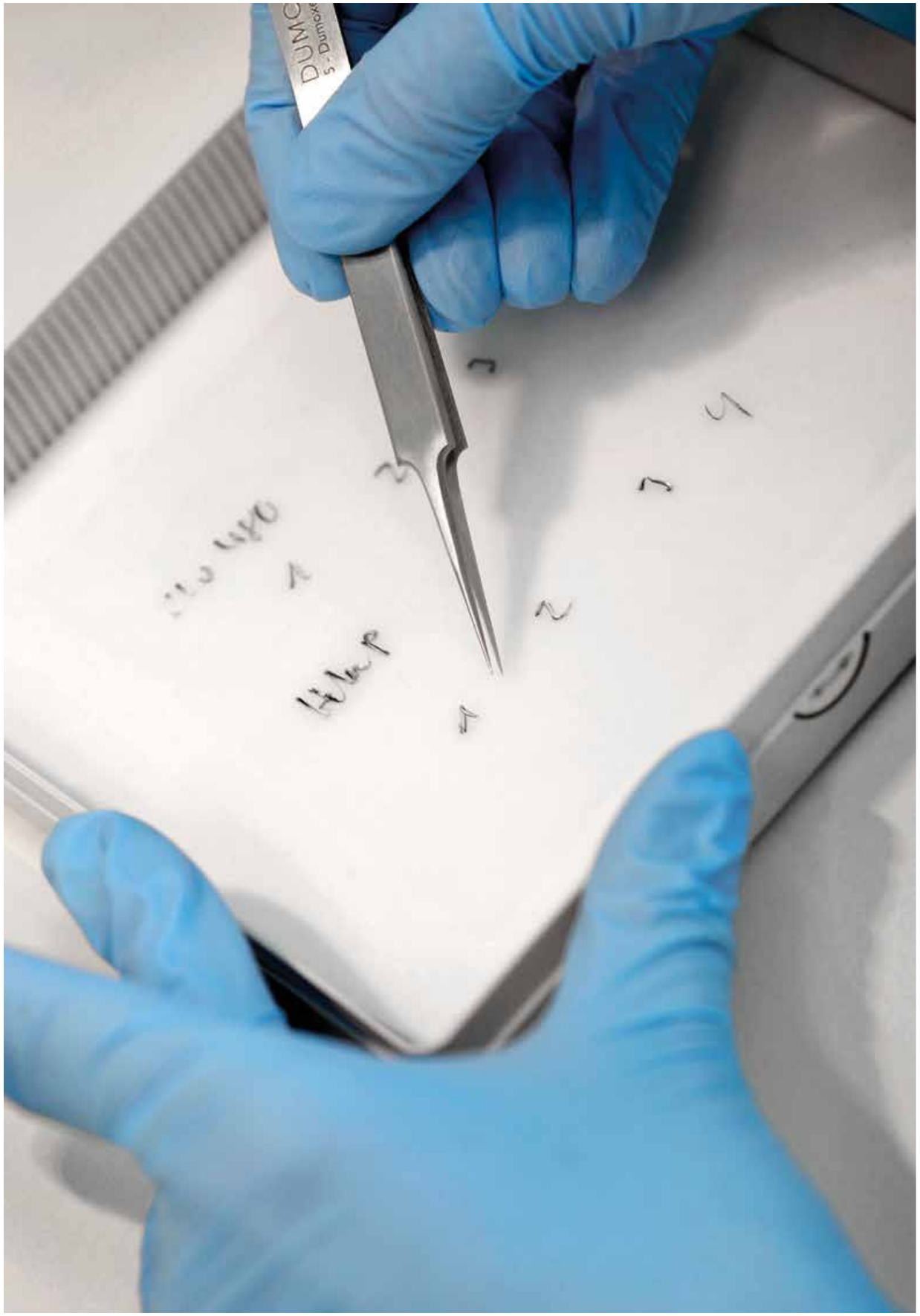
CENTRE FOR CANCER BIOMEDICINE

ANNUAL REPORT 2012

Centre for Cancer Biomedicine



CONTENT

FRONT COVER ART
The fruit fly Drosophila melanogaster is an excellent model to study cancer-relevant processes ranging from stem cells to gene regulation and nutrition. This image shows the upper part of the larval digestive system, where a muscle contracts to allow passage of food into the digestive tract.

Paper: 300g/150g Galerie Art Matt
Design and consept: Fete Typer
Photos: Terje Heiestad – pages 1, 2, 6, 25, 46, 47, 48, 58, 64
Front page: image courtesy of Åsmund Eikenes.

2012 – A MILESTONE FOR INTEGRATED CANCER RESEARCH

September 1st 2012 was an important date in the life of CCB since it marked the transition from the first to the second 5-year period of the Centre. All Norwegian Centres of Excellence receive financial support from the Research Council for a maximum of 10 years. It is thus fair to say that CCB has reached middle age, but our Centre bears no symptoms of midlife crisis. On the contrary, CCB is doing better than ever in terms of science, innovations and education, and the Centre's annual retreat at Leangkollen last autumn was infused by enthusiasm and a genuine team spirit. The Centre has grown to include 178 members/117 man-years among the six Principal Investigator (PI) groups, five associated groups, three clinical associates and three visiting professors.

CCB's researchers have already reached important milestones in basic and translational cancer research as foreseen in the Centre's research plan. With joint efforts towards integration of interdisciplinary competence the Centre has demonstrated improved output and quality of scientific publications and increasing joint work among researchers and clinicians.

Major scientific highlights in 2012 included the identification of prognostic gene expression based signatures for stage II and III colorectal cancers, identification of micro-RNAs that control cell proliferation in colon cancer, development of a novel high-throughput method for nuclear analyses of prostate cancers, identification of a novel mechanism for regulation of the ErbB2 proto-oncogene in breast cancer, identification of novel therapeutic targets in Burkitt's lymphoma, new insights in the biology and tumour suppressor functions of gap junction proteins, identification of protein and RNA contents of microvesicles released from prostate cancer cells, progress in understanding the nuclear translocation of fibroblast growth factor 1, new insight into the regulation of cell polarization, and discovery of novel mechanisms for downregulation of mitogentic receptors in cancer cells.

CCB continues to transfer its research from basic discoveries into innovation paths, and several patent applications describing novel biomarkers for colorectal cancer, prostate cancer and lymphoma were filed in 2012. Furthermore, a license agreement was signed with a British biotech company for development of a non-invasive early detection test for colorectal cancer based on biomarkers identified in CCB. CCB's goal is that its innovations will ultimately become beneficial to the cancer patient.

During the startup years of CCB a strategy was made to recruit excellent associated research groups, young investigators and clinical associates, and this policy has proven very rewarding to the Centre. Research training is also an important objective for CCB. PhD students and postdocs from all over the world have been recruited, and currently 16 nationalities are represented in the Centre. Graduation of PhDs reached an all-time-high in 2012, with 9 PhD degrees obtained by CCB scientists this year. The dedicated work by highly motivated PhD students and postdocs continues to be the driving force of CCB's scientific discoveries. Furthermore, the CCB course in "Advanced cancer biology" open for MSc and PhD students from the Faculties of Mathematics/Natural Sciences and Medicine was running for the second time in 2012. Organized by CCB Young Investigator Guro E. Lind and with contributions form several CCB members this course has already become a great success among students.

The Board and the Scientific Advisory Board (SAB) of CCB have been very important to the success of the Centre so far, and both Boards have been truly supportive in their interactions with the management and scientists of CCB. A particular concern of the SAB has been the career development of postdoctoral scientists and junior group leaders of CCB. Since CCB as such cannot offer any permanent positions, and researcher positions in our host institutions, the University of Oslo and the Oslo University Hospital, are exceedingly scarce, it is a continuous challenge to provide the Centre's most promising junior scientists with the long-time perspectives they demand and deserve. As recommended by the SAB, CCB is now spending a significant amount of its budget for funding support to junior researchers, and as of January 2013 a junior scientist (within 12 years after obtained PhD) will be offered inclusion in the Executive Group of the CCB on an annual basis. Such a position not only means increased funding for the chosen junior scientist, but also increased influence on the Centre's activities and research strategy.

PHOTO BY TERJE HEIESTAD

Director Harald Stenmark and Co-director Ragnhild A. Lothe

– CCB´S RESEARCHERS HAVE ALREADY REACHED IMPORTANT MILESTONES IN BASIC AND TRANSLATIONAL CANCER RESEARCH

CCB has also this year received funding for equal opportunities from the Research Council for CCB's programs for promoting women in science. One of these programs is the funding of bridging fellowships for female postdoctoral scientists in the interim period between two funding periods. Another is the funding of two female adjunct professorships. We are confident that these programmes will contribute to promote the careers of CCB´s talented female researchers, which will also benefit CCB and the cancer research community at large.

Entering the next five-year period CCB aims to contribute even more on the national level, and this is highlighted by CCB's dedicated participation in the Norwegian Cancer Genomics Consortium that aims to provide improved diagnostics and guidance of treatment based on the patient's own tumour genome. Furthermore, CCB's scientists have continuously proven successful in obtaining national funding, but both young and senior CCB members are encouraged to apply for major grants also on the European arena. Each research group in the Centre has documented international collaborations through their publications, and CCB will seek to expand these into interdisciplinary collaborations based on the ideas and project interests of CCB's researchers.

We would like to thank all CCB members, including our excellent associated clinicians and visiting professors, for their great scientific contributions in 2012. The collaborative spirit among all CCB members, and their willingness to help their fellow centre colleagues, are particular assets of CCB. Special congratulations go to those talented men and women who successfully completed their PhD in 2012. On page 63 of this report we highlight our sponsors, whose continued support is instrumental to the success of CCB. Together we will continue to advance cancer research for the benefit of science and the cancer patient.

Director *Harald Stenmark*
Co-director *Ragnhild A. Lothe*

– THE COLLABORATIVE SPIRIT AMONG ALL CCB MEMBERS, AND THEIR WILLINGNESS TO HELP THEIR FELLOW CENTRE COLLEAGUES, ARE PARTICULAR ASSETS OF CCB

JANUARY

Media coverage

NEW PROGNOSTIC TEST FOR IMPROVED CANCER TREATMENT

RESEARCHERS AT THE CENTRE FOR CANCER BIOMEDICINE, OSLO UNIVERSITY HOSPITAL, HAVE DEVELOPED A GENE SIGNATURE THAT IS SUITABLE TO BE DEVELOPED INTO A PROGNOSTIC TEST FOR PATIENTS WITH STAGE II COLORECTAL CANCER.

The test has been named ColoGuideEx and can predict at time of diagnosis whether the patient who has undergone curative surgery in fact has a good or bad prognosis. If he or she belongs to the latter group (25%) chemo therapy may be an option. This remains to be investigated but the prognostic robustness of the gene signature has been shown.

ColoGuideEx measures the activity of 13 genes in the cancer tissue, and each gene contributes with prognostic information. The test is developed through advanced statistics on gene expression measurements of all human genes from cancer patients treated at the hospital. ColoGuideEx has been validated as a robust test in two independent series of patient samples, one from Norway and the other one from USA and Australia.

The research behind ColoGuideEx was published on January 2nd 2012, in the prestigious journal GUT. This work was led by Professor Ragnhild A. Lothe, and is part of a larger collaboration on "prognostic and predictive biomarkers of colorectal cancer" between the Department of Cancer Prevention, Institute for Cancer Research and Department of Gastro Surgery, by Professor Arild Nesbakken. →

PHOTO BY TERJE HEIESTAD

Medical technologist Merete Hektoen

The Norwegian news article about the ColoGuideEx test "Ny test kan gi bedre kreftbehandling" was published on www.oslo-universitetssykehus.no in January.

Furthermore, the website of the Norwegian Cancer Society, www.kreftforeningen.no, published a news article about ColoGuideEx in Norwegian: "Ny genbasert prognostisk test for kreft i tykk- og endetarm".

DISSERTATIONS

HANNE-SOFIE SPENNING DAHLBACK, MD PHD

Cytogenetic and molecular cytogenetic analyses of brain tumours – Faculty of Medicine, University of Oslo, January 2012

INNOVATION

US provisional Patent Application filed January 2012
Prognostic signature for colorectal cancer stage II and III
Ågesen TH, Sveen A, Lind GE, Nesbakken A, Skotheim RI, Lothe RA Serial No.: 61/584,540, INVEN-32274/US-1/PRO

Selected publications →

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

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

SEMINAR

JANUARY 10TH

Regulation of cell function by FGFR3 receptor tyrosine kinase
Dr. Pavel Krejci – Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles

The ER-protein LRRC59 regulates FGF1 nuclear import, cell morphology, and migration
Vigdis Sørensen, PhD – CCB and Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital

COMMENTS TO PUBLICATIONS

1. ESCRTing fibroblasts in the right direction
Since tumours spread by cell migration, it is important to elucidate mechanisms that control this process. PhD student Viola Lobert in Harald Stenmark's group observed that fibroblasts depleted of subunits of the endosomal sorting complex required for transport (ESCRT) machinery lose their sense of direction when trying to migrate towards an open space. She identified a mechanism for how ESCRTs control the directionality of fibroblast migration. This mechanism entails ESCRT-mediated control of kinases that regulate the activity of myosin regulatory light chain, which organizes cell polarization and thereby influences directional migration.

2. Regulating the level of a tumour suppressor
Beclin 1 is a well-known tumour suppressor, and its monoallelic deletion causes spontaneous tumourigenesis. On the other hand, Beclin 1 can also be found overexpressed in some cancers, illustrating the importance of tightly controlled expression of this protein. Postdoc Harald Platta and his co-workers in Harald Stenmark's group have recently discovered a novel mechanism that regulates the cellular levels of Beclin 1. Under conditions when Beclin 1 is separated from its partner proteins, the ubiquitin ligase Nedd4 adds polyubiquitin chains to Beclin 1, thereby targeting it for degradation in proteasomes. These polyubiquitin chains are unusual in that they are linked through lysine-11, and not through the more commonly observed lysine-48.

Highlights

PRIZES TO CCB PHD STUDENTS

THE NORWEGIAN BIOCHEMICAL SOCIETY ARRANGED ITS 48TH CONTACT MEETING AT STOREFJELL, JANUARY 19TH-22ND, 2012, AND HIGH QUALITY SCIENCE WAS PRESENTED BOTH IN LECTURES AND AS POSTERS.

Two PhD students, Simona Kavaliauskiene, from the Sandvig group, working with membrane transport, and Angela Oppelt, from the Wiedlocha group, studying cell movement, were honored by a poster-prize and a prize for an excellent lecture, respectively.

PHOTO BY ØYSTEIN H. HORGMO

From left Angela Oppelt and Simona Kavaliauskiene

FEBRUARY

Selected publications →

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

Media coverage

TV INTERVIEW WITH CCB CO-DIRECTOR ABOUT NATIONAL PROJECT ON PERSONALIZED CANCER MEDICINE.

Interview with Ragnhild A. Lothe and Ola Myklebost in NRK Morning News, 8th of February 2012, about the Norwegian Cancer Genomics Consortium - the first national initiative for personalized cancer medicine – which includes clinicians and several groups from CCB (see October Highlights for further details).

SEMINAR

FEBRUARY 14TH

Lymphomas can escape the inhibitory effects of BMP seen in normal B cells
Kanutte Huse, PhD – CCB and Department of Immunology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital

Flotillin mediated stabilization of the receptor tyrosine kinase ErbB2
Sascha Pust, PhD – CCB and Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital

COMMENTS TO PUBLICATIONS

3. DNA ploidy in endometrial adenocarcinomas
DNA ploidy (chromosome number) analyses are useful for prognostication in cancer patients. Postdoc Wanja Kildal and her co-workers in Håvard Danielsen's group compared ploidy analyses with karyotyping (microscopic analyses of chromosomes) and measurements of DNA copy numbers in 51 endometrial adenocarcinomas. The authors observed a significant correlation between increasing DNA ploidy and increasing number of copy alterations.

INNOVATION

Patent Application filed February 2012:
Prostate cancer markers and uses thereof
Skotland T, Llorente A, Sandvig K
Serial No.: 61/604,145, INVEN-32448/Us-1/PRO.

Innovation

SECURING EXCLUSIVE RIGHTS TO BIOMARKERS

BRITISH BIOTECH COMPANY SIGNS AGREEMENT WITH INVEN2 TO SECURE EXCLUSIVE RIGHTS TO BIOMARKERS IDENTIFIED IN THE LOTHE GROUP.

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

Colorectal cancer is one of the most frequent cancer types in both men and women and more than 3600 new diagnoses are made annually in Norway alone. Less than 60% of the patients are still alive after 5 years. The survival rate is highly dependent on how advanced the cancer is at the time of diagnosis. Detection at an early stage indicates curation by surgery alone.

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

PHOTO BY TERJE HEIESTAD

From left Rolf I. Skotheim, Guro E. Lind, and Ragnhild A. Lothe

Media coverage

THE HUNT FOR PROSTATE CANCER

NEW BIOMARKERS CAN MAKE HUNTING FOR PROSTATE CANCER MORE ACCURATE.

Prostate cancer is the most common form of cancer among men. One in eight men will be affected during their lifetime. But not all forms of prostate cancer are as aggressive, and not all require the same extensive treatment. The challenge is to identify the different types.

Vesicles hold the secret | The answer may lie in vesicles, and scientist Alicia Llorente is working to crack the code.

"Vesicles are small bubbles of liquid found in all biological fluids. All cells secrete vesicles for a specific purpose," she explains.

Just like any motorist trying to find the fastest and least winding road, Llorente is trying to find the easiest and most accurate way of detecting prostate cancer. She wants to drive on the highway, not a crooked county road with an uncertain destination.

Her department is working on intracellular transport. They are studying how molecules are transported into cells and how they move from organelle to organelle inside the cells. The different organelles are like small workshop artisans, each of whom has a special function. There is constant movement in a cell. Proteins and other molecules move constantly, not only inside a cell, but also from cell to cell via the vesicles.

The Norwegian news article "Jakten på prostatakreften" was published on www.forskning.no.

PHOTO BY TERJE HEIESTAD

PhD student Santosh Phuyal

The answer may lie in vesicles. Here a schematic drawing of a microvesicle.

Illustration: Santosh Phuyal

MARCH

Selected publications →

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

Highlights

LLORENTE AND SANDVIG PUBLISH POTENTIAL BIOMARKERS FOR PROSTATE CANCER

ALICIA LLORENTE AND KIRSTEN SANDVIG, DEPARTMENT OF BIOCHEMISTRY AND CCB, HAVE PUBLISHED A PROTEOMIC ANALYSIS OF MICROVESICLES RELEASED FROM A HUMAN PROSTATE CANCER CELL LINE IN THE JOURNAL MOLECULAR AND CELLULAR PROTEOMICS (IMPACT FACTOR 8.4).

Potential new non invasive biomarkers | Most of the 266 proteins identified have previously been reported to be present in vesicles released from other cell types, but several proteins seem to be specific for prostate cancer cells. Since microvesicles can reach biological fluids, these proteins are thus potentially useful as new non invasive biomarkers for detection, diagnosis and/or prognosis of prostate cancer.

Proteomic analysis of microvesicles released by the human prostate cancer cell line PC-3
– Sandvig K, Llorente A. Mol Cell Proteomics. 11(7):M111.012914 [Epub ahead of print 2012 Mar 28].

PHOTO BY PER MARIUS DIDRIKSEN

PHOTO BY TERJE HEIESTAD

From left Alicia Llorente and Kirsten Sandvig

COMMENTS TO PUBLICATIONS

4. Cover story in Journal of Biological Chemistry: Gap junction SUMOylation
One of the ways cells can communicate is by virtue of gap junctions, small channels that connect two neighbouring cells. Since dysfunctional gap junctions are associated with carcinogenesis, it is important to identify mechanisms that regulate these intercellular channels. In a paper presented on the cover of Journal of Biological Chemistry. PhD student Ane Hansen Kjenseth and her co-workers in Edward Leithe's project group showed that gap junction proteins are regulated by conjugation with a small protein called SUMO. SUMOylation of gap junctions was found to control the level of functional levels of functional gap junction channels at the plasma membrane, revealing a new and unexpected mechanism for gap junction regulation. The authors received an Excellent Article Award of NOK 50.000 from Oslo University Hospital.

PHOTO BY TERJE HEIESTAD

From left PhD student Tone Aase Fykerud and Head technician Zeremariam Yohannes

SEMINARS

MARCH 23RD
ESCRT machinery: from membrane remodelling to guardian of the genome
Juan Martin-Serrano, PhD – Guy's King's and St. Thomas' Hospitals, London

MARCH 28TH
CCB Minisymposium on Prostate Cancer – Clinical aspects as well as recent discoveries within research on prostate cancer were presented:

Prostate cancer – an introduction: Treatment stratification and treatment options
Karol Axcrona, MD PhD, Department of Urology, Oslo University Hospital

Biobanking of radical prostatectomy specimens
Kathrine A. Lie, MD PhD, Department of Pathology, Oslo University Hospital

Identification of novel biomarkers therapeutic targets for prostate cancer
Fahri Saatcioglu, Professor, Department of Molecular Biosciences, University of Oslo

Microvesicles as a source of prostate cancer biomarkers
Alicia Llorente, PhD, CCB - Institute for Cancer Research, Oslo University Hospital

From genomics to biomarkers
Rolf Skotheim, Dr. Philos, CCB – Institute for Cancer Research, Oslo University Hospital

DISSERTATIONS

ANNE BERIT DYVE LINGELEM, PHD
Intracellular transport of Shiga toxin and ricin – Faculty of Mathematics and Natural Sciences, University of Oslo, March 2012

MANOHAR PRADHAN, MBBS, MD PHD
DNA ploidy and DNA index in endometrial carcinoma – Faculty of Medicine, University of Oslo, March 2012

ANTONIA SAGONA, PHD
Regulation of cytokinesis and its consequences for human health – Faculty of Medicine, University of Oslo, March 2012

TRUDE HOLMEIDE ÅGESEN, PHD
Genetics of colorectal cancer: new insights to early onset and to prognostication of disease – Faculty of Medicine, University of Oslo, March 2012

ANITA SVEEN, PHD
The transcriptome and prognosis in stage II and III colorectal cancer – Faculty of Medicine, University of Oslo, March 2012

APRIL

Media coverage

PROF. KIRSTEN SANDVIG APPOINTED SCIENTIST OF THE MONTH BY THE SOUTH-EASTERN NORWAY REGIONAL HEALTH AUTHORITY IN APRIL 2012.

The South-Eastern Norway Regional Health Authority (Helse Sør-Øst) aims to profile ongoing excellent research in the region by calling special attention to a "Scientist of the month". For the month of April 2012, this honor goes to CCB's Principal Investigator Kirsten Sandvig from the Department of Biochemistry at the Institute for Cancer Research, Oslo University Hospital.

The Norwegian news article "Jevn kunnskapsoppbygging – ikke store sprang" was published on www.helse-sorost.no.

Educational activities

MBV4160/9160

_Advanced Cancer Biology
Faculty of Mathematics and Natural Sciences
University of Oslo, Spring 2012
Course responsible: Guro E. Lind

THIS IS A CCB ASSOCIATED COURSE OFFERED TO MASTER AND PHD STUDENTS AT THE DEPARTMENT OF BIOSCIENCES (IBV), THE FACULTY OF MATHEMATICS AND NATURAL SCIENCES, AND TO PHD STUDENTS AT THE MEDICAL FACULTY AT THE UNIVERSITY OF OSLO.

The students gain a comprehensive insight into the molecular biology of cancer in general including the underlying biology and clinical challenges of selected diseases studies in CCB.

The vast majority of lectures were provided by the course responsible Guro E. Lind who holds a part time position as an Associate Professor at the University of Oslo. Several additional CCB members contributed to the course including Ragnhild A. Lothe, Edgar Rivedal, Matthias Kolberg, Sharmini Alagaratnam, Edward Leithe, Hilde Abrahamsen, June H. Myklebust, Alicia Llorente, Karol Axcrona, Ole-Christian Lingjærde, Torfinn Nome, Anita Sveen, Kay Oliver Schink, Åsmund Eikenes, Tor Erik Rusten, Rolf Skotheim and Arild Nesbakken. Additional contributors were: Alexander Fosså, Beata Grallert, Pål Selbo, Randi Syljuåsen, and Johanna Olweus.

2012 was the second year the course was running and it has become increasingly popular among the students, underscored by a 64% increase in the number of participants.

MBV3020
_Molecular Genetics and Developmental Biology | Faculty of Mathematics and Natural Sciences
University of Oslo, Spring and Autumn 2012
Course responsible: Fahri Saatcioglu
Responsible for Cancer Biology and Cell Cycle section: Ragnhild A. Lothe | Lecturers from CCB: Edward Leithe, Edgar Rivedal, Guro E. Lind, Rolf Skotheim

MBV4240/9240
_Biochemical Mechanisms in Intracellular Transport | Faculty of Mathematics and Natural Sciences
University of Oslo, Autumn 2012
Course responsible: Kirsten Sandvig
Lecturers from CCB: Kirsten Sandvig, Antoni Wiedlocha, Harald Stenmark

MBV 4270/9270
_Biostruct Advanced Glycobiology – By Glyconor | Faculty of Mathematics and Natural Sciences
University of Oslo, Spring 2012
Lecturer from CCB: Kirsten Sandvig

MF9110BTS
_PhD school, Molecular Biology Research Course | Biotechnology Centre of Oslo
University of Oslo, Autumn 2012
Lecturers from CCB: Rolf Skotheim, June H. Myklebust

MF9120BTS
_Molecular Medicine Research Course, NCMM | Faculty of Medicine
University of Oslo, Autumn 2012
Lecturer from CCB: Anita Sveen

MF9170
_Flow Cytometry In Medical Research And Diagnostics | Faculty of Medicine
University of Oslo, Spring and Autumn 2012.
Lecturer from CCB: June H. Myklebust

MOL8006
_Receptor Signalling and Trafficking | Faculty of Medicine
Norwegian University of Science and Technology, Trondheim, Spring 2012
Course responsible: Harald Stenmark
Lecturers from CCB: Fergal O'Farrell, Jørgen Wesche, Tor Erik Rusten, Lene Malerød

_PBL Course, 9th term, Gynecology, Obstetrics, and Pediatrics | Faculty of Medicine
University of Oslo, Spring and Autumn 2012
Lecturer from CCB: Sverre Heim

DISSERTATIONS

MAREN BAKKEBØ, PHD
Transforming growth factor β superfamily signaling and its role in B-cell lymphoma
– Faculty of Medicine, University of Oslo, April 2012

MAY

Highlights

WEB BASED CANCER ENCYCLOPEDIA

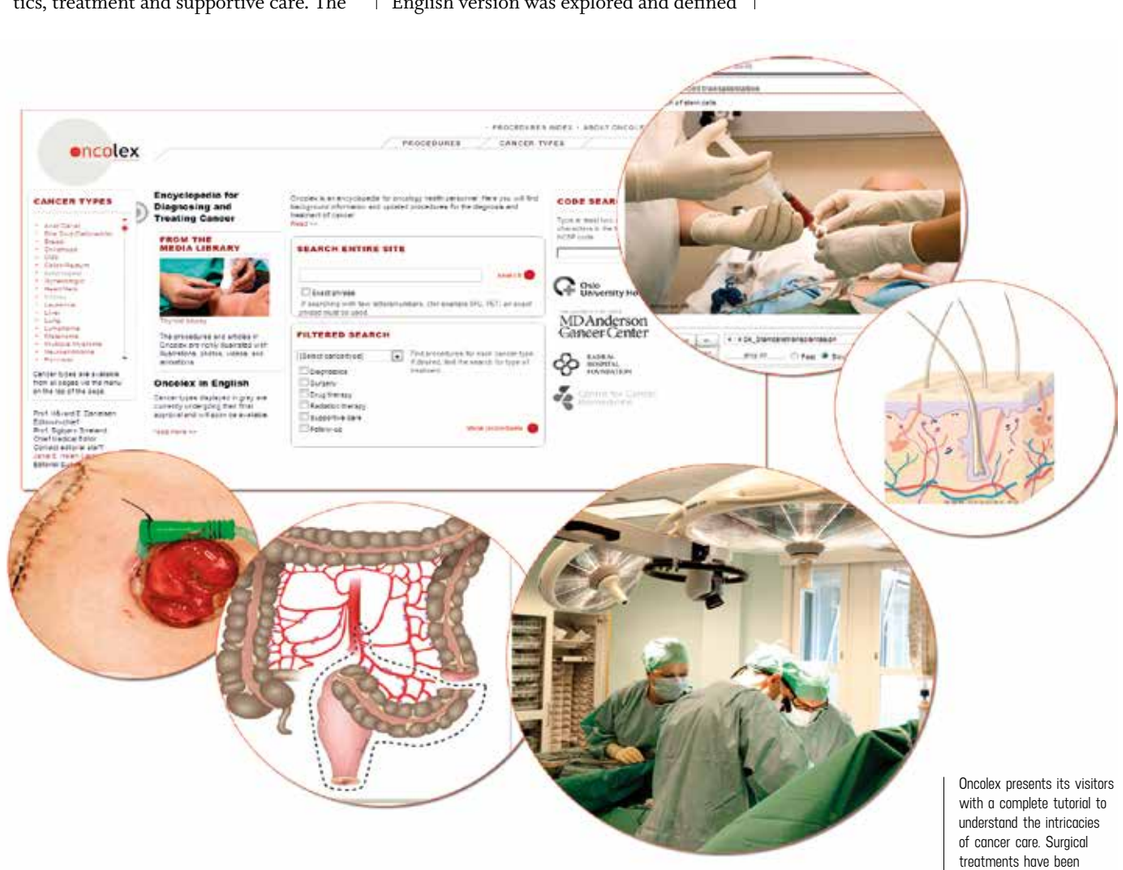
ONCOLEX.ORG IS A WEB BASED CANCER ENCYCLOPEDIA FOR HEALTH CARE PROVIDERS WORLDWIDE, PUBLISHED BY THE INSTITUTE FOR MEDICAL INFORMATICS (IMI) AT OSLO UNIVERSITY HOSPITAL. IMI IS HEADED BY HÅVARD E. DANIELSEN, AND IS PART OF THE CENTRE FOR CANCER BIOMEDICINE.

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

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

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

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



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

SEMINAR

MAY 10TH

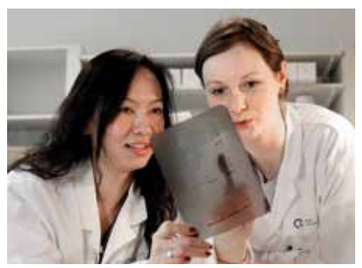
Activation and termination of fibroblast growth factor induced cellular signaling
Antoni Wiedlocha, PhD – Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital

The ribosomal S6 kinase 2 (RSK2) binds and phosphorylates FGFR1
Beata Nadratowska-Wesolowska, PhD – Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital

Selected publications →

5. Zhen Y, Sørensen V, Skjerpen CS, Haugsten EM, Jin Y, Wälchli S, Olsnes S, Wiedlocha A. (2012) **Nuclear import of exogenous FGF1 requires the ER-protein LRRC59 and the importins Kpnα1 and Kpnβ1** Traffic. 13(5):650-64.

PHOTO BY TERJE HEIESTAD



From left: Postdoc Yan Zhen and PhD student Angela Oppelt

5. Chaperoning fibroblast growth factor into the nucleus
Antoni Wiedlocha and Sjur Olsnes in CCB have previously shown that externally added fibroblast growth factor 1 (FGF1) is able to enter the cell nucleus as part of a non-canonical signalling pathway. However, the mechanism by which FGF enters the nucleus has remained elusive. Now, postdocs Yan Zhen and Vigdis Sørensen in Antoni Wiedlocha's group have found that a membrane protein with previously unknown function, the nuclear envelope protein LRRC59, chaperones FGF1 from cytosol into the nucleus by a mechanism that requires the small GTPase Ran and the karyopherins α1 and β1.

JUNE

DISSERTATIONS

ANE HANSEN KJENSETH, PHD
Posttranslational modification of the tumor suppressor protein connexin43 – implications for cell communication and cancer – Faculty of Medicine, University of Oslo, June 2012

MASTER DEGREES

ANE HOEL HØISETH
M.SC. IN BIOTECHNOLOGY
Sorting Nexin 4 mediates chromosome congression – University of Life Sciences at Ås, June 2012

MINNA KIHLSTRÖM
M.SC. IN BIOCHEMISTRY
The effect of radixin on the retrograde transport of Shiga toxin and ricin – Department of Biochemistry, University of Oulu, Finland, June 2012

INA ANDRASSY EILERTSEN
M.SC. IN MOLECULAR BIOSCIENCES
New insights into the regulation of the tumor suppressor proteins PTEN and connexin 43 by post-translational modifications – Faculty of Mathematics and Natural Sciences, University of Oslo, June 2012

INNOVATION

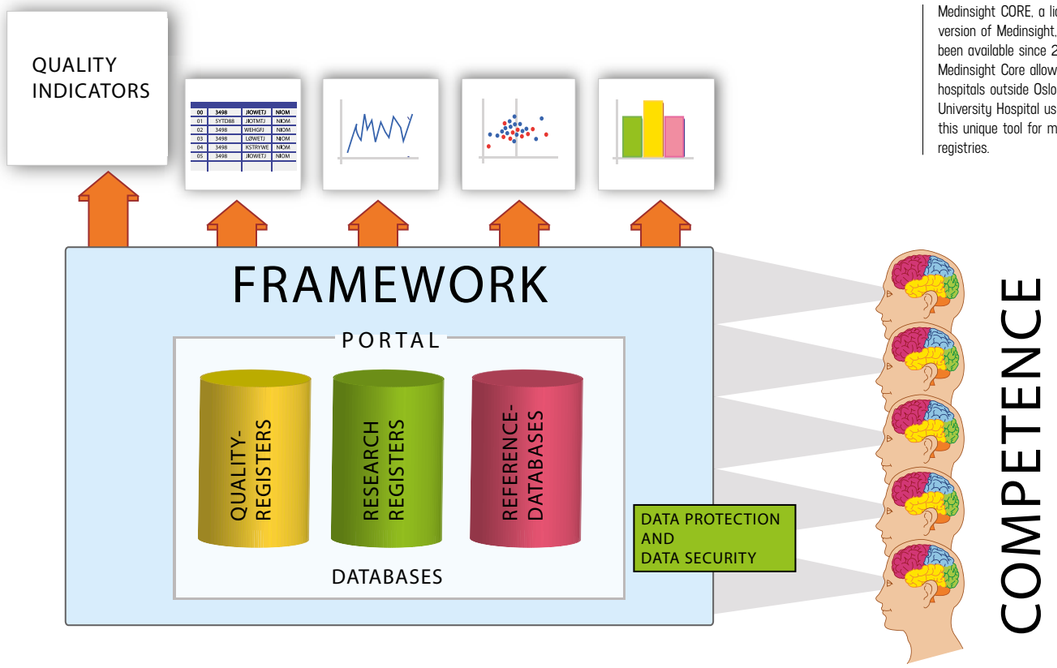
DOFI – Accepted in June 2012
Proteins in microvesicles as biomarkers for prostate cancer
Llorente A, Skotland T, Sandvig K
Inven2 project no. 12037

SEMINAR

JUNE 13TH

Tumor vessels as targets for therapy; histidine-rich glycoprotein (HRG) in regulation of tumor vascularization and anti-tumor immune response
Lena Claesson-Welsh, Professor – Head of Department of Immunology, Genetics and Pathology (IGP), Uppsala University, Sweden

JUNE



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

Highlights

STANDARDIZED DEVELOPMENT OF MEDICAL REGISTRIES

MEDINSIGHT – A CONCEPTUAL FRAMEWORK TO PROVIDE STANDARDIZED DEVELOPMENT OF MEDICAL REGISTRIES, DEVELOPED BY HÅVARD DANIELSEN AND THE INSTITUTE FOR MEDICAL INFORMATICS.

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

Background | National strategies for improving the quality of health services have led to an increased need for documentation of the results of diagnostics and treatment. Medinsight was developed by the Institute for Medical Informatics (IMI) in 2004, in response to clinicians' requirements to carry out quality assurance of patient treatment, as well as to cover researchers' needs for storage and collation of research results.

As of 2013 Medinsight has over 170 implemented registries, 600 users and 40 different disease areas are covered.

Medinsight registries | Medinsight registries are custom built databases based on the individual user's requirements, and are connected to any legal accessible data sources via the Medinsight portal. Technically, Medinsight can contain any type of registry (quality-, research-, biobank-, trial- or clinical registry).

Existing data from other types of databases such as DataEase, Access, Excel and SPPS can all be converted into a Medinsight registry.

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

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

With Medinsight, reports can be created without help from database specialists. Key elements in the report module are functions for counting, filtering and analysis, survival curves and age distribution. Data may be transferred to statistics tools such as SPSS if more advanced analyses are required.

Developers at IMI and healthcare providers work closely together, establishing user-friendly registers adapted to each user's requirements – be in terms of quality assurance or research.

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

JULY

Selected publications →

6. Nielsen B, Albregtsen F, Danielsen HE. (2012) **Automatic segmentation of cell nuclei in Feulgen-stained histological sections of prostate cancer and quantitative evaluation of segmentation results** Cytometry A. 81(7):588-601.

7. Sandvig K, Llorente A. (2012) **Proteomic analysis of microvesicles released by the human prostate cancer cell line PC-3** Mol Cell Proteomics. 11(7):M111.012914.

Highlights

ACQUISITION OF OMX STRUCTURED ILLUMINATION MICROSCOPY FOR SUPER-RESOLUTION IMAGING, THE FIRST SUPER-RESOLUTION MICROSCOPE TO BE INSTALLED IN A NORWEGIAN RESEARCH INSTITUTION

The microscope was funded under the Large-Scale Infrastructure Programme of the Research Council of Norway, with additional support from Bothner's Legacy Foundation.

Structured illumination super-resolution microscopy uses structured light patterns to achieve sub-diffraction limit imaging. The structured light pattern creates interference moiré patterns with the fine structures of the sample which are captured in the resulting fluorescence images. The sample is imaged using several different orientations and phases of the light pattern, then computer algorithms process the data set and generate the final super-resolution image. The resolution that can be obtained with structured illumination microscopy is 90 nm laterally (xy) and 220 nm axially (z). In comparison, with conventional wide-field microscopy, the resolution would be 320 nm in xy and 540 nm in z, and after deconvolution 250/430 nm.

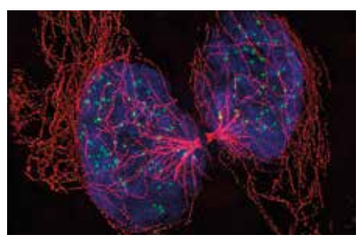


IMAGE BY ELLEN SKARPEN

Superesolution image of a PFA-fixed HeLa cell during cell division stained with antibodies to CREST (green) and Tubulin (red). The image was obtained with an OMX V4 Blaze 3D-SIM Super-resolution microscope from Applied Precision.

COMMENTS TO PUBLICATIONS

6. Towards digital pathology: Automated segmentation of cell nuclei
Manual analyses of tumour specimens by microscopy, as performed by tumour pathologists, requires special expertise and is very time consuming. Therefore, digital analyses of tumours have emerged as an attractive alternative for diagnosis and prognosis of cancer. So far, digital analyses have suffered from lack of reliability, but CCB researchers are now making progress in digital analyses of cell nuclei in cancer diagnosis and prognosis. CCB scientist Birgitte Nielsen and her colleagues in Håvard Danielsen's group have now developed a method for autmated segmentation of nuclei in histological sections of prostate cancer. The automated segmentation performed equally well as manually scored segmentation, demonstrating the potential utility of this method in clinical applications.

7. Specific proteins detected in microvesicles released from prostate cancer cells
Microvesicles released from prostate cancer cells can potentially be used for cancer diagnosis and prognosis, and it is therefore important to characterize the molecular composition. Project leader Alicia Llorente in Kirsten Sandvig's group has performed a proteomic analysis of microvesicles shed by the human prostate cancer cell line PC-3. More than 250 proteins were identified in this analysis, and some of these appear to be specific for microvesicles released from cancer cells. These proteins are thus very interesting as potential biomarkers in prostate cancer.

Media coverage

COVER STORY IN VG ABOUT BREAKTHROUGH FOR CCB RESEARCHERS

THE NEWS ARTICLE "NY TEST KAN REDDE LIV" ON THE COVER OF VG ON THE 30TH OF JULY 2012.

Interview with Group leader Rolf Skotheim about a new gene test for better prognostication of colorectal cancer. Assistant Secretary-General Ole Alexander Opdalshei from the Norwegian Cancer Society applauds the new findings.

Media coverage

The Norwegian newspaper VG published the article "Nordmenn viser hvordan" about the cancer encyclopedia Oncolex on the 1st of July 2012. Read more about Oncolex on page 14.

SØNDAG

HELSE

Nordmenn viser hvordan

Norske kreftleger og forskere står bak internasjonalt legeverktøy for kreftbehandling.

FAKTA

AUGUST

PHOTO BY TERJE HEIESTAD

Erlend B. Smeland

Highlights

CCB PRINCIPAL INVESTIGATOR ERLEND B. SMELAND CO-AUTHORS NATURE ARTICLE ON BURKITT LYMPHOMA

Erlend B. Smeland from the Department of Immunology at the Norwegian Radium Hospital, co-authors an article published online in Nature on 12th of August entitled "Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics"

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

Media coverage

PROF. RAGNHILD A. LOTHE APPOINTED SCIENTIST OF THE MONTH BY THE SOUTH-EASTERN NORWAY REGIONAL HEALTH AUTHORITY IN AUGUST 2012.

The South-Eastern Norway Regional Health Authority (Helse Sør-Øst) aims to profile ongoing excellent research in the region by calling special attention to a "Scientist of the month". For the month of August 2012, this honor goes to CCB's Principal Investigator Ragnhild A. Lothe from the Department of Cancer Prevention at the Institute for Cancer Research, Oslo University Hospital.

The Norwegian news article "Forskning for tidlig oppdagelse av kreft"was published on www.helse-sorost.no.

→

NEWS ARTICLE "NY KREFT-TEST KAN REDDE LIV" ON WWW.VG.NO.

Interview with Rolf Skotheim about a new robust gene classifier, specific for colorectal cancer prognosis, published in the prestigious journal Gut.

Selected publications →

8. Sirnes S, Bruun J, Kolberg M, Kjenseth A, Lind GE, Svindland A, Brech A, Nesbakken A, Lothe RA, Leithe E, Rivedal E. (2012) **Connexin43 acts as a colorectal cancer tumor suppressor and predicts disease outcome** Int J Cancer. 131(3):570-81.

9. Pedersen NM, Raiborg C, Brech A, Skarpen E, Roxrud I, Platta HW, Liestøl K, Stenmark H. (2012) **The PtdIns3P-Binding Protein Phafin 2 Mediates Epidermal Growth Factor Receptor Degradation by Promoting Endosome Fusion** Traffic. 13(11):1547-63.

Highlights

FLOTILLIN-2: A NEW POTENTIAL PREDICTOR FOR PROGNOSIS OF BREAST CANCER

In a new study published in Oncogene (journal impact factor 6.4), Sascha Pust and coworkers from the Centre for Cancer Biomedicine show that flotillins stabilize ErbB2 at the plasma membrane.

Flotillins as regulators of ErbB2 levels in breast cancer | Overexpression of ErbB2 occurs in up to 30% of human breast cancers. ErbB2 is not down-regulated by ligand-induced mechanisms as many other receptors. Sascha Pust from Kirsten Sandvig's group at the Institute for Cancer Research, the Norwegian Radium Hospital, and coworkers show that flotillins stabilize ErbB2 at the plasma membrane. Moreover, microarray analysis of biopsies of 194 breast cancer patients indicated that flotillin-2 is a good prognostic marker for breast cancer. Depletion of flotillins leads to internalization and degradation of ErbB2, thereby inhibiting the ErbB2-triggered signaling.

Flotillins as regulators of ErbB2 levels in breast cancer – Pust S, Klokk TI, Musa N, Jenstad M, Risberg B, Erikstein B, Tcatchoff L, Liestøl K, Danielsen HE, van Deurs B, Sandvig K. Oncogene. 2012 Aug 6 [Epub ahead of print].

COMMENTS TO PUBLICATIONS

8. Gap junction protein as tumour suppressor
Connexin43 is a major constituent of gap junctions that form channels between neighbouring cells. Postdoc Solveig Sirnes and her co-workers in Edgar Rivedal's group found that loss of connexin43 expression in colorectal tumours correlates with significantly shorter survival. This is the first evidence that connexin43 is a tumour suppressor. The study was a collaboration with Guro E. Lind and Ragnhild A. Lothe's groups and with CCB clinical associate Arild Nesbakken.

9. Novel regulator of growth factor degradation and endosome fusion
Postdocs Nina Marie Pedersen and Camilla Raiborg in Harald Stenmark's group have performed a screen for novel PtdIns3P-binding proteins that mediate degradation of the epidermal growth factor receptor. One of the proteins they identified, Phafin2, turned out to promote receptor degradation by stimulating fusion between receptor-containing endosomes. This is of interest since epidermal growth factor receptors are frequently expressed at elevated levels in cancers. The study was a collboration with CCB biostatistician Knut Liestøl.

Sascha Pust, first author

PHOTO BY CHEMA BASSOLS

SEPTEMBER

Selected publications →

10. Cekaite L, Rantala JK, Bruun J, Guriby M, Agesen TH, Danielsen SA, Lind GE, Nesbakken A, Kallioniemi O, Lothe RA, Skotheim RI. (2012) **MiR-9, -31, and -182 deregulation promote proliferation and tumor cell survival in colon cancer** Neoplasia. 14(9):868-79.

11. Sveen A, Ågesen TH, Nesbakken A, Meling GI, Rognum TO, Liestøl K, Skotheim RI, Lothe RA. (2012) **ColoGuidePro: a prognostic 7-gene expression signature for stage III colorectal cancer patients** Clin Cancer Res. 18(21):6001-10.

SEMINARS

SEPTEMBER 20TH–21ST

The annual CCB seminar 2012
Again this year, the annual seminar in CCB was arranged at Hotel Leangkollen in Asker. A record number of CCB members participated in this two day event where scientific presentations and discussions as well as social gathering were the focus of attention. The seminar programme included talks on

- Bioinformatics in cancer research
- Molecular pathology of cancer
- From in vitro to in vivo models in cancer research
- Innovation
- New technologies in cancer research

The annual CCB get-together is certainly of great importance, and it is the perfect way to boost the common CCB spirit.

SEPTEMBER 26TH

Ubiquitin networks in regulation of inflammation and autophagy
Prof. Dr. Ivan Dikic, Buchmann Institute for Molecular Life Sciences, and Goethe University, Frankfurt

COMMENTS TO PUBLICATIONS

10. MicroRNAs in colon cancer development
MicroRNAs are small RNA molecules encoded in the human genome that regulate gene expression. Postdoc Lina Cekaite and her co-workers in Rolf Skotheim and Ragnhild Lothe's groups found that deregulated expression of three microRNAs, miR-9, miR-31 and MiR-182 plays a significant role in the development of colon cancer by promoting proliferation of tumour cells.

11. Strong prognostic classifier for colorectal cancers
Improved prognostic stratification of patients with stage II and III colorectal cancer is needed for better decision making after surgery. PhD students Anita Sveen and Trude H. Ågesen and their collaborators in Ragnhild A. Lothe's group therefore used gene expression profiling to develop a robust prognostic classifier for this patient group. They identified a seven-gene prognostic classifier, ColoGuidePro, which turned out to be a strong prognostic classifier for patients with stage II and III colorectal cancer. This study was a collaboration with the group of Rolf I. Skotheim, CCB biostatistician Knut Liestøl, and CCB associated clinician Arild Nesbakken.

INNOVATION

Patent Application filed September 2012:
Methods and biomarkers for detection of haematological cancers
Bethge N, Smeland EB, Delabie J, Myklebust J, Holte H, Lothe RA, Lind GE
Serial No.: 61/700,021, INVEN-32454/US-1/PRO

14 STEDET

Tirsdag 4. september 2012 Aftenposten

innsikt@aftenposten.no

INNSIKT
NANOTEKNOLOGI

Da laksen fikk nanosølv i vannet, ble gjellene ødelagt, og fisken døde.

Ikke bare nano-glede

Fakta

Nano

Media coverage

MAKING A SAFE AND EFFICIENT NANOMEDICINE REQUIRES CLOSER INTERDISCIPLINARY COLLABORATIONS

THE NORWEGIAN NEWSPAPER AFTENPOSTEN PUBLISHED AN ARTICLE "IKKE BARE NANO-GLEDE" ABOUT HEALTH ISSUES RELATED TO NANOPARTICLES ON 4TH OF SEPTEMBER 2012.

Cross-functional collaboration | CCB's senior scientist Tore-Geir Iversen stated in an interview that it is important with cross-functional collaboration early in the projects in order to reduce any toxic effects and thus bring nanoparticle-based products faster into medical use. In the same article the Minister of the Environment Bård Vegard Solhjell pointed to the need for more research related to pollution aspects.

OCTOBER

PHOTO BY PER MARIUS DIDRIKSEN

Anita Sveen (left) and Trude H. Ågesen, first and second authors.

Highlights

BREAKING ADVANCES IN PROGNOSTIC TESTING OF COLORECTAL CANCER

RESULTS FROM COLORECTAL CANCER RESEARCH AT CCB, DEPARTMENT OF CANCER PREVENTION, INSTITUTE FOR CANCER RESEARCH AND DEPARTMENT OF GASTROINTESTINAL SURGERY HAVE BEEN HIGHLIGHTED FROM RECENT CANCER LITERATURE AS "BREAKING ADVANCES" IN THE AACR JOURNAL CANCER RESEARCH ON 15TH OF OCTOBER 2012.

Important findings | Dr. Anita Sveen and co-workers have shown in a paper published online September 18th in Clinical Cancer Research, that the expression levels of 7 genes can predict the outcome in particular among stage III colorectal cancer patients. About 400 patients from 3 independent clinical series were included in the study. The genetic signature remained significant across technology platforms, in multivariate analyses, and was independent of treatment. The latter opens for guidance on who may benefit from surgery alone and can avoid chemotherapy and the side effects thereof.

This study is part of a translational research programme on colorectal cancer led by Professor Ragnhild A. Lothe.

ColoGuidePro: A prognostic 7-gene expression signature for stage III colorectal cancer patients – Sveen A, Ågesen TH, Nesbakken A, Meling GI, Rognum TO, Liestøl K, Skotheim RI, and Lothe RA. Clin Cancer Res. 18(21):6001-10.

Highlights

40 MNOK IN FURTHER SUPPORT TO THE NATIONAL PROJECT ON PERSONALIZED CANCER MEDICINE FROM THE RESEARCH COUNCIL OF NORWAY THROUGH A MAJOR BIOTEK GRANT.

CCB scientists and clinicians associated with CCB, are also involved in this second phase of the project with regard to exome sequencing of colorectal cancer, prostate cancer and lymphomas.

Read more about the Norwegian Cancer Genomics Consortium and the Personalized Cancer Medicine project on http://cancergenomics.no/

Selected publications →

12. Huse K, Bakkebø M, Wälchli S, Oksvold MP, Hilden VI, Forfang L, Bredahl ML, Liestøl K, Alizadeh AA, Smeland EB, Myklebust JH. (2012) **Role of Smad proteins in resistance to BMP-induced growth inhibition in B-cell lymphoma** PLoS One. 7(10):e46117.

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

SEMINARS

OCTOBER 9TH

Novel roles for FGFR1 signalling in breast and pancreatic cancers
Dr. Richard Grose, Barts Cancer Institute, University of London, UK

OCTOBER 18TH

CCB minisymposium on cellular dynamics

Integrin traffic and cytokinesis
Professor Johanna Ivaska, University of Turku, Finland

Control of cellular dynamics and signaling by reversible ubiquitination
Professor Sylvie Urbé, University of Liverpool, UK

COMMENTS TO PUBLICATIONS

12. Mechanism of apoptosis resistance in lymphoma cells
Postdoc Kanutte Huse and her co-workers in June Myklebust's project group (Erlend Smeland's group) found that the bone morphogenetic proteins (BMPs) are detected in normal and malignant B cells and that some lymphoma cell lines are resistant to the apoptosis-inducing effect of BMPs. The authors found that upregulation of an inhibitory component of BMP signalling, Smad7, is an important mechanism lymphoma cells use to escape the negative effects of BMPs. This work was a collaboration with CCB biostatistician Knut Liestøl.

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

Prizes/Awards

CCB SCIENTISTS AWARDED PRIZE

A STUDY CARRIED OUT AT EDWARD LEITHE'S PROJECT GROUP AT DEPARTMENT OF CANCER PREVENTION HAS BEEN AWARDED A PRIZE FOR EXCELLENT RESEARCH ARTICLE BY THE OSLO UNIVERSITY HOSPITAL. THE PRIZE WAS PRESENTED ON FRIDAY 26TH OCTOBER AND CARRIED AN AWARD OF 50,000 NOK.

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

Edward Leithe's project group is part of the Molecular Cell Biology group led by Edgar Rivedal, which is an associated group in CCB. The study was published in the May 4th issue of Journal of Biological Chemistry, and was featured on the cover of the journal.

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

PHOTO BY JARLE BRUUN

First author and prize winner Ane Hansen Kjenseth

DISSERTATIONS

VIOLA HÉLÈNE LOBERT, PHD
Identification of novel regulators of epithelial polarity and cell migration
– Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology (NTNU), October 2012

NOVEMBER

Highlights

CCB SCIENTISTS IDENTIFY NOVEL LIPID REGULATOR OF CELL MIGRATION

IN A NOVEMBER ISSUE OF EMBO REPORTS, CCB'S PHD STUDENT ANGELA OPPELT AND HER COLLEAGUES IN JØRGEN WESCHE'S PROJECT GROUP AT THE INSTITUTE FOR CANCER RESEARCH PRESENT A NOVEL REGULATOR OF CELL MIGRATION.

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

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

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

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

Production of phosphatidylinositol 5-phosphate via PIKfyve and MTMR3 regulates cell migration – Oppelt A, Lobert VH, Haglund K, Mackey AM, Rameh LE, Liestøl K, Oliver Schink K, Marie Pedersen N, Wenzel EM, Haugsten EM, Brech A, Erik Rusten T, Stenmark H, Wesche J. EMBO Rep. 14(1):57-64 [Epub 2012 Nov 16].

PhD student Angela Oppelt

Selected publications →

14. Nyquist KB, Panagopoulos I, Thorsen J, Haugom L, Gorunova L, Bjerkehagen B, Fosså A, Guriby M, Nome T, Lothe RA, Skotheim RI, Heim S, Micci F. (2012) **Whole-Transcriptome Sequencing Identifies Novel IRF2BP2-CDX1 Fusion Gene Brought about by Translocation t(1;5)(q42;q32) in Mesenchymal Chondrosarcoma** PLoS One. 7(11):e49705.

15. Ågesen TH, Sveen A, Merok MA, Lind GE, Nesbakken A, Skotheim RI, Lothe RA. (2012) **ColoGuideEx: a robust gene classifier specific for stage II colorectal cancer prognosis** Gut. 61(11):1560-7.

PHOTO BY TERJE HEIESTAD

Senior scientist Ioannis Panagopoulos and Postdoc Jim Thorsen

Media coverage

THE FIGHT AGAINST CANCER

Oslo Cancer Cluster has made a supplement on cancer R&D which was distributed with Aftenposten, Norway's largest newspaper, on the 7th of November to around 250,000 recipients and 700,000 readers.

The supplement is called "The Fight Against Cancer", and draws a portrait of how Oslo Cancer Cluster's members work together to improve cancer patients' quality of life by developing new cancer treatments and diagnostic tools.

CCB contributed with the article **"Uniting biology and medicine to improve cancer treatment"** (Forener biologi og medisin for å skape bedre kreftbehandling).

COMMENTS TO PUBLICATIONS

14. Novel fusion gene in mesenchymal chondrosarcoma
PhD student Kaja Nyquist and her collaborators in Francesca Micci's project group (Sverre Heim's group) have used whole-transcriptome sequencing to identify a novel fusion gene in a mesenchymal chondrosarcoma. The fusion gene results in the fusion of the IRF2BP2 gene and the transcription factor CDX1 gene arising from a chromosomal translocation. This study was a collaboration with two other CCB groups, those of Ragnhild A. Lothe and Rolf I. Skotheim.

15. Gene expression classifier for stage II colorectal cancer prognosis
PhD students Trude H. Ågesen and Anita Sveen in Ragnhild A. Lothe and Rolf Skotheim's groups have used gene expression analyses of stage II colorectal cancer to identify a classifier for risk stratification of patients with this cancer. They identified a 13-gene expression classifier, ColoGuideEx, which turned out to be a robust gene classifier specific for stage II colorectal cancer prognosis. The robustness of ColoGuideEx was shown across patient series, populations and microarray versions, demonstrating its potential utility in future clinical applications. This study, which was published in the prestigious journal Gut, was a collaboration with the group of Guro E. Lind and with CCB clinical associate Arild Nesbakken.

INNOVATION

DOFI – Accepted in November 2012
Specific and shared targets of ETS fusion genes in prostate cancer
Paulo P. Teixeira MR, Lothe RA, Skotheim RI
Inven2 project no. B-11096

International networking

CCB'S PROJECT LEADER TORE-GEIR IVERSEN HAS BECOME PART OF THE MANAGEMENT COMMITTEE OF THE MATERIALS, PHYSICS AND NANOSCIENCES (MPNS) COST ACTION TD1204:

Modelling Nanomaterial Toxicity (MODENA)
The MODENA COST Action aims at producing Quantitative Nanostructure-Toxicity relationship models for nanomaterials through the coordination of a network of inter-disciplinary stakeholder parties. This network consists of 18 participating countries funded by the EU during the period of 2013-2016.

COST – European Cooperation in Science and Technology – is one of the longest-running European instruments supporting cooperation among scientists and researchers across Europe. COST gets its budget from the European Union's 7th Framework Programme.

CCB'S PROJECT LEADER ALICIA LLORENTE HAS BECOME PART OF THE MANAGEMENT COMMITTEE OF THE BIOMEDICINE AND MOLECULAR BIOSCIENCES (BMBS) COST ACTION BM1202:

European Network on Microvesicles and Exosomes in Health and Disease (ME-HAD)
Microvesicles and exosomes can have enormous relevance because of their potential functions, use as disease biomarkers and possible therapeutic exploitation. With this COST Action European scientists aim to create a network of experts, fostering a multidisciplinary approach to enhance both basic understanding and translational potential of microvesicles and exosomes.

The network consists at the moment of 15 participating countries and will be funded by the European Union during the period 2013-2016.

PHOTO BY TERJE HEIESTAD

Media coverage

PERSONALISED MEDICINE – INTEGRATING GENOMICS INTO GENERAL HEALTH CARE

International conference in Oslo on the 28th of November 2012 | Invited speaker Ragnhild A. Lothe gave a talk on Genome Medicine of Colorectal Cancer.

The meeting was arranged by The Norwegian Society for Medical Genetics, The Norwegian Society for Human Genetics, and The Norwegian Biotechnology Advisory Board.

The Norwegian journal Dagens Medisin published the news article "Satte fremtidens diagnostikk på kartet" summing up the contributions from the invited international experts.

DECEMBER

Selected publications →

16. Hessvik NP, Phuyal S, Brech A, Sandvig K, Llorente A. (2012) **Profiling of microRNAs in exosomes released from PC-3 prostate cancer cells** Biochim Biophys Acta. 1819(11-12):1154-63.

Highlights

GROUP LEADER GURO E. LIND AWARDED ONE-YEAR PI POSITION IN CCB IN 2013

As part of CCBs strategy for supporting career development of young scientists, the PI group decided earlier this year to announce the following internal call: A one-year PI position in CCB for a young CCB scientist for the year 2013.

We congratulate Guro E. Lind with being awarded the 2013 PI stipend.

CCB plans to announce similar one-year PI positions for the years 2014 to 2017 through internal calls in autumn every year.

National networking

ALICIA LLORENTE IS MEMBER OF THE MANAGEMENT COMMITTEE OF THE SOUTH-EASTERN NORWAY HEALTH AUTHORITY NETWORK "REGIONAL RESEARCH NETWORK ON EXTRACELLULAR VESICLES".

The network is formed by six research groups and was awarded funding for three years by South-Eastern Norway Health Authority in December 2012.

The overall goal of the network is to establish a platform for hitherto fragmented groups in the South-Eastern Norway Health Authority interested in and working with extracellular vesicles, to strengthen the regional quality and production on this area of research.

Other members of the network in the Sandvig group: Kirsten Sandvig, Tore Skotland, Nina Hessvik, and Santosh Phuyal.

Invited lectures

The number of Invited lectures either abroad or at international conferences in Norway by CCB members: 40 lectures in 2012

COMMENTS TO PUBLICATIONS

16. MicroRNAs in microvesicles secreted by prostate cancer cells
Prostate cancer cells are known to shed microvesicles known as exosomes, suggesting the possibility of using exosome-associated molecules as biomarkers in prostate cancer. Postdoc Nina Hessvik and her co-workers in Kirsten Sandvig's group found that exosomes secreted by the prostate cancer cell line PC-3 contain microRNAs, small RNA molecules that regulate gene expression. Moreover, it was found that the microRNA profiles from PC-3 exosomes and exosomes isolated from a non-cancerous prostate cell line, RWPE-1, are similar, although certain microRNAs differed between the two exosome populations. These results suggest that there is sorting of microRNAs into exosomes.

INNOVATION

DOFI – Accepted in December 2012
Epi-markers for early detection and monitoring of patients with hematological cancer
Lind GE, Smeland EB, Lothe RA
Inven2 project no. 12177

PHOTO BY TERJE HEIESTAD

Funding

PRESTIGIOUS CAREER GRANT FOR RESEARCH ON CANCER BIOMARKERS

Associated group leader Guro E. Lind has been awarded a prestigious career grant from Helse Sør-Øst for the proposal "Epigenetic biomarkers in cancer - their function and clinical importance". The grant amounts to NOK 2 million per year and runs for 4 years.

New group in Epigenetics led by Lind | In August 2012 Guro E. Lind was appointed group leader by the Scientific Director of the Institute for Cancer Research. Lind is a young investigator of 35 years and has a strong publication record.

MASTER DEGREES

SHIVA DAHAL-KOIRALA
M.SC. IN MOLECULAR BIOSCIENCES
Regulation of the gap junction protein connexin 43 during mitosis.
– Faculty of Mathematics and Natural Sciences, University of Oslo, December 2012.

Group leader Guro E. Lind (right) and PhD student Deeqa Ahmed

CELLULAR MEMBRANE DYNAMICS

HARALD STENMARK GROUP

Cancer is a disease characterized by uncontrolled proliferation and migration of specific cell types of the body. Stenmark's research group therefore studies cellular pathways that prevent conversion of normal cells into cancer cells.

The group consists of 25 members with research backgrounds in medicine, biology, biochemistry and biotechnology. Group members work together in smaller teams that focus on specific mechanisms in tumour suppression, including uptake and degradation of growth factor receptors, cellular self-consumption pathways, cell migration, and control of cell division.

Researchers in the group are specialists in microscopy, and the group hosts regional core facilities in confocal microscopy and electron microscopy and a national core facility in super-resolution microscopy. Most of the research is done with normal and cancerous cells that are grown in tissue culture flasks, but some group members also use the fruit flies as model organisms for studies of tumour suppression. The group collaborates extensively with CCB groups that specialize in analyses of human tumour samples.

The group has made major discoveries of lipid-binding proteins that promote tumour suppressor pathways.

Stenmark's research group studies cellular pathways that prevent conversion of normal cells into cancer cells.

PHOTO BY TERJE HEIESTAD

THE STATISTICAL ANALYSIS UNIT

KNUT LIESTØL GROUP

The complexity of the data sets produced by modern high throughput technologies makes extraction of information a true challenge. The statistical analysis unit therefore aims at supporting the activity of the CCB groups by providing data analysis, with a focus on high throughput data. The unit has now published together with all the other CCB groups.

The statistical analysis unit at CCB is part of Biomedical Research Group at the Department of Informatics at the University of Oslo. 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 initially focus on a concrete biomedical problem, we then try to solve the statistical challenges in a broader context and finally to develop adapted, easy-to-use software tools. An example of the latter is a system for the analysis of copy number data that allows fast simultaneous estimation from several samples; the system is implemented as a Bioconductor package.

The statistical analysis unit works in close collaboration with the biomedical groups to optimize the information obtained from data.

PHOTO BY TERJE HEIESTAD

LARGE SCALE GENOMIC INSTABILITY

HÅVARD DANIELSEN GROUP

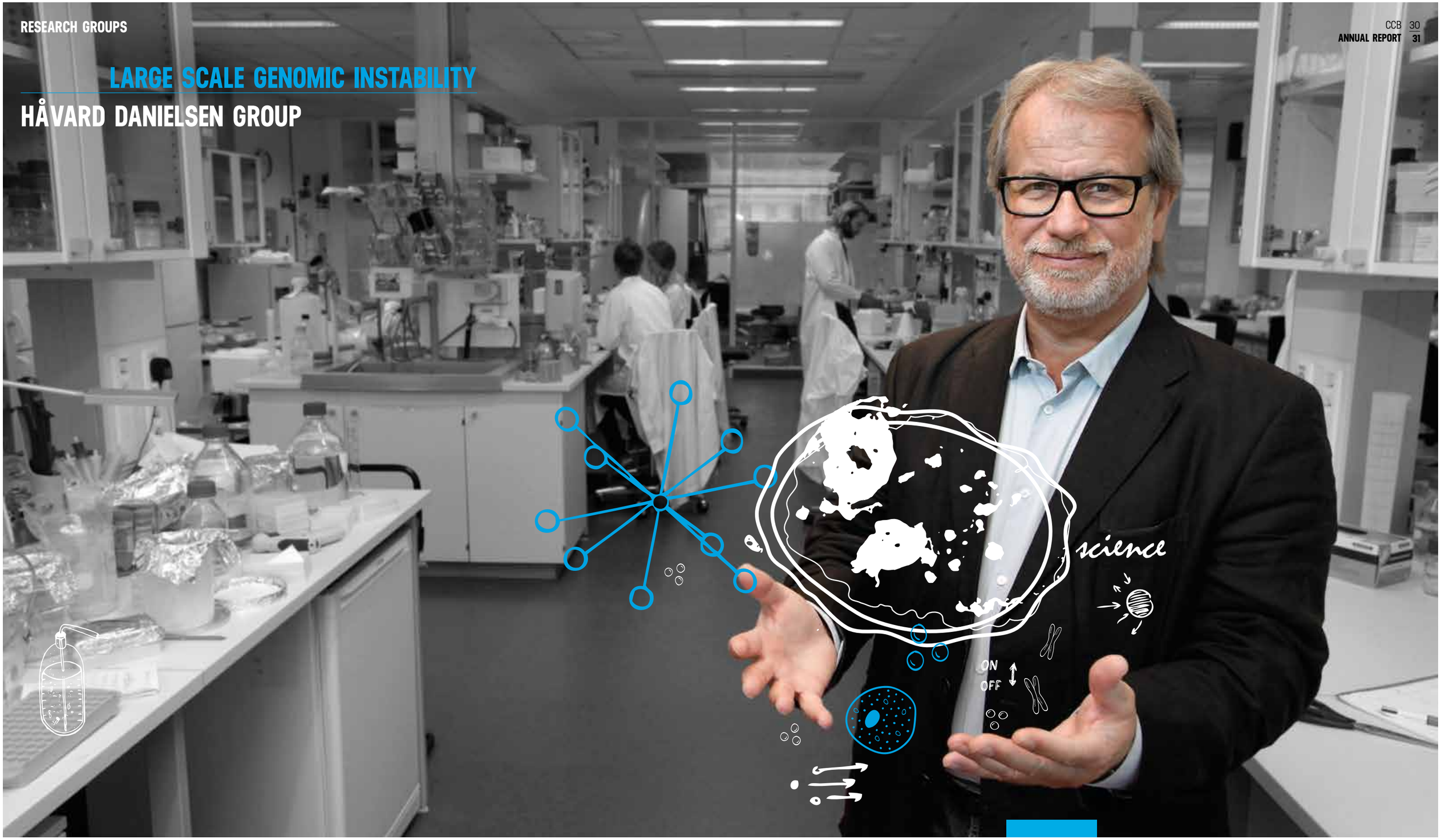


PHOTO BY TERJE HEIESTAD

Cancer is a disease characterized by heterogeneity and genomic instability. Danielsen's research group is therefore developing high throughput methods for detection and characterization of large-scale genomic instability (chromatin structure and DNA ploidy), based on high-resolution digital microscopy and advanced image analysis.

The group consists of 15 members with backgrounds in medicine, biology, mathematics, and computer science. They are studying archival material from the time of diagnosis from cancer patients with proper clinical follow-up and known prognosis. Several methods; such as IHC, FISH, DNA Ploidy, Tissue Micro Array, as well as original methods developed in the group (Nucleotyping, 3D-reconstruction, ImmunoPath and MicroTracker) are used in an attempt to reveal and understand the 3-dimensional organisation of chromatin, and how this organisation controls gene expression. They are engaged in the search for new diagnostic and prognostic markers among these methods and results, and are running clinical validation studies on large series of colorectal, breast, prostate and gynaecological cancers with a minimum of 5, and up to 20, years of clinical follow-up, with emphasis on disease-free survival. The aim is to improve cancer treatment by the identification of better prediction and prognosis of the outcome among these patients.

Danielsen's research group studies how alterations in DNA- and chromatin organization affect cancer patients' outcome.

GENETICS

RAGNHILD A. LOTHE GROUP

The members (n=15) of our group have an interdisciplinary research background and the main activity is translational research of colorectal cancer, which is one of the most common malignancies and one of the major causes of cancer deaths. We combine patient-oriented and biological studies using human biobanks and in vitro models applying a wide range of state-of-the-art technologies.

Understanding molecular mechanisms underlying human tumour development is essential to improve the diagnosis and treatment of the cancer patient. We study the aetiology of selected solid tumors arising in cells that originate from different germ layers, to gain novel knowledge of molecular paths across malignancies.

Within the Centre we collaborate with most of the other groups and clinical associates. During the first period of the Centre we identified biomarkers for early detection and prognostication. Several projects are in innovation paths, and a licensing agreement was signed with international biotech company in 2012 based in biomarkers identified in our group. Lothe is also one of the key investigators of the Norwegian cancer genomics consortium (www.cancergenomics.no), a national collaboration to establish genome-based diagnostics of cancer, which received major grants in 2011 and 2012.

Lothe's research group studies the changes and modifications of the DNA molecule involved in cancer development.

PHOTO BY TERJE HEIESTAD

LYMPHOMA BIOLOGY GROUP

ERLEND SMELAND GROUP

PHOTO BY TERJE HEIESTAD

B-cell lymphomas consist of many different types, which can be identified with a combination of morphological, immunological and genetic methods. Although new therapeutic approaches have steadily improved overall survival for most lymphoma types during the past decades, some patients develop resistance to further treatment.

The group consists of 11 members with research backgrounds in medicine, biology, biochemistry and biotechnology. The members work together in two smaller teams that focus on cell signaling and on genetic and epigenetic changes and immunohistochemical characterization of B-cell lymphoma. We use advanced flow cytometric analysis to characterize cell signaling in B-lymphoma cell lines and in samples from patient biopsies. We also perform genetic and immunohistochemical analyses of frozen and paraffin embedded tissue. Our group has extensive collaboration with the lymphoma program at the hospital, other groups in the CCB and milieus at NCI, Stanford, and Vanderbilt.

We are part of the international lymphoma and leukemia molecular profiling project, led from NCI, which has produced several important papers in top-ranking journals. We have also made important contributions regarding biology and progression of major lymphoma types.

The Smeland/Myklebust group is involved in molecular characterisation of malignant lymphoma in order to optimise diagnosis and treatment of this disease.

INTRACELLULAR TRANSPORT

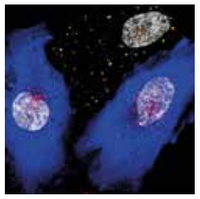
KIRSTEN SANDVIG GROUP

Sandvig's group, counting 17 members from eigth different countries, is interested in the mechanisms of endocytosis, intracellular transport and secretion. Uptake of receptors and ligands and correct intracellular sorting of endocytosed molecules are crucial for maintenance of a normal differentiated phenotype. In some of our studies we are using protein toxins such as ricin and Shiga toxin, which are well established as markers for studies of membrane traffic, and which can be used as agents in cancer diagnosis and therapy.

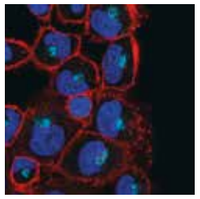
Our expertice is also applied to investigate uptake of nanoparticles and to characterize release of exosomes from prostate cancer cells with the goal of detecting lipid and protein biomarkers. Our research spans all the way from basic to translational medicine, including innovation, and the projects aim at increasing our knowledge about intracellular transport and biomarkers in order to provide a rational basis for diagnosis, treatment and prevention of disease. The group has extensive national and international collaboration.

Sandvig's research group studies membrane dynamics – Intracellular transport of specific proteins and lipids and their potential as biomarkers.

PHOTO BY TERJE HEIESTAD



Stimulation of cancer cells with FGF1 (red) leads to phosphorylation of S777 in FGFR1 (green) but is abolished in cells expressing dominant negative MEK1 (blue). Cell nucleus (white).



Migrating cancer cells polarizing towards the scratch in a wound healing assay. Actin (red), Golgi apparatus (green), and nucleus (blue).

PROTEIN INTERNALIZATION AND SIGNALING GROUP HEADED BY ANTONI WIEDLOCHA

ASSOCIATED WITH THE STENMARK GROUP

PHOTO BY TERJE HEIESTAD

– A DEEPER UNDERSTANDING OF FGF RECEPTOR SIGNALING AND DOWN-REGULATION IS NEEDED TO IMPROVE TREATMENT OF FGF RECEPTOR DEPENDENT CANCERS

Altered cell signaling is of critical importance for cancer development as well as maintaining malignant phenotype. It deregulates normally tightly regulated cellular processes such as proliferation, migration, apoptosis or senescence.

Wiedlocha's group studies the fibroblast growth factor (FGF) signaling system looking at FGFs internalization and signal transduction including intracrine activity. The research of the group is currently focused on three main topics: 1) a better understanding of down-regulation of FGFR signaling in normal and malignant cells, 2) a deeper understanding of the process of cell migration and metastasis formation, 3) a better understanding of the role of intracrine activity of FGF1 and 2 in maintaining the cellular homeostasis.

Today, the group consists of 9 researchers with background in biochemistry, cell biology and medicine. The group members have extensive experience in, among other things, confocal microscopy, protein purification and in analysis of cell growth and migration.

– STUDYING THE RNA FROM CANCER ENABLES US TO POINT OUT GENETIC ERRORS THAT MATTER

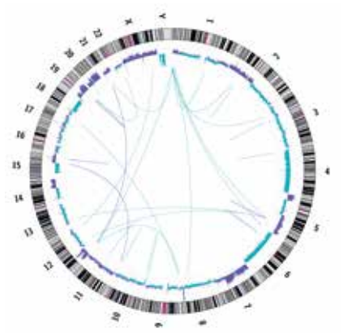
GENOME BIOLOGY GROUP HEADED BY ROLF SKOTHEIM

ASSOCIATED WITH THE LOTHE GROUP

PHOTO BY TERJE HEIESTAD

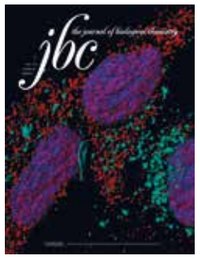
The group investigates cancer genomes by integrated computational and laboratory based approaches. The aim of the Genome biology group is to identify and characterise critical genes involved in the cancer development. Such genes may serve as diagnostic or prognostic biomarkers and also as targets for future molecularly tailored therapy. The group's studies are mainly focused on testicular, prostate and colorectal cancers.

Several of the projects apply deep sequencing, particularly of transcriptomes. The group is specialising in bioinformatics analyses of RNA-seq data, and have recent data on novel transcripts, including fusion transcripts, which are recurrently expressed in colorectal cancers. Further, the group has discovered that a subgroup of colorectal cancers have a phenotype they have named transcriptome instability, meaning that across the genome, these cancers have an exaggerated amount of aberrant RNA splicing. The group is now working on an analysis strategy to use RNA-seq data to explore whether transcriptome instability is a common phenotype across multiple cancer types.



Genome and transcriptome characteristics of a colon cancer cell line

From outside of the circos plot: chromosome numbers, cytogenetic bands, DNA copy numbers, and intra and inter-chromosomal fusion transcripts



SUMOylation has been identified as a novel regulatory mechanism for intercellular communication.
Kjenseth et al., J. Biol. Chem., 287, 15851-61, 2012

The ubiquitin ligase Smurf2 is involved in the loss of gap junctional cell communication induced by cancer causing agents.
Fykerud et al., J. Cell Sci., 125, 3966-76, 2012

– LOSS OF INTERCELLULAR COMMUNICATION IS A POTENTIAL BIOMARKER AND TARGET FOR CANCER PREVENTION

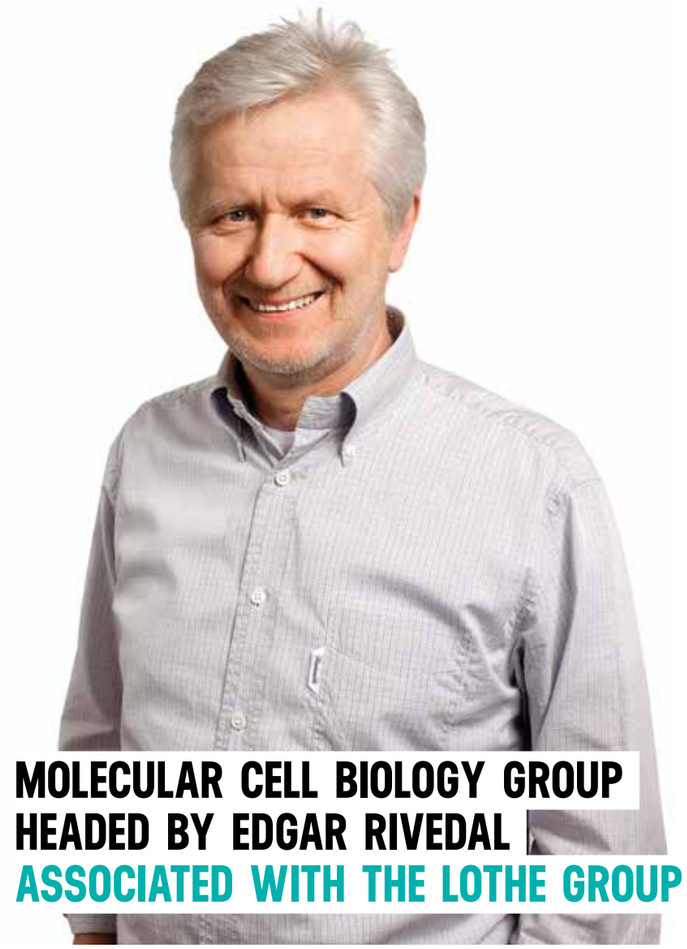


PHOTO BY TERJE HEIESTAD

MOLECULAR CELL BIOLOGY GROUP HEADED BY EDGAR RIVEDAL ASSOCIATED WITH THE LOTHE GROUP

The goal of the research group is to elucidate molecular mechanisms involved in cancer development, with emphasis on intercellular communication and colorectal cancer. Various molecular cell biology methods are used in studies of cell lines derived from normal tissue and tumours, as well as relevant biobank material.

Multicellular organisms have multiple mechanisms for the exchange of information. Connexins are integral membrane proteins that form intercellular channels between adjacent cells. These channels enable cells to communicate via exchange of ions, metabolites and signaling molecules. This type of intercellular communication is often lost during cancer development. Several members of the connexin protein family have been shown to act as tumor suppressors, and are potential biomarkers and targets for chemoprevention and cancer therapy.

The group is also involved in studies of mechanisms involved in regulation of the MAPK and PI3K pathways during colorectal cancer progression, including a better understanding of the post-translational mechanisms involved in loss of the tumor suppressor protein PTEN.

– THE STUDY OF CHROMOSOME ABERRATIONS HOLDS THE KEY TO UNDERSTANDING TUMORIGENESIS

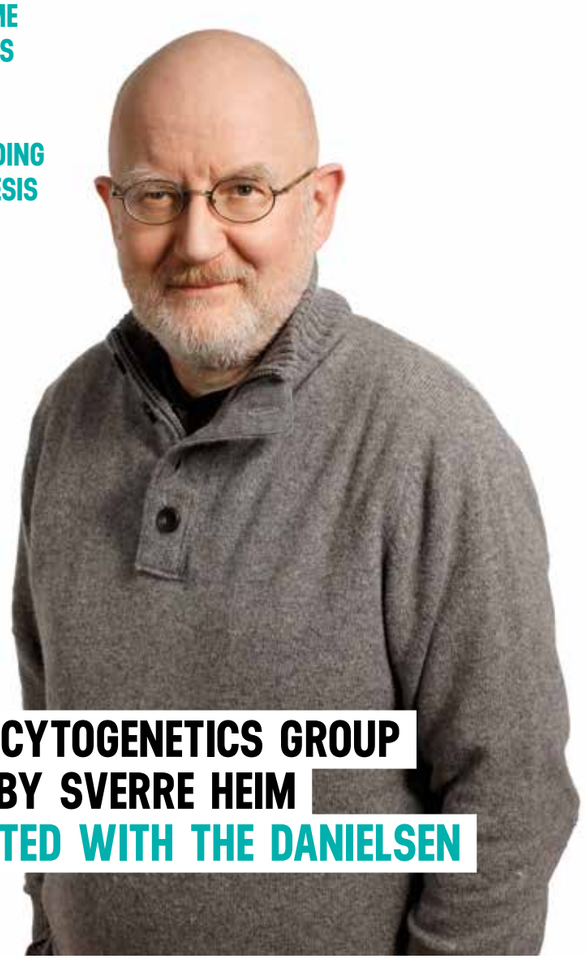


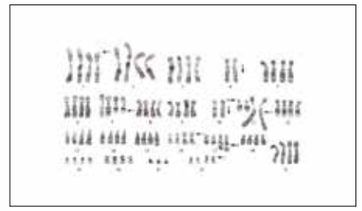
PHOTO BY TERJE HEIESTAD

CANCER CYTOGENETICS GROUP HEADED BY SVERRE HEIM ASSOCIATED WITH THE DANIELSEN GROUP

Heim's research group studies the chromosomal aberrations of cancer cells. The research is done in parallel with diagnostic analyses of leukemias and solid tumors. Of the 14 people involved in research, only five (four PhD-students and one technician) do so full-time. The remainder do diagnostic work half of the time.

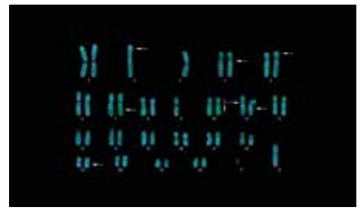
The research begins by finding specific cytogenetic aberrations in various cancers. Then we take the investigation to the molecular level searching for the corresponding changes of genes and DNA primary structure. We have succeeded in all our three main research areas: 1) Gynecologic tumors; 2) Brain tumors; and 3)Analyses of rare tumor-specific translocations.

Our unique area of expertise is the culturing and chromosome analysis of neoplastic cells. We also have extensive experience with fluorescence in situ-based analyses and the search by molecular means for fusion genes brought about by chromosomal translocations. Our approach by combining the two screening techniques G-band karyotyping and next generation sequencing to this end is novel and has led to the discovery of several cancer-specific fusion genes during the past year.



a.

b.

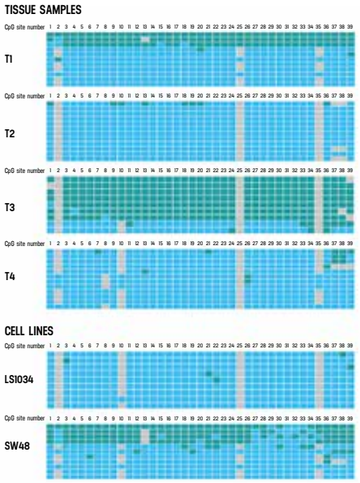


c.

d.

Examples of molecular cytogenetic techniques

a) YAC probes 639c1 (labeled in green) and 763g4 (labeled in red) mapping to chromosomal bands 7p15 and 7p21, respectively. **b)** Normal human karyogram after hybridization with an M-FISH probe. **c)** Normal human karyogram after hybridization with an RxFISH probe. **d)** Normal human karyogram after CGH experiment to detect imbalances in the genome of the breast cancer-derived cell line MA11.



Bisulfite treatment of the DNA enables the methylome to be red by various methods, here exemplified by sequencing.

PHOTO BY TERJE HEIESTAD

EPIGENETICS GROUP HEADED BY GURO E. LIND ASSOCIATED WITH THE LOTHE GROUP

– FEW WOULD HAVE PREDICTED HOW OUR VIEW OF THE HUMAN EPIGENOME HAS EXPANDED OVER THE PAST 10 YEARS

STEPHEN BAYLIN AND PETER JONES 2011

Cancer results from the accumulation of genetic and epigenetic changes. We focus our research on the cancer epigenome and DNA methylation in particular. By integrating large-scale analyses with detailed candidate gene characterization we aim at identifying DNA methylation biomarkers with clinical impact.

The group consists of seven people and was established in august 2012 after existing as a project group since 2009. We are specialists in designing and performing DNA methylation analyses of candidate genes using various quantitative and qualitative methods. In close collaboration with clinical partners we study the methylome of various cancer types. Relevant cancer cell lines are also studied, representing in vitro models for particular cancer types, which allows for a modification of the epigenome.

The group has several active collaborations within CCB and the Institute for Cancer Research.

– Challenges for the next decade include bringing DNA methylation markers to full clinical use...

STEPHEN BAYLIN AND PETER JONES, 2011

VALUABLE COLLABORATION BETWEEN CCB AND CLINICAL ASSOCIATES

CCB has three clinicians associated to the Centre:

HARALD HOLTE
MD, PhD, Senior Consultant, Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Oslo University Hospital.

Harald Holte is head of the lymphoma treatment programme at the Norwegian Radium Hospital.

KAROL AXCRONA
MD, PhD, Consultant, Department of Urology, The Norwegian Radium Hospital, Oslo University Hospital.

Karol Axcrona has a key position in the prostate cancer treatment programme at the Norwegian Radium Hospital.

ARILD NESBAKKEN
Professor, MD, Senior Consultant, Department of Gastrointestinal Surgery, Oslo University Hospital.

Arild Nesbakken is responsible for colorectal cancer surgery at the Oslo University Hospital, Aker.

PHOTOS BY TERJE HEIESTAD

HIGHLIGHTS FROM CCB´S FIRST 5-YEAR TERM

What has CCB been achieving during its lifetime so far? The most important milestone, at least when considering the Centre's funding situation, was the rank as "exceptionally good" by the mid-term evaluation carried out by the Research Council. This score, which ensures sustained funding from the Research Council until September 2017, was based on the Centre's achievements during the first 3 ½ years. As pointed out in the report, CCB has been delivering what could be expected from a Centre of Excellence, namely research results of top class, combined with excellent research training and international research exchanges. In addition, the Centre's scientists have made several innovations that are getting close to entering the clinic for the benefit of the cancer patient.

The founding idea of CCB was to join cell biological research aimed at discovering new mechanisms in carcinogenesis and tumour suppression with translational cancer research aimed at discovering novel molecular and phenotypic hallmarks of cancers that can be exploited in diagnostics, prognostics and therapy. Aided by experts in biostatistics, this has indeed proven to be a fruitful strategy, and a number of cutting-edge joint papers across these disciplines have emerged during CCB´s first 5-year term. As predicted in CCB´s original research plan, basic research on the signalling and intracellular trafficking of growth factor receptors, combined with molecular analyses of tumour biopsies, has advanced our understanding of cancer development and provided new strategies for cancer therapy. A recent example comes from a collaborative study between the groups of Kirsten Sandvig, Håvard E. Danielsen and Knut Liestøl, which established that flotillin-2 regulates the levels of the receptor tyrosine kinase ErbB2 in breast cancer and can be used as a predictor of survival. An emerging topic, not foreseen in the original research plan, concerns the importance of cytokinesis, the final stage of the cell division process, in maintaining genome stability and thereby contributing to tumour suppression. A collaboration between the groups of Harald Stenmark, Knut Liestøl and Rolf I. Skotheim resulted in the identification of a novel regulator of cytokinesis, FYVE-CENT, and the demonstration that this protein is required for fidelity in cell division and is downregulated in advanced breast cancers. Another collaborative study between the groups of Ragnhild A. Lothe (with Guro E. Lind) and Harald Stenmark (with Camilla Raiborg) showed that methylation of the SPG20 gene can be used as a biomarker for early detection of colorectal cancer and established the gene product, Spartin, as a novel regulator of cytokinesis. As highlighted elsewhere in this Annual Report, recent CCB collaborations led by Ragnhild A. Lothe´s group have resulted in identification of gene expression signatures that can be used for prognosis and classification of colorectal cancers, studies led by Erlend B. Smeland and his project leader June H. Myklebust have revealed novel signalling pathways that might be exploited therapeutically in lymphomas, and studies spearheaded by Håvard E. Danielsen´s group have provided the exciting prospect of using automated nuclear analyses in diagnosis and prognosis of prostate cancers. The overall picture is that CCB´s research is well on track in providing an outcome that will prove beneficial to the cancer patient.

In order to make scientific discoveries useful to the patient, it is essential to secure intellectual property rights that attract cooperations with biotech companies, and CCB collaborates with the technology transfer office of its host institutions, Inven2, to patent all its innovations. CCB´s partnership with Oslo Cancer Cluster, a Norwegian Centre of Expertise, is part of the Centre´s innovations strategy. During the first 5-year term, CCB´s scientists have filed 2 patents and 18 patent applications within the areas of cancer biomarkers, image analyses and data sharing, demonstrating the Centre´s high activity within scientific innovation.

Involvement in international collaborations is critical to the success of any Centre of Excellence, and CCB scientists have indeed been very active on the international arena. A particularly successful international cooperation is the Lymphoma/Leukemia Molecular Profiling Project, which is coordinated by Louis Staudt at the National Institutes of Health (USA) with CCB PI Erlend B. Smeland and CCB clinical associate Harald Holte as central partners. During the past 5 years this multi-centre project has resulted in substantial knowledge on pathogenesis and therapeutic targets in distinct lymphoma subtypes. Results from these studies have been published in top journals, including 3 papers in *Nature*, one in Science and one in the *New England Journal of Medicine*. Adding to this, CCB scientists have published a large number of papers in other international peer-reviewed journals of high reputation, and CCB´s total output of 313 publications during its first 5-year term is an indication of the high activity in the Centre.

A sign that CCB´s science is appreciated by the scientific community is that several CCB scientists have been awarded prestigious prizes during the first 5-year term of CCB. A recent example is the 2011 award of H.M. The King´s gold medal for outstanding cancer research to Sverre Heim. Examples of international recognitions include an honorary doctorate at the University of Copenhagen to Kirsten Sandvig (2007) and the award of the Sir Hans Krebs Medal to Harald Stenmark (2010). CCB´s junior researchers have also been receiving prizes, including the Oncology Forum young investigator prize to Guro E. Lind (2011) and the Mørk Legacy prize for excellent cancer research to Anne Simonsen (2007), Tor Erik Rusten (2008), Rolf I. Skotheim (2009) and Camilla Raiborg (2011).

Since the Centre of Excellence funding from the Research Council only amounts to approx. 14% of CCB´s total budget, CCB is highly dependent on grants from various sources. Indeed, CCB´s scientists have been very successful in obtaining substantial grants from the South-Eastern Norway Regional Health Authority, the Research Council of Norway, and the Norwegian Cancer Society. In addition, the Radium Hospital Foundation has been an important partner by sponsoring essential equipment used by CCB scientists. CCB researchers have also been successful in securing international funding from the European Union (including an Advanced Grant from the European Research Council), the National Institutes of Health, the European Science Foundation, and the Poland-Norway Research Foundation. In the future it will become even more important to increase the portfolio of international grants, and CCB´s scientists are now in a very good position to achieve this.

One of the hallmarks of a Centre of Excellence is that its scientific discoveries are important enough to attract attention worldwide. Publication in the most influential journals is one way to achieve this, and CCB has been very successful in this respect. For example, during the first 5-year term CCB has published as many as 7 papers in *Nature* (4 of these with CCB scientists as corresponding author), including 3 original articles, 3 commentary articles and one review. Other top journals that have been featuring contributions from CCB scientists include *Science, New England Journal of Medicine, Cell, Journal of Clinical Oncology, Immunity, Developmental Cell, Molecular Cell, Nature Cell Biology, Nature Structural and Molecular Biology, Nature Chemical Biology, Journal of Experimental Medicine, Gastroenterology, Gut, Blood, Journal of Cell Biology,* and *EMBO Journal*. With few exceptions, these papers have had CCB scientists as main authors, and several of the papers have been dedicated commentary articles written by leading authorities in the respective fields, thereby increasing their visibility even further. Another way to make CCB´s research visible is to target a more general audience in the form of popular-scientific lectures and journal articles, interviews in newspapers, magazines and broadcasts, and participation in popular-scientific fairs. CCB scientists have been active in all these arenas, and as the Centre´s collaborative research is breaking new grounds, these activities are expected to expand further in the near future.

In summary, the first 5-year term of CCB has been exciting, and it has been inspiring to witness all the progress that has been made. With the entry into CCB´s second 5-year term we hope the success will continue.

Director *Harald Stenmark*
Co-director *Ragnhild A. Lothe*

– IT HAS BEEN INSPIRING TO WITNESS ALL THE PROGRESS THAT HAS BEEN MADE

FACTS AND FIGURES 2012

CENTRE FOR CANCER BIOMEDICINE WAS ESTABLISHED IN SEPTEMBER 2007 AS A CENTRE OF EXCELLENCE APPOINTED BY THE RESEARCH COUNCIL OF NORWAY WITH THE UNIVERSITY OF OSLO AS HOST INSTITUTION.

The majority of our Centre is located at Oslo University Hospital, the Norwegian Radium Hospital. A consortium agreement regulates cooperation between the University of Oslo and Oslo University Hospital with the intention to make conditions favourable for fulfilling the scientific aims and strategic plans of CCB.

The Research Groups

CCB consists of six research groups and five associated groups embracing an average of 150 people in 2012.

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

Five independent groups are associated with CCB. These are the groups of Antoni Wiedlocha, Edgar Rivedal, Rolf Skotheim, Guro E. Lind, and Prof. Sverre Heim.

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.

The board members are:

Prof. Hilde Irene Nebb, Chairperson
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
Department of Gastrointestinal & Paediatric Surgery, Divison of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital.

Prof. Ole M. Sejersted
Head of Institute for Experimental Medical Research, Oslo University Hospital.

Chairperson Hilde Irene Nebb about CCB:

"Due to scientific vision and a clear strategic focus, CCB has excelled notably in the area of unifying basic and translational research for the benefit of the cancer patient. 2012 has been a particularly active year with multiple scientific breakthroughs. Focus on technology development has had an immediate impact on the quality of fundamental research.

Since its establishment CCB has raised a number of outstanding young scientists and the specific focus to secure the scientific career of the best talents is impressive. The Faculty of Medicine is proud of hosting CCB and will, together with our partner Oslo University Hospital, support environments that will further foster excellence in science and research educations."

Scientific Advisory Board

The Scientific Advisory Board supports our Centre with valuable input on strategy and science which helps us achieve our goal of becoming one of Europe's leading centres for cancer research. SAB visited CCB for the 4th time in June 2012.

An extract from SAB's 2012 report:

"The SAB is impressed by the development of the CCB, both scientifically and structurally. The ambition by the directors to implement previous SAB suggestions was demonstrated in several ways. The CCB has very clearly shown its potential to serve as a model for other centres of excellence in Norway, in particular with regard to efforts to create new collaborative research constellations and to promote the career development of young scientists."

Prof. Hilde Irene Nebb, Chairperson.

The SAB members are:

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

Professor Lena Claesson-Welsh
Head of Immunology, Genetics and Pathology, IGP, Uppsala University, Sweden.

Professor Marja Jäättelä
Head of Unit Cell Death and Metabolism, Danish Cancer Society Research Center, Copenhagen, Denmark.

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

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

Visiting Professors

CCB has three professors associated to the Centre.

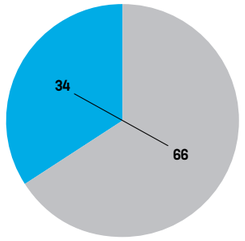
Professor Bo van Deurs
Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.

Professor Manuel Teixeira
Portugese Oncology Institute, Porto, Portugal.

Professor Marco Novelli
University College London Hospitals, London, UK.

Administrative coordinator
Anette Sørensen

GENDER DISTRIBUTION
PERCENT %



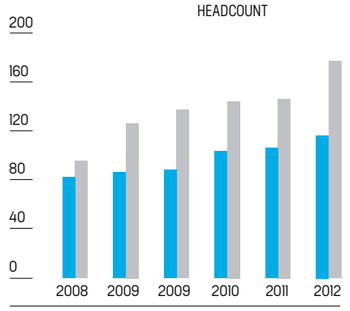
Male
Female

From 2011 to 2012 the number of female employees in our centre has increased from 61 to 66%.

Based on the fact that 66% of CCB members are female, an analysis of the representation of female scientists in CCB is conducted again this year. CCB actively supports the promotion of talented female scientists through various means where the overall strategy is to create predictability and continuity, and thereby motivating women to stay in their current career path.

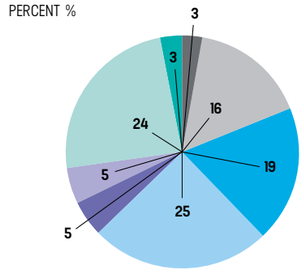
Earlier, we identified one problem area, namely the promotion of women to the highest scientific category, the project leader/senior scientist level. Again this year we are happy to report stable figures for this category: The female representation at the project leader/senior scientist level has dropped slightly from 45% in 2011 to 40% in 2012. However this is due to the promotion of one female project leader to the independent group leader level. This results in a female share of 20% in the group leader category in 2012.

CCB STAFF DEVELOPMENT
IN MAN-YEARS/
HEADCOUNT



Since CCB's inauguration in 2007, the number of man-years has increased with approx. 40%. Our current infrastructure restricts further expansion of the centre, and we therefore plan to keep the number of CCB staff stable in the years to come. The total number of people registered in the centre in 2012 is 178, corresponding to 117 man-years. CCB currently houses 21 different nationalities.

CCB STAFF CATEGORIZED
BY POSITION
PERCENT %

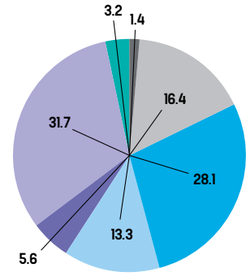


Principal Investigators
Professors and researchers
Postdocs
PhD students
Guest researchers
Master students
Technical staff
Administrative staff

We have counted 178 CCB members in 2012, corresponding to 117 man-years. The pie chart shows the categorization of our staff by position.

– VALUABLE ADMINISTRATIVE SUPPORT FROM OUR TWO HOST INSTITUTIONS ENABLES US TO OFFER OUR EXCELLENT RESEARCHERS THE EXCELLENT ADMINISTRATION THEY DESERVE!

FUNDING
MNOK



The Research Council of Norway
The Norwegian Cancer Society
South-Eastern Norway Regional Health Authority
Centre of Excellence
University of Oslo
Oslo University Hospital
The Radium Hospital Legacy Foundation

The funding situation for CCB is good in the sense that the centre has been obtaining sufficient financial resources to implement all its planned activities. The total funding for 2012 is 99.7 MNOK excluding in-kind contributions.

Again in 2012, the funding from the South-Eastern Norway Regional Health Authority has increased dramatically, from 19.5 MNOK in 2011 to 28.1 MNOK in 2012.

CCB's international funding in 2012 includes an ERC Advanced Grant. Due to 18 months instalments, no ERC funding was transferred to CCB in 2012. However, costs attributed to international funding in 2012 exceeded 3 MNOK.

The overall funding for CCB has increased with 7.5 MNOK from 2011 to 2012.

TOTAL NUMBER OF CCB PUBLICATIONS IN 2012
77 PUBLICATIONS
–
NUMBER OF PUBLICATIONS WITH CCB SCIENTISTS AS CORRESPONDING AUTHOR
50 PUBLICATIONS
(65%)
–
NUMBER OF COLLABORATION PUBLICATIONS WITH CLINICIANS AND PATHOLOGISTS
39 PUBLICATIONS
(51%)
–
NUMBER OF PUBLICATIONS WITH INTERNATIONAL PARTNERS
27 PUBLICATIONS
(35%)

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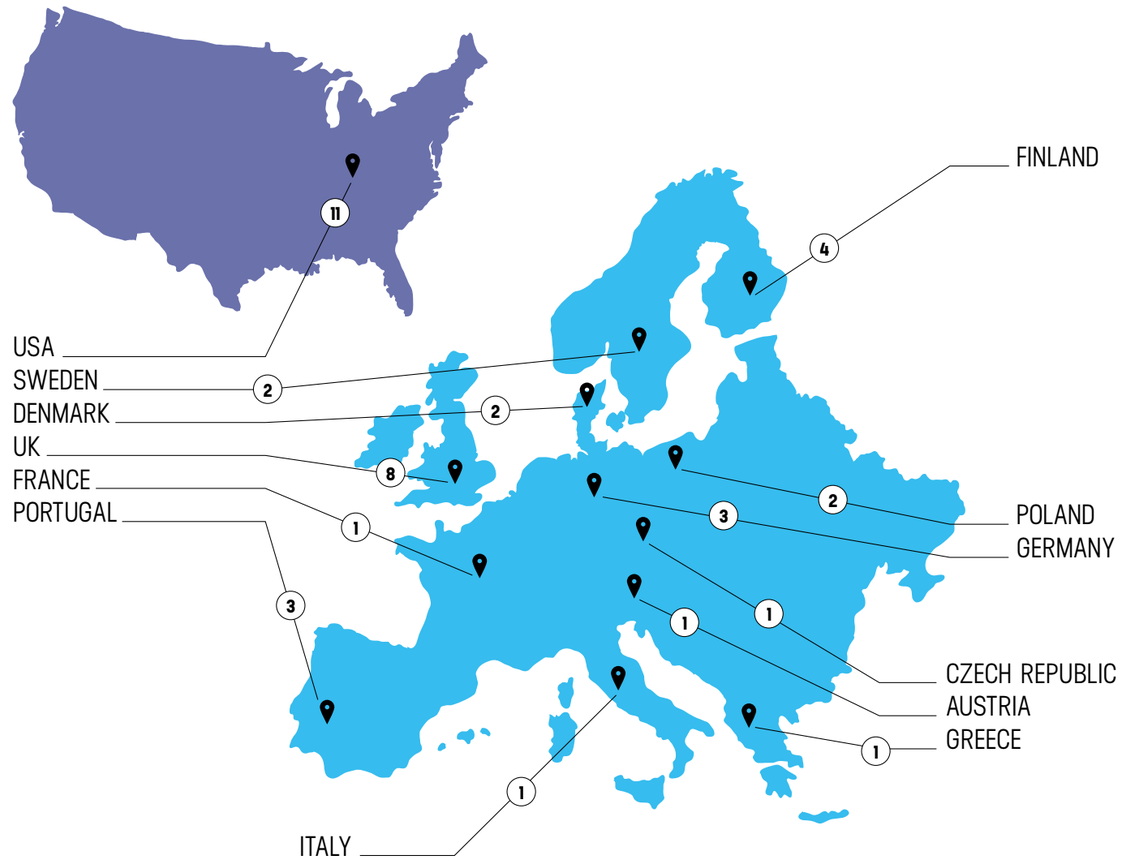
INTERNATIONAL COLLABORATION



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

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

Prof. Katherine Nathanson, University of Pennsylvania, Philadelphia, USA

Dr. Juha Rantala, Knight Cancer Institute, Oregon Health and Science University, Portland, USA

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

Assistant Prof. Ash A. Alizadeh, Division of Oncology, Stanford University, USA

Prof. Ronald Levy, Division of Oncology, Stanford University, USA

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

Assistant Prof. Joshua Brody, Director of Lymphoma Immunotherapy Program, Mount Sinai School of Medicine, New York, USA

Dr. Louis M. Staudt, Head of the Lymphoma and Leukemia Molecular Profiling Project (LLMPP), National Cancer Institute, USA

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

Prof. Peter Andrews, University of Sheffield, UK

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

Dr. Tobias Zech, The Beatson Institute for Cancer Research, Glasgow, UK

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

Dr. Jason Dunn, St Thomas' Hospital, London, UK

Dr. Jude Fitzgibbon, Barts Cancer Institute, Barts and The London School of Medicine and Dentistry, UK

Prof. Daniel St Johnston, University of Cambridge, UK

Prof. Marco Novelli, University College London, UK

Dr. Kim Ekroos, Zora Biosciences Oy, Espoo, Finland

Prof. Ilpo Vattulainen, Dept. Physics, Tampere University of Finland, Tampere, Finland

Dr. Marika Ruponen, School of Pharmacy, University of Eastern Finland, Kuopio, Finland

Dr. Johanna Ivaska, University of Turku, Finland

Prof. Fredrik Mertens, University of Lund, Sweden

Prof. Gert Auer, Karolinska Institutet, Stockholm, Sweden

Prof. Ewa Rajpert-De Meyts, Rigshospitalet, Copenhagen, Denmark

Prof. Bo van Deurs, University of Copenhagen, Denmark

Prof. Paula Soares, IPATIMUP, Porto, Portugal

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

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

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

Dr. Graça Raposo-Benedetti, Curie Institute, Paris, France

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

Prof. Jacek Otlewski, Faculty of Biotechnology, University of Wroclaw, Poland

Prof. V. Gerke, University of Münster, Germany

Prof. Dr. Torsten Steinmetzer, Inst. of Pharmaceutical Chemistry, Phillips University, Marburg, Germany

Prof. Ivan Dikic, Goethe University, Frankfurt, Germany

Dr. Pavel Krejci, Institute of Experimental Biology, Masaryk University, Brno, Czech Republic

Dr. Barbara Hausott, Division of Neuroanatomy, Innsbruck Medical University, Austria

Dr. Philos Nikos Pandis, Department of Genetics, Saint Savvas Hospital, Athens, Greece

NAME	POSITION	GROUP	NATIONALITY	EMPLOYER	ACADEMIC TITLE
Abrahamsen, Hilde	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Ailte, Ieva	PhD student	Sandvig	Latvia	University of Oslo	MSc
Alagaratnam, Sharmini	Postdoc	Lothe	Malaysia	Oslo University Hospital	PhD
Ali, Deeqa Ahmed Mohamed	PhD student	Lind	Norway	Oslo University Hospital	MSc
Amoasii, Leonela	Guest PhD student	Stenmark	France	I.G.B.M.C., Strasbourg	MSc
Andersen, Hege Kilen	Technician	Heim	Norway	Oslo University Hospital	
Andresen, Kim	PhD student	Lind	Norway	Oslo Univ. Hosp./University of Oslo	MSc
Annese, Valentina	Guest PhD student	Stenmark	Spain	University of Seville	MSc
Askevold, Kaja	PhD student	Wiedlocha	Norway	Oslo University Hospital	MSc
Bakkebø, Maren	PhD student/Postdoc	Smeland	Norway	Oslo University Hospital	MSc/PhD
Bakken, Anne Cathrine	Research fellow	Skotheim	Norway	Oslo University Hospital	MSc
Bassols, Jose Maria	Computer specialist	Stenmark	Spain	Oslo University Hospital	
Berg, Kaja Christine Graue	Research fellow	Lothe	Norway	Oslo University Hospital	MSc
Bergan, Jonas	PhD student	Sandvig	Norway	Oslo University Hospital	MSc
Bergersen, Anne Gro	Technician	Stenmark	Norway	Oslo University Hospital	
Bethge, Nicole	PhD student	Smeland	Germany	Oslo University Hospital	MSc
Bjønness, Heidi Plum	Laboratory Assistant	Stenmark	Norway	Oslo University Hospital	
Blaker, Yngvild Nuvin	PhD student	Smeland	Norway	Oslo University Hospital	MD
Bollum, Lise Kristin	Master student	Smeland	Norway	Oslo Univ. Hosp./University of Oslo	
Brabrand, Sigmund	PhD student	Skotheim	Norway	Oslo University Hospital	MD
Brandal, Petter	Scientist	Heim	Norway	Oslo University Hospital	PhD
Brech, Andreas	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Bredahl, May Kristin Lyamouri	Senior scientist	Smeland	Norway	Oslo University Hospital	PhD
Bruun, Jarle	PhD student	Lothe	Norway	Oslo University Hospital	MSc
Bævre, Mette	Research fellow	Danielsen	Norway	Oslo University Hospital	MSc
Børø, Siri	Research fellow	Danielsen	Norway	Oslo University Hospital	MSc
Campsteijn, Coen	Postdoc	Stenmark	Holland	Oslo University Hospital	PhD
Cekaite, Lina	Postdoc	Lothe	Lithuania	Oslo University Hospital	PhD
Celestino, Ricardo	Guest PhD student	Skotheim	Portugal	University of Porto	MSc
Christ, Liliane	Guest master student	Stenmark	Switzerland	University of Bern	MSc
Cordara, Gabriele	PhD student	Sandvig	Italy	University of Oslo	MSc
Cyll, Karolina	Master student	Danielsen	Polish	Oslo Univ. Hosp./University of Oslo	
Dahlback, Hanne-Sofie Spenning	PhD student/Postdoc	Heim	Norway	University of Oslo	MD PhD
Danielsen, Håvard	P.I., professor	Danielsen	Norway	Oslo University Hospital	PhD
Danielsen, Stine Aske	Postdoc	Lothe	Norway	Oslo University Hospital	PhD
Eibak, Anne Mette	Technician	Heim	Norway	Oslo University Hospital	MSc
Eide, Marianne Brodtkorb	PhD student	Smeland	Norway	Oslo University Hospital	MD
Eide, Peter Andreas Wold	Research fellow/PhD student	Lothe	Norway	Oslo University Hospital	MSc
Eikenes, Åsmund Husabø	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Eilertsen, Ina Andrassy	Master student/Research fellow	Lothe	Norway	Oslo University Hospital	MSc
Eknæs, Mette	Technician	Lothe	Norway	Oslo University Hospital	
Engen, Anne	Technician	Stenmark	Norway	Oslo University Hospital	
Erling, Hilde Lie	Administrative head	Danielsen	Norway	Oslo University Hospital	MSc
Ersvær, Elin	PhD student	Danielsen	Norway	Oslo University Hospital	MSc
Fiskvik, Idun Hege	PhD student	Smeland	Norway	University of Oslo	MD
Fjelldal, Marthe Fredheim	Research fellow	Danielsen	Norway	Oslo University Hospital	MSc
Forfang, Lise	Technician	Smeland	Norway	Oslo University Hospital	MSc
Fosslie, Madeleine	Technician	Danielsen	Norway	Oslo University Hospital	MSc
Fykerud, Tone	Research fellow	Rivedal	Norway	Oslo University Hospital	MSc
Gargul, Anne Grete	Master student	Sandvig	Norway	Oslo Univ. Hosp./University of Oslo	
Gehrken, Hege Brandt	Technician	Heim	Norway	Oslo University Hospital	MSc
Gorunova, Ludmila	Scientist	Heim	Russia	Oslo University Hospital	PhD
Guriby, Marianne	Research fellow	Lothe	Norway	Oslo University Hospital	MSc
Haglund, Kaisa	Project leader, Senior scientist	Stenmark	Sweden	Oslo University Hospital	PhD
Haugom, Lisbeth	Research fellow	Heim	Norway	Oslo University Hospital	
Haugsten, Ellen Margrethe	Postdoc	Wiedlocha	Norway	Oslo University Hospital	PhD
Heim, Sverre	Group leader, Senior scientist	Heim	Norway	Oslo University Hospital	PhD
Hektoen, Merete	Technician	Lothe	Norway	Oslo University Hospital	MSc
Hermansen, Lene Cecilie	Technician	Stenmark	Norway	Oslo University Hospital	MSc

NAME	POSITION	GROUP	NATIONALITY	EMPLOYER	ACADEMIC TITLE
Herrman, Carolina	Laboratory Assistant	Stenmark	Norway	Oslo University Hospital	
Hessvik, Nina Pettersen	Postdoc	Sandvig	Norway	Oslo University Hospital	PhD
Hilden, Vera Irene	Technician	Smeland	Norway	Oslo University Hospital	MSc
Hoff, Andreas Midbøe	PhD student	Skotheim	Norway	Oslo University Hospital	MSc
Honne, Hilde	Research fellow	Lind	Norway	Oslo University Hospital	MSc
Huse, Kanutte	Postdoc	Smeland	Norway	Oslo University Hospital	PhD
Hveem, Tarjei Sveinsgjerd	PhD student	Danielsen	Norway	Oslo University Hospital	MSc
Høimyr, Helene	Research fellow	Danielsen	Norway	Oslo University Hospital	MSc
Høiseth, Ane Hoel	Master student	Stenmark	Norway	Oslo Univ. Hosp./University of Oslo	
Høland, Maren	PhD student	Lothe	Norway	University of Oslo	MSc
Håvik, Annette Bentsen	PhD student	Heim	Norway	Oslo University Hospital	MSc
Iversen, Tore-Geir	Project leader, Senior scientist	Sandvig	Norway	Oslo University Hospital	PhD
Jacobsen, Jørn	PhD student	Danielsen	Norway	Oslo University Hospital	MSc
Jenstad, Monica	Postdoc	Danielsen	Norway	Oslo University Hospital	PhD
Johannessen, Bjarne	PhD student	Skotheim	Norway	Oslo University Hospital	MSc
Johannessen, May Elisabeth	Secretary		Norway	Oslo University Hospital	
Karerwa, Jeanne D'Arc	Technician	Danielsen	Norway	Oslo University Hospital	
Katheder, Nadja Sandra	PhD student	Stenmark	Switzerland	Oslo University Hospital	MSc
Kavaliauskiene, Simona	PhD student	Sandvig	Lithuania	Oslo University Hospital	MSc
Kihlstrøm, Minna	Master student	Stenmark	Finland	Oslo Univ. Hosp./University of Oslo	
Kildal, Wanja	Head technician	Danielsen	Norway	Oslo University Hospital	PhD
Kjenseth, Ane Hansen	PhD student/Postdoc	Rivedal	Norway	Oslo University Hospital	MSc/PhD
Kjæreng, Marna Lill	Technician	Danielsen	Norway	Oslo University Hospital	
Kleppe, Andreas	PhD student	Danielsen	Norway	University of Oslo	MSc
Klokk, Tove Irene	Postdoc	Sandvig	Norway	Oslo University Hospital	PhD
Koirala, Shiva Dahal	Master student	Rivedal	Nepal	Oslo Univ. Hosp./University of Oslo	
Kolberg, Matthias	Scientist	Lothe	Norway	Oslo University Hospital	PhD
Kostas, Michal	Guest PhD student	Wiedlocha	Poland	University of Wroclaw	MSc
Kraggerud, Sigrid M.	Scientist	Lothe	Norway	Oslo University Hospital	Dr. Philos
Kvalvaag, Audun Sverre	PhD student	Sandvig	Norway	Oslo University Hospital	MSc
Kvamme, Linko Sigrid Izumi	Laboratory Assistant	Stenmark	Norway	Oslo University Hospital	
Leithe, Edward	Project leader, Senior scientist	Rivedal	Norway	Oslo University Hospital	Dr. Philos
Liestøl, Knut	P.I., professor	Liestøl	Norway	University of Oslo	Dr. Philos
Lind, Guro Elisabeth	Group leader, Senior scientist	Lind	Norway	Oslo University Hospital	Dr. Philos
Lingelem, Anne Berit Dyve	PhD student/Postdoc	Sandvig	Norway	Oslo University Hospital	MSc/PhD
Lingjærde, Ole Christian	Associate Professor	Liestøl	Norway	University of Oslo	PhD
Llorente, Alicia Martinez	Project leader, Senior scientist	Sandvig	Spain	Oslo University Hospital	Dr. Philos
Lobert, Viola	PhD student/Postdoc	Stenmark	France	Oslo University Hospital	MSc/PhD
Lothe, Ragnhild A.	P.I., professor	Lothe	Norway	Oslo University Hospital	Dr. Philos
Løvf, Marthe	PhD student	Skotheim	Norway	University of Oslo	MSc
Malerød, Lene	Postdoc	Stenmark	Norway	Oslo University Hospital	PhD
Manfroi, Elisabetta	Guest scientist	Heim	Italy	Azienda Ospedaliera Ternni	PhD
Martinsen, Janne	Laboratory Assistant	Stenmark	Norway	Oslo University Hospital	
Merok, Marianne Aarstad	PhD student	Lothe	Norway	University of Oslo	MD
Micci, Francesca	Scientist	Heim	Italy	Oslo University Hospital	PhD
Mjøen, Linda Uv	Advisor		Norway	Oslo University Hospital	
Mohn, Hans Martin	Software Developer	Danielsen	Norway	Oslo University Hospital	
Musa, Nagham	PhD student	Sandvig	Sweden	Oslo University Hospital	MSc
Myklebust, June Helen	Project leader, Senior scientist	Smeland	Norway	Oslo University Hospital	PhD
Myrann, Anne Grethe	Technician	Sandvig	Norway	Oslo University Hospital	
Nadratowska-Wesolowska, Beata	Postdoc	Wiedlocha	Poland	Oslo University Hospital	PhD
Nesheim, John Arne	Head of developement	Danielsen	Norway	Oslo University Hospital	MSc
Nezis, Ioannis	Postdoc	Stenmark	Greece	Oslo University Hospital	PhD
Nielsen, Birgitte	Scientist	Danielsen	Norway	Oslo University Hospital	PhD
Nilsen, Gro	PhD student	Liestøl	Norway	University of Oslo	MSc
Nome, Torfinn	PhD student	Skotheim	Norway	Oslo University Hospital	MSc
Nordtun, Silje	Technician	Danielsen	Norway	Oslo University Hospital	MSc
Norgren, Axel	Med. Student	Stenmark	Norway	Oslo Univ. Hosp./University of Oslo	
Norman, Ingrid Louise	Technician	Heim	Norway	Oslo University Hospital	MSc

NAME	POSITION	GROUP	NATIONALITY	EMPLOYER	ACADEMIC TITLE
Nymark, Carl-Martin	Technician	Sandvig	Norway	Oslo University Hospital	MSc
Nyquist, Kaja Beate	PhD student	Heim	Norway	Oslo University Hospital	MD
Oeste, Clara L.	Guest PhD student	Stenmark	Spain	CIB-CSIC, Madrid	MSc
O'Farrell, Fergal	Postdoc	Stenmark	Ireland	Oslo Univ. Hosp./University of Oslo	PhD
Oksvold, Morten	Postdoc	Smeland	Norway	Oslo University Hospital	PhD
Olsen, Thale Kristin	PhD student	Heim	Norway	Oslo University Hospital	MD
Olsen, Therese	Master student	Smeland	Norway	Oslo Univ. Hosp./University of Oslo	
Olsnes, Sjur	Professor emeritus	Wiedlocha	Norway	Oslo University Hospital	MD, PhD
Oppelt, Angela	PhD student	Wiedlocha	Germany	Oslo University Hospital	MSc
Panagopoulos Ioannis	Senior scientist	Heim	Hellas	Oslo University Hospital	PhD
Pedersen, Anne-Mari Gjestvang	Technician	Sandvig	Norway	Oslo University Hospital	MSc
Pedersen, Nina Marie	Postdoc	Stenmark	Norway	Oslo University Hospital	PhD
Petersen-Øverleir, Marte	Master student	Stenmark	Norway	Oslo Univ. Hosp./University of Oslo	
Phuyal, Santosh	Research fellow	Sandvig	Nepal	Oslo University Hospital	MSc
Pradhan, Manohar	PhD student/Postdoc	Danielsen	Nepal	Oslo University Hospital	MD, PhD
Pretorius, Maria	Administrative head	Danielsen	Norway	Oslo University Hospital	MSc
Pust, Sascha	Postdoc	Sandvig	Germany	Oslo University Hospital	PhD
Raiborg, Camilla	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Rivedal, Edgar	Group leader, Senior scientist	Rivedal	Norway	Oslo University Hospital	Dr. Philos
Rusten, Tor Erik	Project leader, Senior scientist	Stenmark	Norway	Oslo University Hospital	PhD
Rødland, Einar	Scientist	Liestøl	Norway	University of Oslo	PhD
Rønning, Eva	Head technician	Stenmark	Norway	Oslo University Hospital	
Sagona, Antonia	PhD student/Postdoc	Stenmark	Greece	Oslo University Hospital	MSc/PhD
Sandve, Geir Kjetil	Scientist	Liestøl	Norway	University of Oslo	PhD
Sandvig, Kirsten	P.I., professor	Sandvig	Norway	Oslo University Hospital	Dr. Philos
Schink, Kay Oliver	Postdoc	Stenmark	Germany	Oslo University Hospital	PhD
Schultz, Sebastian	Postdoc	Stenmark	Sweden	Oslo University Hospital	PhD
Sem Wegner, Catherine E.	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Sheikh, Danial	Software Developer	Danielsen	Norway	Oslo University Hospital	MSc
Simm, Roger	Lab.manager	Sandvig	Sweden	Oslo University Hospital	PhD
Sirnes, Solveig	Postdoc	Rivedal	Norway	Oslo University Hospital	PhD
Skarpen, Ellen	Scientist	Stenmark	Norway	Oslo University Hospital	PhD
Skotheim, Rolf I.	Group leader, Senior scientist	Skotheim	Norway	Oslo University Hospital	Dr. Philos
Skotland, Tore	Senior scientist	Sandvig	Norway	Oslo University Hospital	Dr. Philos
Sletten, Torunn	PhD student	Wiedlocha	Norway	Oslo University Hospital	MSc
Smedbye, Marianne Lislerud	PhD student	Heim	Norway	Oslo University Hospital	MD
Smeland, Erlend Bremertun	P.I., professor	Smeland	Norway	Oslo University Hospital	MD, PhD
Smestad, Marianne	Technician	Stenmark	Norway	Oslo University Hospital	
Sneeggen, Marte	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Steen, Chloe B.	Master student	Stenmark	Norway	Oslo Univ. Hosp./University of Oslo	
Stenmark, Harald	P.I., professor	Stenmark	Norway	Oslo Univ. Hosp./University of Oslo	Dr. Philos
Sveen, Anita	PhD student/Postdoc	Skotheim	Norway	Oslo University Hospital	MSc/PhD
Syvertsen, Rolf Anders	Software Developer	Danielsen	Norway	Oslo University Hospital	MSc
Sørensen, Anette	Administrative coordinator		Denmark	University of Oslo	
Sørensen, Vigdis	Postdoc	Wiedlocha	Norway	Oslo University Hospital	PhD
Thomassen, Gard O. Sundby	Postdoc	Skotheim	Norway	Oslo University Hospital	PhD
Thoresen, Sigrid Bratlie	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Thorsen, Jim	Postdoc	Heim	Norway	Oslo University Hospital	PhD
Thorvaldsen, Tor Espen	PhD student	Stenmark	Norway	Oslo University Hospital	MSc
Vedeld, Hege Marie	PhD student	Lind	Norway	Oslo University Hospital	MSc
Vietri, Marina	PhD student	Stenmark	Italy	Oslo University Hospital	MSc
Våtsveen, Thea	Guest scientist	Smeland	Norway	NTNU	PhD
Wenzel, Eva	Postdoc	Stenmark	Germany	University of Oslo	PhD
Wesche, Jørgen	Project leader, Senior scientist	Wiedlocha	Norway	Oslo University Hospital	Dr. Philos
Wiedlocha, Antoni	Group leader, Senior scientist	Wiedlocha	Poland	Oslo University Hospital	Dr. Philos
Wæhre, Håkon	Medical consultant	Danielsen	Norway	Oslo University Hospital	MD, PhD
Yohannes, Zeremariam	Technician	Rivedal	Norway	Oslo University Hospital	
Yri, Olav Erich	PhD student	Smeland	Norway	Oslo University Hospital	MD
Zhen, Yan	Postdoc	Wiedlocha	China	Oslo University Hospital	PhD
Ågesen, Trude Holmeide	PhD student/Postdoc	Lathe	Norway	Oslo University Hospital	MSc/PhD

CCB WOULD LIKE TO THANK THE FOLLOWING FUNDING ORGANIZATIONS AND SPONSORS FOR THEIR VALUABLE COMMITMENT AND FINANCIAL SUPPORT:

UiO : Universitetet i Oslo

IVAR P. GLADHAUG
Head of Institute
Institute of Clinical Medicine
University of Oslo

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SIGBJØRN SMELAND
Head of Division
Divison of Cancer Medicine, Surgery and Transplantation
Oslo University Hospital

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JOHN TORGILS VAAGE
Director
Research and Innovation
South-Eastern Norway Regional Health Authority

Helse Sør-Øst RHF (the South Eastern Norway Regional Health Authority) promotes research that aims to be of the highest quality, is based on collaboration, and of benefit to our patients. The Centre for Cancer Biomedicine fulfills this vision by bridging frontline interdisciplinary research with clinically useful applications and innovations. The Centre for Cancer Biomedicine has received solid financial support from Helse Sør-Øst RHF in the form of competitive research grants. This will help the centre to reach its long-term goal of providing "benefit to the cancer patient".

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General inquiries
E-mail: post@ccb.uio.no
Tel: +47 22 78 18 27
www.uio.no/ccb

Postal address
Oslo University Hospital
The Norwegian Radium Hospital
P. O. Box 4953 Nydalen
N–0424 Oslo
Norway

Visiting address
The Norwegian Radium Hospital
The Research Building
Dept. of Biochemistry, 5th floor
Ullernchausseen 70
0379 Oslo