	Norway	Oslo University Hospital	
Guha, Nirmalendu	Laboratory assistant	Olsnes	Norway	Oslo University Hospital	
Guldsten, Hanne	Technician	Olsnes	Norway	Oslo University Hospital	

Name	Position	Group	Nationality	Employer	Academic title
Guriby, Marianne	Master student	Lothe	Norway	Oslo University Hospital	
Haglund, Kaisa	Project leader, Senior scientist	Stenmark	Sweden	HFSP/ Oslo University Hospital	PhD
Haugsten, Ellen M.	PhD student/Postdoc	Olsnes	Norway	Oslo University Hospital	MSc
Hektoen, Merete	Technician	Lothe	Norway	Oslo University Hospital	MSc
Hilden, Vera Irene	Technician	Smeland	Norway	Oslo University Hospital	MSc
Høland, Maren	Master student	Lothe	Norway	Oslo University Hospital	
Honne, Hilde	Research fellow	Lothe	Norway	Medinnova AS	MSc
Huse, Kanutte	PhD student	Smeland	Norway	Oslo University Hospital	MSc
Hveem, Tarjei S.	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
Jin, Yi-xin	Postdoc	Olsnes	China	Oslo University Hospital	PhD
Johannessen, May E.	Secretary		Norway	Oslo University Hospital	
Karerwa, Jeanne D'Arc	Technician	Danielsen	Norway	Oslo University Hospital	
Kildahl, Wanja	PhD student	Danielsen	Norway	Oslo University Hospital	MSc
Kjæreng, Marna Lill	Technician	Danielsen	Norway	Oslo University Hospital	
Kjeldby, Brage Braathen	Laboratory assistant	Olsnes	Norway	Oslo University Hospital	
Kjenseth, Ane Hansen	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Klokk, Tove Irene	Postdoc	Sandvig	Norway	Oslo University Hospital	PhD
Kolberg, Matthias	Scientist	Lothe	Norway	Oslo University Hospital	PhD
Kraggerud, Sigrid M.	Postdoc	Lothe	Norway	Oslo University Hospital	Dr. Philos
Leithe, Edward	Project leader, Senior scientist	Lothe	Norway	Oslo University Hospital	Dr. philos
Lemus, Dafne	PhD student	Stenmark	Mexico	Oslo University Hospital	MSc
Liestøl, Knut	Group leader, professor	Liestøl	Norway	University of Oslo	Dr. philos
Lind, Guro Elisabeth	Project leader, Senior scientist	Lothe	Norway	Oslo University Hospital	Dr. philos
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.	Group leader, professor	Lothe	Norway	Oslo University Hospital	Dr. philos
Løvf, Marthe	PhD student	Lothe	Norway	University of Oslo	MSc
Ludt, Jannikke	Adm. coord., Research fellow	Olsnes	Norway	Oslo University Hospital	PhD
Malerød, Lene	Postdoc	Stenmark	Norway	Oslo University Hospital	PhD
Merok, Marianne Aa.	PhD student	Lothe	Norway	Oslo University Hospital	MD
Mesquita, Barbara	Guest PhD student	Lothe	Portugal	Portuguese Oncology Institute	MSc
Mikalsen, Svein-Ole	Scientist	Lothe	Norway	Oslo University Hospital	Dr. philos
Mjøen, Linda Uv	Advisor		Norway	Oslo University Hospital	
Myklebust, June Helen	Project leader, Senior scientist	Smeland	Norway	Oslo University Hospital	PhD
Myrann, Anne Grethe	Technician	Sandvig	Norway	Oslo University Hospital	
Nesheim, John Arne	Head of development	Danielsen	Norway	Oslo University Hospital	
Nezis, Ioannis	Postdoc	Stenmark	Greece	Oslo University Hospital	PhD
Nielsen, Birgitte	Postdoc	Danielsen	Norway	Oslo University Hospital	PhD
Nilsen, Gro	Research fellow	Liestøl	Norway	University of Oslo	MSc
Nome, Torfinn	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Nybøen, Åsmund	Head of lab	Danielsen	Norway	Oslo University Hospital	
Oksvold, Morten	Scientist	Smeland	Norway	Oslo University Hospital	PhD
Olsnes, Sjur	Group leader, professor	Olsnes	Norway	Oslo University Hospital	MD, PhD
Oppelt, Angela	PhD student	Olsnes	Germany	Oslo University Hospital	MSc
Parmo, Herman Ludt	Laboratory assistant	Olsnes	Norway	Oslo University Hospital	
Paulo, Paula	Guest PhD student	Lothe	Portugal	Portuguese Oncology Institute	MSc

Name	Position	Group	Nationality	Employer	Academic title
Pedersen, Anne-Mari G.	Technician	Sandvig	Norway	Oslo University Hospital	
Pedersen, Nina Marie	Postdoc	Stenmark	Norway	Oslo University Hospital	PhD
Platta, Harald	Postdoc	Stenmark	Germany	EMBO	
Pretorius, Maria	Administrative head	Danielsen	Norway	Oslo University Hospital	MSc
Pust, Sascha	Postdoc	Sandvig	Germany	Oslo University Hospital	PhD
Raa, Hilde	PhD student	Sandvig	Norway	Oslo University Hospital	MSc
Raiborg, Camilla	Postdoc	Stenmark	Norway	Oslo University Hospital	PhD
Rasmussen, Ida Løver	Laboratory assistant	Olsnes	Norway	Oslo University Hospital	
Ribeiro, Franclim	Guest Postdoc	Lothe	Portugal	Portuguese Oncology Institute	PhD
Rivedal, Edgar	Senior scientist	Lothe	Norway	Oslo University Hospital	Dr. philos
Rodahl, Lina W.	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Rødland, Einar	Scientist	Liestøl	Norway	University of Oslo	PhD
Rønning, Eva	Head technician	Stenmark	Norway	Oslo University Hospital	
Roxrud, Ingrid	PhD student/Postdoc	Stenmark	Norway	Oslo University Hospital	MSc
Rusten, Tor Erik	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Sagona, Antonia	PhD student	Stenmark	Greece	Oslo University Hospital	MSc
Sandvig, Kirsten	Group leader, professor	Sandvig	Norway	Oslo University Hospital	Dr. Philos
Sem Wegner, Catherine E.	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Silva, Diogo	Guest PhD student	Lothe	Portugal	Portuguese Oncology Institute	MSc
Simonsen, Anne	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Sirnes, Solveig	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Skånland, Sigrid Strand	PhD student	Sandvig	Norway	Oslo University Hospital	MSc
Skiple Skjerpen, Camilla	Postdoc	Olsnes	Norway	Oslo University Hospital	Dr. Philos
Skotheim, Rolf I.	Project leader, Senior scientist	Lothe	Norway	Oslo University Hospital	Dr. philos
Smeland, Erlend Bremertun	Group leader, professor	Smeland	Norway	Oslo University Hospital	MD, PhD
Smestad, Marianne	Technician	Stenmark	Norway	Oslo University Hospital	
Stuffers, Susanne	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Sørensen, Anette	Administrative coordinator		Denmark	University of Oslo	
Sørensen, Vigdis	Postdoc	Olsnes	Norway	Oslo University Hospital	PhD
Stenmark, Harald	Group leader, professor	Stenmark	Norway	Oslo University Hospital/ UiO	Dr. Philos
Stork, Bjørn	Guest scientist	Stenmark	Germany	University Hospital Tübingen	PhD
Sundet, Kristine Ingrid	Master student	Sandvig	Norway	Oslo University Hospital	MSc
Sveen, Anita	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Tcatchoff, Lionel	Postdoc	Sandvig	France	Oslo University Hospital	PhD
Thomassen, Gard O.S.	PhD student	Lothe	Norway	Medinnova AS	MSc
Thoresen, Sigrid Bratlie	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Torgersen, Maria Lyngaas	Postdoc	Sandvig	Norway	Oslo University Hospital	PhD
Utskarpen, Audrun	PhD student	Sandvig	Norway	Oslo University Hospital	MSc
Vedeld, Hege Marie	Master student	Lothe	Norway	Oslo University Hospital	
Vietri, Marina	PhD student	Stenmark	Italy	Oslo University Hospital	MSc
Wæhre, Håkon	Senior scientist	Danielsen	Norway	Oslo University Hospital	MD, PhD
Wesche, Jørgen	Project leader, Senior scientist	Olsnes	Norway	Oslo University Hospital	Dr. Philos
Wiedlocha, Antoni	Project leader, Senior scientist	Olsnes	Norway	Oslo University Hospital	Dr. Philos
Yadollahi, Mandana	Laboratory assistant	Olsnes	Iran	Oslo University Hospital	
Yohannes, Zeremariam	Technician	Lothe	Norway	Oslo University Hospital	
Zakrzewska, Malgorzata	Postdoc	Olsnes	Norway	Oslo University Hospital	PhD
Zhen, Yan	PhD student	Olsnes	Norway	Oslo University Hospital	MSc
Ågesen, Trude H.	PhD student	Lothe	Norway	Oslo University Hospital	MSc





ANNUAL REPORT 2009

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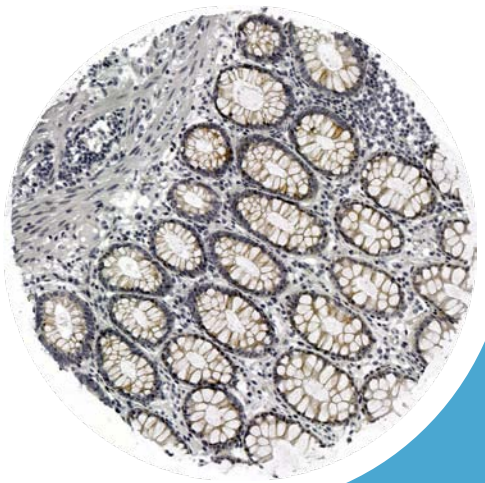
Norwegian Centre of Excellence

Oslo University Hospital

UNIVERSITY OF OSLO



Cover photo front | Immunohistochemical staining of the gap junction component connexin-43 in intracellular vesicles in colon cancer tissue

Cover photo back | Cross section of normal colon mucosa

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