INSTITUTE FOR CANCER RESEARCH

ANNUAL REPORT
2014

Oslo University Hospital

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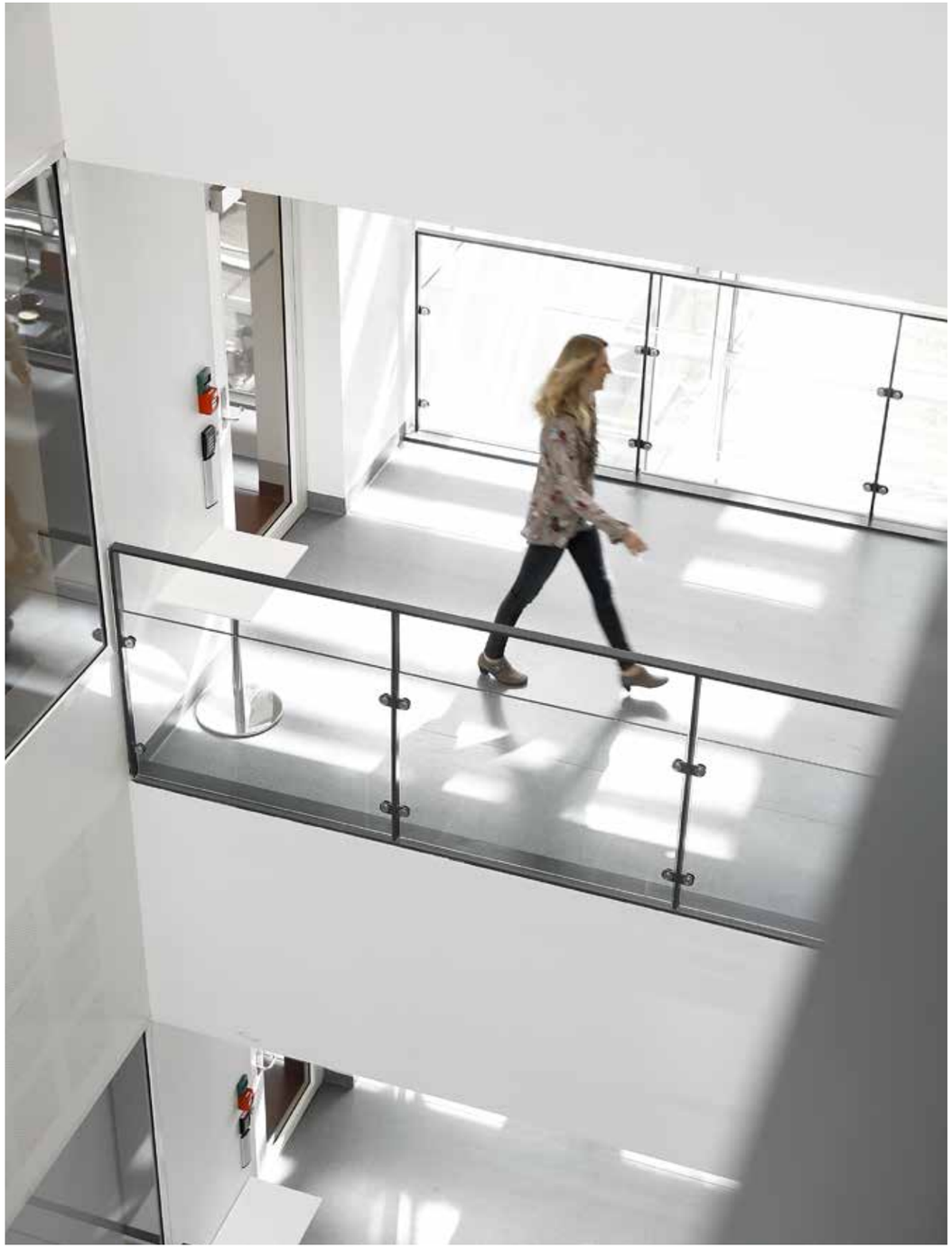


PHOTO BY TERJE HEIESTAD

CONTENT

The Institute for Cancer Research (ICR) was founded in 1954, and has since then been integrated with The Norwegian Radium Hospital (NRH) which delivers highly specialized clinical cancer care and cancer research.

The ICR has over the years been a central player in the national medical research community and been internationally competitive in many cancer research areas.

In 2009 Oslo University Hospital (OUH) was established through the merger of four Oslo University hospitals (including NRH), resulting in an increase of the total institutional cancer patient volume to approximately 7500 new patients a year. The same year ICR moved into a new and dedicated cancer research building. ICR is now part of the Division of Cancer, Surgery and Transplantation in OUH, and the organizational structure of the Division is harmonized with the University of Oslo (UiO) structure.

Following the appointment of the new ICR Director in August 2013, the Institute´s organization and research in 2013-14 underwent an internal revision. ICR is now organized in 6 Research Departments with 24 research groups, and a dedicated Department of Core Facilities. The strategic and operational priorities for our research were revised with a resultant emphasis on to further strengthen and harmonise research quality, to increase the translational focus and internationalization, and to optimize internal collaboration, including strengthened collaboration with OUH clinical cancer scientists.

ICR currently has 294 full time positions, including 68 researcher positions, and 28 of these hold part time professorships at the University of Oslo. Also, 11 senior physicians at the departments of Oncology, Tumour Surgery or Pathology in OUH hold part time positions at ICR. The total financial expenditure in 2014 was NOK 278 mill (approx. € 32 mill), of which 68% was competitive funding from external sources.

This report is focused on the ICR research activity for 2014, and key metrics are compared for the last three years. The results for 2014 are encouraging, with increased production of publications and with an indication of increased quality and merit.

ICR is an integrated part of a university hospital with advanced cancer care, and going forward the Institute has an obligation to focus on transforming excellent science into patient benefit. However, this does not reduce the need to perform excellent basic research to increase the biological understanding of cancer and form the basis for future translations. In order to succeed we need to combine strengthening of our own skills with increased collaboration with the very best international groups and institutions. A pre-requisite for this is to develop our own attractiveness as a partner for the best actors within science, clinical care and industry. Important progress in cancer research is also dependent on extensive multidisciplinary interaction on an institutional level, and ICR will fully support the further development of the Comprehensive Cancer Center model at OUH. Our goal is to be perceived as one of Europe´s very top cancer research institutes and CCC´s within 2020.

One of Norway´s strengths is the ability to perform nation-wide population based studies, including on the molecular level. Several groups at the Institute have over the recent years taken important initiatives to establish state- of- the art technology and to share their competence with other national milieus – examples are NGS and advanced microscopy. This has been followed up by leaderships in national research programs like the Norwegian Cancer Genomics Consortium (NCGC), and ICR groups will initiate and support further programs of this nature.

2015 will see the opening of the Oslo Cancer Cluster Innovation Park just next door to the Institute, which will include housing the Norwegian Cancer Registry and the Incubator for new start-up companies. This development will strengthen both the collaboration on population-based studies and the further development of ICR innovations.

Finally, to support ICR in its further development an external Scientific Advisory Board (SAB) was appointed in 2014, and the first SAB evaluation will take place in September 2015. The members of the ICR SAB are:

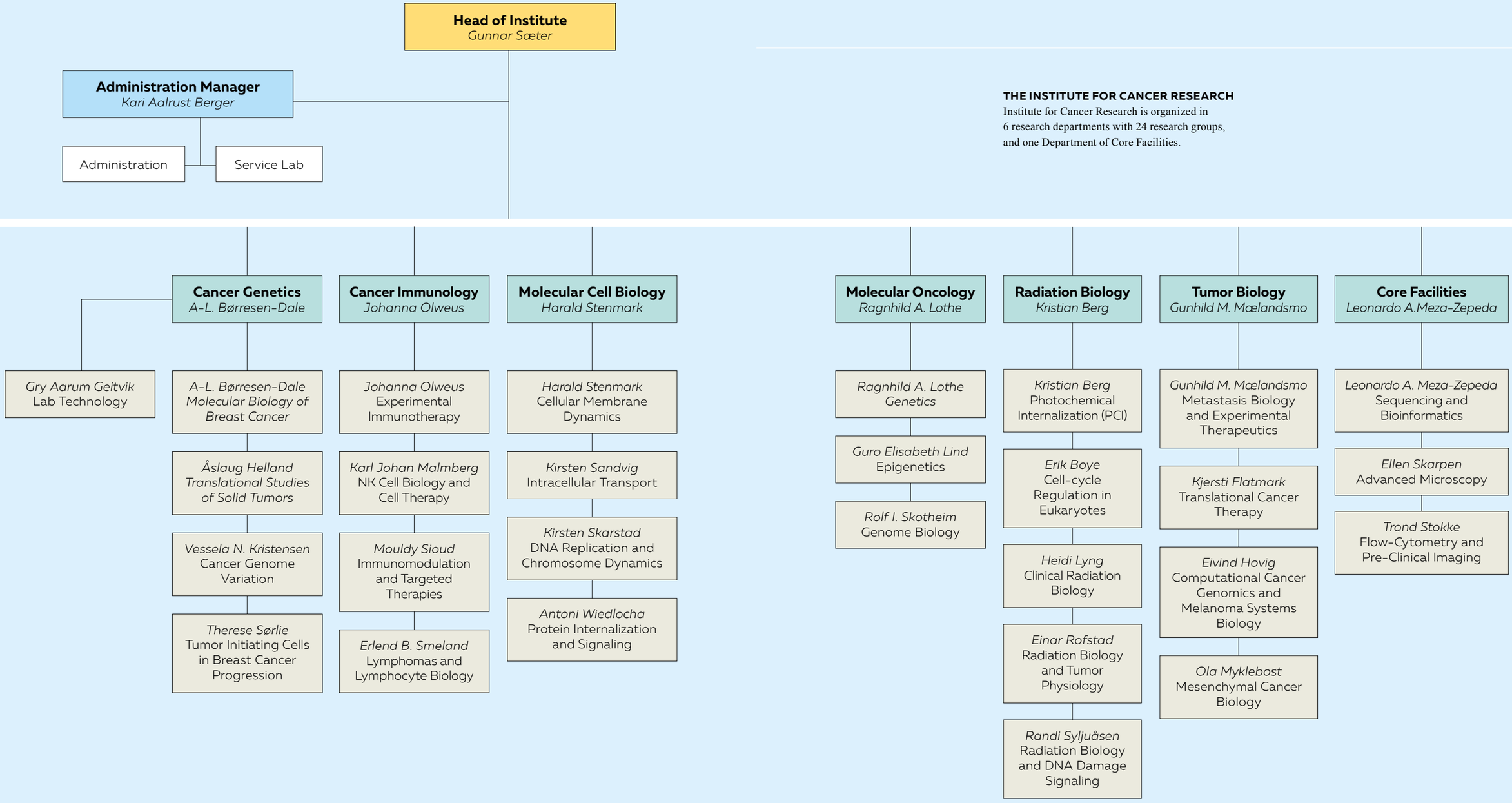
- Professor Carl-Henrik Heldin, Ludwig Institute of Cancer Research, Uppsala (Chair)
- Professor Josep Tabernero, Director, Vall d´Hebron Institute of Oncology, Barcelona
- Professor Eric Solary, Director of Research, Institut Gustave Roussy, Paris
- Professor Mef Nilbert, Head, Regional Cancer Centre South, Lund
- Professor Per Eystein Lønning, Haukeland University Hospital, Bergen
- Professor Odd Stokke Gabrielsen, University of Oslo

April 2015
Gunnar Sæter

PHOTO BY TERJE HEIESTAD

DIRECTOR
Gunnar Sæter

ORGANISATION CHART

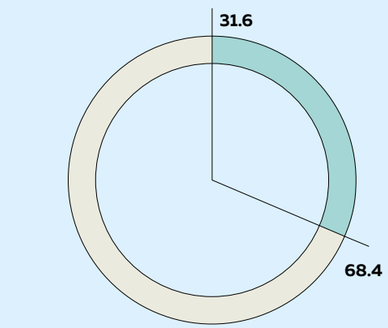


THE INSTITUTE FOR CANCER RESEARCH

Institute for Cancer Research is organized in 6 research departments with 24 research groups, and one Department of Core Facilities.

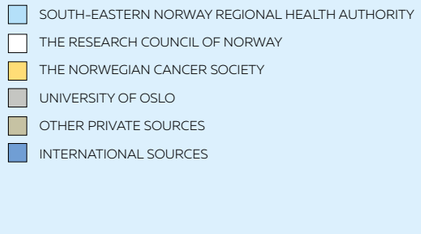
KEY FIGURES 2014

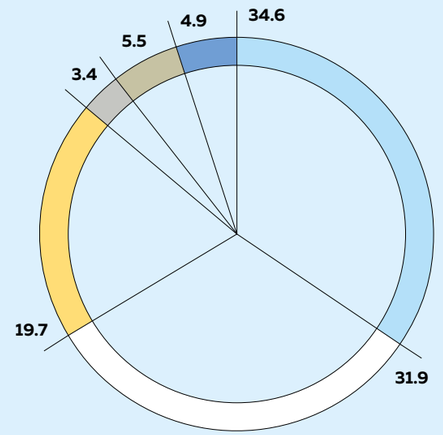
Funding
Percent



Actual Institute expenditure for 2014 by internal and external funding sources (total 278.5 MNOK = approx. 32.0 M€). The corresponding figures for budget allocation was 25% vs. 75%. This discrepancy is caused by external funds being transferable to the subsequent year, whereas internal funds are not.

External funding by source
Percent

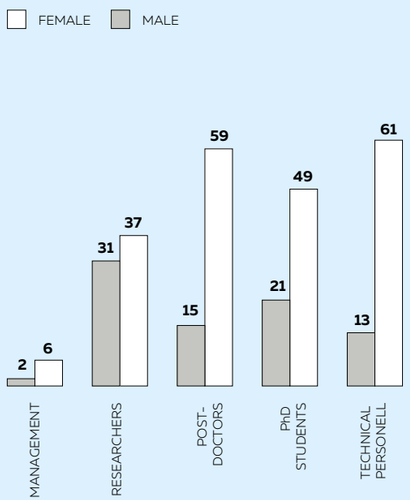




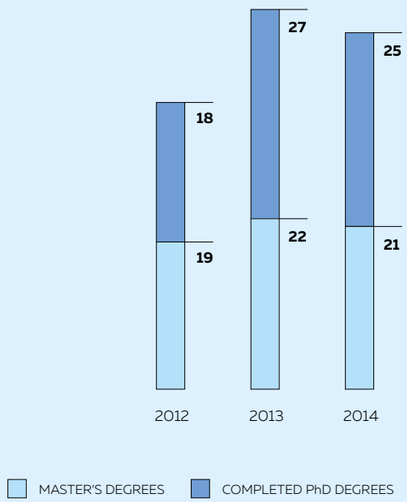
Sources of external competitive funding for 2014, based on actual expenditure (total 190.5 MNOK = approx. 22 M€)

Employees
Number

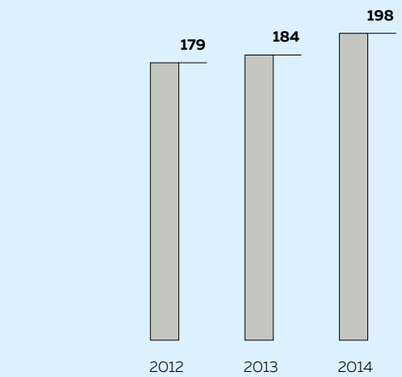
Full time employees by type of position



Completed PhDs and Master degrees
Number



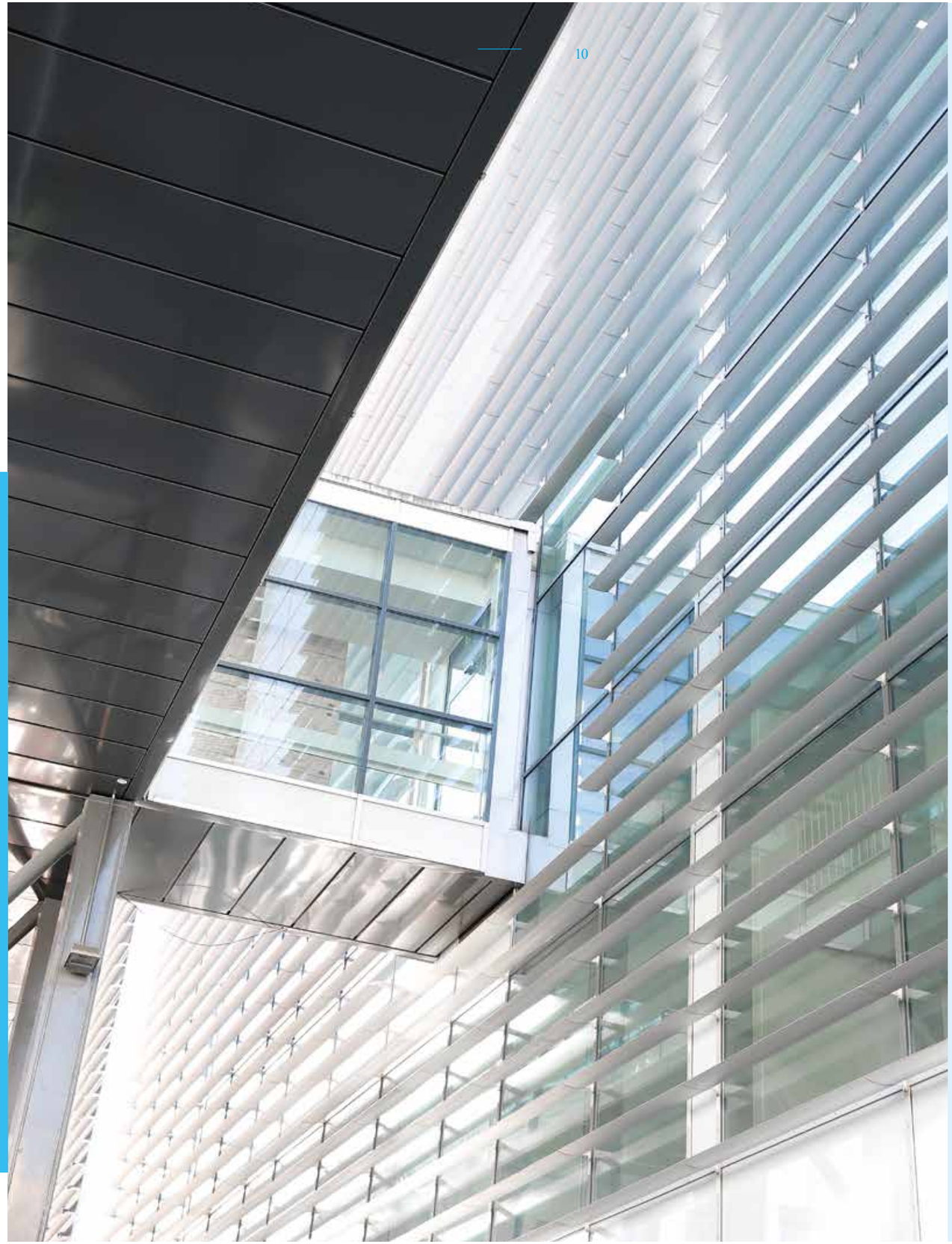
Articles published
Number



IMPACT FACTOR

	2012	2013	2014
MEAN	5.8	5.4	6.1
MEDIAN	3.8	3.7	4.5

The number of publications for 2014 are based on the actual lists of publications from the ICR research groups. The numbers for 2012 and 2013, and the Impact Factors, are based on the OUH Publika database (2013 is corrected for print date).



DEPARTMENTS AND RESEARCH GROUPS

PHOTO BY TERJE HEIESTAD

CANCER GENETICS

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Headed by
Anne-Lise Børresen-Dale

Our vision is to perform integrated molecular and epidemiological studies to reduce risk, achieve early diagnosis, improve prognosis, and to tailor the treatment for the individual patient with breast, lung, pancreatic and ovarian cancer.

The department consists of four research groups and one laboratory technology group. In total there are 43 FTEs and 51 employees (12 males and 39 females). There are 37 scientific employees, of which 13 are MDs, and 5 recruited from abroad.

The research focus is on molecular classification, data integration, translation, and pan-cancer analyses of breast, lung, pancreatic and ovarian cancer, with a common goal of achieving a deeper molecular understanding of inter- and intra-tumor heterogeneity, both between different tumor entities, between tumor subgroups, and within a single tumor. Our strategy has been to establish a pipeline for high-quality biobanking and data-handling of patient cohorts with long-term, high quality follow-up data and perform multilevel molecular characterization down to the single-cell level. Mouse modeling of human cancers to understand the cancer evolution, heterogeneity and therapy resistance is part of the department's project portfolio. We are an interdisciplinary team performing integration of biological data with clinical variables, with the aim of developing prognostic and predictive signatures and designing assays that can be translated into clinical management.

We were pioneers in expression profiling of breast cancer leading to clinical important molecular subtypes, which has been followed by multilevel characterization of larger cohorts, setting the stage for large scale data integration. This approach has formed the basis for the analyses of the other tumor types, paving the way for Pan-cancer analysis. Development of computational algorithms has been a strong focus and led to important tools receiving international recognition like the ASCAT and CAAI algorithms (PNAS and Science Transl Med), and led to the invitation to review principles and methods of integrative genomic analyses in cancer (Nat. Cancer Rev 2014).

We have an extensive institutional, national and international collaboration, and are involved in several programs within the ICGC (International Cancer Genome Consortium). We are WP-leaders in multiple EU funded projects (Eurocan, BASIS, GlycoHit, EpiMark, Cancer-ID).

The Department hosts the K.G. Jebsen Center for Breast Cancer Research and The National Competence Center for Lung Cancer, and is involved in several national and institutional networks (The Regional Research Network on Extracellular Vesicles (RRNEV), Personalized Cancer Treatment and Metaflammation).

The total number of peer reviewed publications in 2014 was 48.

PHOTOS BY TERJE HEIESTAD

MOLECULAR BIOLOGY OF BREAST CANCER

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Group leader
Anne-Lise Børresen-Dale

PHOTO BY TERJE HEIESTAD

ABOUT

The group consist of 4 scientists, 3 postdocs, 6 phD students (of which one is an MD), and 6 research engineers.

We seek to reach a more fundamental understanding of the biological dynamics of breast cancer through high-throughput molecular analyses of DNA, mRNA, miRNA and protein. We perform ”state of the art” analyses of patient material, both on bulk tumors, single cells and liquid biopsies, at various stages of the disease from consecutive patient series (OsloVal, Oslo0, Oslo1 and Oslo2), and from clinical trials with sampling before, during and after therapy (the NeoAva and the IBCT-studies).

AIMS

The biggest challenge in order to reach an earlier and more accurate diagnosis, to improve tailoring of treatments and to predict drug response and patient prognosis, and to pave the ground for development of new therapeutic approaches, is the huge heterogeneity of breast cancer. To understand the role and impact of the huge both inter- and intra- tumor heterogeneity on response to therapy and patient outcome, we are aiming towards a patient directed multi-level approach in a “systems biology framework”. Our ultimate goal is to translate the biological findings into clinical management.

PROJECTS

- Single level classification at DNA/RNA/protein/metabolic level of both primary tumors and metastases in large cohorts of patients at various stages of the disease (from normal breast to advanced stage)
- Somatic Genetics of Breast Cancer, from single genes (TP53 and PIK3CA) to genome panels (IonTorrent) to whole genome sequencing
- Genomic alterations to elucidate the genomic landscape in breast cancer with impact on prognosis, therapy prediction and clinical follow-up
- Intra-tumor heterogeneity and its implication for diagnosis and treatment
- HER2 postitive cancer and treatment response
- Genomic and functional analysis of therapeutic targets in breast cancer
- Functional screens elucidating the role of miRNA’s
- Glycans and miRNA as serum biomarkers
- Integrated classification

RECENT ACHIEVEMENTS

- *Publication activity*: 40 original publications, 2 invited reviews in 2014. One paper (Silwal-Pandit, Vollan et al., TP53 Mutation Spectrum in Breast Cancer Is Subtype Specific and Has Distinct Prognostic Relevance) published in Clinical Cancer Research received the prize for outstanding publication from the Regional Health Authorities in 2014
- Two successful PhDs defenses in 2014
- The group leader received The Helmholtz International Fellow Award for 2014

TRANSLATIONAL STUDIES OF SOLID TUMORS

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Group leader
Åslaug Helland

PHOTO BY TERJE HEIESTAD

ABOUT

The group focuses on translational studies on solid tumours, with a special interest in pancreatic, lung, ovary and colorectal cancers. We do whole genome analyses on patient material, aiming at identifying predictive and prognostic biomarkers. We are analysing mRNA, miRNA, DNA, methylation, glycosylation, mutations and proteins. By increasing the understanding of the underlying biology of tumour development, we aim at improving cancer care. Several of our projects include material from patients included in clinical studies, and we have clinical and follow-up data from all patients.

The group has three project groups, with a total of 17 members (14 women) and four associate members. Eight of these 17 are MDs, and India, Great Britain and Israel are represented. We are three researchers, two postdocs, nine PhD-students, one study nurse and two research engineers.

AIMS

The ultimate goal is to personalise cancer treatment and improve prognosis.

- Identification of biomarkers in blood samples, for diagnostics, follow-up and prognostication
- Identification of tumour biomarkers for prediction of therapy response and for prognosticaton

PROJECTS

- Serum miRNA-signatures for the detection of lung and pancreatic cancers
- Molecular characterisation of lung adenocarcinomas
- Molecular characterisation of pancreatic cancers
- MiRNA in ovarian cancer
- Improving radiotherapy in lung cancer
- Identification of biomarkers in colorectal cancers
- Protein (TMA) analyses in lung cancers
- Genome-wide detection of diagnostic plasma miRNAs in pancreatic cancer
- Exosome profiles of proteins and miRNAs in plasma of pancreatic cancer patients
- Serum N-glycans as prognostics markers in pancreatic and colorectal cancers

RECENT ACHIEVEMENTS

In 2014, the group was involved in several EU-applications, published 20 papers in peer-review journals, and filed one DOFI. We were appointed “The Norwegian Cancer Society’s National Centre of Expertise for Lung Cancer”, funded with 11 mill NOK. We are also part of the division’s Focus Area for Personalised Cancer Therapy. We have had several oral presentations at national and international meetings, and are PIs on >20 translational and clinical studies.

CANCER GENOME VARIATION

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Group leader
Vessela N. Kristensen

PHOTO BY TERJE HEIESTAD

ABOUT

The group at ICR: 1 senior scientist, 3 postdocs, 2 PhD students and 1 research technician in 2014. Vessela Kristensen is a professor I at the Faculty of Medicine, UiO, and works towards an intensive and fruitful collaboration between ICR and University of Oslo, where she also leads a group of 2 postdocs, 2 PhD students and 1 research technician. Totally these represent 3 male and 9 female individuals, mostly Norwegian, but also from India, Pakistan and Serbia. Both groups work closely together and in collaboration to breast clinicians, pathologists and oncologists. Vessela N. Kristensen is on the advisory committee of 3 PhD students in Princeton University.

AIMS

The Cancer Genome Variation group is working to understand how genetic variation affects occurrence of somatic alterations, gene expression patterns and genome wide copy number alterations in human tumours. Understanding inherited genetic variability and how it affects crucial biological pathways is likely to lead to new successful prevention and treatment strategies. http://ous-research.no/kristensen/

PROJECTS

- Genome variation; fine mapping characterization of susceptibility loci in mitotic regulatory pathway genes and in genes shown to lead to aggressive epithelial cancers.
- DNA methylation in the early phases of disease progression and their clinical impact on treatment response. DNA methylation has an impact on immune signaling in radiation therapy.
- Data integration summarized in the work entitled Principles and Methods of Integrative Genomic Analyses (Nature Rev Cancer). Integrated analysis of high-resolution DNA methylation profiles, gene expression, germ-line genotypes and clinical end points in breast cancer.
- Non-canonical transcriptomes. Long non-coding RNAs in normal versus primary breast tumor tissues; converse changes to breast cancer-related protein-coding genes.
- Immune signaling. Interleukin signaling is in focus since our 2012 discovery of massive cytokine signaling. Lymphocyte Invasion in IC10/Basal-Like Breast Tumors Is Associated with Wild-Type TP53.

RECENT ACHIEVEMENTS

Publication activity: 22 publications and 2 PhD dissertations in 2014.

TUMOR INITIATING CELLS IN BREAST CANCER PROGRESSION

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Group leader
Therese Sørlie

PHOTO BY TERJE HEIESTAD

ABOUT

The group consists of 6 people including one postdoc, three PhD students, one research engineer and one MD-PhD student.

Our group is interested in development and progression of breast cancer, and we focus on the earliest tumor stages, in particular the transition from ductal carcinoma in situ (DCIS) to invasive cancer. We are interested in the role of tumor heterogeneity in progression and invasion, and in culmination into the various molecular breast cancer subtypes. We use both patient material and animal models (transgenic and patient-derived xenograft - PDX) in our studies. We apply high-throughput genomic technologies, functional assays, lineage-tracing, in situ techniques and associated statistical and bioinformatics methods.

AIMS

Our aim is to identify critical molecules, regulatory pathways and cell types involved in breast cancer development and progression to invasive disease. Through an increased understanding of how tumors progress to more advances stages, improved strategies for early intervention and more precise treatment can be developed.

PROJECTS

- Characterize progression pathways of pre-invasive lesions in the breast
- Identify and test potential molecular progression markers in large patient cohorts
- Characterize genetic, phenotypic and functional heterogeneity in breast tumors using PDX models representing luminal-like and basal-like breast cancer subtypes
- Identify and test novel targetable markers of tumorigenic cell populations in PDX models
- Investigate the role of Hedgehog/GLI1 signaling in breast cancer development
- Explore the tumorigenic potential of LGR5 expressing cells in the mammary gland
- Study tissue homeostasis upon anti-cancer treatment by in vivo lineage tracing
- Define genetic and epigenetic regulatory events in breast cancer progression, using transgenic animal models

RECENT ACHIEVEMENTS

- 9 publications in 2014 (one review article)
- Co-organized workshop “Precursors to breast cancers and tumor evolution”, 14th annual BCI-McGill workshop, Jan 23-30, Barbados

CANCER IMMUNOLOGY

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Headed by
Johanna Olweus

DCI has 4 research groups. Among the PIs, 3 are full professors at The University of Oslo (MD, PhD) and one is visiting professor (DEA pharm, PhD). One PI was recently recruited from Karolinska Institute (2011). Groups in the DCI are partners of: Center of Excellence for Cancer Biomedicine (CCB), two K.G. Jebsen Centers (Cancer Immunotherapy and Inflammation Research, and leader of the former) and OUH focus area for Cancer Immunotherapy. With emphasis on translation and extensive involvement in clinical trials, the DCI is the department with the highest number of MDs at the Institute. The DCI counts 39 members (62% women); 5 scientists, 11 postdocs, 8/1 PhD/Master students, and 10 technical staff, with 36% of the employees being recruited from abroad.

Our aim is to improve cancer diagnostics and therapy through cutting edge research on tumour immunology and lymphocyte biology.

This is done through projects on:

LYMPHOCYTE BIOLOGY, BY DECIPHERING
- ontogeny of B, T and NK cells
- tumor heterogeneity (signaling and mutanome)
- immune cell recognition elements (antigen discovery)

BIOMARKERS, BY PROFILING OF
- lymphocyte repertoires
- the tumor and its microenvironment
- T-cell receptors and humoral immunity

THERAPEUTICS, BY
- genetically engineered T and NK cells
- immune priming with siRNA and antigen-targeting to DC
- genetically engineered peptibodies
- cell therapy across HLA barriers to overcome immune tolerance
- clinical trials using local immunotherapy in lymphoma (LYMVAC)

In 2013-14, an average of 18 original publications/year were published (12.5 as first/last authors, of which 5 with IF>5 (mean IF 5.5)) and 4.5 DOFI/Patent applications were filed. In 2013 NOK 83 mill and in 2014 NOK 13 mill were achieved in external funding. Two articles were awarded among “Best publications from OUH” in 2014. Two articles were subjects of commentaries in Blood (IF=10) and Eur J Immunol (IF=5), respectively. One PI (KJM) met all criteria for excellence in the ERC consolidator grant evaluation, releasing an incentive grant from The Research Council of Norway (NOK 12 mill).

PHOTOS BY TERJE HEIESTAD

EXPERIMENTAL IMMUNOTHERAPY

/

Group leader
Johanna Olweus

PHOTO BY TERJE HEIESTAD

ABOUT

The group counts 12 members (67% women); 1 full professor (JO), 1 scientist, 3 postdocs, 4 PhD students and 2.5 engineers. Four members have MD background. Seven members are recruited from abroad (six different countries) and five are Norwegians. The group is partner of two K.G. Jebsen Centers (2013-); "Cancer Immunotherapy" and "Inflammation Research", respectively, and Olweus is Director of the former.

The main focus is to develop new strategies for cancer immunotherapy and to couple clinical trials with penetrating mechanistic analyses.

AIMS

To find new immunotherapeutic T-cell based strategies that overcome the major challenge of self-tolerance in cancer. Two principally distinct approaches are pursued in an interdisciplinary and translational program
Strategy 1: Use of T cell-based alloreactivity to target self-antigens.
Strategy 2: Identification and targeting of cancer-specific neo-antigens.

PROJECTS

Strategy 1

- Identify cell-type specific T-cell epitopes from self-antigens, T cells reactive with such epitopes and their TCRs for future genetic transfer in adoptive cellular therapy

Strategy 2

- Target neo-antigens neglected by melanoma patients
- Use TCR profiling as a tool to identify T-cell reactivities
- Identify neo-antigens and reactive T cells in biobanked material from patients responding to immunotherapy in LYMVAC trial
- Identify auto-antibody targets by protein arrays

RECENT ACHIEVEMENTS

6 original articles accepted for publication with Olweus as senior author and group member as first author on 4; 2 in journals with IF=10 (Blood, PNAS) and 2 in Eur J Immunol (EJI). Two articles selected by Faculty of prime (EJI:1 star, PNAS: 2 stars), and two were subject of commentaries (Blood, EJI). The Blood paper additionally resulted in an invited author-view in OncoImmunology (IF=6, in press). The PNAS article was awarded "Best article from OUH" for the 1st half and the Blood paper for the 2nd half of 2014 (100 000NOK). Two filed patent applications.

NATURAL KILLER CELL BIOLOGY AND CELL THERAPY

/

Group leader
Karl-Johan Malmberg

PHOTO BY TERJE HEIESTAD

ABOUT

The group counts 16 members (50% women); 1 full professor (KJM), 2 scientists, 4 postdocs, 5 PhD students, 2 engineers, 2 master students. Four members have MD background. Malmberg is a visiting Professor at the Karolinska Institutet (KI) and the group is partner of the K.G. Jebsen Center for Cancer Immunotherapy (2013–) and three focus area centers in Immunotherapy and Regenerative Medicine at both KI and OUH. The main focus is to develop new strategies for cell-based immunotherapy based on insights into the molecular regulation of natural killer (NK) cells.

AIMS

1. To gain insights into how killer cell immunoglobulin-like receptors (KIR) influence the function of human NK cells. We combine high-dimensional single cell assays with immune informatics to examine the dynamic shaping of human NK cell repertoires during viral infection, tumor transformation and following stem cell transplantation.

2. To implement new insights into the adaptive behavior of NK cells in the next generation of NK cell-based immunotherapy for patients with refractory or relapsing malignancies.

PROJECTS

- Deciphering the functional regulation of NK cells
- Integrative profiling of NK cell repertoire diversity
- Harnessing adaptive NK cells in cancer therapy

RECENT ACHIEVEMENTS

7 original articles accepted for publication with Malmberg as senior author on 3; 4 in journals with IF=10 (Bloodx2, Immunity, Gut) and 1 in J Immunology. Participated as expert reviewer for the NIH: RFA-AI-14-012/013 "HLA and KIR region genomics in immune-mediated diseases". One patent application concerning a novel platform for selective expansion of adaptive NK cells.

IMMUNOMODULATION AND TARGETED THERAPIES

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Group leader
Mouldy Sioud

PHOTO BY TERJE HEIESTAD

ABOUT

The group counts 5 members; 1 senior scientist, 2 engineers, 1 PhD student and 1 veterinary student. Since 97 Sioud has been a visiting professor in immunology and molecular biology at the University of Tunis. The main thematic areas are immunotherapy and gene technology. Both cell and molecular biology techniques are used, including RNAi technology, peptide phage libraries, scFv antibody libraries, and various prokaryotic and eukaryotic expression platforms. Animal studies are done in collaboration with Dr. Qian Peng (Department of Pathology-OUH) and Prof. Dietmar Abraham (University of Vienna, Austria).

AIMS

To engineer new therapeutic proteins, enhance dendritic cell function, and identify new cell surface markers. Recent research in the group has lead to the discovery of new targeting peptides used worldwide, the development of better cancer vaccines and therapeutic siRNAs without off-target effects. Cancer patients treated with one of the optimized cancer vaccines that we have developed together with Dr. Gunnar Kvalheim (Dept. Cell Therapy-OUH) showed objective clinical responses. Notably, we have significantly contributed to the understanding of RNA sensing by the immune system, as well as the response of human hematopoietic stem cells to infection [Sioud, 2006, Trends Mol. Med. (IF=10.1), Sioud 2006, Nature Biotech (IF=39), Sioud 2007 ADRR (IF=12.7)].

PROJECTS

- Block inhibitory pathways in the immune system and tumor microenvironment via RNAi
- Engineer new targeted therapeutic proteins and better vaccine formulations

RECENT ACHIEVEMENTS

- Optimized dendritic cell cancer vaccines (Hum Vaccin Immunother. 2014)
- New targeting peptides for antigen delivery (FASEB J. 2013)
- New signaling pathway for microRNA via TLRs (J Innate Immun. 2014)
- New mucosal cancer vaccines (Human Vaccin Immunother. 2015)
- New peptide-Fc fusion proteins for cancer therapy (submitted)
- So far the group has published 178 PubMed-indexed papers, including 10 papers in 2014-15. One filed patent and 1 book on RNAi technology edited by Sioud in 2014.

LYMPHOMAS AND LYMPHOCYTE BIOLOGY

/

Group leader
Erlend Bremertun Smeland

PHOTO BY TERJE HEIESTAD

ABOUT

The group consists of 12 members with research background in medicine, biology, biochemistry and biotechnology, and includes 1 professor (EBS), 1 assistant professor (JHM), 1 senior scientist (50% position), 5 postdocs, 3 PhD students and 1 technician. Four of the members are recruited from abroad (USA, China, Switzerland, Sweden), and 75% are women. The group is partner of a Centre of Excellence, Centre for Cancer Biomedicine (CCB). We focus our research on B-cell lymphoma, a malignancy originating from B cells of the immune system. B-cell lymphoma is a heterogeneous group of diseases, and even patients with identical diagnosis can have remarkably variable prognosis. Although new therapeutic approaches have improved overall survival for many lymphoma types, some types are still considered incurable.

AIMS

To identify biomarkers and to develop novel therapeutic strategies in B-cell lymphoma.

PROJECTS

- Proteomics characterization of tumor cells and tumor microenvironment in follicular lymphoma (FL), mantle cell lymphoma (MCL) and diffuse large B-cell lymphoma (DLBCL) by use of immuno-histochemistry, flow cytometry and CyTOF
- Characterize how crucial mutations affect drug responsiveness in B-cell lymphoma (through drug assays, phospho-specific flow cytometry and genetic manipulation)
- Identify abnormal cell signaling in MCL by phospho-specfic flow cytometry
- Exome and RNA sequencing project in diffuse large B-cell lymphoma to identify recurrent mutations associated with therapy relapse
- Exome and RNA sequencing to describe clonal evolution and disease progression in serial biopsies of FL

RECENT ACHIEVEMENTS

- Ten publications with 7 as first and 2 as last author (1 in Blood) and coauthorship in top Journals (1 Nature, 1 Cancer Disc)
- *1 paper awarded best OUH paper*: Brodtkorb et al. Blood 2014; Whole-genome integrative analysis reveals expression signatures predicting transformation in follicular lymphoma
- 2 PhD dissertations (M. Brodtkorb April 2014 and N. Bethge June 2014)
- 1 new DOFI

MOLECULAR CELL BIOLOGY

/
Headed by
Harald Stenmark

The department has a staff of about 60 and hosts 4 research groups and 7 project groups. It was previously known as Department of Biochemistry and has recently acquired the Skarstad group from the previous Department of Cell Biology. Research in the department comprises various aspects of cancer relevant cell biology, including membrane traffic, receptor signalling, and cell division. A common goal for researchers in the department is to uncover novel molecular mechanisms that control cellular functions related to cancer. The department's research strategy is to combine molecular cell biology with biochemistry and advanced imaging in order to address relevant scientific questions. Recent key achievements from the department's scientists include the identification of novel molecular mechanisms for control of DNA replication, cell division, growth factor signalling, cell migration, and intracellular transport. In general, the department's groups have been successful in obtaining national and international external funding. The groups of Stenmark, Sandvig and Wiedlocha are associated with a Centre of Excellence (Centre for Cancer Biomedicine), and Kirsten Sandvig heads a national project on Biodegradable Nanoparticles in Cancer Diagnosis and Therapy.

PHOTOS BY TERJE HEIESTAD

CELLULAR MEMBRANE DYNAMICS

/

Group leader
Harald Stenmark

PHOTO BY TERJE HEIESTAD

ABOUT

The group has 28 members, of which 12 are of foreign nationalities. The main focus is the dynamics of cellular membranes and their relevance to cancer. Cellular processes studied by the group include endocytosis, autophagy, and cell division. Initially focusing on the membrane lipid phosphatidylinositol 3-phosphate (PtdIns3P) and its downstream effectors, the group has also contributed to our understanding of how the endosomal sorting complex required for transport (ESCRT) machinery controls processes as different as receptor downregulation and sealing of the nuclear envelope during mitotic exit. The group employs standard and advanced molecular biology methods in combination with biochemistry and imaging technologies such as electron microscopy, live-cell microscopy, confocal microscopy and super-resolution microscopy. As model systems it uses cell cultures, organoid models, fruit flies and zebrafish.

AIMS

The principal aim of the group is to understand how membrane dynamics contribute to tumour suppression and how their dysfunction may promote cancer development.

PROJECTS

- Mechanisms of carcinogenesis
- Endocytosis in control of tumour suppression and promotion
- Tumour-microenvironment interactions
- Control of cell polarity by membrane dynamics
- Centrosome dynamics in cancer
- Cytokinesis in development and carcinogenesis
- The β-catenin destruction complex in physiology and cancer
- Membrane dynamics in promotion of genome integrity

RECENT ACHIEVEMENTS

The group has recently contributed to our understanding of how cytokinesis, the final step of the cell division process, is regulated. In 2014, PhD student Sigrid Bratlie Thoresen and her co-workers identified a novel component of the cytokinetic abscission checkpoint, ANCHR, and characterized its mechanism of action (Thoresen et al., Nature Cell Biology, 2014). The finding that ANCHR is required to prevent accumulation of cells with abnormal chromosome numbers (aneuploidy) makes it interesting in the context of tumour suppression.

INTRACELLULAR TRANSPORT

/

Group leader
Kirsten Sandvig

PHOTO BY TERJE HEIESTAD

ABOUT

Sandvig's group, counting 17 members from six 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 on membrane traffic, and which can be used as agents in cancer diagnosis and therapy. Our expertise is also applied to investigate uptake of nanoparticles, and in 2013 we obtained a five year grant from the Norwegian Research Council to build national competence in nanomedicine. This project, "Biodegradable nanoparticles in cancer diagnosis and therapy", headed by Sandvig, involves collaboration with ten other Norwegian groups working in academia, research institutes, hospitals and industry. We also characterize 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. The work published by the Sandvig group is well cited, and Sandvig's H-index is now 68 (~300 publications). The group has extensive national and international collaboration.

AIMS

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.

PROJECTS

- Characterization of intracellular transport
- Biodegradable nanoparticles in cancer diagnosis and therapy
- Exosomes and prostate cancer

RECENT ACHIEVEMENTS

Sandvig received in 2014 "The Fridjof Nansen Award for outstanding research in science and medicine". In 2014 the group published 12 articles, two PhD students completed their degrees, and four master students obtained their M.Sci. degrees during the year. The work on exosomes from prostate cancer patients resulted in 2014 in a DOFI and the patent application was submitted in January 2015.

DNA REPLICATION AND CHROMOSOME DYNAMICS

/

Group leader
Kirsten Skarstad

PHOTO BY TERJE HEIESTAD

ABOUT

The group has 6 members. Stability of the genome is important to prevent development of cancer. We study proteins which act on DNA in order to discover the mechanisms by which DNA is replicated, moved and repaired. Of special interest is replication fork collapse which contributes to genome instability, and also how initiation of replication and segregation are controlled and coordinated with cell growth. Most of our projects are basic science projects using the model organism Escherichia coli.

AIMS

The principal aim is to increase the knowledge about DNA transactions and use this knowledge to combat disease.

PROJECTS

- Mechanisms of replication fork collapse and repair
- The roles of the beta clamp and PCNA proteins in replication fork rescue
- The roles of SeqA, topoisomerases and Dam methylase in stabilization of the replication fork and daughter chromosome segregation
- The roles of the DnaA initiator protein and RNA polymerase transcriptional activity in control of replication frequency

RECENT ACHIEVEMENTS

The SeqA protein organizes newly replicated DNA in a large stabilizing complex. The complex keeps the new DNA at a distance from the replication fork and contributes to proper segregation of DNA to the daughter cells (Fossum-Raunehaug et al., PLoS One, 9(10):e110575).

Although the SeqA structures trail the replication forks at a distance, the two sister SeqA structures were kept close together indicating that they may form a barrier through which precatenanes will not diffuse. The stretch of DNA between the SeqA structures and the replisome will thus form a defined substrate for topoisomerases. In addition the result means that homologous DNA molecules are kept in close proximity to each other facilitating recombination and repair (Helgesen, et al., Nucleic Acids Res (in press).

During the E. coli DNA damage response the DNA is extensively repositioned and more compacted than normal. We find that the main actor in this process is the SMC protein RecN (Odsbu and Skarstad, Microbiology 160(Pt 5):872-82).

PROTEIN INTERNALIZATION AND SIGNALLING

/

Group leader
Antoni Wiedlocha

PHOTO BY TERJE HEIESTAD

ABOUT

The group is composed of 6 members from 3 nationalities. Maintenance of tissue homeostasis depends on complex intercellular growth factor- mediated signaling networks that control basic cell functions. The fibroblast growth factor (FGF) signaling system represents one of the fundamental tools of such cell to cell communication. The FGFs-FGFRs signaling system exerts a powerful combination of biological effects during development and in maintaining a malignant phenotype. FGF signaling is strongly oncogenic once the tight regulation on its physiological function is lost; it is enabled to be a central driver of tumor progression. FGFs as well as their receptors are frequently and abundantly expressed in various cancers and recognized as mediators of the epithelial-mesenchymal transition, tumor cell survival, migration/metastasis and neoangiogenesis, Therefore, the interest of FGF-induced signaling as a promising target for cancer therapy has systematically been increasing.

AIMS

The main goal of the research group is to elucidate differences in mechanisms of signaling induced by FGF in normal cells and in tumour cells.

PROJECTS

- Activation and termination of FGF-FGFR induced signaling
- Endocytosis, sorting and intracellular transport of FGF1 and FGFRs
- Mechanisms of FGF-induced cancer cell migration
- Identification of new interaction partners involved in regulation of FGF-induced signaling

RECENT ACHIEVEMENTS

We propose a novel feedback mechanism for FGFR1 activity through active RSK2.These findings indicate the FGFR1-RSK2 signaling loop as a potential target in cancer therapy (Nadratowska al., Oncogene, 2014).

We explore the role of the FGF1-nucleolin interaction in intracellular trafficking of FGF1 and demonstrate that nucleolin regulates phosphorylation of FGF1 and thereby regulates nuclear export of FGF1 (Sletten et al., PLoS One, 2014). We demonstrated that PIKfyve (phosphoinositide 5-kinase, FYVE finger containing) and MTMR3 (myotubularin-related protein 3), together with PtdIns5P are important for cell migration. Thus PIKfyve and MTMR3 could represent novel therapeutic targets in metastatic cancer (Oppelt et al., Biochemical Journal, 2014). Deregulated FGFR4 signalling has been associated with the progression of a number of types of cancer. We have developed photoactivation approaches to directly visualize FGFR trafficking and use them to show that recycling of FGFR4 is Rab11 dependent (Haugsten et al., Traffic, 2014).

MOLECULAR ONCOLOGY

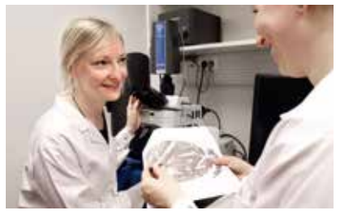
/
Headed by
Ragnhild A. Lothe

The department is the youngest at the ICR, established in May 2006 as Cancer Prevention and recently renamed Molecular Oncology (MO). The staff includes 3 research groups and 1 project group with a total of 36 employees and 5 master students. In the first 5 year period we systematically built a trans-disciplinary competence through recruitment and education, and established a broad range of state-of-the-art technologies. Two of the ICR´s youngest group leaders were appointed to the department in 2010 and 2012. As part of the research quality, we emphasize work satisfaction and the department has had the highest possible score in the three employee surveys from South-East Health Regional authorities. The three group leaders are P.I.s and in the management of the Centre of Excellence for Cancer Biomedicine (2007-17), the Norwegian Innovation Centre for Cancer Stem Cells (2007-14), the K.G. Jebsen Colorectal Cancer Research Centre (2014-18), and the OUH Priority Area for Colorectal Cancer (2014-18). The groups are also partners in the Norwegian Cancer Genomics Consortium and the Global Testicular Cancer Research Consortium.

The MO research activity comprises the molecular evolution of solid tumors, with particular focus on unsolved clinical challenges in colorectal cancer. Following high quality biobanking and development of protocols/study designs during the previous three years, the MO research strategy in the coming three years is in depth analyses of tumor heterogeneity and its potential implications for practical oncology.

During the last 3 years, we have published 83 papers, with 1st and/or last authorships on two-thirds. The mean IF = 7.4 in the 3 year period, including 7 papers with IF> 10. The MO total innovation activity include 13 patent applications, several innovation grants, and three signed license agreements, two with a British biotech company and one with a small Norwegian start-up company.

The group leaders are affiliated with the University of Oslo, holding professorships at the Institute for Biosciences, the Institute for Clinical Medicine, and the Institute for Informatics. The MO scientists teach at several PhD/MSc/undergraduate level courses, and 10 PhDs and 7 MSc have received their academic degrees during the last 3 years (2012-2014) with supervisors from MO.



PHOTOS BY TERJE HEIESTAD

GENETICS

/

Group leader
Ragnhild A. Lothe

PHOTO BY TERJE HEIESTAD

ABOUT

The group members hold expertise in cancer genetics, genomics, molecular cell biology, bioinformatics, and medicine. We collaborate actively with clinical partners to secure active translational research and are partners in the Norwegian Cancer Genomics Consortium. We work with various-omics approaches to identify clinically important molecular subgroups and to identify and develop prognostic and predictive biomarkers for selected malignancies. Last year, funding for translational colorectal cancer (CRC) research was supported by the K.G. Jebsen Foundation and OUH, granting us a research centre and 5 year priority area, respectively. The group has altogether 26 members, including the project group (8 members) of Edward Leithe.

AIMS

To identify important molecular changes in the complex dynamics of cancer development and to transfer such knowledge into practical oncology.

PROJECTS

- Molecular biology and identification of biomarkers for CRC and malignant peripheral nerve sheath tumors (MPNST)
- Genomic tumor heterogeneity and clonal evolution in space and time for CRC and ovarian cancer
- miRNA expression and function in CRC
- Ubiquitin system in intercellular communication and CRC pathogenesis
- Identification of drug targets and drug sensitivity by in vitro screens

RECENT ACHIEVEMENTS

During the last year our group has identified and validated prognostic biomarkers for CRC and for MPNST. Our gene signature for stage III CRC has particular clinical potential for elderly patients (Sveen at al., 2013 CCR), and is included in a recent protocol for a randomized clinical trial. In a large population representative series of CRCs, the prognostic potential of selected Wnt signaling factors and the cell cycle protein RCC2 was investigated (Bruun et al., Frontiers in Oncol, 2014; ClinCancerRes, 2015). RCC2 is a novel cancer biomarker, and the first to show prognostic value for both the MSI and MSS subgroups of CRC. For MPNST patients, methylated RASSF1A - an effector of KRAS signaling, had prognostic value for individuals with neurofibromatosis type 1 (Danielsen et al., Neuro-Oncol, 2014). Independent of NF1 status an expression profile of three proteins encoded by 17q genes identified patients with inferior prognosis even after assumed complete resection. Notably all three proteins are drug targets (Kolberg et al., Mol Oncol 2015). Seventeen papers were published in the period 2014–April 2015, four people received their academic degrees and Edward Leithe received the early career award from OUH in 2014.

EPIGENETICS

/

Group leader
Guro E. Lind

PHOTO BY TERJE HEIESTAD

ABOUT

In the group of Epigenetics we are studying DNA methylation alterations by integrating carefully selected methylome approaches with detailed candidate gene characterization. The research is performed across cancer types, but with a main focus on colorectal cancer. The group has all together six members. Two additional postdoctoral bioinformaticians have been recruited in 2015.

AIMS

1. To identify epigenetic biomarkers with clinical impact, including markers for early detection and monitoring of cancer.
2. To analyze and understand the underlying biology of these aberrations and how they affect the cancer development.

PROJECTS

- Epigenetic subclassification and prognostic markers for colorectal cancer
- Mechanisms of the DNA methylation machinery
- Methylome-based early detection and monitoring of urological cancers
- Epimutations and epigenetic drivers of tumor development

RECENT ACHIEVEMENTS

In addition to novel biomarkers in colorectal (Vedeld et al., Epigenetics) and gastrointestinal cancer (Vedeld et al., Int J Cancer) the group has the last year identified a DNA methylation biomarker panel for early detection of the rare malignancy cholangiocarcinoma (Andresen et al., Hepatology). Due to the late clinical presentation and high mortality, early detection of cholangiocarcinoma is valuable as more patients at Oslo University Hospital could qualify for curative treatment by liver resection or transplantation. This is the first biomarker panel that can accurately detect this disease by using minimally invasive biliary brush samples. The research has been done in collaboration with the NoPSC center. In collaboration with the Smeland group we have identified novel biomarkers for Non-Hodgkin lymphomas (Bethge et al., Epigenetics and PLoS One). These findings will be followed up in a newly established collaboration with NIH.

During 2014, three MSc- and two associated PhD-students graduated from the group. For the fifth year, the PI Guro Lind is leading an inter-faculty course in Advanced Cancer Biology at the University of Oslo. Lind received the early career award from Oslo University Hospital in 2013 and a Young Researcher Talent grant from the Research Council of Norway in 2014.

GENOME BIOLOGY

/

Group leader
Rolf Skotheim

PHOTO BY TERJE HEIESTAD

ABOUT

The Genome Biology group studies how genomes and transcriptomes are altered in cancer cells by using both computational biology and wet-lab based approaches. Mutation analyses in cancer clearly benefit from knowing which genes and variants that are actually expressed. In this line, the group has particularly specialized in RNA-level analyses, and the projects focus on prostate, testicular and colorectal cancers. An interdisciplinary set of competences is required to perform meaningful genome-scale cancer research. As such, personnel in the group have their basic education across the disciplines of biology, informatics, and medicine. The group has all together nine members including 2 master students.

AIMS

The research aim is to identify and characterise genes that are critical for the development of cancer. Such genes may serve as diagnostic or prognostic biomarkers and as targets for future molecularly tailored therapy.

PROJECTS

- Genome-based prostate cancer biomedicine
- Fusion transcripts and other qualitative RNA variation in cancer
- Modelling heterogeneous solid tumours from multi-omics data

RECENT ACHIEVEMENTS

During 2014, Marthe Løvf defended her PhD thesis, «Detection of fusion genes and novel RNA variants in cancer». We have established bioinformatics pipelines for high-throughput sequencing data, and during the past year, we have published on both exome-sequencing and RNA sequencing. Our exome-sequencing study was the first such publication on testicular germ cell tumours. This revealed a low mutation frequency, resembling that of childhood cancers, and that bilateral testis cancers have independent developmental lineages (Brabrand, Johannessen et al., Neoplasia 2015). RNA-sequencing of colorectal cancers revealed novel fusion transcripts and splice variants of the WNT-effector *TCF7L2* (Nome, Hoff et al., PLoS ONE 2014). Further, we have identified a novel transcript, *VNN1-AB*, as a biomarker for colorectal cancer (Løvf et al., Int. J. Cancer 2014). Finally, we have identified transcriptome instability as a common characteristic of solid cancers, including prostate and colorectal (Sveen et al., BMC Genomics 2014).

PHOTO BY TERJE HEIESTAD

RADIATION BIOLOGY

/
Headed by
Kristian Berg

The Department has more than 60 employees organized in 5 research groups. The research at the department is focused on the biological responses to electromagnetic radiation, including γ-radiation, ultraviolet radiation and visible light. Our department is actively engaged in revealing the mechanisms involved in DNA repair, cell-cycle regulation and genomic instability after radiation, the impact of hypoxia on radioresponse and predictive markers for the radiosensitivity of neoplastic tissue. Another research area is the use of visible light to activate photosensitive compounds that are used for cancer detection and therapy. In that respect a technology has been developed, photochemical internalization (PCI), which may be utilized for site-directed intracellular delivery and activation of therapeutics into cancer cells. This technology induces reactive oxygen species that has similarities to the biological response to ionizing radiation. The department is also involved in revealing the impact of solar radiation on cancer development and protection by UV-induced vitamin D formation.

Our vision is to develop a radiobiological understanding of response to ionizing and non-ionizing radiation on the molecular, cellular and physiological level, and to utilize this knowledge to design new strategies for the treatment of cancer. Our research strategy involves basic radiobiological research, translational and clinical studies.

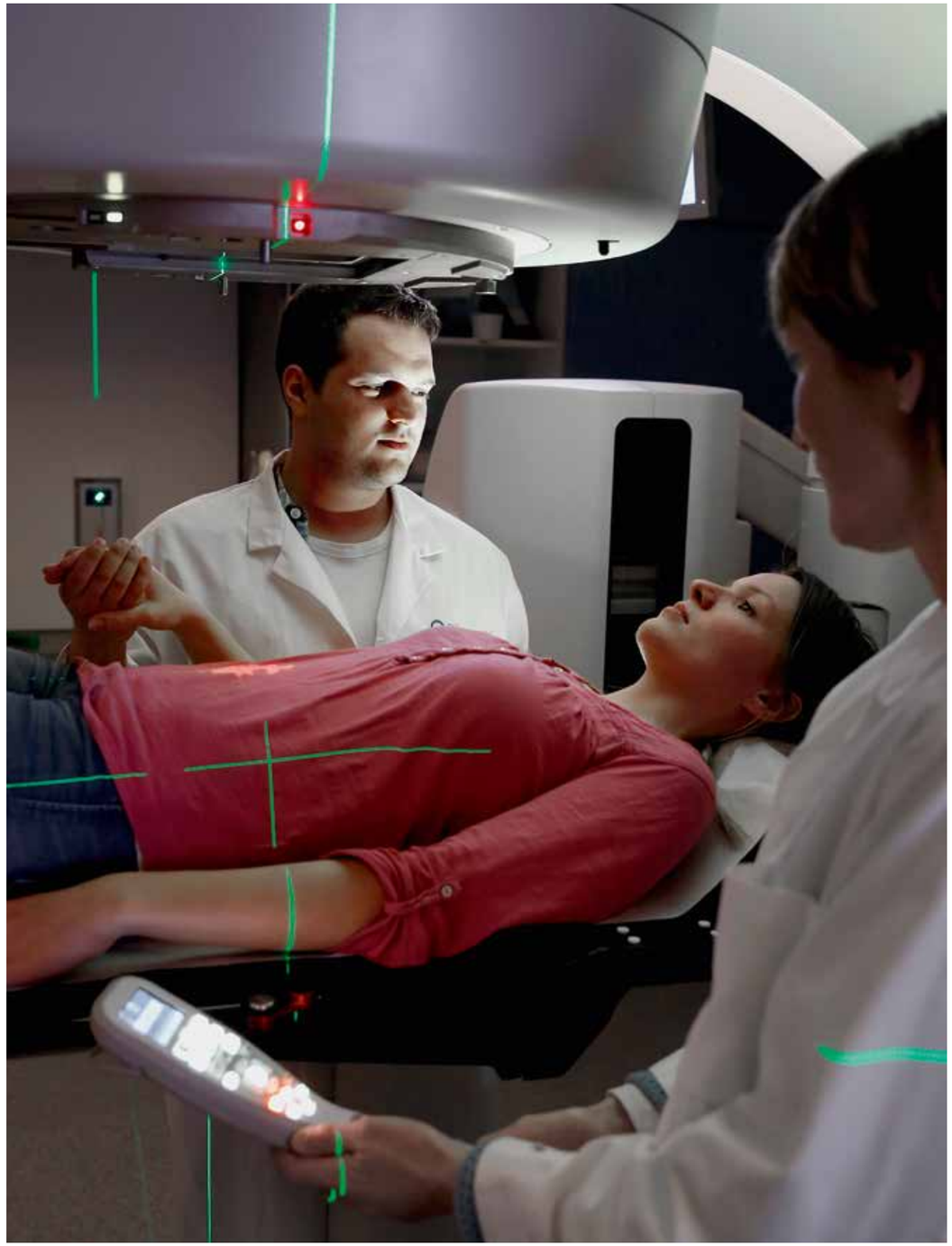
OUR GOALS ARE

- to understand the molecular and physiological mechanisms behind tumour response to radiation, and to develop predictive methods and treatment strategies
- to utilize aquired knowledge to establish new radiation-based treatment regimens with improved specificity and efficacy towards malignancies
- to develop treatment strategies utilizing non-ionizing radiation combined with photosensitizing agents, either to induce tumour cell kill directly or via internalization of therapeutic or sensitizing agents

KEY ACHIEVEMENTS THE LAST 3-4 YEARS INCLUDE

- Novel theory has been established explaining apparently conflicting clinical observations on associations between lymph node metastasis and tumor interstitial fluid pressure, hypoxia, and microvascular density.
- The efficacy of CHK1-inhibitors has been found to increase after reoxygenation following hypoxia.
- PCI has been found efficient as a methodology to enhance antigen presentation during anti-cancer vaccination.
- A prognostic hypoxia biomarker has been found for patients with cervical cancer.
- A G1-S checkpoint has been identified in fission yeast which is not only dependent on the DNA repair capacity of repair-deficient cells, but also the nature of the repair deficiency.

PHOTOS BY TERJE HEIESTAD



PHOTOCHEMICAL INTERNALIZATION

/

Group leader
Kristian Berg

PHOTO BY TERJE HEIESTAD

ABOUT

Group members: 12, including 3 researchers, 1 postdoc and 5 PhD students

Photochemical internalisation (PCI) is a novel technology for release of endocytosed macromolecules into the cytosol. The technology is based on the use of photosensitizers located in endocytic vesicles that upon activation by light induce rupture of the endocytic vesicles and thereby release of the macromolecules into the cytosol. PCI has been shown to enhance the biological activity of a large variety of macromolecules and other molecules that do not readily penetrate the plasma membrane, including type I ribosome-inactivating proteins (RIPs), gene-encoding plasmids, adenovirus and oligonucleotides. For clinical utilization a novel photosensitizer has been developed and evaluated for PCI of bleomycin. PCI is currently evaluated in 2 phase I and II clinical trials.

AIMS

The main aim of our group is to develop and optimize the PCI technology for treatment of solid cancers with a curative endpoint.

PROJECTS

- Design and develop recombinant immunotoxins based on type I ribosome-inactivation protein toxins to achieve high treatment efficacy and specificity
- Reveal the potential of the PCI technology as a treatment option for therapy resistant cancers, including cancer stem cells
- Utilize new vehicles for targeted delivery of small molecular drugs to endocytic vesicles for activation by PCI
- Evaluation of the vasculature as a target for PCI treatment and seek treatment options to further utilize these effects to reach a curative endpoint
- Document and utilize the anti-tumor immunity potential of the PCI technology;
- Develop PCI as a strategy for boosting anti-cancer vaccines

RECENT ACHIEVEMENTS

No. of papers in 2014: 13

Papers of special importance

1. EGF was found to be a superior ligand in recombinant fusion constructs for PCI-induced delivery of the protein toxin gelonin (Berstad et al., Oncogene in press)
2. PCI was found highly efficient to deliver and activate tamoxifen caged by cyclodetrin to estrogen receptor positive breast cancers (Theodossiou et al., Angewandte Chemie Int. Eds. in press)
3. Photosensitisation facilitates cross-priming of adjuvant-free protein vaccines and stimulation of tumour-suppressing CD8 T cells. (Håkerud et al., Journal of Controlled Release, 2014).

PROJECT GROUP PHOTOBIOPHYSICS

Project leader Asta Juzeniene

ABOUT

This project group with 4 members has been added to Prof. Berg's research group following the restructuring of the Institute in in 2014 and the retirement of group leader Johan Moan. Solar ultraviolet (UV) radiation is the main source of vitamin D production and also the most important environmental risk factor for skin cancer development. Vitamin D deficiency is a causal risk factor for several types of cancer. Since the dominant source of vitamin D is UV exposure, there is a need to understand what a balanced level of sun exposure is to maintain an adequate level of vitamin D with a minimal risk for skin cancer.

AIMS

We want to contribute improving the public health strategies regarding sun exposure, skin cancer, vitamin D status and sun protection.

PROJECTS

- Cutaneous vitamin D synthesis versus skin cancer development
- The role of UV radiation in melanoma development, progression and metastasis
- Vitamin D levels and cancer
- Skin cancer epidemiology

RECENT ACHIEVEMENTS (2014)

One PhD thesis defended (Emanuela Micu, "Solar radiation and melanoma epidemiology in Norway").

Four scientific publications in 2014.

CELL-CYCLE REGULATION IN EUKARYOTES

/

Group leader
Erik Boye

PHOTO BY TERJE HEIESTAD

ABOUT

Group members: 10.5, including 2 researchers, 3 postdocs, and 2 PhD students

THEME

To characterize the molecular mechanisms regulating cell-cycle progression in the model organisms yeast and mammalian cells in culture. The methods used are molecular genetics, cell synchronization, flow cytometry and different in vitro analyses.

AIMS

Our main interest is the G1-S transition, which is central in cancer development. We are characterizing a checkpoint that we discovered a few years ago (Genes Dev 2007, PNAS 2012) and which involves the kinase Gcn2 and also affects protein translation. Our aims are to fully understand the molecular interactions involved, including the activation mechanism of Gcn2 and its role in cancer.

PROJECTS

- Regulation of the G1-S transition in fission yeast cells
- Regulation of the G2-M transition in fission yeast cells
- Regulation of the G1-S transition in mammalian cells
- Regulation of translation after stress
- The function of Gcn2 in cancer

RECENT ACHIEVEMENTS

Three PhD theses defended (Knutsen, Anda, Rødland) and two MSc degrees.

Two scientific publications in 2014:

Rødland, G.E., Tvegård, T., Boye, E. and Grallert B. Crosstalk between the Tor and Gcn2 pathways in response to different stresses. Cell Cycle, 13, 453-61(2014)

Anda, S., Boye, E. and Grallert, B. Cell-cycle analyses using thymidine analogues in fission yeast. PLoS ONE e88629. doi: 10.1371 (2014)

Three popular science articles.

CLINICAL RADIATION BIOLOGY

/

Group leader
Heidi Lyng

PHOTO BY TERJE HEIESTAD

ABOUT

Group members: 8, including one researcher, 4 postdocs and one PhD student

THEME

To develop molecular biomarkers that can identify patients at risk of radiotherapy failure and to find targets for therapeutic intervention in a combined radiotherapy regimen. The research projects are run in close collaboration with clinicians. The work is based on tumor biopsies and blood samples collected at diagnosis or during therapy. Whole genome methodology is used, including microarray and sequencing techniques, which provides new insight into the disease and enables identification of novel biomarkers and drug targets. In collaboration with Department of Medical Physics, we also explore whether functional tumor images (MRI/PET) can aid the translation of the molecular findings into radiotherapy practice.

AIMS

- Understand molecular mechanisms behind radioresistance of cervical and prostate cancers
- Develop biomarkers and find drug targets for personalized radiotherapy of patients with these diseases

PROJECTS

- Genetic alterations and chemoradioresistance of cervical cancer
- Molecular hypoxia biomarkers in cervical and prostate cancer
- Combined molecular and imaging biomarkers in cervical and prostate cancer

RECENT ACHIEVEMENTS

Publications in 2014: 4

Selected paper: Ragnum HB, Vlatkovic L, Lie AK, Axcrona K, Julin CH, Frikstad K-AM, Hole KH, Seierstad T, Lyng H. The hypoxia marker pimonidazole reflects a transcriptional program associated with aggressive prostate cancer. British Journal of Cancer, 112, 382-390, 2015, Epub 2014.

PhD thesis in 2014: 1
Harald Bull Ragnum: “Hypoxia in prostate cancer: Gene expression profiling in relation to disease aggressiveness and treatment intervention.”

Patent application submitted in 2014
“Prognostic gene methylation test for cervical cancer”, (US 61/928,120).

RADIATION BIOLOGY AND TUMOR PHYSIOLOGY

/

Group leader
Einar K. Rofstad

PHOTO BY TERJE HEIESTAD

ABOUT

Group members: 9, including 2 researchers, 3 postdocs, 2 PhD students and 2 technicians.

The focus of the group is to reveal mechanisms causing tumor resistance to radiation therapy. The research is based on the hypothesis that radiation resistance is primarily a consequence of microenvironmental abnormalities in the tumor tissue. Xenografts of human cervical carcinoma, pancreatic carcinoma, malignant melanoma, and soft tissue sarcoma are used as preclinical tumor models. In addition to standard molecular biology methods, important methods include intravital microscopy, magnetic resonance imaging, and probe measurements of physiological parameters.

AIMS

The main aim is to develop strategies for personalized radiation therapy of cancer to improve the outcome for patients with treatment-resistant tumors. To reach this goal, the research is divided into two arms with the following aims:

- To develop MRI-based methods that can provide information on the physiological micro-environment of tumors and, hence, biomarkers of tumor radiocurability.
- To develop antiangiogenesis-based treatment strategies for normalizing the physiological micro¬environment of tumors and, hence, enhancing the effect of radiation therapy.

PROJECTS

- Mechanisms Governing the Microenvironment and Radiocurability of Tumors
- Interstitial Fluid Pressure and Hypoxia in Tumors: Causes and Consequences
- Preclinical and Clinical Magnetic Resonance Imaging
- Antiangiogenic Treatment of Experimental Tumors

RECENT ACHIEVEMENTS

The group published 6 papers in 2014.
A paper published in Neoplasia presented a novel theory explaining apparently conflicting clinical observations on associations between lymph node metastasis and tumor interstitial fluid pressure, hypoxia, and microvascular density. Moreover, we showed in 2012 that peritumoral interstitial fluid flow velocity (V_0) measured by magnetic resonance imaging correlates with interstitial fluid pressure in tumors. In 2014, we published a paper in Radiotherapy and Oncology showing that V_0 predicts survival in cervical carcinoma, independent of established prognostic factors.

RADIATION BIOLOGY AND DNA DAMAGE SIGNALING

/

Group leader
Randi G. Syljuåsen

PHOTO BY TERJE HEIESTAD

ABOUT

Group members: 12.5, including 3.5 researchers, 3 postdocs and 2 PhD students.

Ionizing radiation is used to cause DNA damage in cancer cells. The DNA damage is rapidly sensed and a network of intracellular DNA damage signaling cascades is activated. These signaling cascades influence whether the cells die or survive, through regulation of DNA repair, cell cycle checkpoint and cell death pathways. Our group works on the border between basic and translational radiation research. We conduct basic projects to identify novel mechanisms of DNA damage checkpoint signaling, in addition to more applied projects to understand how inhibitors of checkpoint signaling can be used in an optimized manner for cancer treatment. In the beginning of 2015 the Molecular Radiation Biology group was merged into this group.

Methods: We study human cancer and normal cell lines and use many different techniques including immunofluorescence microscopy and live cell imaging, multiparameter flow cytometry, immunoblotting, immunoprecipitation, protein overexpression, siRNA transfection, hypoxia treatment, X-ray irradiation, and robot-automated flow cytometry large-scale screening.

AIMS

Obtain new knowledge about DNA damage signaling, with focus on the S and G2 checkpoints, and explore how such knowledge can be used to improve cancer therapy.

PROJECTS

- Pre-clinical exploration of checkpoint kinase inhibitors (Chk1, Wee1, Atr, Plk1) as a strategy for cancer treatment in normoxic and hypoxic cancer cells in the absence and presence of ionizing radiation.
- The functional role of Protein phosphatase 1 (PP1) targeting subunits in regulation of checkpoint signaling after radiation.
- Identification of novel regulators of DNA damage signaling through flow cytometry-based large-scale compound screens.
- The function of the centrosome and selected centrosomal proteins in cell cycle regulation and genome integrity.

RECENT ACHIEVEMENTS

Number of articles in 2014: 4

Selected articles

1. C. Lund-Andersen, S. Patzke, V. Nähse-Kumpf, R.G. Syljuåsen. ”Plk1-inhibition can cause radiosensitization or radioresistance dependent on the treatment schedule” Radiation Therapy and Oncology, 110, p.355-361, 2014.
2. J. Sternemalm, H. G Russnes, X Zhao, B Risberg, S. Nord, C. Caldas, A. L Børresen-Dale, T. Stokke, S. Patzke. “Nuclear CSPP1 expression defined subtypes of basal-like breast cancer” British Journal of Cancer, 111, 326–338, 2014.

PhD completed in 2014

C. Lund-Andersen “The radiation-induced G2 checkpoint: impact on genome stability and cancer treatment”

New grants in 2014

In 2014 our group was awarded new grants from the Norwegian Cancer Society and from the EEA Czech-Norwegian Research Programme.

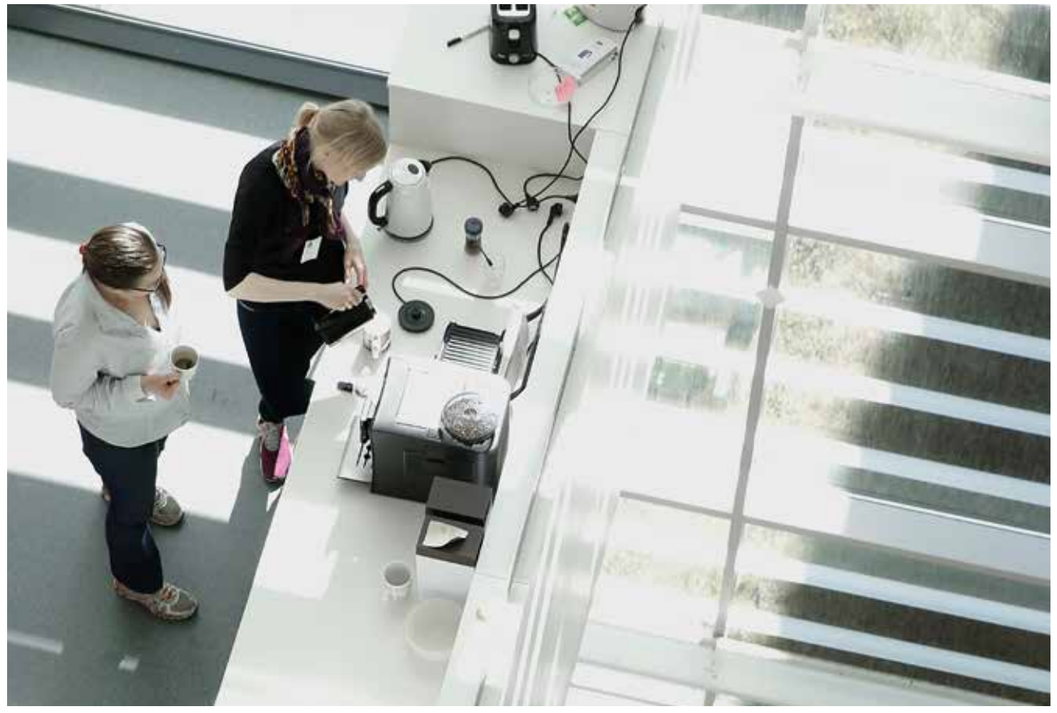


PHOTO BY TERJE HEIESTAD

TUMOR BIOLOGY

/
Headed by
Gunhild M. Mælandsmo

The department has 4 research groups and 52 employees, with a common vision to better understand the biological mechanisms involved in cancer development, progression and metastasis, and to utilize this knowledge to improve cancer treatment.

We are mainly performing translational research, and the main pillars in our research program are cancer genomics, computational science and investigations on biological mechanisms underlying metastatic progression. Our ambition is to identify candidate biomarkers and therapeutic targets, followed by validation in preclinical models and clinical trials.

To foster high quality translational research we emphasize a close collaboration with clinical scientists, and have several researchers holding part-time clinical positions. Another prerequisite for the ongoing research is a huge collection of patient-derived tumour models established from different types of human cancer. The models are utilized for biological studies of disease progression, and for preclinical evaluation of novel drugs and drug combinations. We expect such patient-derived xenografts (PDX) to be crucial for clinical translation of precision medicine and the department aims to actively participate in this effort. In that regard it will be of high priority to maintain the national and international networks and collaborations as mentioned below.

Key achievements over the last 3-4 years include external funding of several large collaborative projects in the area of precision oncology:

NCGC
The Norwegian Cancer Genomics Consortium, funded by The Research Council of Norway, (RCN), a national project aiming to sequence tumors across nine tumor types

NoSarC
Norwegian Sarcoma Consortium, funded by The Norwegian Cancer Society (NCS), a national project studying disease development and treatment of sarcoma

MetAction
Actionable targets in cancer metastasis (RCN), the first clinical trial in Norway offering targeted treatment based on biomarker detection in metastatic lesions

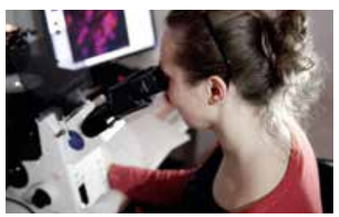
MOVEMBER
Identifying biomarkers distinguishing indolent and aggressive prostate cancer (NCS)

Other clinical intervention studies with substantial collateral research;

NeoAva
Bevacizumab in combination with neoadjuvant chemotherapy in breast cancer

I-BCT
DNA targeted chemotherapy to breast cancer patients with an aggressive phenotype

ImmunoPeCa
Immunotoxin in Peritoneal Carcinomatosis



PHOTOS BY TERJE HEIESTAD

METASTASIS BIOLOGY AND EXPERIMENTAL THERAPEUTICS

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Group leader
Gunhild M. Mælandsmo

PHOTO BY TERJE HEIESTAD

ABOUT

Employees: The group has 22 members with multidisciplinary background and experience as cell- and molecular biologists, medical doctors, physicists and animal technicians.

Research focus: Metastasis biology and therapeutic targets/experimental drugs.

Methodology: Molecular and functional analysis utilizing clinical samples, human cell cultures and in vivo models.

AIMS

Metastatic progression is the major clinical challenge and the principal cause of death in cancer patients. To combat metastatic cancer our goal is to understand the underlying biological mechanisms causing therapy resistance, invasion and re-growth. Knowledge on these processes is vital for identification of molecules that can be utilized as prognostic and predictive biomarkers or targets for therapy. We are mainly working with malignant melanoma, breast cancer and prostate cancer.

PROJECTS

1. *Basic research revealing mechanisms causing metastasis or treatment resistance*
   - Metastasis associated proteins and regulators, with special emphasis on tumor-stroma interactions and effects on invasion, metabolic state and immune responses
   - Cellular plasticity in disease progression
2. *Preclinical research evaluating novel drugs and drug combinations*
   - Efficacy and mechanistic studies in vitro and in vivo
   - Biomarker detection by molecular and functional (PET, MRS, MRI) techniques
3. *Clinical trials for precision medicine*
   - *NeoAva:* bevacizumab in combination with neoadjuvant chemotherapy for patients with locally advanced breast cancer
   - *I-BCT:* additional DNA-targeted chemotherapy to breast cancer patients with an aggressive phenotype
   - *MetAction:* Actionable molecular target identification in metastatic cancer patients for palliative targeted drug therapy

RECENT ACHIEVEMENTS

- *Metrics:* Group members were credited with 18 publications in 2014; 2 PhD degrees completed.
- Two clinical intervention trials were initiated (MetAction and I-BCT)
- *Papers that underscore our research activities:* Kristian, Acta Oncol 2014; Hidalgo, Cancer Discovery 2014; Bettum, Cancer Letters 2014; Haugen, Eur J Cancer 2014; Grytli, Eur Urol 2014; Skrbo PLosOne 2014; Lindholm Clin Cancer Res 2014; Grinde Breast Cancer Res 2014

TRANSLATIONAL CANCER THERAPY

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Group leader
Kjersti Flatmark

PHOTO BY TERJE HEIESTAD

ABOUT

The Translational Cancer Therapy group comprises 21 members; it was relatively recently established, and several projects are still in an early phase. Our strength is a broad variety of competencies spanning from basic biologists through translational scientists to clinicians; this year, 7 group members were MDs. The approach to research is translational, encompassing methods from biochemistry and cell biology, preclinical drug testing in animal models, biomarker studies in clinical cohorts and interventional clinical trials. Extensive collaboration has been established within the Institute, with clinical departments, nationally and internationally.

AIMS

Our long-term aim is to develop new prognostic and predictive biomarkers and implement improved cancer therapy using a collaborative, transdisciplinary, and translational approach.

PROJECTS

1. *Colorectal cancer (CRC)* – a majority of the projects in the group focus on locally advanced and metastatic CRC, involving basic, preclinical, translational and interventional clinical trials
2. *Cancer metastasis projects* – employ basic, translational and clinical methodology to identify and characterize factors of importance in the metastatic process
   - Exosomes in cancer metastasis
   - Experimental models and therapy in ovarian carcinoma
   - B7H3 protein in metastasis and therapy resistance
   - MetAction clinical trial – actionable targets in cancer metastasis
   - Brain metastasis project
3. *Sarcoma*
   - Gastrointestinal stromal tumors – therapy resistance and circulating DNA
   - NoSarC; DNA sequencing of annual cohorts of sarcoma patients in Norway

RECENT ACHIEVEMENTS

- Group members were credited with 14 publications in 2014; 1 PhD completed.
- Two clinical intervention trials were initiated (ImmunoPeCa and MetAction)
- Establishment of a public, revised database of all human miRNAs (MirGeneDB.org; http://invitro.hpc.uio.no/mirgenedb/)
- FRIPRO mobility grant was awarded one postdoctoral researcher (RCN/COFUND-Marie Curie Actions- FP7)
- Establishment of AcredIT regional (HSØ) research network (http://acredit.no/)
- Commercialization MOC31PE immunotoxin

COMPUTATIONAL CANCER GENOMICS AND MELANOMA SYSTEMS BIOLOGY

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Group leader
Eivind Hovig

PHOTO BY TERJE HEIESTAD

ABOUT

The group has strong interest in the development of computational approaches in cancer genomics in general, and in melanoma systems biology more specifically. Currently, activity is centered on computational aspects of deep sequencing pipelines for cancer, and downstream analysis. The lab biology focus is on understanding various aspects of melanoma, with an emphasis on the MITF master switch of melanocytes, and studies on key signaling systems in melanoma.

AIMS

The overarching approach is to feed the computational and wet-lab activities reciprocally, using high-throughput genomic technologies and computational modeling, to understand important signaling systems in melanoma. Another aim is to develop novel methodology for computational studies of cancer-related processes. The main wet-lab approach is the use of a well-characterized panel of melanoma cell lines representing different stages of melanoma progression, as well as normal melanocytes to chart causative molecular features. The group also uses lentiviral constructs to build lab models of melanoma. Among the computational aspects addressed are immune aspects of melanoma, chromatin, including 3D models of nuclear DNA, understanding of mutational processes and signal modeling.

PROJECTS

- The MITF transcriptional master switch of melanocytes. Use of lentiviral systems with bi-cistronic MITF constructs with ChIP-seq mapping of active signal pathways.
- Oncogene-induced senescence in melanoma by introduction of perturbation of signaling systems, including BRAF and CDKN2A aberrations. Understanding the consequences for modulation of immune responses.
- Approaching digital molecular pathology towards the immune system component of solid tumors. This is achieved by development of computational deciphering of transcription.
- Further development of statistical genomics based on our software, the Genomic HyperBrowser. This is an internationally used tool for multipurpose integrated statistical analysis of genomic data, that is being further developed.
- Implementation of computational aspects of sequencing towards diagnostics.

RECENT ACHIEVEMENTS

Publications: 12
PhDs completed: 3
Partner of SFI: Big insight for big data

MESENCHYMAL CANCER BIOLOGY

/

Group leader
Ola Myklebost

PHOTO BY TERJE HEIESTAD

ABOUT

The 14-member group has a long standing interest in the biology of mesenchymal tumours (sarcomas). The current focus is on precision medicine for these tumours, and Ola Myklebost is head of the Norwegian Cancer Genomics Consortium (NCGC, www.kreftgenomikk.no) and Norwegian Sarcoma Consortium (NoSarC, www.nosarc.no).

AIMS

As an overall approach, the group is combing genetic characterization by deep genomic analysis of patient material with preclinical investigation in cell cultures and human tumour models in mice. The generation and characterization of in vitro and in vivo sarcoma models make the framework for the pre-clinical analyses. Sarcomas are rare cancers, with poor treatment options, and can gain much from personalized cancer treatment. The choice of treatment would be based on the tumor's mutations, opening for the opportunity to use treatments currently approved for other cancers with similar mutations. The ultimate aim is to work towards future precision medicine for sarcomas.

PROJECTS

- Norwegian Sarcoma Consortium (NoSarC) - Biobanking and genomic characterization of patient material of 2-3 national cohorts of sarcomas, estimated to at least 500 samples. The project will provide unique, population-based datasets including the many rare subtypes of sarcomas.
- Preclinical investigation – Using in vitro and in vivo models to evaluate the therapeutic potential of drugs that target mutations identified in patient tumors.
- Sarcoma biology – Gaining further understanding of the development and progression of osteo- and liposarcomas, and potentially identify biomarkers and novel drug targets.
- Studies of metabolic reprogramming in sarcomas and during mesenchymal transformation of breast cancer.
- Implementation of sequencing in diagnostics.
- Exploration of "liquid biopsies", the detection of tumour-derived DNA in blood, to monitor disease progression and therapeutic markers.

RECENT ACHIEVEMENTS

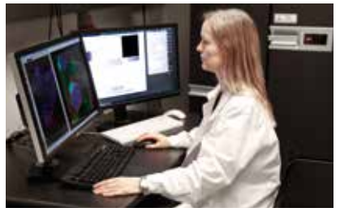
Publications: 9
PhDs completed: 1
Prizes: Prize for one of the best 12 publications from OUH, Håkelien et al.

CORE FACILITIES

/
Headed by
Leonardo A. Meza-Zepeda

PHOTO BY TERJE HEIESTAD

PHOTOS BY TERJE HEIESTAD



The core facilities within the Institute were from 2014 organized in a separate Department to improve function and visibility of the services provided by the different core facilities. The Department today runs seven regional core facilities financed by the Southern-Eastern Regional Health Authorities, providing advanced services to regional, national and international users. The Department of Core Facilities aims to deliver easy access to state-of-the-art advanced technologies, to improve research quality through assistance by experienced personnel and optimal choice of technology, and ultimately increase the scientific competitiveness of our users. The Department is organised in three units; Flow Cytometry and Pre-Clinical Imaging, Advanced Microscopy, and Genomics and Bioinformatics, with a total of 14 employees. More information at http://ous-research.no/corefacilities/

ADVANCED LIGHT MICROSCOPY

Ellen Skarpen

The Core Facility for Advanced Light Microscopy (ALM) offers services in various types of ALM, including confocal microscopy, live-cell microscopy and super-resolution microscopy. Current instruments include a Zeiss LSM710 confocal microscope, a DeltaVision live-cell microscope and an OMX Blaze structured illumination (and STORM) super-resolution microscope. The core facility cooperates with nodes at the Rikshospitalet and Ullevål campuses of Oslo University Hospital, as well as the light microscopy core facility at the Institute for Biosciences, University of Oslo. Services include training, courses, access to microscopes and microscopy performed by core facility personnel.

ADVANCED ELECTRON MICROSCOPY

Ellen Skarpen

The Core Facility for Advanced Electron Microscopy includes nodes at the Radium Hospital and Rikshospitalet, and provides service, training and access to microscopes for ultrastructural studies. The core facility offers a wide range of techniques including conventional plastic embedding, immune EM, correlative light/electron microscopy (CLEM), high pressure freezing and electron tomography. Our current instrumentation includes 3 transmission electron microscopes and sample preparation tools such as microtomes (cryo), high-pressure freezers and freeze substitution units. We actively cooperate with the imaging platform at the Institute for Biosciences, University of Oslo.

BIOINFORMATICS

Leonardo A. Meza-Zepeda

The Bioinformatics Core Facility provides service, support and advice on most aspects of bioinformatics, including a wide array of topics ranging from simple identifier mapping tasks to mathematical modeling of biological processes, sequence and sequencing data analysis, analysis protein structure, DNA variation, genetic linkage, microarrays, association studies, statistical genomics, database access, web services and network analysis. The complementary competence of the core facility personnel is backed by strong links to leading bioinformatics and biostatistics research groups in the region. The operation of the Bioinformatics Core Facility is aligned with the national and local Elixir bioinformatics infrastructure project, and also interacts with USIT, University of Oslo, for facilitating use of high-performance computing resources.

FLOW CYTOMETRY

Trond Stokke

The Flow Cytometry Core Facility (FCCF) provides analysis and sorting services for users within the Southern-Eastern Health Region of Norway. Flow cytometry analysis can be performed by users themselves, but sorting experiments are done by one of the 2 employees working in the facility in addition to the leader. The facility also offers high-throughput screening, processing and staining of cells in 96- or 384-well plates, followed by automated flow cytometry and/or microscopy analysis. We are now installing a new mass-spec ”flow cytometer”, the CyTOF. This instrument will increase the number of parameters that may be measured to 50-60, i.e. several times what is achievable by regular flow cytometry. The FCCF collaborates with facility nodes at the Rikshospitalet and Ullevål campuses of OUH.

GENOMICS

HIGH-THROUGHPUT SEQUENCING AND MICROARRAYS

Leonardo A. Meza-Zepeda

The Genomics Core Facility (GCF) provides state-of-the-art laboratory technology and high-throughput genomic services to the Norwegian scientific community. Today, GCF is an Illumina CSPro certified service provider, and offers an extensive set of complex technologies to study genome structure, dynamics and function using high-throughput sequencing (Illumina) and different commercial microarray platforms. Our highly competent and experienced service personnel provide advanced support to clinical, translational and basic researchers. Our services include standard and custom solutions to study the transcriptome, genome and epigenome from multi-gene to genome-wide analysis. The core facility collaborates with similar nodes at the Ullevål campus for sequencing and microarray services. The GCF is a member of the Norwegian Genomics Consortium, and provides the sequencing infrastructure and competence for the National Personalised Medicine initiative.

PRECLINICAL MAGNETIC RESONANCE IMAGING (MRI)

Trond Stokke

The Preclinical MRI Core Facility provides access to a state-of-the-art 7T Bruker MRI system and all the necessary equipment for in vivo research on small animals or tissue/organ samples from larger animals or humans. A comprehensive library of standard off-the-shelf protocols are available, and custom-protocols can be developed upon user request. The service offered by the core facility includes design, development and running of the MRI experiment, as well as post-processing of the data in addition to instrument-specific training. The core facility collaborates with the Preclinical MRI node at the Ullevål campus.

RESEARCH CENTRES OF ICR

The Centres of Excellence (CoE) scheme is a national programme under the auspices of the Research Council of Norway. The granted CoE is funded for 5 + 5 years (if recommended following a mid-term evaluation). The total basic funding is ~100 million NOK.

The K.G.Jebsen Foundation supports Centres for Medical Research of high international quality as part of its program for translational medicine. The centres are selected in collaboration with the Norwegian medical faculties and University Hospitals for a period of 4 years. The selected Centres receive 16 million NOK in basic funding from the Foundation.

The establishment of Norwegian Cancer Genomics Consortium was recommended by the Regional Health Authorities and the Universities. The consortium includes research groups and clinicians from the Norwegian University Hospitals, and its total basic funding is 75 million NOK received from the Norwegian Research Council.

PHOTO BY TERJE HEIESTAD

CENTRE OF EXCELLENCE FOR CANCER BIOMEDICINE (CCB)

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Headed by

Harald Stenmark and
Ragnhild A. Lothe

PHOTO BY TERJE HEIESTAD

Centre for Cancer Biomedicine

CCB was inaugurated in September 2007 with the vision of joining 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 CCB scientists have made several discoveries and innovations that promise to be useful for future patients with lymphoma, colorectal cancer and prostate cancer.

The centre has two principal investigator (PI) groups that specialize in various aspects of cancer relevant cell biology – Kirsten Sandvig's group focusing on intracellular transport and Harald Stenmark's group studying cellular membrane dynamics. It also includes the three PI groups of Ragnhild A. Lothe, Håvard E. Danielsen and Erlend B Smeland which work on translational research with particular focus on colorectal cancer, prostate cancer and lymphomas. A PI group led by Knut Liestøl and Ole Christian Lingjærde contributes with biostatistical analyses. CCB, assisted by external evaluators, yearly appoints a young investigator as the seventh member of the PI group. In 2013 and 2014 this was granted Guro E. Lind, a specialist in cancer epigenetics. Four associated groups, headed by Sverre Heim, Antoni Wiedlocha, Rolf I. Skotheim and Guro E. Lind contribute to the success of CCB's research programme, as do the three associated clinicians Arild Nesbakken (colorectal cancer), Karol Axcrona (prostate cancer) and Harald Holte (lymphomas). Four visiting professors participate in international collaborations and provide valuable input to CCB's research strategy. *These are:* Manuel Teixeira, Porto; Marco Novelli, London; Jan Delabie, Toronto; and Bo van Deurs, Copenhagen.

The Board consists of the Chair and three members. Hilde Irene Nebb (chair) and Svein Stølen representing CCB's host the University of Oslo and Karl-Erik Giercksky and Ole M. Sejersted represent the consortium partner, Oslo University Hospital.

An international scientific advisory board (SAB) has been instrumental in developing CCB's scientific and organizational strategy. The SAB members are Professors Manuel Sobrinho-Simões (Porto), Olli Kallioniemi (Helsinki), Marja Jäättelä (Copenhagen) and David J. Kerr (Oxford).

CCB was prolonged for a 2nd 5 year period after an excellent mid-term evaluation by the review panel of the Research Council. The interdisciplinary collaboration has resulted in a steep increase in joint publications from the researchers of the centre. Most importantly, several of these publications can be classified as real breakthroughs. Amongst the 476 papers published during the first 7 years (76 in 2014), CCB has published as many as 11 papers in Nature, of which the majority has CCB scientists as corresponding authors. 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.

A large number of innovations have surfaced from CCB scientists, including patent applications, patents and licenses. Several of the innovations involve technologies and biomarkers with potential clinical impact.

CCB has been an important training ground for Norway's new cancer researchers, and as many as 42 PhD candidates have been graduated during CCB's first 7 years (10 in 2014). We have also initiated an inter-facultary PhD course in Advanced Cancer Biology, a very successful course led by Guro E Lind and running for the fifth year.

CCB´s research also targets 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.

K. G. JEBSEN CENTER FOR BREAST CANCER RESEARCH

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Headed by

Anne-Lise Børresen-Dale

PHOTO BY TERJE HEIESTAD

Kristian Gerhard Jebsen Foundation

VISION

Towards personalized therapy for breast cancer; integrated molecular and epidemiological studies of breast cancer to reduce risk, improve prognosis, and tailor the treatment.

The Center was established in the fall of 2011, it builds on the Oslo Breast Cancer Consortium (OSBEAC) and consists of 6 research groups:

- *Clinical group:* Dr.Med Ellen Schlichting, Prof. Em. Rolf Kåresen (surgery), Prof. Torill Sauer, Dr.Med Elin Borgen, Dr.Med Hege G. Russnes (pathology), Prof. Erik Wist, Dr.Med Olav Engebråten og Prof. Bjørn Naume (oncology)
- *Molecular group:* Prof. Anne-Lise Børresen-Dale (director) and Prof. Vessela N. Kristensen (deputy director)
- *Micro-metastases group:* Prof. Bjørn Naume and Prof. Em. Øystein Fodstad
- *Model-systems and functional group:* Prof. Gunhild M. Mælandsmo and Prof. Em. Øystein Fodstad
- *Metabolic profiling and imaging group:* Prof. Tone F Bathen NTN University, Trondheim
- *Bioinformatics/biostatistics group:* Prof. Ole Christian Lingjærde, University of Oslo

The overall aim is to foster collaboration between clinical and basic scientists and motivate exchange of ideas on how to best utilize the huge collection of patient materials and data generated for the benefit of patients. By such synergism we have been able to explore genes/pathways/networks involved in basic processes like cell cycle, DNA repair, apoptosis, and immune response and their impact on breast cancer development, progression and response to therapy. By performing longitudinal studies of samples at different stages of the disease and characterize such patient materials in full molecular details, we are moving towards a more individual treatment protocols.

THE SPECIFIC AIMS

- Develop validated stratification criteria based on phenotypic/genotypic profiling of tumours
- Use validated phenotypic and genotypic stratification criteria for assessing individual response and prognosis
- Identify molecular pathways and biomarkers predicting treatment response and/or resistance using cell lines and orthotopic xenograft models representing the various subgroups of breast cancer
- Translate and validate molecular and imaging biomarkers from preclinical models into clinical trials

The research project utilizes a number of previously and newly collected clinical cohorts and consists of several well integrated activities:

1. High throughput molecular characterisation of primary tumours
2. Detection and characterization of occult tumour cells in bone marrow (DTC), blood (CTC) and sentinel lymph nodes (SLN) as well as detection of cell free tumour DNA (ctDNA) in blood as a new development
3. Functional studies in experimental model systems
4. Metabolic and physiological characterization
5. Data integration

THE FOLLOWING RESULTS ARE HIGHLIGHTED

- Analyses of mRNA, miRNA, copy number and DNA-methylation have been performed on > 1500 cases from consecutive series and form clinical trials (samples before, during and after treatment). NGS of selected samples have identified new genes and novel mutational processes that evolve across a tumour's lifespan with subtype-specific signatures of point mutations and chromosomal instability. Another 2000 cases with long-term follow-up (>20 years) have been partly analysed and data used as the main validation cohort in a worldwide computational competition to predict outcome.
- Single DTCs have been analysed by NGS, and comparing to primary tumours, and clonality and cell diversity estimated.
- DTC analysis for monitoring purposes during follow up for selection of patients for a secondary treatment intervention within clinical trials has proven reliable.
- A method for in-situ RNA expression in DTCs (by Quantigene ViewRNA) is established.
- Heterogeneity is studied by advanced in-situ techniques (ImmunoFish). A Novel software has been developed and applied to a series of HER2+ cases who received neo-adjuvant treatment with HER2-targeted agents.
- A proof of principle detection of cell-free tumour DNA (ctDNA) in blood has been performed using targeted massive parallel sequencing and digital PCR.
- Orthotopic xenograft models have been established and characterized at many molecular, metabolic and physiological levels and used to assess therapeutic effects.
- Combined analyses of molecular data have pointed to biological functions and molecular pathways being deregulated in multiple cancers, and will be used to identify novel patient subgroups for tailored therapy and monitoring.

In the period 2011-2014 there have been 13 PhD students who have successfully defended or recently submitted their thesis, 10 PhD student projects are ongoing, 4 of which are directly funded by the Center.

More than 150 Scientific publications have been published from the Center.

K. G. JEBSEN CENTER FOR CANCER IMMUNOTHERAPY

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Headed by

Johanna Olweus

PHOTO BY TERJE HEIESTAD

STIFTELSEN KGJ Kristian Gerhard Jebsen Foundation

ABOUT

The K.G. Jebsen Center for Cancer Immunotherapy (JCIT) was awarded center status in June 2013 following international evaluation organized by the Norwegian universities. In this center five Norwegian and one Dutch research group have come together to find new immunotherapeutic strategies that overcome the major challenge of self-tolerance in cancer. This consortium of PIs is assembled based on 1) Highly complementary expertise, in areas ranging from basic immune cell biology, including proteomics (FLJ), cell signaling (KT, FLJ) and T-cell receptor (TCR) and HLA-engineering (TS, JO), to translational research leading to results of high relevance for human disease (all partners), expertise in animal models (TS), and experience as PI for clinical trials in immunotherapy including lymphoma patients (AK, KJM). The center has recuited 55% of the 53 center employees from abroad. The gender balance is 60/40 (w/m). The center is part of Oslo University Hospital Focus Area for Cancer Immunotherapy, lead by partner AK.

AIMS

Three principally distinct approaches are pursued in an interdisciplinary and translational program to find novel immunotherapeutic strategies that overcome immunological tolerance: 1. Use of T-cell and NK-cell based alloreactivity to overcome self-tolerance. 2. Identification and targeting of cancer-specific neo-antigens. 3. Enhancement of effector T-cell function by counteracting inhibitory mechanisms.

PROJECTS

- Epitope discovery to identify targets for immunotherapy (WP 1)
- Identify T cells that recognize and kill cells that express the identified targets (WP 2)
- Molecular cloning, genetic transfer and profiling of immune receptors (WP 3)
- Enhance effector cell function by overcoming inhibitory mechanisms (WP 4)
- In vivo evaluation of immune modulating therapies (WP 5-6)

KEY ACHIEVEMENTS

In-center generated frontline technologies for:

- identification of tumor-specific neo-antigens from cancer exome data (JCO 2013)
- high-throughput discovery of T-cell targets, antigen-specific CD8+ and CD4+T cells and T-cell receptors (PNAS 2014, Nat Med 2015, JCO 2013, and one patent application)
- use of reference T-cell receptor libraries to identify disease-driving antigens (Eur J Immunol 2014 and one patent application)
- measurement of anti-tumor T cell reactivity in clinical trials (Blood 2015)
- bead-based, highly multiplexed proteomics, including protein- and antibody array technology combined with state-of-the-art mass spectrometry
- tracing adaptive NK-cell responses in the human (Eur J Immunol 2014)
- selective expansion of adaptive NK cells (Patent application)
- delineating signaling cascades of inhibitory Tregs as compared with activating effector T cells (Biochem J 2014 and ms submitted)
- robotized flow cytometry-based chemical biology screening (Assay Drug Dev Technol, 2014; J. Thromb. Haemostasis, 2014)

CLINICAL TRANSLATION

A key strength of the center is the ability to couple clinical trials with penetrating mechanistic analyses, facilitating the continuous refinement of experimental immunomodulatory therapeutic trials.

Examples include

- The LYMVAC cancer vaccine trial was recently completed in which a novel local immunotherapeutic strategy resulted in 36% clinical responses, including complete responders, in patients with follicular lymphoma. Remarkably, clinical responses were strongly correlated with systemic CD8 T cell-mediated anti-tumor responses. (Blood 2015, commentary same issue)
- *Adoptive NK cell trial (ongoing):* Based on previous studies in the Malmberg group, a first phase I/II clinical trial based on adoptive transfer of haploidentical NK cells to patients with high-risk hematological malignancies (MDS and AML) who have no other treatment options has been started with promising results.

Home page
http://www.med.uio.no/klinmed/english/research/centres/kgj-cancer-immunotherapy/

GROUP LEADERS / STEERING COMMITTEE

Professor Johanna Olweus (JO)
(MD, PhD, Director), Dept of Cancer Immunology, Institute for Cancer Research, Oslo University Hospital (OUH)-Radiumhospitalet and University of Oslo (UiO)

Professor Karl Johan Malmberg (KJM)
(MD, PhD, deputy Director), Dept of Cancer Immunology, Institute for Cancer Research, OUH-Radiumhospitalet and UiO

Senior Consultant Arne Kolstad (AK)
(MD, PhD), Dept of Oncology, OUH-Radiumhospitalet

Professor Kjetil Tasken (KT)
(MD, PhD), Centre for Molecular Medicine Norway, Nordic EMBL Partnership and Biotechnology Centre, UiO and Dept of Infectious Diseases, OUH

Senior scientist Fridtjof Lund-Johansen (FLJ)
(MD, PhD), Dept of Immunology, OUH-Rikshospitalet

Professor Ton Schumacher (TS)
(PhD), The Netherlands Cancer Institute, Amsterdam

K. G. JEBSEN CENTRE FOR COLORECTAL CANCER RESEARCH

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Headed by

Ragnhild A. Lothe

PHOTO BY JARLE BRUUN

Kristian Gerhard Jebsen Foundation

ABOUT

The K.G.Jebsen Colorectal Cancer Research Centre was opened in August 2014. Colorectal cancer (CRC) remains a major health challenge. The Centre is hosted by the Clinic for Cancer, Surgery and Transplantation, Oslo University Hospital. The in-hospital availability of advanced technology, patient volume, tumour material and clinical facilities provide added value by shortening the time to clinical implementation of novel personalized medicine for this large and increasing patient group. The Centre's research groups are also part of the SMART-Colorectal Institutional Cancer Priority Area, granted for the period 2014-18, and is lead by Ragnhild A. Lothe and professor Arild Nesbakken. The projects include clinical co-investigators from all four main OUH sites and at Haukeland University Hospital in Bergen. The research leads have competence in running various types of clinical trials, and in biomarker research and development. Ongoing international collaborations include researchers at Harvard, MD Anderson and Oxford University.

Home page: www.colorectalcancer.no

P.I.s/steering committee of the Centre

- Professor Ragnhild A. Lothe (MSc, PhD, leader), Department of Molecular Oncology, Institute for Cancer Research, Oslo University Hospital (OUH) and University of Oslo (UiO)
- Professor Michael Bretthauer (MD, PhD), Institute of Health and Society, UiO, and Department of Transplantation medicine, Section of Gastroenterology, OUH
- Professor Arild Nesbakken (MD,PhD, deputy leader), Department of Gastrointestinal Surgery, OUH and Institute for Clinical Medicine, UiO
- Professor Rolf I. Skotheim (MSc, PhD), Department of Molecular Oncology, Institute for Cancer Research, OUH
- Professor Kjell M. Tveit (MD, PhD)/ Senior Consultant Marianne Guren (MD, PhD), Department of Oncology, OUH and Institute for Clinical Medicine, UiO

Administrative coordinator (20% position): Anette Sørensen, K.G.Jebsen Colorectal Cancer Research Centre, Oslo University Hospital

AIMS

The research groups unite a translational multidisciplinary research environment with high quality standards at all steps of the disease process aiming to transfer biomedical research results into improvements in prevention and treatment of CRC.

PROJECTS

- The design of improved personalised drug treatment of CRC patients through biologically justified use of chemotherapy and/or targeted drugs
- Identify biomarkers for monitoring early relapse of CRC by exploring the molecular intra- and inter-tumour heterogeneity of primary and metastatic lesions
- Identify novel molecular changes in families with a high risk for CRC, where the heritability cannot be explained by known genetic risk factors
- Generate molecular profile for high risk precursor lesions and apply novel biomarkers in population-based screening studies

KEY ACHIEVEMENTS

On the opening day of the Centre (28th August 2014) the group of Michael Bretthauer published a NEJM paper (Løberg et al., 2014) about colorectal cancer mortality after adenoma removal, and recently Bretthauer was the senior author on a review article in GUT (Robertson et al., 2015 March) about effectiveness and quality of colonoscopy screening for colorectal cancer, demonstrating their strong impact in the field of cancer prevention. Previous collaboration between the Lothe, Nesbakken and Bretthauer group have identified DNA methylation based biomarkers suitable for early detection of colorectal tumors (Lind et al., Mol Cancer 2011). Currently we are setting up a collaborative project aiming to identify novel biomarkers for risk assessment of adenomas.

Several of the researchers in the Centre wrote a recent review about the PI3K/AKT pathway, summarizing the known alterations at different regulatory levels and their prognostic and predictive role in colorectal cancer (Danielsen, Eide et al., BBA-Reviews on Cancer 2015). The Centre partners are now setting up both a randomised adjuvant study for selected elderly (>75 years) with stage III colorectal cancer (Ommundsen et al., Oncologist 2014), and a national collaboration for a population based biomarker study of colorectal cancer. Centre partners have published a systematic review on re-irradiation of recurrent rectal cancer and a report presenting the outcome data for rectal cancer in Norway in the period 1993-2010 (Guren et al., Radiother Oncol 2014; Guren et al., Acta Oncol 2015 April). Recently, Centre researchers identified the cell cycle protein regulator of chromosome condensation 2 as a prognostic marker in stage II CRC independent of molecular phenotypes (Bruun et al., Clin Cancer Res 2015).

NORWEGIAN CANCER GENOMICS CONSORTIUM

/

Headed by

Ola Myklebost

PHOTO BY TERJE HEIESTAD

FOCUS AREA

The use of tumor genome analysis to better tailor cancer treatment.

The Norwegian Cancer Genomics Consortium (NCGC) is a group of oncologists and researchers from all health regions of Norway, who are collaborating to determine the potential of cancer genome analysis for prediction of therapeutic outcomes or selection of novel targeted therapies.

Precision oncology, or personalized cancer medicine, promises huge benefits to the patients by better adapting the treatment, especially by targeted drugs, to the disease of the individual. The hope is that this will at least give prolonged survival and better quality of life to the patients, and at the same time reduce the morbidity, expense and wasted resources on unsuccessful treatments. A main obstacle is the difficulty to prove the efficacy in ever smaller patient groups, and thus the reluctance of the public health services to introduce the new treatments.

PROJECTS

- Exome sequencing of nine selected cancer types
- Establishment and characterisation of relevant preclinical models
- Validation of novel targets in preclinical models
- Design of small-scale trials to identify potential of candidate drugs
- Develop decision support tools for pathologists and oncologists to better interpret genome diagnostic data for therapeutic interventions.

The projects include the determination of the sequence of all genes in the patient and the tumour, identification of mutations that reveal mechanistic insights or can suggest specific treatments. Promising targets for which drugs are available but without documentation of effect in the cancers investigated, will be investigated preclinically in relevant cell or xenograft models. The intention is then to propose small, exploratory clinical trials to indicate activity in selected patients, and that promising results could lead to proper phase II studies.

The NCGC has received two major grants from the Research Council, and has embarked on projects to sequence tumour material from selected biobanks from 9 cancer types; melanoma, colorectal, breast, ovarian and prostate cancer, leukemia, lymphoma, multiple myeloma, and sarcoma. The main hub of NCGC is at the ICR and its core facility for genomics, and five of the co-principal investigators are from the ICR. The other main nodes are at the University of Oslo, Haukeland University Hospital, St Olav University Hospital, University Hospital of Northern Norway, and the University of Tromsø.

The NCGC also has an ELSA work package, which addresses important societal issues including innovation, health economy, law and ethics, as well as professional and societal dialogue.

NCGC PIs and their focus areas are:

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Head NCGC, Sarcomas, ICR
Ragnhild A Lothe
Colorectal and Prostate Cancer, ICR
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Multiple Myeloma
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Jan helge Solbakk
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Ivar Sønbø Kristiansen
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Dag Wiese Schartum
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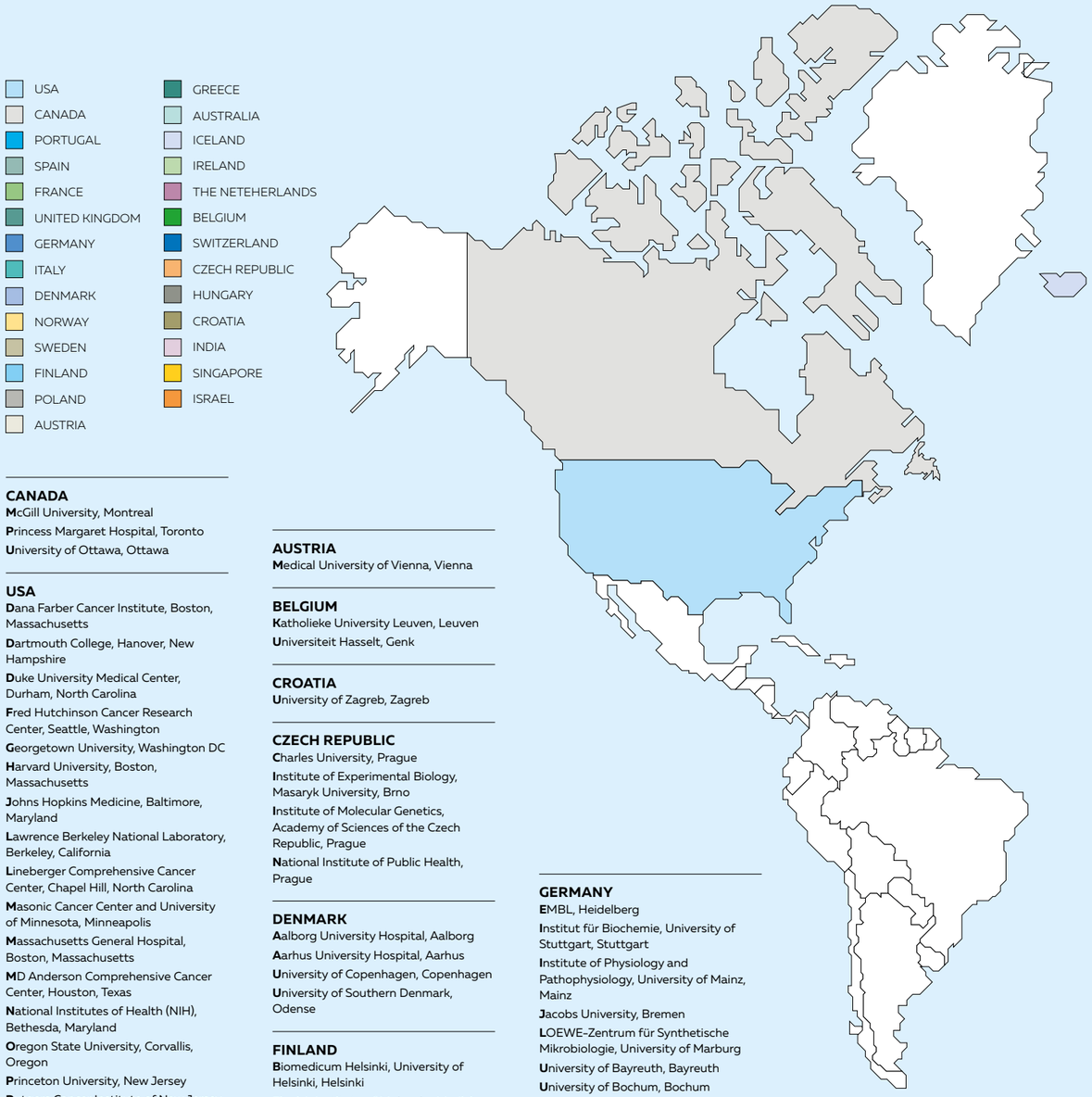
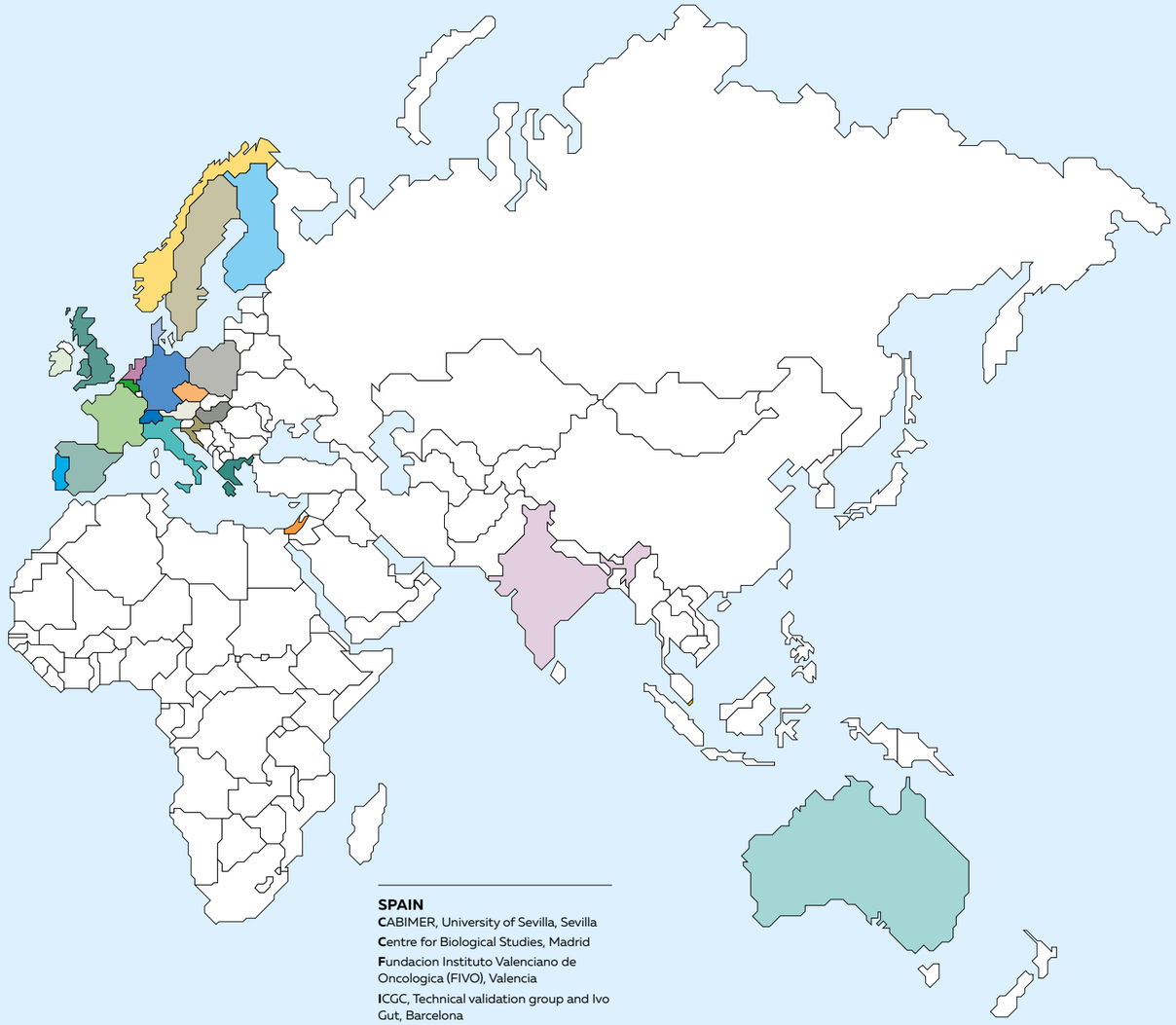
Sissel Rogne
(Biotechnology Advisory Board)
Societal Dialogue
Oslo Cancer Cluster,
Innovation Network
PubGene
Oncology decision support
BerGenBio
Drug trial, Target development





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Princess Margaret Hospital, Toronto
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Dartmouth College, Hanover, New Hampshire
Duke University Medical Center, Durham, North Carolina
Fred Hutchinson Cancer Research Center, Seattle, Washington
Georgetown University, Washington DC
Harvard University, Boston, Massachusetts
Johns Hopkins Medicine, Baltimore, Maryland
Lawrence Berkeley National Laboratory, Berkeley, California
Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina
Masonic Cancer Center and University of Minnesota, Minneapolis
Massachusetts General Hospital, Boston, Massachusetts
MD Anderson Comprehensive Cancer Center, Houston, Texas
National Institutes of Health (NIH), Bethesda, Maryland
Oregon State University, Corvallis, Oregon
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Rutgers Cancer Institute of New Jersey
Stanford University, California
The Mount Sinai Hospital, New York
The University of Kansas Hospital, Kansas
Tisch Cancer Institute, New York
UCSF, Helen Diller Family Cancer Centre, San Francisco, California
University of Albany, New York
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HUNGARY
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ADMINISTRATION AND SERVICE LAB

The responsibilities of the Administration and the Service Lab include budgeting, human resources, grants and external funding management, facilities management, health and safety, lab services and the development of administrative IT services.

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Administration from left: Anne S. Uhnger, Peter Wiedswang, Siri Mette Jebsen, Kari Aalrust Berger, May Elisabeth Johannessen, Linda Uv Mjøen and Mona Hagen.

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Service Lab from left: Yong Fang Po, Marit Osland Haugli and Kari Aalrust Berger.

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