SCIENTIFIC REPORT 2006-2007

Comprehensive Cancer Centre

Cancer Registry of Norway established in 1951

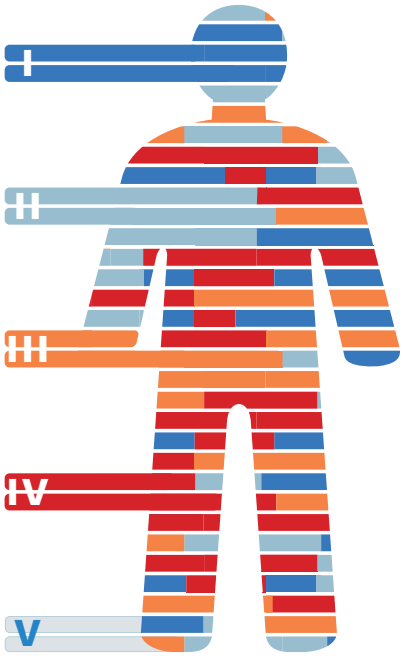
The Norwegian Radium Hospital founded in 1932

The National Hospital founded in 1826

RIKSHOSPITALET

Rikshospitalet University Hospital

Rikshospitalet University Hospital



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Rikshospitalet University Hospital

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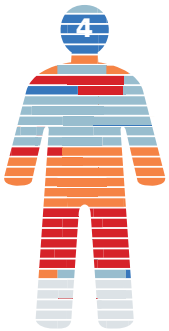
Content



Introduction

In 2005 The National Hospital and The Norwegian Radium Hospital merged and got named Rikshospitalet-Radiumhospitalet Medical Centre. Since we edited The Scientific Report from the Comprehensive Cancer Centre for 2005, the name of the institution has been changed to Rikshospitalet University Hospital.

Today the hospital meets all the necessary requirements for the status as a Comprehensive Cancer Centre (CCC). The present CCC report is the second from our institution and attempts to give an overall summary of the cancer research activities of the merged hospital. Through clinical treatment and research programs, the close interaction with our Institute for Cancer Research, the associated Cancer Registry of Norway (Institute of Population-based Cancer Research) and the University in Oslo, the Rikshospitalet University Hospital generates an extensive activity within clinical, basic, translational and epidemiologically/preventive cancer research. The cancer care in the hospital is organized in disease-based programs. All relevant clinical disciplines involved in the diagnosis, treatment and research of specific cancer entities are organized in multidisciplinary teams, as in the breast cancer or lung cancer programs. The diagnosis-specific programs are headed by a senior consultant with scientific competence. The overall activities of the Comprehensive Cancer Centre are coordinated by the CCC-council consisting of altogether 17 clinic and department chairs.

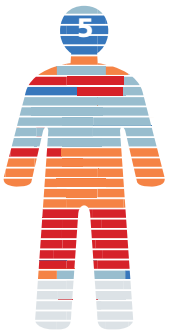
The semi-annual report is divided into four main sections: In the first section we present the different treatment programs and the collaborating research groups, named CCC-programs. In the second section the projects of the basic and/or translational research groups are presented according to their main focus of interest. Some of the research groups will therefore be represented in more than one CCC-program and/or in both sections. In the third section you will find a presentation of some of the hospital's dedicated research centers. The fourth section presents The Cancer Registry of Norway.

This report has been compiled and coordinated by Wenche Reed, editor, with the following editorial board members: Trond Olav Berg, Ragnhild A. Lothe and Finn Wesenberg. We are very grateful to all the contributors of this report.

Oslo, April 2008

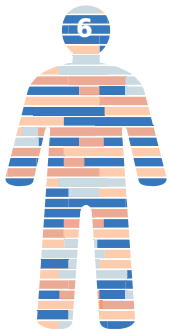
Morten Reymert
CEO

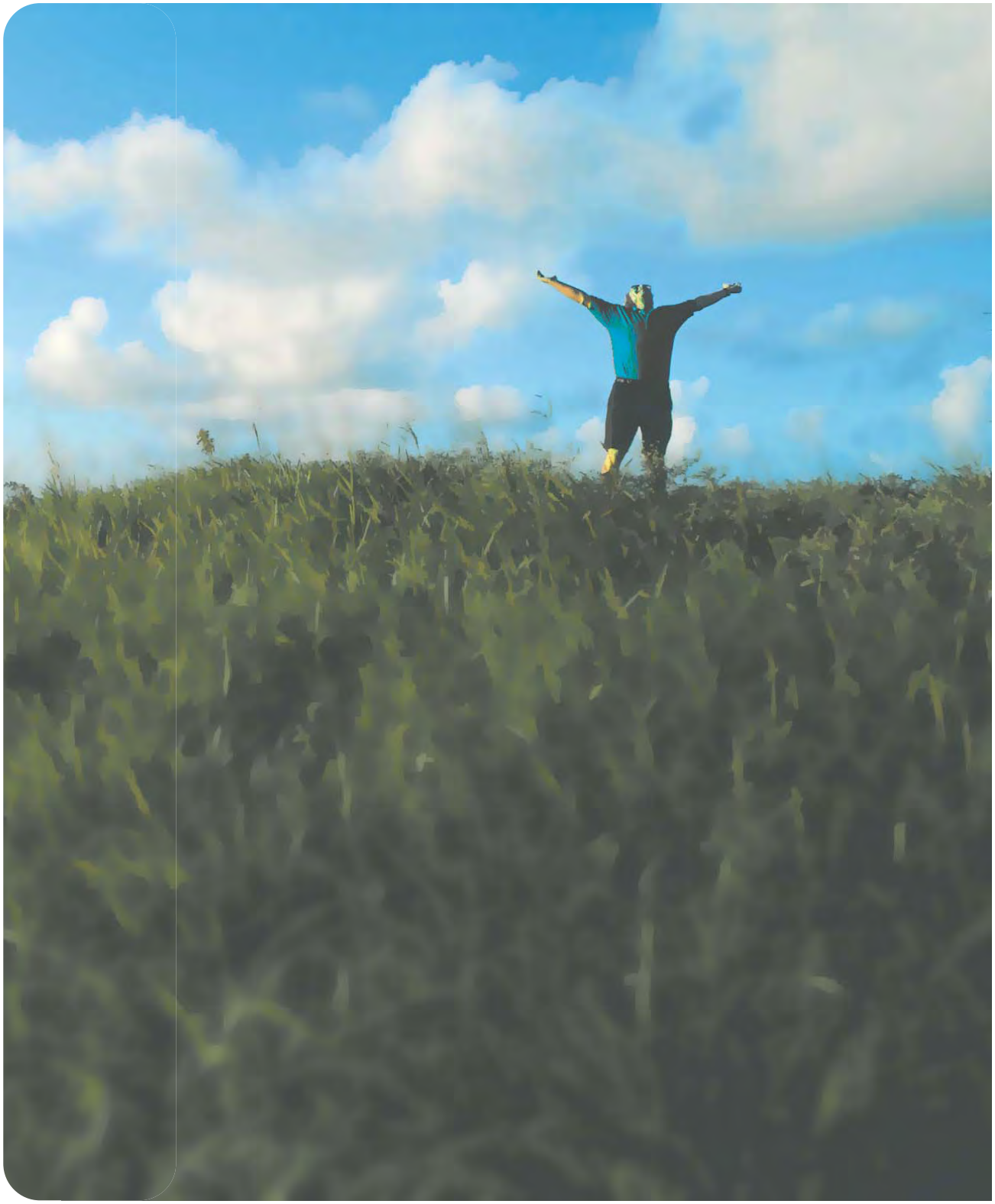
Øystein Fodstad
CCC-council Chair



I CCC-Programs

Brain tumor



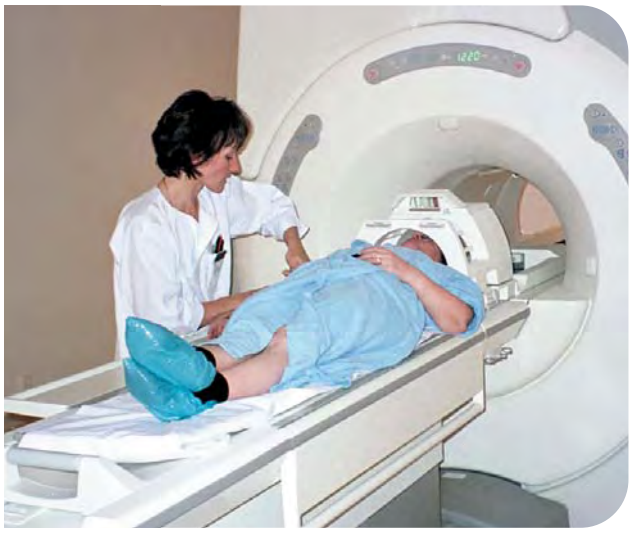


Ill. photo

Brain tumor

Treatment program

The brain tumor treatment program is led by ***Knut Lote.*** Primary tumors of the CNS are highly heterogeneous with regard to histology, biology, and prognosis. Annual incidence in Norway (with a population of 4.5 millions) is around 900 patients, comprising 3 % of all new cancer cases. Registered incidence has doubled over the last 50 years. The prevalence of CNS - tumors has also increased. In 2005, 7394 Norwegian patients were alive with a CNS - tumor, and 2815 of these were alive more than 10 years following diagnosis.



The tumors are of neuroepithelial (60 %), meningeal (20 %), sellar (10 %), or other (6 %) origin. Intracranial germinal tumors and lymphomas may also occur. Very few CNS - tumors metastasise outside the CNS, although many subtypes infiltrate locally and may metastasise within the CNS. About 30 % of all paediatric cancers arise in the CNS, and 40 to 50 children are diagnosed annually in Norway.

Modern imaging modalities using CT and MRI including MRI spectroscopy have greatly improved preoperative diagnostic accuracy. Histological confirmation of the radiological diagnosis was available for more than 90 % of all cases diagnosed in Norway during the last decades.

Neurosurgery and radiotherapy remain the standard therapeutic modalities, although chemotherapy is increasingly important in high grade gliomas, paediatric tumors, lymphomas and germinomas.

The prognosis in patients with primary CNS - tumors is highly variable, the most important prognostic factors being histological subtype and age at diagnosis. Generally, the prognosis has considerably improved in childhood CNS - tumors, with 10-year-survival now exceeding 60 %. Survival at 15 years for adult patients with neuroepitelial tumors in the age group 15-49 years is lifted to 35 %. In contrast, the prognosis for patients > 50 years with neuroepitelial tumors is only marginally improved during the last 30 years. Patients with tumors of meningeal or sellar origins enjoy much better long-term prospects following neurosurgery or for some patients with additional conformal or stereotactic radiotherapy.

PATIENT GROUPS

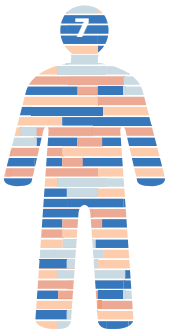
Primary CNS - tumors are of neuroepithelial (60 %), meningeal (20 %), sellar (10 %), or other (6 %) origin. High-grade gliomas are aggressively infiltrative tumors, low grade gliomas less so. Most meningeomas and sellar tumors as well as cranial nerve tumors are benign. Very few primary tumors metastasise outside the CNS. However, metastases to the brain are very common (15-30 % of cancer patients. The treatment modalities are neurosurgery, radiotherapy, radiosurgery, chemotherapy and hormonal treatment. None of the patients are enrolled in treatment protocols. National guidelines with regard to the treatment of gliomas are not formally implemented, but glioblastoma patients in Norway are since September 1st 2004 treated following the regime described by Stupp R et al (N Engl J med 2005, 352:987-96).

MAIN CLINICAL RESEARCH PROJECT

A phase 2 study evaluating the use of tumor mRNA dendritic cell vaccination is in preparation and is expected to be activated early 2008. A number of doctoral projects are at present under work (1 in neuroradiology, 2 in neuropathology, 2 in neuroendocrinology, and 2 in basic science).

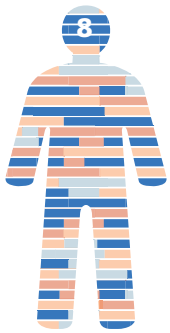
NATIONAL FUNCTIONS

The Division of Clinical Neuroscience performs about 50 % of all adult and 70-80 % of all pediatric tumor craniotomies in Norway. The Division of Clinical Neuroscience, in collaboration with the Division of Pathology and others, is building a tissue bank for basic research and histological diagnoses. Institutional clinical databases on CNS - tumor patients have since long been established separately at Rikshospitalet University Hospital .These databases will be amalgamated as far as possible in cooperation with the Cancer Registry of Norway. The long-term aim is also to establish a national quality register at the Cancer Registry including clinical and epidemiological data for all CNS - tumor patients in Norway, to facilitate the follow-up for these patients who often are in need of multidisciplinary care



Breast cancer

Treatment program

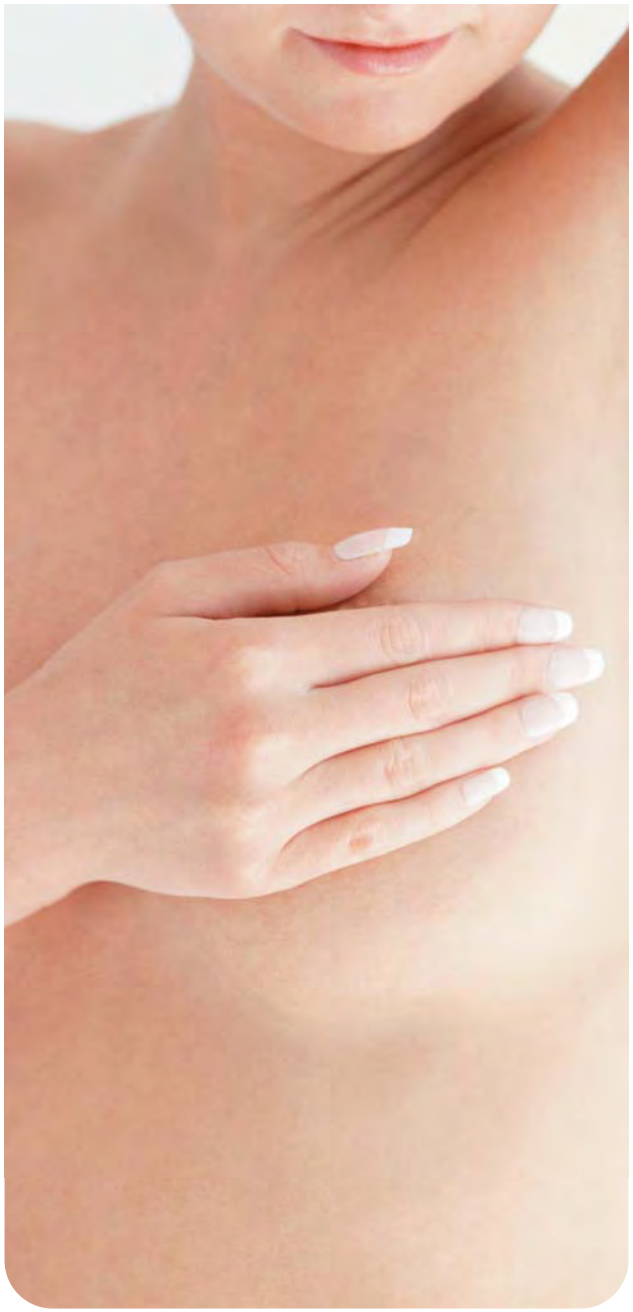


The breast cancer treatment program is led by ***Bjørn Naume.*** Breast cancer is the most common malignancy among women both globally and in Norway. It comprizes about 24 % of all cancer causes among Norwegian women, 2780 new cases were reported in year 2005. About 5-10 of the cases are strictly due to genetic reasons (e.g. mutation in the BRCA-1 and BRCA-2 genes). The age adjusted incidence rate has doubled during the last 40-50 years, reaching for the period 2001-2005 76.3 new cases per 100 000 women. In contrast, the death rates have been constant over many years, and appear now to drop. In year 2004, 694 women died of breast cancer. This is in line with a significantly improved breast cancer survival during these years. The reason for improved survival is a combination of the following factors: Mammography screening resulting in early detection, adjuvant systemic therapy (hormonal therapy and chemotherapy, reducing mortality between thirty to fifty percent), and radiation therapy in lymph node positive disease. Due to extensive research activities, new knowledge about prognostic and predictive factors is evolving and gives new opportunities for further improvements in treatment selection and survival. As a consequence, the introduction of taxanes and trastuzumab in adjuvant treatment is expected to further improve the survival figures in the next years.

The breast cancer disease is more frequently detected in early stages with reduced lymph node involvement. Therefore, a major challenge in the future management of patients with this disease is the combination of increasing number of active therapies and, in contrast, the increased number of patients with high probability for non-disseminated disease with no need for systemic treatment. There is a need for better prognostic tools for identification of both patients with no need for additional treatment and patients with high risk for systemic relapse using the current treatment regimens. The latter patients may be candidates for intensified or alternative experimental treatments.

PATIENT GROUPS

The majority of the primary cases are detected by the mammography screening program. Also, a relatively large proportion of the patients are referred for locally advanced disease (~50). Of those that receive radiotherapy, the majority have early breast cancer (~500). Patients in all stages of metastatic disease are controlled and treated (~500). In 2006 the hospital treated 6111 as outdoor patients and 2496 as hospitalised patients. The treatment modalities are surgery, plastic surgery, oncoplastic surgery, radiotherapy, endocrine therapy, chemotherapy, targeted therapy. 10% of the patients are enrolled in treatment protocols.



THE MAIN PROTOCOLS ARE:

SATT-study: bone marrow (BM) aspiration for detection of disseminated tumor cells (DTC) is performed after ended adjuvant chemotherapy. DTC+ patients receive docetaxel with monitoring of DTC and clinical outcome after end of treatment, to evaluate DTC as a surrogate marker for effect of treatment.

Oslo2 study: Detection and characterization of breast cancer (BrCa) cells in sentinel nodes (SN), blood and BM – Comparison with molecular signatures in the primary tumour. A broad sampling and analysis of biological material aims at increasing the molecular understanding of the metastatic cascade and identifying markers for prediction of adjuvant therapy response.

Exploration of late effects of radiotherapy (RT) in BrCa: Patients treated with locoregional RT are controlled at 3 years and 10 years, analyzing shoulder/arm morbidity, pulmonary and cardiovascular side effects and QoL.
(Neo)ALTTO studies: HER2+ patients who are candidates for adjuvant trastuzumab are randomized between this treatment and lapatinib, their sequence or combination.

MAIN CLINICAL RESEARCH PROJECTS

Our main goal is to initiate (see"#" below), perform and participate in translational studies. Several studies have been designed to disclose the clinical relevance of early dissemination, the characteristics of DTC and how to eradicate these cells:

- Oslo1 study#: BM aspiration (BMA), DTC analysis, primary tumour analysis and clinical FU of 920 early BrCa patients.
- SATT study# (NBCG9): BMA is performed in patients after adjuvant chemotherapy for selection of DTC+ patients to receive docetaxel (rescue) treatment. 1064 patients included.
- @FAME study#. BMA has been performed in ER+ postmenopausal patients at surgery for identification of DTC+ high risk patients. These patients receive anastrozole +/-fulvestrant for endocrine treatment optimization. So far 273 patients are BM screened, 26 at our institution.
- Oslo2 study#. A new study of tumor dissemination, including SN, blood, BM and primary tumor, started in 2007 (in collaboration with Ullevål University Hospital). The sampling of tissue is performed at surgery and further processed at the collaborative research groups. 143 patientshave so far been included.
- Collaboration with MDAnderson for initiation of metastatic circulating tumor cell (CTC) studies#.

Neoadjuvant studies, aiming at detection of predictive markers for adjuvant treatment have been initiated. Fresh tumor tissue is collected before and during treatment for detailed analyses and comparison to tumor response, outcome and other parameters:

- A large number of patients was included in NBCG6 (Neotax) randomizing pts between epirubicin and paclitaxel. Clinical FU is still updated.
- In the NICE-study, patients with operable ER- T2/T3 tumours received +/- gefitinib, a tyrosine kinase inhibitor, in combination with chemotherapy (EC).
- The NeoALTTO study is recently initiated, to clarify the effects of lapatinib in HER2-positive patients. Includes CTC analysis.
- A new neoadjuvant study# is prepared at our hospital (in collaboration with Ullevål University Hospital) for HER2-negative patients, which includes molecular array analyses, MRI/MRS, MR-metabolomics, DTC, anti-angiogenic treatment (bevacizumab) and evaluation of the methods of surgery.

REGIONAL FUNCTIONS

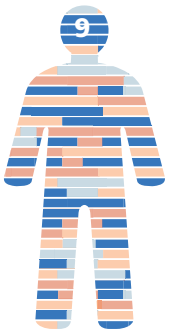
The breast cancer program has regional functions in the research and treatment of locally advanced breast cancer. Patients with large tumors or regionally extended disease are referred to our hospital for examination, treatment and if possible inclusion into ongoing studies. The patients are followed closely during preoperative therapy and in the following surgery, radiotherapy and follow up. The hospital also has regional roles in adjuvant and metastatic studies.

We have regional responsibility for locoregional radiotherapy after breast conserving surgery or after completed surgery for lymph node positive disease, although the radiotherapy satellites at Sykehuset Innlandet. Gjøvik and Sørlandet Sykehus also treat these patients. We function as reference institution for these satellites.

The hospital is also a regional centre for inherited breast cancer (see under Research programs), which includes identification, counselling, surveillance and initiation of prevention steps to this group of high risk women. The clinical procedures include mammography, ultrasound, MRI, prophylactic oophorectomy and prophylactic mastectomy with concomitant reconstructive surgery.

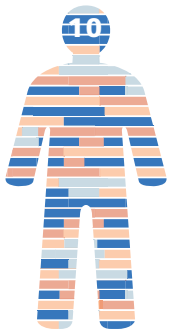
Patients are also referred to the hospital for primary oncoplastic surgery, where the breast tumor surgery is combined with primary reconstruction. In addition, secondary reconstructive surgery for breast cancer survivors is part of our regional responsibility.

A multimodal approach is often the basis for treatment of breast cancer. In metastatic disease, the decision of what treatment option should be used for an individual patient can be difficult. In such cases, we are the regional reference institution for treatment decisions.



Research programs

Breast cancer



Anne-Lise Børresen-Dale is the head of the Department of Genetics, Institute for Cancer research, with a large range of projects:

I) FUNCTIONAL GENOMICS

Breast cancer (BC) is the leading cause of cancer morbidity in women. Both germline and somatic mutations are involved in tumor initiation, development and progression. In principle it should be possible to derive at a complete catalog of mutations to understand fully the functional consequences of these alterations to develop/implement preventative/interventional strategies. The challenge lies in the complexity and needs to be attacked by means of systems biology. This complexity arises from the fact that BC genomes are dynamic and tumors are complex organ systems, shaped by gene aberrations, cellular biological context, characteristics specific to the person, and environmental influences. The biological dynamics of BC, the interaction with host factors and environmental factors, need to be understood at a more fundamental level than of today. The completion of the human genome sequence, the high quality registries with full patient follow-ups and our extensive use of the various National FUGE platforms for large-scale cancer genomics studies have allowed us to accumulate huge amount of data. Functional studies of the genes identified will be performed by different strategies. Systematic investigation of mutations, gene expression patterns, genome wide copy number alterations and their correlation to specific phenotypic variations will provide the basis for an improved molecular taxonomy of BC. Recognizing expression "motifs" that represent important clinical phenotypes, like resistance or sensitivity to specific therapies, invasiveness, or metastatic potential, will be an important challenge in these studies. The project is divided in 7 activities:

1. Gene environment interaction in breast cancer risk,
2. Tumor initiation and early diagnosis,
3. Tumor progression and metastasis,
4. Prediction of treatment response and targeted therapy,
5. Integrated approaches.
6. Functional validation.
7. Biostatistical challenges and approaches.

II) IDENTIFYING MOLECULAR PORTRAITS OF BREAST CANCER

The group studying whether the genomics can be translated into clinical practice is led by ***Therese Sørlie***, also part of the Department of Genetics. The goal of this project is to identify individual gene targets and sets of genes that contribute to the potential of breast cancer to be aggressive and metastatic, and which reflect and predict treatment responses in the patient. We will apply state-of-the-art microarray tools, novel functional technologies and associated statistical and bioinformatics methods to profile breast tumors at the DNA, RNA and protein level. More specifically, the research over the next years will be carried out in the context of the following four subprojects:

- Sub-project 1. Classification of breast tumors by their variation in genome-wide expression patterns. Aim: Validate and optimize the robustness of our previously described breast cancer classification in various breast cancer cohorts.

- Sub-project 2. Prediction of micro-metastases in early breast cancer. Aim: To determine whether primary tumor gene expression profiles will enable us to predict the presence of micro-metastatic disease and systemic relapse.

- Sub-project 3. Identification and validation of genes predictive of therapy response. Aim: Identify genes and/or gene expression profiles that may contribute to resistance to specific therapies and extract information on molecular pathways involved in tumor sensitivity and resistance.

- Sub-project 4. Identification of individual gene targets undergoing somatic genetic mutations in breast cancer. Aim: To identify genes that carry non-sense mutations in breast cancer using a genome-wide method called non-sense mediated RNA decay microarray analysis (NMD microarrays).

III) SIDE EFFECT OF RADIATION TREATMENT IN BREAST CANCER

Expression profiles that can predict response and adverse effect of radiation treatment. In breast cancer patients with regional lymph node metastases radiotherapy to the breast, thoracic wall and regional lymph nodes is an established adjuvant treatment. Acute skin toxicity can be a problem for some of these patients. Typical post-mastectomy target field covers the ipsilateral lymph node regions in the axilla, the fossa supraclavicularis, along the arteria mammaria interna and the thoracic wall. Irradiation of normal tissue may cause adverse side effects. Acute side effects emerge during or shortly after radiotherapy (RT) and these early reactions are often transient. Late effects occur months and years after treatment and may persist, and are typical irreversible. Late adverse effects include teleangiectacies and atrophy of the skin, subcutaneous fibrosis, rib fractures, thickening of the pleura and lung fibrosis and costa fractures. The degree of adverse effects varies with the total dose, the number of fractions, the volume of the exposed area, the organ at risk as well as the time period since irradiation. The clinical importance of late side-effects increases with increasing long-term survival after cancer therapy. Extensive research is the-

refore needed to explore the causes and identify risk factors and predictive factors that can identify patients with a high risk of developing late side-effects in response to radiotherapy.
The aim of this project is to investigate
1. Can gene expression profiles in blood and tumors after radiation treatment predict short term response and side effects?
2. Can gene expression profiles in blood cells at the time of treatment start predict outcome?
3. Does gene expression profiles in blood cells 6-8 years after treatment correlateith any persistent adverse effect?

IV) CANCER GENETICS

Vessela N. Kristensen and her group have looked at SNPs and pharmacogenetics of breast and lung cancer in a clinical setting. SNPs have proven a functional effect and clinical relevance for the response to the following anticancer drugs: 5-Fluorouracil, Doxorubicin, Methotrexate, Etoposide, 6-Mercaptopurine, Azothiopurin, Thioguanine, Irinotekan, Docetaxel/Paclitaxel need to be introduced for routine analysis. Validation of the importance of these candidate SNPs was performed on samples collected from 90 breast cancer patients treated with doxorubicin, 35 breast cancer treated with 5-Fluorouracil and 65 osteosarcoma patients treated with Methotrexate abd 27 lung cancer patients treated with docetaxel. The presence and the exact location of the SNPs have been verified through databases such as Ensembl http://www.ensembl.org/ and UCSC (http://genome.ucsc.edu/). Methods were developed for high precision genotyping and aplied on clinical sample collections. We are also in the process of selecting candidate genes for the study of the effect of genetic variance on the response to other drugs such as: bevacizumab, gefitinib, epirubicin, cyclophosphamide, paclitaxel, docetaxel and carboplatin in order to identify markers of treatment response and cytotoxity that can be included in the clinic.

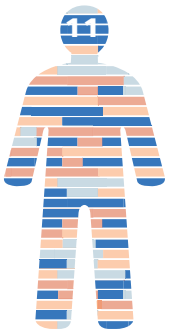
V) RADIATION BIOLOGY

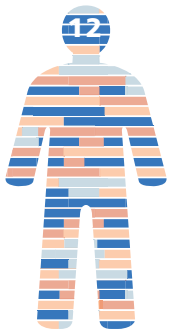
Vessela N. Kristensen and her group have a project on genetic polymorphism in the ROS signalling pathway, DNA repair genes, genomic instability and radiation response in patients with breast, cervical and head and neck cancer. Radiotherapy exerts its antineoplastic effect either by directly attacking cellular macromolecules or indirectly by generating ROS and ROS products that induce antioxidant enzymes (AOE) and DNA-damage repair pathways. ROS in turn signal to the cell cycle and apoptosis. Genetic variation in the genes involved in these processes mentioned above may increase or decrease individual radiation response. Our current studies on breast and cerivcal cancer cancer cases point to the existence of a signature of SNPs that predicts for lung fibrosis (8 SNPS) and pleural thickening (11 SNPs) with significant p-values). These SNPs are very good candidates for further analyses in the new cohort that has been collected in collaboration with Prof. Sophie D. Fosså. This cohort consists of 317 women with breast cancer stage II, who have received radiotherapy as adjuvant treatment. Post-operative adjuvant radiotherapy has been applied for many years at the hospital, using manual simulator-based dose planning (so called 5-field technique [5-FT]). Radiotherapy, either as a single modality or in combination with surgery or chemotherapy, is integral to current therapy for the majority of SCCHN (Squamous cell carcinoma of the head and neck). Together with Å. Helland we have initiated a project to identify genes and variations of genes that increase adverse effects during and after radiation therapy of SCCHN.

VI) CANCER PREVENTION

Vessela Kristensens group studies the variation in oestradiol pathway in relation to mamnographic breast density in high risk individuals under observation at DNR. The goal of this project is to identify SNPs in individuals and studied genes using iPlex assays for Sequenom (Collaboration core genotyping facility, Ås) in 1200 control individuals with known metabolic levels and mammographic density (prospective study, in collaboration with I. Gram, University of Tromsø, G. Ursin, University in Oslo, as well as with the clinical study of Å. Helland and M. Holden. 1000 SNPs in the ER/PR signalling and metabolic pathway have been selected and the first 500 in four different sample sets are genotyped. In this pilot we have confirmed some of the associations from our previous studies, and identified several SNPs associated to the same or related metabolites as well as mammographic density in all studied materials. These studies will hopefully lead us to given genetic profiles which predispose to increased mammographic density, which will add another dimension to mammographic screening and help diagnosis with problematic cases with unclear mammograms or small and uncertain observations.

Øystein Fodstad and his group, in the Department of Tumor Biology, Institute for Cancer Research, focus on
TARGETED THERAPY OF CANCER USING IMMUNOTOXINS
Residual disease in the form of dormant metastatic cells is a considerable problem in the adjuvant treatment of patients with high risk of disease relapse. Conventional treatment with chemotherapy have reduced, but not eradicated this problem. Immunotoxins are composed of a targeting part, a monoclonal antibody, and a toxin part – which inhibit the protein synthesis, and also trigger the apoptotic process in the cells. Treatment with immunotoxins targeted to the epithelial glycoprotein 2 (Ep-CAM) and the MUC-1 glycoprotein prevent the development of metastatic disease in clinically representative animal models. Based on these results and extensive toxicity testing in rodents and non-human primates, a clinical phase I trial have been started. A total of 24 patients have been treated with injections of the immunotoxin targeted toward the Ep-CAM molecule. No serious side effects have been observed, and the ongoing trial will





recruit patients for the establishment of a safe dose level for further clinical phase II trials. The trial also include response evaluation of metastatic and micrometastatic disease in order to document clinically relevant anticancer activity of the compound. Preclinical research is ongoing, focusing the potential for the use of the immunotoxin as a part of a combined treatment regimen, including cyclosporin and new small molecule therapeutics. Combined treatment with cyclosporin has been shown to reduce the immunogenicity of the immunotoxin, with a concomitant increase in the apoptosis inducing activity of the compound. In addition, the possibility for concomitant treatment using immunotoxin and conventional chemotherapy is now investigated.

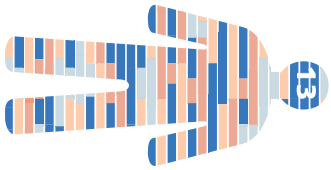
Guttorm Haraldsen, from the Division of Pathology, leads a project on the REGULATION OF NUCLEAR IL-33 IN BREAST CANCER. We propose to characterize the role of interleukin-33 (IL-33) in vascular morphogenesis/ angiogenesis as it is globally expressed in endothelial cell nuclei of resting blood vessels but almost completely absent in vessels of a wide array of human malignant tumors. We also have preliminary data that support the view that IL-33 is involved in transcriptional regulation and that its expression is strongly linked to the maintenance of vascular stability. Here we describe a coherent line of in vitro and in vivo experiments to shed more light on this putative drug target of angiogenic activation. The proposed studies should expand our understanding of the complex mechanisms regulating endothelial cell function during angiogenesis.

Gunhild Mælandsmo's and *Øystein Fodstad's* groups, in the Department of Tumor Biology, Institute for Cancer Research, participate in the collaborative project

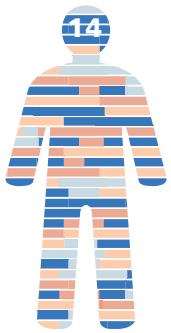
TOWARDS PERSONALIZED THERAPY FOR BREAST CANCER

The project involves groups at Institute for Cancer Research, Division of Cancer Medicine and Radiotherapy, Ullevål University Hospital and NTNU. Breast cancer is a complex disease where inherent heterogeneity and diverse contribution from the normal microenvironment together constitute each tumors phenotype, and thus dictate the molecular portrait of the tumors. Currently, only a handful of clinical, pathologic and molecular factors help clinicians decide upon diagnosis, prognosis and selection of therapy. The heterogeneity is only partially apprehended by these parameters, making therapeutic strategies less than perfectly adapted to each patient. Current cytotoxic drugs do not differentiate between malignant and normal cells. Thus, developing molecular therapies selectively targeting the tumor cells, and also adapted to each individual patient, are highly prioritized research areas.

The aim of the present project is to collect matched material from primary tumor, sentinel lymph nodes, bone marrow, blood and distant metastases, analyze the samples in an integrative approach and collect information of diagnostic, prognostic or therapeutic value. The project has the following work packages: 1) Global characterization of the primary tumor; 2) Detection and characterization of disseminated cancer cells; 3) Studies of cancer stem cells; 4) Functional studies of possible targets; 5) Targeted therapy utilizing cell lines and in vivo models. At present more than 150 patients (from Ullevål University Hospital) has been enrolled (the Oslo II protocol). A neoadjuvant clinical trial examining the effect of chemotherapy and endocrine therapy in combination with antiangiogenic treatment will be initiated at the Cancer Clinic during 2008. A similar preclinical study is at present performed and in both studies extensive molecular analysis are planed in an attempt to identify markers that can be utilized for predictive or prognostic purposes



Breast cancer



Colorectal and oesophagus cancer

Treatment program

Svein Dueland heads the colorectal and oesophagus treatment program.

• *Colorectal cancer*

The focus colorectal cancer is multidisiplinary treatment of locally advanced rectal cancer, local relapse of rectal cancer, cancer ani and intraperetoneal heated chemotherapy of pseudomyxoma peritoneii and adenocarcinoma (metastases from colorectal cancer). Data from the Cancer Registery of Norway for 2005, show that the number of new cases of colon cancer was 1052 males and 1168 femals. Similar data for combined cancers of rectosigmoid, rectum and ani were 675 males and 553 females. 5 years survival for combined rectosigmoid, rectum and ani with regional disease at the time of diagnosis was about 65 % and with metastatic disease at time of diagnosis about 10 %. At the end of year 2005, 14692 males and femals were alive and diagnosed with colon cancer: Similar data for rectosigmoid, rectum and ani cancers were 8883. Wiig and Larsen et al have reported the results from our institution in patients with locally advanced rectal cancer and in patients with relapse of rectal cancer. Our results in cancer ani patients will be included in a national database and published in 2008-2009.

PATIENT GROUPS

The types of patient groups are locally advanced rectal cancer that in accordance with national guidelines will receive preoperative chemoradiation, rectal cancer patients with relapse, colorectal cancer patients with metastatic disease and cancer ani patients that will receive primary treatment or treatment for metastatic disease. The treatment modalities are chemotherapy, radiation therapy and surgery.

A large fraction of these patients are treated according to different protocols:

All cancer ani patients that receive their primary chemo-radiation treatment are treated according to a Nordic chemo-radiation protocol.

About 70% of rectal cancer patients with locally advanced disease who receive their primary chemo-radiation treatment are included in a study (LARC-RRP).

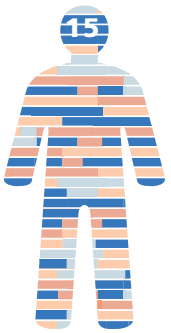
About 10 % of patients with metastatic colorectal cancer are included in different chemotherapy studies.

LARC-RRP: The patients receive 2 cycles of Oxaliplatin containing chemotherapy (FLOX) before start of radiation treatment and weekly Oxaliplatin and capecitabine twice a day during radiation therapy (5 weeks). In addition to clinical outcome (effect and side-effects) histopathological examinations describing tumor regression (TRG) and resection margin (obtaining complete microscopic and marcoscopic resection) are given. Patients with different pelvic tumors that will receive palliative local radiation therapy are included in a phase I trial with standard radiation treatment (3 Gy x 10) combined with a histonedeacetylase inhibitor during the radiation treatment periode. Cancer ani patients with advanced disease (T3-4 and or N+) receive 2 cycles of cisplatin/5-FU before radiation therapy and one cycle during start of 5-6 weeks of radiation therapy. Patients with less advanced disease (T1-2 and N0) receive one cycle of mitomycine C and 5-FU during.

MAIN CLINICAL RESEARCH PROJECTS

• LARC-RRP. Standard treatment of locally advanced rectal cancer (LARC) is multimodal, involving preoperative chemoradiation therapy (CRT) aimed at down-staging the tumor to facilitate subsequent complete surgical removal. However, the tumor response to the preoperative therapy varies greatly, from pathological complete response (pCR) to lack of objective response. To possibly increase the number of patients obtaining pCR, LARC patients included in this phase II protocol will receive a new combination of chemotherapeutics in the preoperative CRT setting. This project also aims at identifying molecular and metabolic signatures, by means of oligonucleotide microarray analysis and magnetic resonance spectroscopy (MRS), respectively, in pre-CRT biopsies. The pharmacological component of CRT is intended to radiosensitize the tumor cells, and in addition to 5-fluorouracil (5-FU) routinely used today, we will introduce oxaliplatin. Surgery is performed 6–8 weeks after completion of CRT. The surgical specimens are assessed by the study pathologist and CRT response graded according to a validated tumor regression-scoring model. The clinical endpoints are to determine the safety profile, particularly grade 3 and 4 toxicity, and quality of life scorings, according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) and EORTC questionnaires, respectively.

• PRAVO. Radiation as therapeutic modality has well-documented palliation effects on advanced pelvic tumors. The combination of radiotherapy and chemotherapy is advocated primarily because of the independent effect of each modality. Cellular treatment with histone deacetylase (HDAC) inhibitors causes hyperacetylation of histone proteins by



which these compounds enhance tumor cell sensitivity to radiation treatment. Primary objectives is to determine toxicity of HDAC inhibitor (vorinostat) when administered concomitantly with palliative pelvic radiation

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versity Hospital. Most cases are squamous cell carcinoma, but adenocarcinoma on the basis of Barrett's oesophagus is increasing and accounts for 40 % of the cases. 25 % of patients with oesophageal cancers seen at oncological centers are candidates for radical surgery, long term survival for these are about 50 % in many publications, higher in highly selected series. However, with a median overall survival of 10-12 months and a cure rate of 10 % for the whole goup, the prevalence is accordingly low. Challenges for the program are on one hand diagnostic to find the cases for radical treatment and to give these patients optimal treatment in addition to surgery - on the other hand to give good palliation to the gross number of patients with pain, dysphagia and short expected time to live. The hospital has explored different ways to optimize radiotherapy and to give the high radiation doses required for squamous cell carcinomas. The addition of chemotherapy regimens has been considered toxic, and the introduction of these have subsequently been delayed. Which way to choose for the future, will depend on institutional results as well as on publications from other centers.

NATIONAL/REGIONAL FUNCTIONS

National functions:

- Heated isolated pelvic perfusion chemotherapy (HIPEC) after macroscopic radical surgery of patients with pseudomyxoma peritoneii and colorectal cancer patients with pelvic only metastatic adenocarcinoma - only microscopic disease is left in place at surgery and HIPEC is performed after surgery the same day or next day.

- Pelvic excenteration of locally advanced or recurrent rectal cancer - the patients have previously received radiation therapy and the multmodal treatment may involve surgerns with speciality in: gastroenterology, urology, plastic surgery, ortopedic surgery.

Regional functions:

- Chemoradiation therapy for patients with locally advanced or or local relapse of rectal cancer.
- Primary chemoradiation treatment of anal cancer and surgical treatment of local relapse or disease progression after chemoradiation of patients with anal cancer.

• *Oesophagus cancer*

The incidence of this entity is increasing, with 200 new cases in Norway 2006, of which 50 was seen at Rikshospitalet Uni-

PATIENT GROUPS

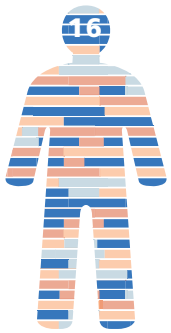
Local tumors (50%) are candidates for radical surgery or radiotherapy. Advanced tumors with or without distant metastases (50%) are candidates for palliation. Treatment modalities:

- PDT for early stage/ Barretts oesophagus
- Radical surgery and preoperativly radiotherapy
- Hyperfractionated radiotherapy and intracavitar brachytherapy, total dose 72 Gy, with curative intent
- Moderate to low dose external radiotherapy, endocavitary brachytherapy, stent for palliative treatment

None of these patients are enrolled in protocols yet. Brachytherapy vs stent and brachytherapy for palliation, phase III study will be started early 2008.

MAIN CLINICAL RESEARCH PROJECTS

- Longterm effect of PDT treatment of premalignant lesions/ Barrett's oesophagus and tumours in early cancer, including patients in China. The follow-up will be 5 years.
- A retrospective study of results from a 10 year experience of all stages, 452 cases.
- A study of biological prognostic markers in development



premalignant and invasive squamous cell carcinomas and adenocarcinomas Brachytherapy vs stent and brachytherapy for palliation, randomized phase III study

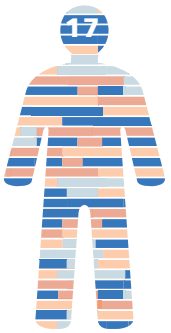
NATIONAL/REGIONAL FUNCTIONS

Brachytherapy with endoscopically placed radioactive source for pallation, or boost in curative situations, is a procedure that gives durable palliation and short stay in hospital.

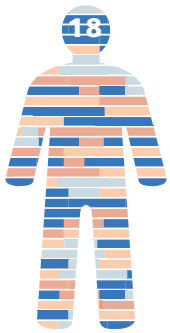
Research programs

Ole Petter F. Clausen from the Division of Pathology focuses on **TUMOR BIOLOGI OF NEOPLASIAS OF THE GASTROINTESTINAL TRACTUS AND SKIN**. Mutations in genes that regulate cell growth, programmed cell death (apoptosis) and DNA repair may be linked to carcinogenesis. How and why mutations occur is largely unknown, but it is often related to chromosomal instability (CIN). CIN indicates that the tumor cells have an increased risk for accumulating genetic damage through tumorprogression. This is again linked to the development of aneuploidy which is associated with bad prognosis. We are studying geno-and phenotypic alterations in tumors and their precursor lesions in the gastrointestinal tractus and skin to elucidate patogenetic mechanisms for tumordevelopment. In particular we analyze genetic aberrations and altered protein expression associated with CIN and development of aneuploidy in colorectal cancer. Such information may reveal markers related to the early phase of tumordevelopment and make radical treatment possible. In addition we want to find markers related to tumor agressivness and prognosis. Recently we have shown that amplification of 20q occurs early during aneuploidization in colorectal adenocarcinomas, because this amplification is seen also in the diploid component of carcinomas harbouring aneuploidy. We will with genomic arrays and FISH analyze genes within the consensusregion 20q13 to find candidate genes related to aneuploidization. By CGH technique we have recently shown that there are significant differences in in genetic aberrations between keratoacanthomas (KA) and squamous cell carcinomas (SCC) in skin. We are currently studuying such differences in more detail with genomic arrays, FISH, and tissue micro arrays with protein expression.

Ragnhild A. Lothe and her group, in the Department of Cancer Prevention, Institute for Cancer Research, study **NOVEL DIAGNOSTIC MARKER IN COLORECTAL CARCINOMA.**The incidence of CRC is increasing, and approximately 3400 new cases are diagnosed yearly in Norway.The lack of non-invasive methods to identify the precursor lesions and to pinpoint the ones with malignant potential, call for novel molecular diagnostic markers. The high mortality rate among those with this malignancy suggests the need for new informative predictive and prognostic markers to aid in the identification of those who will benefit from more aggressive therapy and those who is best treated with surgery alone. We have in series of polyps stratified according to size, architecture, in vivo growth and multiplicity identified gene mutation and gene methylation profiles in order to identify common and early events in the development of these tumors. We aim to identify a set of bio-markers suitable for analyses of DNA from feces in order to pinpoint tumorigenic changes potentially present. Furthermore, the time of clinical intervention may be assessed from the type and number of changes present in the DNA. To identify yet undiscovered genes predisposing to colorectal cancer the genome biology of series of young at onset are compared with those of late at onset patients. To identify differences among carcinomas of the various large bowel segments we are analysing the genome, epigenome and transcriptome, and from this we select single components and targeted pathways for further detailed studies. Novel biomarkers are being clinically validated by use of existing tissue microarrays. This is a synopsis of several protocols each involving many active partners in the clinic and in pathology from national hospitals as well as from international basic research laboratories.



Gunhild Mælandsmo and her group in the Department of Tumor Biology, Institute for Cancer Research, are studying **RADIATION BIOLOGY IN THE LARC-RRP (LOCALLY ADVANCED RECTAL CANCER – RADIATION RESPONSE PREDICTION) STUDY.** LARC encompasses rectal tumors that grow through the rectal wall to an extent that precludes surgical removal with sufficient microscopic margins. Standard treatment of LARC is multimodal, involving preoperative chemoradiotherapy (CRT), which intends to achieve down-staging of the tumor to allow complete surgical removal. However, radiotherapy also causes damage to healthy tissues, which confers the risk of short- and long-term complications. Importantly, CRT responses vary greatly, from complete response, with no remaining tumor cells in the surgical specimen, to lack of objective response. Hence, it would be useful to select and treat only those patients likely to benefit from preoperative CRT. We have hypothesized that the intrinsic biology of the individual tumor may determine CRT response, but with involved biological mechanisms that are both complex and largely unknown. The project aims at identifying molecular and metabolic signatures of tumors before CRT that are associated with CRT response, assessed as Tumor Regression Grade. Magnetic resonance spectroscopy (MRS) and diffusion weighted magnetic resonance imaging are two in vivo non-invasive methods for monitoring of tumor physiology and metabolism. Kinase activity microarray analysis and ex vivo MRS will provide molecular and metabolic profiles of tumor biopsies that may correlate to CRT response. The multiplex profiling of kinase activity in protein lysates from tissue biopsies is performed using microarrays with peptide substrates (Tyrosine Kinase PamChip® arrays), a novel technology that provides the opportunity to monitor multiple kinase/substrate interactions in one experimental run with real-time kinetic read-out of the reactions. Currently (January 2008), 75 of intended 100 LARC patients are enrolled into the LARC-RRP study.



Gynecological cancer

Treatment program

The leader of the gynecological program is ***Claes Tropé.*** Age adjusted incidents of ovarian cancer in Norway is 14 per 100.000 women. 490 new patients were diagnosed in 2005. The age adjusted incidents rates in endometrical cancer is 16 per 100.000 women. 530 new cases were diagnosed 2005. The age adjusted incidents for cervical cancer is 10 per 100.000 women. Number of new cervical cancer diagnosed in 2005 was 297. Incidents of vulva and vagina cancer are not registrated. The number of new vulva cancer in 2005 was 34 and the new number of vaginal cancer was 18. Number of choriocarcinoma was 6.

At the hospital the 5 year survival rate for ovarian cancer is 44%, for cervical cancer 76%, for corpus cancer 82%, for vulva cancer 75%, for vaginal cancer 60%, and for choriocarcinoma 98%.

PATIENT GROUPS

In 2006, the hospital treated 230 new patients with ovarian cancer, 145 with cervical cancer, 165 with endometric carcinoma, 6 with vaginal carcinoma, 26 with vulva carcinoma, and 7 patients with choriocarcinoma. Still about 70% of ovarian cancer patients have stage III-IVdisease. 30% of cervical cancer, 15% of corpus cancer and 50% of vulva cancer patients have stage III-IV disease.

The hospital treated 3400 policlinic patients with cervical cancer, 30 choriocarcinoma, 3300 ovarian cancer, and 640 vulva/vagina patients. Hospitalized patients were 760 with ovarian cancer, 400 with cervical cancer, 360 with corpus cancer, 43 with vaginal cancer and 158 with vulva cancer. 65 Wertheim operations, 50 total hysterectomies, 200 ovarian cancer operations, 28 vulva/vagina cancer, 40 bowel resections, 6 exenterations, 8 trachelectomies, and 15 laparoscopic operations whereof 10 laparoscopic robotic Wertheim operations were done in 2006. The treatment modalities are surgery, radio therapy, IV and IP, chemotherapy and hormon therapy.

30-40% is treated in prospective protocols, with the research goals:

- Develop our role as the strongest research milieu in the country on gynecologic oncology with an extensive international interface.
- Clinical medicamental research: 20 various ongoing studies, with 6 prospective multinational randomized studies with NSGO, EORTC, MRC, GOG and GCIG.
- Translation research within ovarian cancer, endometrial cancer, cervical cancer and vulva cancer. Collaboration projects with the Institute for cancer research.
- Collaboration project with the Cancer Registry of Norway: a prospective quality register on ovarian cancer
- Develop ultramodern molecular biology laboratory for ovarian cancer patients
- Pre-operative molecular biological and dynamic MR report at endometrial cancer
- Prospective quality of life studies in treatment of gynecologic oncology patients
- Introducing Leonardo da Vinci robotic surgican techniques, especially in cervical cancer with radical hysterectomy plus lymph adenectomy.
- Fertility saving surgery in early ovarian and borderline ovarian cancer and in early cervical cancer.

Ongoing quality of life studies

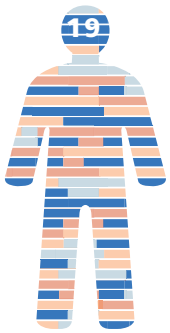
1. Somatic and mental health status in women who have performed prophylactic oophorectomy because of risk of ovarian cancer, a follow-up study.
2. Morbidity and quality of life in epithelial ovarian cancer survivors.

Ongoing clinical studies for ovarial cancer

1. EORTC 55971. A randomized phase III study comparing upfront debulking surgery vs neoadjuvant chemotherapy in patients with Stage IIIc or IV epithelial ovarian carcinoma
2. NSGO-OC 0101. A randomized study of chemotherapy vs hormonal treatment in patients with ovarian cancer, resistant or refractory to platinium and taxane.
3. NSGO-OC-0401: CalypsoA Multi-National, randomized, phase III, GCIG Intergroup study comparing pegylated liposomal Doxorubicin (Caelyx®) and Carboplatin vs. Paclitaxel and Carboplatin in patients with epithelial ovarian cancer in late relaps (<6 months)
4. ICON7: A randomised two-arm, multi-centre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer.
5. Trial designed to evaluate the safety and efficacy of adding bevacizumab, a humanised monoclonal antibody against Vascular Endothelial Growth Factor (VEGF), to standard chemotherapy with carboplatin and paclitaxel.

Ongoing clinical studies for endometrial cancer

1. NSGO-EC-9501. A randomized trial of adjuvant treatment with radiation plus chemotherapy vs radiation alone in high risk endometrial carcinoma.
2. NSGO-EC-0302: Exemestane in advanced and recurrent endometrial carcinoma. A multicentre non-randomized Phase II study.



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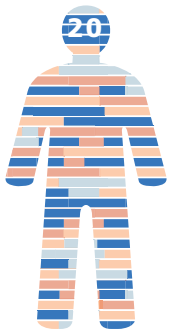
3. Molecular biological and dynamic MR as preoperative account to find optimal treatment of patients with early endometrial cancer
4. Laparoscopic robotic surgery of endometrial carcinoma

Ongoing clinical studies for cervical cancer

1. Fertility preserving surgery (Trachelectomi).
2. Laparoscopic robotic surgery of cervical cancer.
3. EORTC protocol 55994: Randomized phase III study of neoadjuvant chemotherapy followed by surgery vs. concomitant radiotherapy and chemotherapy in FIGO Ib2, IIa>4 cm or IIb cervical cancer.
4. Weekly Taxol in cisplatin resistant residue of cervical cancer.
5. Dynamic MRI of cancer cervicis uteri as method for prediction of residual, metastatic disease and radiation sensitivity.
6. Radiation induced late effects in the pelvis region after combined external and intracavitary radiation therapy by cancer cervicis uteri. Patients who receive curative radiation therapy are included in this study, where radiation biological data and data from dynamic MR are coupled against clinical data and follow-up with registration of radiation discomfort and quality of life.
7. Hyperbar oxygen treatment for injuries among gyneacological patients caused by radiaton.
8. NSGO-CC-0304: Combretastatin Phase I-II-III studies of Cisplatin and Combretastatin (CA4P) in recurrent or advanced cervical cancer.
9. The primary objective (Phase I) is to establish the maximally tolerated dose (MTD) of Combretastatin combined with weekly Cisplatin in patients with advanced cervical cancer.



Ongoing clinical studies for vulva cancer

1. Evaluation of the total material from the hospital from 1990, 500 cases
2. Sentinal node study in order to find optimal non-mutilating treatment.
3. NSGO-CC-0301: Vulva A phase II study of management of the patients with locally advanced (FIGO III & IVa or stage II unfavorably located lesion) or relapsed vulvar carcinoma.
4. A non-randomized, open, multi-centre, phase II study to evaluate the effect of radiotherapy and concomitant cisplatin in patients with locally advanced or relapsed vulvar cancer.

MAIN CLINICAL RESEARCH PROJECTS

• Molecular pathology

Image cytometric DNA ploidy analysis of endometrial carcinoma with effect

1. To determine the reproducibility of different DNA ploidy parameters using manual and automatic high resolution analysis.
2. To evaluate local heterogeneity of DNA ploidy and related parameters with special reference to curettage and resection specimens of endometrial carcinoma.
3. To study the correlation of DNA ploidy and related parameters with histologic subtypes of endometrial carcinoma.
4. To evaluate the prognostic significance of DNA ploidy and its parameters in different histologic subtypes and grades of endometrial carcinoma.

To study the prognostic significance of molecular markers in DNA ploidy categorized groups of endometrial carcinoma

• Radiation biology

Molecular markers in radiotherapy of cervical cancer are studied. Molecular methods based on microarrays will be combined with MR and PET techniques to find biomarkers that can be utilized for biologically optimized therapy. The aims are to

- Identify predictive biomarkers for the therapeutic outcome, including patient survival, locoregional tumor control and normal tissue side effects.
- Identify key radiation regulated pathways in tumors and possible targets for molecular intervention.
- Explore how the molecular findings can be combined with functional (MR and PET) and molecular imaging in treatment planning and response monitoring.

• Cancer genetics

Molecular mechanisms in development and progression of vulvar cancers are studied with the main aims:

- Identify genes and gene products, which may be important for the development and metastasis of vulvar cancers.
- Search for prognostic markers which may help the clinician to tailoring the treatment.

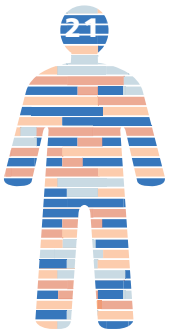
Sub aims:

1. Examining cell cycle markers which are involved in G1/S- and G2/M-checkpoint (p15, p57, CDC25C, CDC25A, CDC25B, 14-3-3 sigma, chk1, chk2, cdk1, cyclin B).
2. Investigate connection between p53, mdm2 and p33 or p14.
3. Study apoptotic markers (bax, noxa, puma, bcl-2, bcl-XL, Mcl-1, aktivert caspase-3, -8, -9, XIAP).
4. Examining E-cadherin, catenins, matrix metalloproteinases.
5. Analyzing the importance of the markers from numbers 1-4 in development, metastasing and prognosis.

NATIONAL/REGIONAL FUNCTIONS

Since 1987 the Division of Obstetrics and Gynaecology has been the National Competence Center for Gynecologic Oncology in Norway, and Claes Tropé is the leader of this competence center. The division has the national function for pelvic excenteration and rare ovarian tumors and choriocarcinomas, and is a regional center for gynecologic cancer for Health Regions South and East.

Research programs



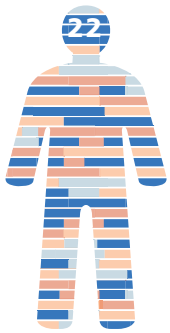
Ben Davidson, from the Division of Pathology, is involved in METASTASIS BIOLOGY. The project focuses on characterization of metastatic cancer cells in effusions, the primary tumor type being ovarian carcinoma, with comparative models of breast carcinoma and malignant mesothelioma. The project utilizes established methods (immunohistochemistry, western blotting, flow cytometry, PCR) and high-throughout technology (Affymetrix arrays, Proteomics and SNP arrays) for identification of novel biomarkers related to cancer cell survival and chemoresistance, with correlation to patient outcome. Additional part of the project deals with analysis of chemoresistance and anti-apoptotic mechanisms in tumor cells in vitro and in clinical material, using flow cytometry as the main quantitative method. Finally, novel markers are evaluated for the diagnostic role in effusions cytology.

Vivi Ann Flørenes, from the Division of Pathology, focuses on **CANCER PREVENTION.** Ovarian cancer is the leading cause of death from gynecological cancers. 5-years survival is disappointingly low since most patients present with metastatic disease and to primary or acquired drug resistance. The aim of this project has been to develop a test to screen fresh tumor material for resistance to chemotherapy treatment. In brief, fresh tumor material are minced and single cell suspensions are plated out in polyhema-coated round-bottom 96-plates.Polyhema prevents cells to attach, thus preventing the growth of normal cells. Very high doses of drugs or combination of drugs are added to the cells and proliferation are measured after 5 days following labeling of the cells with 1 µCi [3H]Thymidine (American Radiolabeled Chemicals, Inc, St. Louis, MO) for the last 24 hours before harvesting using a Filtermate harvester (Packard Instrument Company, Meriden, CT). [3H]Thymidine incorporation was assessed in a Packard Microplate Scintillation Counter (Packard Instrument Company). Controls were incubated with medium containing solvent only. So far tumor material from approximately 150 patients has been tested, and we are currently evaluating our results by comparing with clinical response.

Ruth Holm, from the Division of Pathology, studies **FACTORS INVOLVED IN DEVELOPMENT AND METASTASIS OF GYNECOLOGICAL CANCERS.** Malignant tumors of the female gynecological system includes cancers of the ovarian and tube (450), corpus uteri (350), cervix uteri (350), vagina (10) and vulva (60). The number in brackets shows approximate number of new cases each year in Norway. Several of these gynecological cancers have an aggressive malignancy and high mortality rate. Studies of biomolecular factors are important in understanding the biology of a given disease (genesis and progression). Furthermore, knowledge of prognostic factors could help tailor treatment so that overtreatment can be avoid in low risk groups and adjuvant treatment only is given to patients with a high risk of relapse. The aims of the present project were to identify genes and gene products which may be involved in the development and metastasis of gynecological cancers. Furthermore, we wanted to search for prognostic markers which may help the clinician to tailoring the treatment. In our project we focus on cell cycle proteins, apoptosis markers, human papillomavirus, adhesion molecules and matrix metalloproteinases. Several methods will be used: Immunohistochemistry (single-, double- and triple-staining), immunoblotting, in situ hybridization, PCR, temporal temperature gel electrophoresis, microarray, Southern blotting combined with PCR techniques and NASBA method.

Einar K. Rofstad and his group, from the Department of Radiation Biology, Institute for Cancer Research, are studying **NON-INVASIVE DETECTION OF TUMOR HYPOXIA BY DCE-MRI.** Tumor hypoxia is the primary cause of radiation resistance in several histological types of cancer. The main aim of the project is to develop a non-invasive method for detection of hypoxic regions within tumors. Our hypothesis is that dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) may be a useful method. Amelanotic human melanomas and human cervix carcinomas xenografted into BALB/c-nu/nu mice are used as preclinical models of human cancer. Clinical studies are performed in cervix carcinomas. DCE-MRI is performed at 1.5 T by using a clinical MR-tomograph. Gd-DTPA is used as contrast agent. Oxygen tension is measured by using oxygen electrodes and hypoxia markers (pimonidazole).

The ovarian cancer research group led by ***Clas Tropé*** has a wide range of interests. One project focuses on the biology of metastatic cancer cells originated from ovarian cancer (main area), breast cancer and malignant mesothelioma, three tumors that frequently involve the serosal surface of the peritoneum and the pleural cavity. Our work focuses on differences in the expression of metastasis- and cancer-associated molecules in the progression from primary tumor to effusion/solid metastasis, including events related to transcriptional regulation and signaling. Recent focus in our lab is on mediation of cancer cell survival and proliferation in effusions, as well as chemo resistance. Collaborative work with centers in the USA focuses on genetic profiling of these tumors using cDNA arrays, digital kariotyping and SNP arrays. Work is also done with collaborators in Israeli centers on regulation of metastasis. We collaborate with several research groups (in molecular genetics, pathology and tumor biology) at the The Rikshospitalet University Hospital, together with research groups at universities abroad, around the investigation of biological conditions around ovarian cancer. The parameters we study are:



A. 1 GROWTH FACTORS AND TYROSINE KINASE RECEPTORS

These growth factors are expressed in any ovarian tumors and their membrane receptors are often altered (mutated or over-expressed) in this cancer type. They are responsible for cancer cell proliferation and growth and aid in inhibiting tumor cell death following chemotherapy. We will analyze mRNA and/or protein expression and activation of several receptors that have shown to be expressed in ovarian cancer. Some of them are also involved in blood vessel formation (angiogenesis), an important factor in tumor growth. Drugs that inhibit these growth factors or their receptors (Iressa, Gleevac, Avastin) are in clinical trials at present. The following receptors will be studied:

- Epidermal growth factor (EGFR) family - EGFR, c-erbB-2, c-erbB-4
- Platelet-derived growth factor receptor (PDGFR)
- c-met (receptor for hepatocyte growth factor)
- Fibroblast growth factor (FGF) and its receptors (1-4)
- Vascular endothelial growth factor (VEGF) and its receptors (KDR and flt1)

2. MULTIDRUG RESISTANCE (MDR) MOLECULES

These are proteins that are involved in resistance of cancer cells to chemotherapy. Tumors expressing these markers do not respond to one or more drugs used in chemotherapy. We will study the expression of several molecules in this family (P-glycoprotein, LRP, others).

3. STUDY OF INTRACELLULAR SIGNALING

Growth signals from the cell membrane are transferred into the cell nucleus via proteins that put phosphate groups on their targets (kinases). In the nucleus, they activate the synthesis of molecules involved in cancer growth and metastasis. Many of these signal transduction molecules are now studied as therapeutic agents, and this approach will get more and more common in the future. We will analyze the activation (phosphorylation) of the proteins involved in signaling. We hope to use a novel chip with antibodies against many of these molecules (AKT, mitogen-activated protein kinases, others) that will provide the "profile" of the tumor.

4. IMMUNE RESPONSE PARAMETERS

In some patients, the immune response is not activated once tumor is present, making the body defense against cancer much weaker. Some of these patients can benefit from stimulation of the response. In other cases, we may get important prognostic information that will aid in treating the patients more or less aggressively. We wish to study the expression of two families of these molecules, cytokines and chemokines, in the tumors.

5.IN VITRO CULTURES FOR CHEMOTHERAPY SENSITIVITY

We culture cancer cells and test their sensitivity for the drugs that are most often used in chemotherapy for ovarian cancer. The recommendations from ONCOTECH will be followed.

6. ANALYSIS OF CHEMOTHERAPY EFFECTS

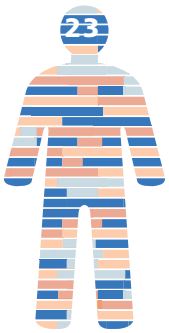
Some patients receive treatment that is not affecting the tumor and suffer from the effects of chemotherapy with no benefit. In order to avoid this, we consider analyzing the expression of molecules involved in cell death (apoptosis). This is a good parameter for evaluating chemotherapy responses.

7. DETECTION OF MICROMETASTASES

We have more than 10 years experience with the diagnostics of micrometastases. We have worked mainly with breast cancer, prostate cancer and colorectal cancer. Tumor cells enter the bloodstream and may remain in the bone marrow for longer periods. These cells may return to the blood and spread to distant organs, a process that results in high mortality. We wish to analyze the bone marrow of the patients and learn about the prognostic role for finding cancer cells there. We do have preliminary study of micrometastases in ovarian cancer patients, but did not find any prognostic significance. However, technology has changes since then, and now we have the intention to include a larger series of patients. We do know that for breast cancer patients, prostate cancer patients and colorectal cancer patients it is an important prognostic factor and also a tool to analyze treatment response. The laboratory and equipment needed is already in routine use. The bone marrow aspirations are standard procedures and their handling in the Micrometastasis Laboratory is also standard, with the use of immunocytochemistry on cytospins made from mononuclear suspensions. For detection we apply cytokeratins, a marker present in epithelial cells and usually not present in the normal bone marrow. In the future we will characterize the tumor cells detected, so that we can explore the possibility to tailor the treatment after the phenotype expressed on the surface of the tumor cells. This will also be done in close collaboration with Gustav Gaudernack and his team, designing immunotherapy for the individual patient.

8. PROTEOMICS

This is another novel method that allows us to evaluate many (up to hundreds) proteins simultaneously and see the profile of the cancer cells. In this manner we can apply the best therapy. We will analyze the tumor material with this technique, in collaboration with Professor Gert Auer at the Karolinska Institute in Stockholm. Protein expression profiles and gene expression profiles are very valuable for exploring the mechanisms in cancer development and will also be important in designing treatment for the patients.



B. OBJECTIVES FOR TRANSLATIONAL RESEARCH OF ASCITES AND PLEURAL EFFUSIONS

- Studying molecular mechanisms of tumor progression in ovarian carcinoma (OC)
- Studying OC cell survival mechanisms and chemotherapy resistance
- Analyzing the biology of OC cells in effusions
- Optimizing cancer diagnosis in effusions

• Tumor progression studies using Affymetrix arrays

1. Prognostic segregation of patients with OC effusions based on array signatures (60 patients, in progress)
2. Patient-matched analysis of primary tumors, effusions and solid metastases (30 patients, planned 2008-2009)

• Analysis of chemo resistance in OC

1. Immediate profiling of tumor sensitivity to chemotherapy in order to optimize patient treatment (>50 patients, ongoing)
2. Molecular analysis of cellular anti-apoptotic and pro-survival mechanisms in patient material and in vitro (200 patients, ongoing. Studying the clinical role of bone marrow micrometastasis in OC
1. To study the presence, extent and clinical role of micrometastases in the bone marrow of OC patients, planned 2008-2009)

• Optimizing OC diagnosis in effusions

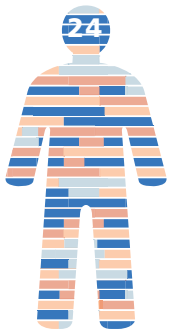
1. To study potential markers for identifying OC (and other cancer) cells in effusions (ongoing, work based on Affymetrix study with Johns Hopkins)
2. To analyze the site-related expression and prognostic role of the new markers

C. MOLECULAR MECHANISMS IN DEVELOPMENT AND PROGRESSION OF OVARIAN CANCERS.

Main aims: Identify genes and gene products, which may be important for the development and metastasis of ovarian cancers. Search for prognostic markers which may help the clinician to tailoring the treatment.

Sub aims:

1. Examining cell cycle markers which are involved in G1/S- and G2/M-checkpoint (p15, p57, p18, CDC25C, CDC25A, CDC25B, 14-3-3 sigma, chk1, chk2, cdk1, cyclin B).
2. Investigate connection between p53, mdm2 and p33 or p14.
3. Study apoptotic markers (bax, noxa, puma, bcl-2, bcl-XL, Mcl-1, aktivert caspase-3, -8, -9, XIAP).
4. Examining E-cadherin, catenins, matrix metalloproteinases
5. Study the changes of G2/M-phase and apoptotic markers after chemotherapy treatment.
6. Analyzing the importance of the markers from numbers 1-4 in development, metastasing and prognosis.



Head and neck cancer

Treatment program

Jan Folkvard Evensen is the head of the head and neck tumor treatment program. Squamous cell carcinoma in the head and neck region is becoming a still more frequent disease and is now the fourth most common malignant disease worldwide. A total of 550-600 cases of cancer in this region are annually registered in Norway. Excessive use of tobacco and alcohol are among the causative factors for this. Another increasingly important causative factor is human papilloma virus (HPV). Today, approximately ¼ of oropharyngeal carcinomas are HPV induced. However, this disease seems to differ from the tobacco- and alcohol induced disease, with different histology and different prognosis. Five years survival for localized disease in oral cavity and throat is 75% for women, 63 % for men. Five years survival for locoregional disease is 35 % for both genders. The prevalence in Norway is 4500. Since 1983 clinical data on treatment and follow-up have been recorded prospectively (database CAHN).

PATIENT GROUPS

Characteristically squamous cell carcinoma in the head and neck region is a loco-regional disease, whereas distant metastases are rarely seen at time of diagnosis. One third of the patients are in stage I + II (T1-2N0M0) and 2/3 in stage II-IV (T1-4N2-3M0-1). Ten to fifteen percent of the patients will develope distant metastases. The treatment modalities of choice are radiotherapy and surgery, but chemotherapy has become still more important during the last years. The Fraction of patients in protocols is 10-20 %.

The main protocols:

DAHANCA: Since 1994, the hospital has co-operated with The Danish Head and Neck Cancer Study Group through the DAHANCA protocols. This co-operation has given good results and, as in Denmark, our treatment policy is now to give concomitant accelerated chemoradiotherapy with cisplatin given weekly. In addition the radiosensitizer nimorazole is given 11/2 hours before radiation, in line with the results from the DAHANCA studies.

MAIN CLINICAL RESEARCH PROJECTS

Unfortunately, treatment of cancer in the head and neck region is usually accompanied by acute as well as long term side effects, this holds true for surgery as well as radiotherapy. Much

effort is therefore put into research aimed to improve the therapeutic ratio for the respective treatment modalities. For the time being, DAHANCA 19 (Undersøgelse af betydningen af EGFr antistoffet
Zalutumumab for effekten af strålebehandling til patienter med primært planocellulært hoved-hals karcinom) is under preparation.

REGIONAL FUNCTIONS

Rikshospitalet University Hospital is one of 4 centres in Norway that treat head and neck cancer with more than 300 patient treated each year.

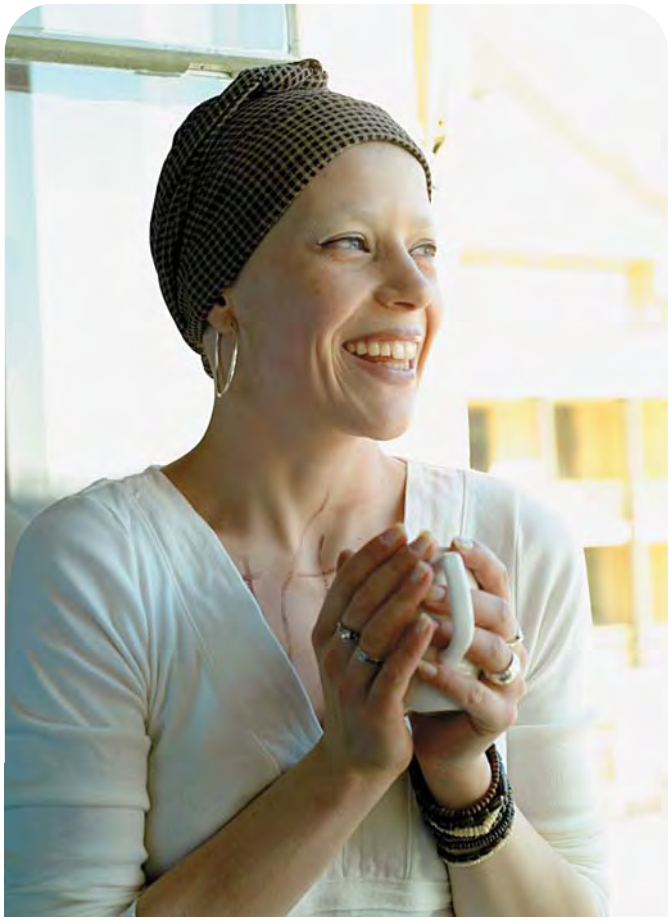
Hematological malignancies

Treatment program

Lorentz Brinch is head of the treatment program for hematological malignancies.
The main focus is on leukemias, in particular patients with acute leukemia that are candidates for potentially curative chemotherapy and/or allogeneic blood stem cell transplantation. Because of this restriction, we mainly see patients below ca. 60 years of age.

PATIENT GROUPS

We see about 20 patients per year with newly diagnosed acute leukemia from our health region, and perform 30-40 allogeneic blood stem cell transplants every year, the largest group is patients with acute leukemias in different stages. Furthermore we are following approximately 50 patients with chronic lymhoproliferative diseases (CLL, LGL; cryoglobulinaemia, CAD), about the same number of patients with CML and other myeloproliferative diseases- in coooperation with local hospitals. We perform approximately 20 high dose treatments with autologous stem cell support in myeloma patients per year. We give advice on diagnosis and treatment of patients with myelodysplastic syndromes. It should be added that we are part of the Medical Division, and we also have important functions in the diagnosis and treatment of non-malignant heamatological diseases, such as haemostasis, thromboembolic diseases, bone marrow failure, cytopenias, and haematological problems in patients with non-hematological diseases.



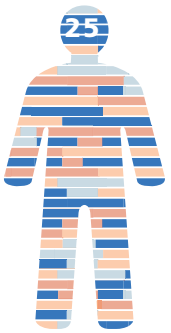
Treatment modalities are:
Allogeneic blood stem cell transplantation- myelo- and non myeloablative conditioning.
High dose treatment with autologous stem cell support.
High dose combination chemotherapy for patients with acute leukemias.
Tyrosin kinase inhibitors in patients with CML and other myeloproliferative diseases Monoklonal antibodies in patients with lymphoproliferative disorder Immunosuppressive treatment.
The fraction of patients in protocols is 100% for patients with acute leukemia, CLL, CML and myeloma, as they are treated within national programs. Less than 50% are treated within formal research protocols.

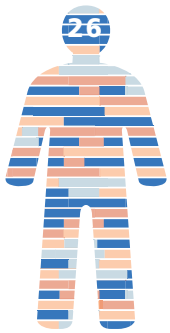
The main protocols:

- Patients with high risk CLL are treated with intensive combination chemotherapy within a nordic/HOVON protocol.
- Patients with CML not responding adequately to imatinib may be included in protocols with 2.generation tyrosine kinase inhibitors(dasatinib, nitotinib), parients with cryoglobulinemia and CAD may be included in intensive chemotherapy studies.
- Patients with LGL are treated with cyclosprin or metotrexate.
- Older patients (essentially 60-70 years) with AML in CR1 may be included in a study comparing allogeneic stemcell transplantation with dose reduced conditioning with conventional chemotherapy

NATIONAL/REGIONAL FUNCTIONS

Fomally, we have a multiregional function for allogeneis stem cell transplants, and national function for transplants with unrelated donors. We have more or less formal regional function in the diagnosis and treatment of chronic lymphoproliferative diseases and CML, and regional responsibilities in the diagnosis and treatment of acute leukemias, in particular patients below ca. 60 years, and for practical purposes also MDS.

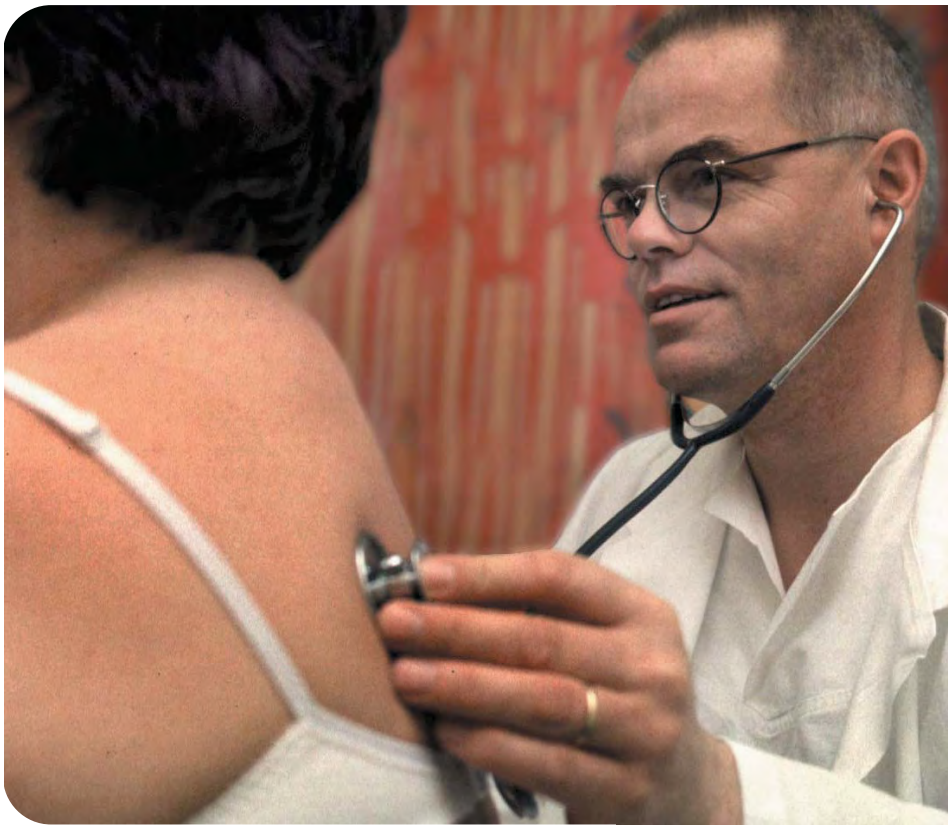




Lung cancer

Treatment program

Johny Kongerud is head of the lung cancer treatment program. The hospital is responsible for a population of approximately 0.9 million people.In 2005, 2252 new cases of lung cancer were diagnosed in Norway. The 5 year survival rate for lung cancer in Norway is about 10% for men and 13 % for women. For stage I and II the 5-year survival is 40-60% and 20-40%, respectively. For advanced disease however, the 5-year survival is only 5-10% in stage III and less than 1% in stage IV. Almost 75% of the patients are still diagnosed with advanced disease, despite the increasing use of sophisticated diagnostic tools.



About 900 new patients with lung cancer are registered annually at the hospital. Surgery is the only modality for curative treatment. At the present time only 17% of all cases are treated with surgery. The hospital has all the relevant disciplines necessary for treating patients with lung cancer; i.e. pulmonologists, thoracic surgeons, medical oncologists.etc. A PET unit is also available for the preoperative work up and follow up of patients with lung cancer.

PATIENT GROUPS

Most patients are referred to the hospital for surgery or some sort of palliative treatment. The treatment modalities are surgery, radiotherapy, chemotherapy. In 2006 and 2007 (pr. 20 Nov), 100 and 87 patients with primary lung cancer were operated at the hospital. In addition, 47 and 53 patients, respectively, were operated for lung metastases. Patients from Health Region South are treated with radiotherapy at our institution and in Kristiansand. The estimated need for radiotherapy is 64 % of the total number. Only 40% of the patients are treated ambulatory. About 10 % of the patients are treated with radiotherapy with a curative intention. Chemotherapy is given at a specialized unit or at the ward for lung cancer, but most patients are referred back to their local hospital for adjuvant chemotherapy. The treatment for all patients is discussed at regular multidisciplinary meetings twice a week with video- transmission to the local hospital. The Norwegian Lung Cancer-Group, NLCG, has established National Guidelines for the treatment of patients with lung cancer. All patients are treated according to these guidelines and protocols for different stages oflung cancer. The fraction of patients in protocols is 10%. Our phase I/II/III studies are carried out in cooperation with Department of Clinical Cancer Research and Studies and NLCG.

The main protocols are:

- Telomerase peptide vaccination in patients with NSCLC. Phase II study. A total of 15 patients included. The patients are trteated with vaccination after having finishing concurrent chemo-radiotherapy.
- Pharmacokinetic and pharmacogenetic analysis of docetaxel at different dose levels.
- Micrometastasis in patients with NSCLC. 200 patients included.
- Radiofrequency ablation in patients with tumors of the lung (Division of Medical Imaging and Intervention)
- Studies in cooperation with NLCG: Phase III in both Small cell and non small cell lung cancer
- Studies in cooperation with pharmaceutical industry
- Studies in patients with brain metastases with palliative team

MAIN CLINICAL RESEARCH PROJECTS

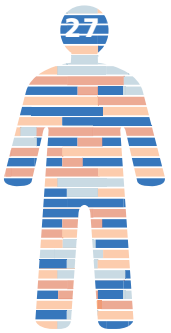
- LuCan - a Medinsight database: Establishment of a lung cancer biobank and clinical database•
- Diagnostic value of PET/CT scan in lung cancer diagnosis and treatment. Department of Respiratory Medicine.
- Immunotherapy targeting lung cancer stem cells. Department of Immunology, Institute for Cancer Research
- Identification and evaluation of new markers for early detection of lung cancer. Department of Clinical Oncology, Division of Cancer Medicine and Radiotherapy
- Early detection and characterization of metastatic cells. Department of Tumor Biology, Institute for Cancer Research
- Isolation and characterization of cancer stem cells from lung cancer. Department of Cell Therapy, Division of Cancer Medicine and Radiotherapy, and Division of Pathology

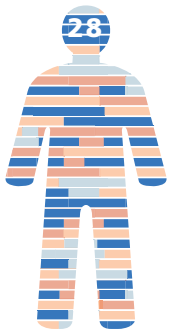
NATIONAL/REGIONAL FUNCTIONS

Rikshospitalet University Hospital is the only centre with phase I/II studies where patients with lung cancer also can be included. The Clinical Research Unit, Division of Cancer Medicine and Radiotherapy, has 2-4 beds localized in our ward. Lung cancer surgery is carried out for the all the Health Region South.

Research programs

Trine Bjøro and her group, from the Division of Laboratory Medecine, have a cooperation project with the lung cancer treatment program in immunobiology. Our group is affiliated to the project **"MOLECULAR HALLMARKS OF LUNG CANCER RELATED TO OUTCOME AND SURVIVAL"**. Small cell lung cancer (SCLC) accounts for approximately 20% of new cases of lung cancer, and advanced disease is prevalent at the time of diagnosis. This cancer displays high sensitivity to chemotherapy and radiotherapy and tumor markers play an important role in monitoring of treatment efficacy and in supporting diagnosis. Neuron specific enolase (NSE) has been the primary prognostic marker in SCLC. We have previously developed an immunological method for this marker, being applied in our routine. However, NSE has a relatively low sensitivity in early stage disease and alternative or complementary markers are needed. Serum proGRP has been shown to be a useful marker in a number of studies. ProGRP is the precursor of neuropeptide GRP and is produced frequently by small cell carcinomas. GRP was first isolated from porcine gastric fundus, and described as a gut hormone belonging to the bombesin family. We have succeeded in generating high affinity monoclonal antibodies for proGP and recently established a sensitive and robust assay for this marker. The assay is now ready for evaluation using samples from lung cancer patients.





Lymphoma

Treatment program

The head of the lymphoma program is ***Harald Holte.*** The program focuses on updated standard treatment guidelines as well as clinical, translational and basic lymphoma and –normal B-lymphocyte research. Malignant lymphoma consists of Hodgkin's lymphoma (HL, 113 new cases in Norway 2005) and non-Hodgkin's lymphoma (NHL; 777 new cases in Norway 2005). By the end of 2005, 1862 patients were alive with HL and 5375 with NHL. The survival of HL has increased steadily during the last decades, and 5-year relative survival approaches 90%. NHL is a heterogeneous group of lymphoid malignancies with 5-year relative survival ranging from 20% to 90%, depending on histology, age and other risk factors like stage, performance status and results of blood tests. HL was centralized toThe Norwegian Radium Hospital (now part of Rikshospitalet University Hospital) up to the early 1980'ies, but since then, each Health Region has taken over the responsibility for their own patients. As the hospital has had the responsibility for Health Region South and most of Health Region East, approximately 50% of the Norwegian patients have been treated at our hospital since the early 1980'ies. Similarly, the hospital has the treatment responsibility for almost 50% of the NHL-patients. During the last decade, new diagnotic tools like immunohistochemistry and molecular pathology ensures a more reliable tumor tissue diagnosis. At the same time, results from well-designed clinical trials world-wide increases the importance of a correct diagnosis as the treatment differs more and more between different histological entities. We foresee a tailored individualized treatment in the near future based on correct diagnosis including gne expression profiling, risk stratification and staging procedures.

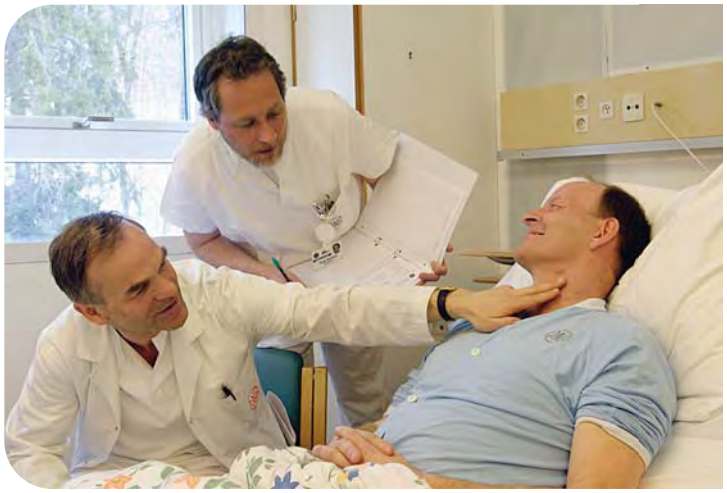
PATIENT GROUPS

Patients for whom there is a curative treatment intention are referred to Rikshospitalet University Hospital: Patients with primary and relapsed HL, aggressive primary and relapsed NHL (numerous subentities) and indolent localized NHL. In addition, many patients with indolent NHL (for whom there is no curative treatment) are referred for inclusion in clinical trials, treatment advice and radiotherapy. More than 300 new lymphoma patients are admitted yearly, with approximately 2500 outdoor consultations and 1500 hospital admissions.

MAIN CLINICAL RESEARCH PROJECTS

Radioimmunotherapy as part of the conditioning regimen before autologous stem cell transplantation in first-line treatment of mantle cell lymphoma. A Nordic phase III study. The Nordic lymphoma group has recently initiated a third phase II study, which will include radioimmunotherapy (RIT) employing Yttrium-labelled anti-CD20 antibody as part of the high-dose regimen for patients in remission after induction chemotherapy with dose intensified CHOP-Rituximab alternating with high dose Ara-C. Arne Kolstad is the head of the writing committee and the Office for Clinical Research, Department of Research Services, has the formal central responsibility for the study. We aim to treat 5-10 patients every year at our institution.

CHOEP-14 + rituximab with CNS prophylaxis in patients less than 65 years with Diffuse Large B-Cell Lymphoma/Follicular Lymphoma grade III, stage II-IV with risk factors (age adjusted IPI) A Nordic phase II study (NLG-LBC-04). The Office for Clinical Research has the formal responsibility for the study. The study for this group of patients introduces immunotherapy, intensifies chemotherapy compared to previous studies and introduces systemic CNS prophylactic chemotherapy. 130 of 160 projected patients have been included. The results will be compared to results from a previous Nordic study on a similar patient population. Several molecular and immunohistochemical projects will be performed on this homogeneous patient cohort.



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Randomized Study of Sirolimus (Rapamycin) generated donor Th2 cells and in vivo Sirolimus for GVHD prevention after allogeneic HSCT for hematologic malignancy. The study is initiated at National Cancer Institute, US. Rikshospitalet University Hospital takes part in the study as the only non-NCI institution. The clinical results of the treatment are promising. The investigational part of the study focuses on immunomodulation which from in vitro and animal in vivo studies reduces GVH while maintaining GVL effect.

Neurophysiological and pharmacokinetic studies of vincristine in chemotherapy-induced peripheral neuropathy

(in patients receiving CHOP-based chemotherapy).In this study, lymphoma patients given CHOP - like chemotherapy, the degree of peripheral neuropathy induced by vincristine will be related to: vincristine pharmacokinetics, P-glycoprotein single nucleotide polymorphism (SNP) and function of the liver enzyme CYP3A4 which is the rate limiting step in the degradation of vincristine. 100 patients will be included from the lymphoma section, in the Division of Cancer Medicine and Radiotherapy.

VACCINE STUDIES

Gene expression microarray studies and immunohistochemical analyses of tumor tissue as well as clinical histories indicate that immune surveillance plays an important role in follicular lymphomas. This surveillance is sought enhanced in a phase II study on patients with follicular lymphoma with measurable lymphoma manifestations and a wait and see policy: The patients are given a single fraction of radiotherapy to an isolated lymphoma manifestation followed by autologous dendritic cell tumor and GM-CSF injections twice. Animal studies indicate that necrotic and apoptotic tumor tissue (radiation effect) exposed to dendritic cells are phagocytosed and exposed on the surface of the dendritic cells in conjunction with MHC class II. As these dendritic cells are drained to the regional lymph nodes, the tumor antigens are presented to T-cells whereby a general immunological response is elicited. The immune response will be measured by in vivo and in vitro studies as well as by evaluating the patients for clinical responses. Planned recruitment of 20 patients will take place over a two-year period. The first patient will be treated in December 2007.

PILOT STUDY ON DIETARY INTERVENTION IN PATIENTS WITH INDOLENT LYMPHOMAS OBSERVED WITHOUT TUMOR DIRECTED TREATMENT INTERVENTION ("WAIT AND SEE POLICY").
We want to study the effect of dietary supplements on the rate of tumor growth, apoptosis, inflammation and infiltrating immune cells. Epidemiological studies suggest a link between certain food products and NHL. The patients are given dietary supplements rich in antioxidants, omega 3 polyunsaturated fatty acids, selenium and garlic.

OTHER STUDIES: The lymphoma program is by far the most prominent contributor to patient inclusion in the presently ongoing four Nordic Lymphoma Group studies not mentioned above:
-Phase II study on T-cell lymphoma including high dose therapy with autologous stem cell research (HDT).
-Phase III study in follicular lymphomas with two immunotherapies compared as first line: rituximab versus rituximab + interferon alfa.
-Phase II study in primary CNS lymphoma with intensified chemotherapy. Radiotherapy to the brain, which is associated with a high frequency of dementia, is not used as first line treatment.
-PET in diffuse large B-cell lymphomas: a blinded study of 18F-FDG-PET examination after one course of chemotherapy: If the result from early PET discriminates well enough, subsequent studies will focus on therapy intervention based on early PET results.

A pan-European phase III study in pediatric and adolescence Hodgkin's disease, further aiming at reduced long term side effects and maintained excellent event free and overall survival.

Industry sponsored study: A randomized, double blinded study of rituximab +/-galiximab (antiCD80) in relapsed follicular lymphoma. Anti CD80 is effective as monotherapy in relapsed follicular lymphoma. Will patients with relapsed follicular lymphoma benefit from combined immunotherapy compared to rituximab alone?

IMMUNOTHERAPY FOR LYMPHOMA

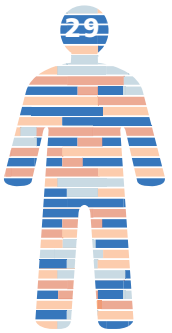
Vaccibodies

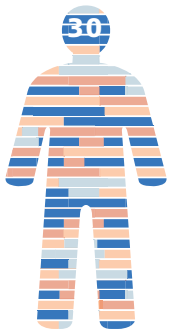
Our gene expression study has shown that the immune reaction against the tumor is the most important prognostic factor for patients with follicular lymphoma. The immune response in these patients alters survival with as much as 15 years. It is therefore very likely that boosting the immune response in these patients will result in improved survival. In collaboration with Bjarne Bogen, at the Institute of Immunology, we have started a project aiming to elicit immune responses in patients with indolent, follicular B-cell lymphomas. The project is studying responses to a newly developed vaccine formulation called Vaccibodies, which are partly made of the proteins or alternatively of the genes coding for the variable fragment of the immunoglobulin molecule of the malignant B cells (see application from B. Bogen under Research programs). The study is at a preclinical stage, but will form the basis of a phase I study where patients with indolent, follicular lymphomas in complete remission induced by chemotherapy will undergo vaccination with Vaccibodies made from their own tumor immunoglobulin molecules.

Autologous T-cells with transient expression of B-cell antigens

The lymphoma/immunology/immunotherapy group at our hospital has considered different options for development of immunoterhapy for patients with malignant lymphoma. During the last year, there has been considerable progress in the area of T-cell expansion and transient transfection with artificial mRNA constructs. Artifical T-cells which transiently express receptors for surface markers on tumor cells (eg CD19) have been produced and tested in vitro for abilities to kill tumor cell lines of B-cell origin. The group now seeks to expand this work and to set up a phase I/II trial in patients with relapsed/refractory B-cell lymphomas using mRNA transfected autologous T-cells expressing different artificial receptors.

CT contrast enhancement characteristics of lymphomatous lymph nodes. The project is headed by ***Trond Hagtvedt*** at the Division of Medical Imaging and Intervention. In a previous pilot-





study we found lymphomatous lymph nodes of the neck to have significantly less CT contrast medium enhancement than presumably normal neck nodes. These findings are confirmed in a prospective larger study of untreated lymphoma patients. Lymph nodes with Hodkin and lymph nodes with non-Hodgkin lymphoma had similar enhancement curves in the corresponding time span.

These enhancement patterns of lymphomatous neck nodes should be compared to the enhancement pattern of lymphomatous lymph nodes of other anatomic regions as mediastinum and retroperitoneum. The specificity compared to diseases as granulomatous diseases, mononucleosis and squamous cell carcinoma should also be elucidated. Dynamic contrast-enhanced CT studies may result in better and more differentiated interpretation of head and neck CT in patients with lymphoma

INTERNATIONAL COLLABORATION

Lymphoma/Leukemia Molecular Profiling Project

The lymphoma milieu at our hospital is one of four European groups participating in a large international collaborative project regarding molecular profiling of B-cell lymphomas (headed by Dr. Louis Staudt at NCI, ***Erlend. B. Smeland,*** head of the Institute for Cancer Research, is site PI). So far, these studies have revealed and charactereized 3 previously unrecognized subgroups of Diffuse Large B-Cell Lymphomas (DLBCL); ABC, GCB and PMBCL, with distinct gene expression profiles, distinct genetic abnormalities and different prognosis. Importantly, we have shown for DLBCL, Mantle Cell Lymphomas and FL that gene expression profiles correlate to prognosis. Interestingly, in FL expression of two gene signatures reflecting infiltrating non-tumor cells in biopsies strongly correlate to prognosis. Importantly, gene expression profiling allows a precise distinction of Burkitt lymphoma and DLBCL with c-myc translocations, in contrast to current diagnostic methods for which speration of these entities is difficult. Several other subprojects have been performed, including genome-wide CGH analysis and analysis of specific translocations. The CGH data have been correlated to microarray RNA expression data and the clinical dataq from the same data set. Moreover, immunohistochemical analysis (TMA), which by itself may lead to better routine diagnostic practice, has been initiated to validate some of the results at the protein level. We have recently received NCI support for a broad prospective LLMPP study to test the diagnostic accuracy and robustness of a diagnostic lymphoma microarray with approximately 3000 genes, selected from the previous studies of the main subgroups of B cell lymphomas. The study has started and analysis of Norwegian samples are being analysed at our hospital. We have received approval for this study from relevant authorities. The array has been tested and there is excellent concordance of the data between the centers taking part in the study. The study will continue for several years involving a retrospective and a prospective part with consecutive cases. The clear advantage of the array is that diagnoses will be objective and accurate, which we can offer our patients already within a few months. Of even greater importance, the array includes prognostic parameters which by far surpass all other prognostic parameters brought forward in the two last decades, including the International Prognostic Index or adapted clinical indices. The use of the diagnostic array allows objective and accurate risk stratification for the purpose of clinical trials. We can therefore expect novel treatment modalities that will results in improved patients survival and well-being.

Retrospective Immunohistiochemical and clinical study of follicular lymphoma

For years, there has been a discussion in the international lymphoma milieu whether grading of FL (1-3) is of clinical interest or not. The grading is based on the percentage of blastic B-cells in the tumor (centroblasts) compared to centrocytes with lower proliferation rate. For the last decade, most centers (including our) have treated follicular lymphomas grade 3 as DLBCL, that means with aggressive immunoradiotherapy with cutrative intent. Molecular studies and studies employing karyotyping indicate that there is a shift between subcategories of FL3; grade 3a versus grade 3b. However, no clinical study with adequate design and power (number of patients) has answered which therapy should be given to the different categories of grade 3 disease. In cooperation with dr Eva Kimby at Huddinge, we will perform this analysis retrospectively as we have treated several hundred patients according to the same protocol. The grading of all follicular the lymphomas treated since year 2000 will be performed by the same person at both institutions.

Characterization of signaling networks in B-cell lymphoma and B-cell acute lymphoblastic leukemia by the use of flow cytometry

Analysis of phosphorylated proteins by flow cytometry, a method developed by Garry Nolan and coworkers at Stanford, has emerged as a powerful tool to analyze intracellular signaling events at the single cell level. The ability to simultaneously measure different cell surface markers and the levels of intracellular phosphoproteins, makes it possible to study intracellular pathways specifically in the malignant cells.This method has successfully been used to study phospho-protein responses after stimulation with relevant cytokines in acute myeloid leukemia (AML) by Nolan and coworkers. Based upon the cytokine responses, they designed bio-signatures which divided the AML samples into 4 different groups of which one of them correlated with response to chemotherapy. We will use this method to obtain a comprehensive overview over constitutive activated and inducible signaling pathways in different subtypes of B cell lymphomas (Burkitt, DLBCL and MZ) and B cell acute lymphoblastic leukemia. Our aim is to obtain different signaling profiles within each subgroup and explore whether any of these correlate with prognosis, genetic aberrations or response to therapy.

Research programs

The lymphoma treatment program is involved in several projects in collaboration with ***Jan Delabie,*** the Division of Pathology:

I) ONCOGENES INVOLVED IN SPLENIC MARGINAL ZONE LYMPHOMA

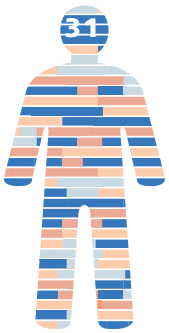
This is a preclinical research project by characterization of a recurrent translocation.

Specific oncogenes have been discovered to play a role in specific types of lymphoma. No oncogenes have as yet been discovered in splenic marginal zone lymphoma, one of the lymphoma entities. We have recently found a recurrent chromosome translocation in this lymphoma type, the t (4;14)(p11;q32). In the current project, we will characterize the oncogene localized on chromosome 4p11, which has been translocated to the immunoglobulin heavy chain locus on chromosome 14q32. The discovery of this oncogene will lead to a better understanding of the carcinogenesis of splenic marginal zone lymphoma and therefore will allow research into novel treatment strategies.

II) THE DEVELOPMENT OF A DIAGNOSTIC TEST FOR THE DETECTION OF PROMISCUOUS TRANSLOCATIONS

Human B-cell lymphomas are in large part characterized by specific gene translocations in the genome of these tumors. The identification of the translocation has become an integral part of the diagnosis and hence for treatment of the disease. In addition, knowledge of the variable partner gene in a translocation can be important for the prognosis but is the condition sine qua non for the design of molecular minimal residual disease follow-up. It is therefore our aim to develop a test to rapidly identify fusion genes in human lymphomas for the purpose of diagnosis and to allow the identification of targets for possible minimal residual disease detection. For this test, magnetic beads are coated with synthetic oligonucleotides specific to one gene or a set of genes known to be involved as constant partners in translocations. The extracted gene sequence can subsequently be used as a probe for hybridization on genomic arrays to identify both the constant and fusion partner sequences of a translocation. Gene expression patterns in T-cell lymphoma are also studied.

Harald Holte and his group study LONG TERM SURVIVORS AFTER LYMPHOMA TREATMENT. During previous years, we have investigated long term side effects after treatment for Hodgkin's disease focusing on cardiovascular effects of radiotherapy and on chronic fatigue. We have also performed quality of life studies on patients with leukaemia and lymphoma after allogeneic and autologous stem cell transplantation. Presently and in collaboration with the National Competence Center for studies on long term cancer survivors, we are performing examinations on hypophyseal and gonaldal function and fertility after curative lymphoma treatment.In collaboration with Division of Cardiovascular and Respiratory Medicine and Surgery we are also performing a longitudinal study of cardiovascular disorders at a median of 20 years after radiotherapy to the neck and chest. The results show clearly that these patients are at a lifetime considerably increased risk for developing valvular regurgitation and stenosis as well as coronary and other types of artery stenosis and trombosis. These studies are important for future studies aiming at reducing the risk of side effects as well as for designing schedules of follow up examinations.



The aim of the research group lead by **Erlend B Smeland** (also head of the Institute for Cancer Research) is genetic and molecular characterization of malignant B-cell lymphoma. In collaboration with the lymphoma milieu at our institution, they are involved in several studies using tumor material:

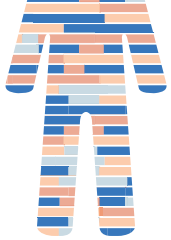
I) GENOME-WIDE CGH ARRAYS ON SERIAL BIOPSIES OF FOLLICULAR LYMPHOMA

Follicular lymphoma (FL) often transforms to a more aggressive lymphoma. However, many patients also experience relapse without apparent changes in morphology. We have access to a unique material with serial biopsies from 35 patients with FL and have performed in-house genome-wide CGH arrays with high resolution to examine if genetic changes occur during progression without transformation. The molecular findings are correlated to clinical parameters.

II) TISSUE MICROARRAY ON SERIAL BIOPSIES FROM PATIENTS WITH TRANSFORMED B-CELL LYMPHOMAS INCLUDED IN A PROSPECTIVE NATIONAL STUDY.

The Norwegian Lymphoma Group has performed a multi-institutional study on patients with transformed B-cell lymphomas employing high dose chemotherapy with autologous stem cell support for responders. Seventy-five patients (50 patients from our institution) were included. Using tissue array methodology, we want to identify changes in protein expression that are linked to transformation and correlate protein expression with clinical parameters. We will also investigate if the tumor microenvironment is of crucial importance, as previously implicated from gene expression profiling. Tissue blocks have been collected from the different hospitals and cut and are ready for examination.

Similar examinations will be performed on tumor material from the ongoing Nordic phase II studies on DLBCL and the phase III study on follicular lymphomas. These studies are dependent on the expertise at the Dep of Pathology



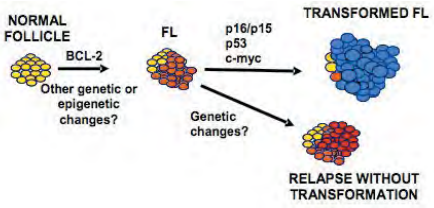


Figure: Most Follicular Lymphomas (FL) carry the t14:18 translocation where the BCL2 locus comes under control of the IgH promoter.

One third of the patients relapse with morphological transformation to secondary high-grade lymphoma with a more aggressive clinical course. Several genetic changes are associated with transformation, and c-myc and proliferation-associated genes have been reported to be involved in approximately half of these cases. In contrast, most of FL patients experience relapse without change in morphology, and less is known regarding the molecular events involved in disease progression without transformation.

III) SNP ANALYSIS OF CYTOKINE GENES IN PATIENTS WITH MALIGNANT LYMPHOMA – EPIDEMIOLOGICAL AND CLINICAL ASPECTS

Single nucleotide polymorphisms (SNP) represent the most common variation in the genome, occurring at on average every 300 base in the DNA. SNPs are found both in coding and non-coding sequences, and both types can lead to different phenotypes based on altered expression or function of the gene product. Available data suggest that SNP in genes involved in immune responses and cell growth can influence the risk of cancer development and /or influence the prognosis in different cancer types. It has been speculated that a dysfunctional balance between different cytokines can contribute to the progression from chronic infection to cancer. Such a dysbalance can be caused by polymorphism in genes encoding cytokines. Thus, it has recently been shown that polymorphism in the promoter of the IL-10 gene is associate with an increased risk of developing aggressive, malignant B cell lymphomas. We have collected blood samples from approximately 1000 patients with malignant lymphoma treated at our hospital during the past years and have blood samples from 6000 healthy control blood donors. DNA will be extracted from the blood samples and the following SNPs will be examined: IL-1 beta (-35 and -511), IL-2 (-330), IL-4 (-590), IL-6 (-174), IL-8 (-251), IFN-gamma (+874) and TGF-beta (+915). In addition IL-10 and TNF-alpha polymorphisms will be added. The analyses will be performed by a recently developed assay using denaturating capillary gel electrophoresis (established by Ekstrøm/Gaudernack), which allows high sample throughput. The data will be correlated to explore1) if polymorphisms in these genes will be correlated to the development of different types of malignant lymphoma and 2) if the polymorphisms are associated with prognosis in the different subgroups.

IV) FUNCTIONAL STUDIES

Several functional studies are ongoing in the laboratory. Of specific interest are studies on the TGF-β family members which are structurally related secreted cytokines including TGF isoforms, activins and bone morphogenetic proteins (BMPs). They are multifunctional cytokines involved in many aspects of cell function including proliferation, apoptosis, differentiation and cell fate decisions, and have an essential role in early emryogenesis and subsequent organogenesis. In contrast to the extensive work related to TGF-β, few studies have explored the role of BMP signalling in hematopoietic cells. However, the findings of Staudt and collaborators from gene expression profiling of DLBCL identifying BMP-6 as a gene with prognostic value, suggested that exploring the role BMPs in lymphomagenesis might be of value. We have in the recent years explored the role of BMP induced growth suppression in normal primary B and T lineage cells from blood and bone marrow.

These previous studies constitute a basis for our new focus to investigate the implications of BMP/TGF-☼ signalling pathways for diagnosis, prognosis and possibly as new therapeutic targets in lymphomas. At present, we are exploring whether the expression of BMPs and BMP signalling components might have prognostic impact in lymphomas. In DLBCL, survival analysis showed that whereas high BMP-6 levels correlated with poor prognosis, high BMP-7 expression correlated with good prognosis (obtained from data set of 240 DLBCL, http://llmpp.nih.gov/DLBCL/). This finding led us to further investigate whether the combination of these two markers could be an even better predictor, and found that patients that had high levels of BMP-6 and low expression of BMP-7, was associated with extremely poor prognosis, with median survival of 1.7 years. In contrast, patients with low BMP-6 and high BMP-7 had good prognosis with median survival of 9.8 years.The future focus for this project will be to identify the mechanisms for how B lymphoma cells can evade BMP-mediated growth suppression and include BMP receptors in TMA analysis of tumor blocks from clinical studies.

Trond Stokke is the head of the Section of Molecular Radiation Biology at the Department of Biophysics, Institute for Cancer Research, and studying **EFFECTS OF RADIATION AT THE MOLECULAR LEVEL.** This is studied on various tumor tissues, including lymphoma. During recent years, they have also studied the effects of radioimmunotherapy with 227Th, a targeted therapy with alfa-emitting radioimmunoconjugate, The aim of this project is to provide an alfa-emitting molecule that can be attached to various carrier molecules, including antibodies and peptides, exploiting the extreme, selective cytotoxicity of alfa particles. Thus, a radioimmunoconjugate, 227Th-rituximab, has been developed. In vitro data are very promising compared to rituximab alone. A phase I study will be started when the toxicity of the treatment is determined.

Pediatric cancer

Treatment program

Marit Hellebostad is head of the treatment program for pediatric cancer.

PATIENT GROUPS

The hospital treats children with leukaemias, lymphomas, all solid tumours inside and outside the central nervous system and histiocytoses. The treatment modalities are chemotherapy, surgery, irradiation, stem cell transplantation. Near 100 % of children with cancer are included in clinical trials, either Nordic (leukaemias and lymphomas) through NOPHO or international (solid tumours), mostly through SIOP. The follow-up into adulthood is almost complete.

The main protocols are:

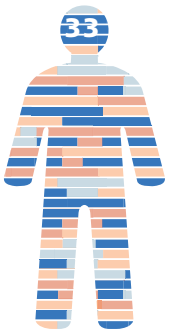
- ALL: Common Nordic protocol for various risk groups / therapy groups. Currently we use the NOPHO ALL-2000 protocol. The stratification between therapy groups is based on age, immune phenotype, peripheral WBC count, cytogenetics, specific gene rearrangements, and therapy response. For Philadelphia chromosome positive patients a specific European protocol for Ph+ ALL is used. For infants (< 1 year of age) a separate protocol (Interfant 2004). All patients are included in the clinical and biological studies linked to the protocols.
- AML: Nordic protocol NOPHO AML-2004.
- Solid tumours: Various Nordic and international protocols with associated clinical and biological studies.
- Histiocytosis (LCH and HLH): International protocols through the Histiocyte Society.

MAIN CLINICAL RESEARCH PROJECTS

1. Clinical studies: Registration and follow-up of included patients. Several biological studies linked to the protocols.
2. Follow-up: Psychosocial follow-up of adolescent and adult survivors of Acute Myelogenous Leukaemia (AML), Wilms' tumour and astrocytoma in childhood - a Nordic collaborative study.
3. Generating cancer-targeted T cells reactive with cell type-specific peptides.
4. Optimizing of dendritic cell based vaccines for therapy of paediatric cancer.
5. European neuroblastoma study: 1) Prognostic significance of genetic markers in neuroblastoma, 2) MRD in high-risk neuroblastoma.
6. ALL 2000 MRD study

NATIONAL FUNCTIONS

The program is the National Centre for Allogeneic Stem Cell Transplantation in Children.



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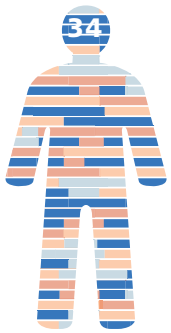


Prostate, urological and testicular cancer

Treatment program

Karol Axcrona is head of the prostate, urological and testicular cancer treatment program. At our hospital we have a multimodal treatment approach to the patient with urological cancer. Surgeons, oncologists, radiologists and pathologists work in close cooperation in pretreament and posttreatment decision making. Prostate cancer (PCa) is the most common type of cancer in men, with an incidence of 3.600 patients (pts.) and a prevalence of 20.000 in Norway. The 5 year survival is 75%. There is evidence that surgery with (robot-assisted) radical (laparoscopic) prostatectomy (RLRP/'DaVinci') and external beam radiation therapy (EBRT)/combined with high dose-rate brachytherapy (HDR-BT) can cure patients with localised and locally advanced PCa. Patients with advanced PCa disease, i.e. metastatic and/or with hormonal refractory disease are included in diverse oncological protocols. Quality of life is a substantial task.

Urinary bladder cancer is the fifth most common cancer type in Norway, incidence of 1100 patients / year. Most often the cancer is superficial, less than 10% of all urinary bladder cancers progress to muscle invasion. That necessitates surgical removal of the urinary bladder and a urinary diversion. Selected patients are treated with curative intended EBRT. Chemotherapy is added in patients in a palliative situation, or adjuvant as part of clinical protocols.

Renal cancer treatment has developed substantially the last decade. The incidence is 580 patients / year. Minimal invasive surgery is implemented. Progress has been made in treatment with chemotherapeutics interfering with cell signalling in advanced, i.e. metastatic, renal carcinoma.

The incidence of testis cancer is 270 patients / year. With a survival rate of >95%, it is an example of a multidisciplinary approach with a close cooperation of the above specialties.

Penile cancer is the least common urologic cancer- 40 patients / year. The last 5 years progress in treatment has been made in surgery with organ sparing surgery and improved survival rates through implementation of the sentinel node technique.

PATIENT GROUPS

The hospital treated 410 patients with radical surgical and radiation treatments and 180 patients with palliative radiation treatments for PCa.

The number of outdoor patients was 5250; the number of hospitalised patients1051.

Treatment modalities:

- Radical surgical treatment, e.g. 'DaVinci' prostatectomy, RPLND, Cyst(oprostat)ectomy and urinary diversion (cutaneous, orthotopic bladder).
- EBRT and/or combined HDR-BT.

- Salvage radiation treatment.
- Palliative radiation for metastases.
- Adjuvant or palliative chemotherapy, hormon therapy.

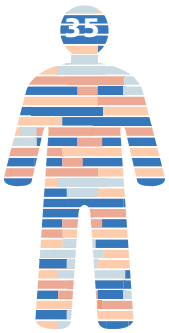
40% of the patients were in protocols. The main protocols are:

- EBRT and combined HDR-BT protocol: PCa patients are continuously included in a database for assessment of side effects and long term outcome.
- 'DaVinci': continuous monitoring of quality with respect to surgical complications, pathological outcome in patients operated with RLRP and long term results.
- AdPro: Adjuvant docetaxel chemotherapy in operated high risk patients.
- Quality of life assessment in PCa patients treated with EBRT and RLRP
- EORTC: urinary bladder- adjuvant chemotherapy
- EORTC: testicular cancer- TIP chemotherapy protocol
- NEPRO: Docetaxel in hormon resistant PCa
- IMRT: Intensity modulated radiotherapy in localised/locally advanced PCa with N+ sickness
- PFPI: Pomegranate juice in primary PCa

MAIN CLINICAL RESEARCH PROJECTS

The last years' main focus of the urologic cancer program has lied on the establishment of new clinical treatment modalities for localised and locally advanced prostate cancer, i.e. high dose-rate brachytherapy combined with EBRT and RLRP. This includes establishment of protocols, databases and logistics of patient flow in the clinical departments involved.

1. Quality of Life (QoL) study: PCa patients treated with curative intention with EBRT and RLRP.
2. PCa micrometastasis study: in collaboration with **Øystein Fodstad** from the Department of Tumor Biology, Institute for Cancer Research, the relevance of micrometastases after radical treatment of PCa is ananysed.
3. PCa stem cell/vaccine study: identification, isolation of PCa stem cells as part of the PCa vaccine project in collaboration with **Gustav Gaudernack** from the Department of Immunology, Institute for Cancer Research, **Steinar Aamdal** from the Phase I unit and **Gunnar Kvalheim** from the Stem Cell Research group, the Division of Cancer Medicine and Radiotherapy.



4. IMRT study: patients with primary PCa and lymph node positive sickness in the pelvic area are treated with EBRT towards the prostate in addition to a pelvic field with 50Gy. Pts. are monitored with regard to radiation side effects, QoL and long term outcome.
5. 'DaVinci' study: PCa patients operated with RLRP are monitored with regard to preoperative cancer data, peroperative parameters, and postoperative complications and histopathological results as well as long time survival results. MR of the prostate as preoperative stageing in PCa is evaluated in a separate study.
6. PFPI study: randomises PCa patients for treatment with curative intention to ingestion of pomegranate juice. Influence of substances in that juice are analysed in biopsies taken from PCa's, that are treated with curative intention, with regard to molecular biologic markers as a response to ingestion of that juice.
7. Photodynamic therapy in penile carcinoma in situ, planned Phase II study.
8. Testicular cancer: EORTC protocols and collaboration with **Ragnhild A. Lothe,** head of the Department of Cancer Prevention, Institute for Cancer Research.
9. Hormon resistant PCa: Chemotherapy (docetaxel) in oncologic protocols.

NATIONAL/REGIONAL FUNCTIONS

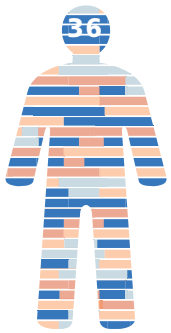
The last decade the urologic cancer program has been in the frontline on a national basis in introducing new techniques for treatment of localised/locally advanced PCa. Rikshospitalet is the only institution that has introduced HDR-BT combined with EBRT in Norway so far. At our hospital the first RLRP in Norway was performed in 2004. The technique has then been implemented in cooperation with Telemark Sentralsykehus, where a surgical team from the hospital trained surgeons at the other institute. The program is involved in several international chemotherapy protocols mainly in high risk/hormon refractory PCa, testicular cancer and urinary bladder cancer. There is a fruitful ongoing collaboration with the Cancer Registry of Norway regarding registration of PCa and epidemiology of PCa. A national study of long term side effects of radical treatment of PCa will also be initiated in collaboration with the Cancer Registry.

The potential of realising urologic cancer translational research projects through the near cooperation with the Institute for Cancer Research at the hospital is unique on a national level. Rikshospitalet University Hospital has along with Ullevål University Hospital a regional function in EBRT of localised/locally advanced PCa in Health Region South - East. The department of urology at The RikshospitaletUniversity Hospital has had the main responsibility for urologic cancer treatment in Health Region South. The department of oncology has the main responsibility for training of oncology residents in Health Region South - East. The urologic cancer program has also fulfilled the function of a second opinion instance on a regional/national level.

Research program

Ragnhild A. Lothe, head of the Department of Cancer Prevention, Institute for Cancer Research, and her group study **TGCT TUMORIGENESIS.**

Testicular cancer (usually of germ cell origin, TGCT) is the most common cancer type among young and adolescent males and the incidence has almost quadrupled during the past 50 years. The TGCT tumorigenesis is in many respects analogous to the early embryogenesis. We and others have collected strong evidences for this also being the case for the transcriptional and epigenetic programs of these tumors. By follow-up studies using our TGCT tissue microarray, which contains more than 500 tissue samples from the various histological subtypes, we are able to relate our genetic findings to clinicopathological information in a large series of patient samples. We are also investigating the TGCT patients' constitutional genotypes at polymorphic loci near or within cancer relevant genes. By integrating the tumor characteristics with the patients' genotypes, we may understand these tumors high sensitivity to drugs, predict long-term effects for the patient, and provide the tools for molecularly assisted diagnostics. TGCT is generally treatable (surgery and cisplatin), even in the presence of distant metastases. Therefore, understanding the molecular biology of these tumors could enlighten response mechanisms to chemotherapy which may be applicable to cancer in general. Furthermore, due to the young age of onset, correlations between genetics and long term effects can be investigated for this patient group. This summarises several integrated ongoing studies and include many active partners including the key clinician, Prof. Sophie D. Fosså, and pathologist Dr. Vera M. Abeler.



Sarcoma

Treatment program

Kirsten Sundby Hall is head of the sarcoma treatment program. Sarcomas are rare and only about 200 sarcoma patients are treated annually in Norway. The sarcoma program is an active multidisciplinary team consisting of specialists with high level of competence in radiology, pathology, genetics, oncology (chemotherapy and radiotherapy) and surgery. Sarcoma patients are treated at four central hospitals in Norway, but the majority is treated at Rikshospitalet University Hospital. The hospital has status as a National Resource Centre for Sarcomas for this group of patients. This status implies a continuous demand for research and development of high quality treatment. A higher degree of centralization to fewer centres is one focus for the program. The rarity of sarcomas requires collaboration with international groups on treatment protocols and research. The outcome of sarcoma patients treated at the hospital has been shown to increase over time. Improved outcome appears partly to be due to refinements in the use of existing modalities and improved quality and integration of multidisciplinary approaches. Improved formalized organization of the sarcoma program may also have contributed to improved quality.

The sarcoma program uses extensive resources on evaluation of images from local hospitals of uncertain bone and soft tissue lesions. This service seems essential for selecting patients who need further investigations. Being a national resource centre for sarcoma the program considers this service function to be important. In total 939 patients were referred in 2006. Of these 388 patients had their images evaluated without visiting the clinic. The final diagnosis was: 33 bone sarcomas, 156 soft tissue sarcomas and other malignancies/uncertain benign/malignant in 59 patients. The remaining were benign lesions. Some aggressive benign tumors however, have to be operated by sarcoma specialized orthopedic surgeons. The records from 2007 are incomplete and will not be reported.

PATIENT GROUPS

Treatment modalities in 2006:

• Bone sarcomas

Surgery only	11 patients
Surgery+ chemotherapy	14 patients
Surgery+chemotherapy+radiotherapy	2 patients
Surgery+radiotherapy	2 patients
Radiotherapy + chemotherapy	2 patients

• Soft-tissue sarcoma

Surgery	128 patients
Chemotherapy	38 patients

Radiotherapy, incomplete records and will not be reported
Surgery in benign bone-and soft tissue lesions - 109 pts

Fraction of patients in protocols:
a. Almost all bone sarcoma patients
b. A subgroup of STS with defined risk-factors
c. A subgroup of GIST with defined risk-factors
c. Most other patients are treated after treatment recommendations which are common for all sarcoma centers in Scandinavia (members of Scandinavian sarcoma group)

The main protocols are:

• Bone sarcoma

EURAMOS 1 (SSG (Scandinavian Sarcoma Group, EOI (European Osteosarcoma Intergroup), COSS (sarcoma centres in Germany. Austria and Switzerland), COG (The North American Childrens Oncology Group)): A randomized trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy. This European-American trial protocol was activated 2005. The trial is open to all patients with resectable high-grade osteosarcoma of the limbs and the axial skeleton, localized or primary metastatic. All patients are to receive a standard induction chemotherapy regime (cisplatin, doxorubicin and high-dose methotrexat). Postoperatively, the patients are randomized according to the chemotherapy response of their tumours. The good responders (<10% viable tumour) continue to receive the same regimen as they obtained before their operations, but they are then randomized to receive pegylated recombinant IFN alpha 2b in addition or not. The poor responders undergo other randomizations not involving IFN. The end-point of the trial is event free survival. The inclusion rate is on target and the aim is 1400 pts in Jan 2009. Rikshospitalet University Hospital is the leading centre in Scandinavia regarding inclusion of patients(12).
Research projects:
- Biology and genetics of osteosarcoma (leader: **Ola Myklebost**, Department of Tumor Biology, Institute for Cancer Research, coordinator SSG and Eurobonet=European Network of pathology and genetics of Bone tumors).
- Immunomagnetic isolation of tumor cells present in peripheral blood and bone marrow aspirates in osteosarcoma patients (leader **Øyvind S. Bruland**, Division of Cancer Medicine and Radiotherapy)

Euroboss I (SSG, COSS, ISG (Italian Sarcoma Group)): A European treatment protocol for bone sarcoma in patients older than 40 years. By 2006 in total 121 pts were included. No tre-

atment related death has been reported. The study will continue to the end of 2009.

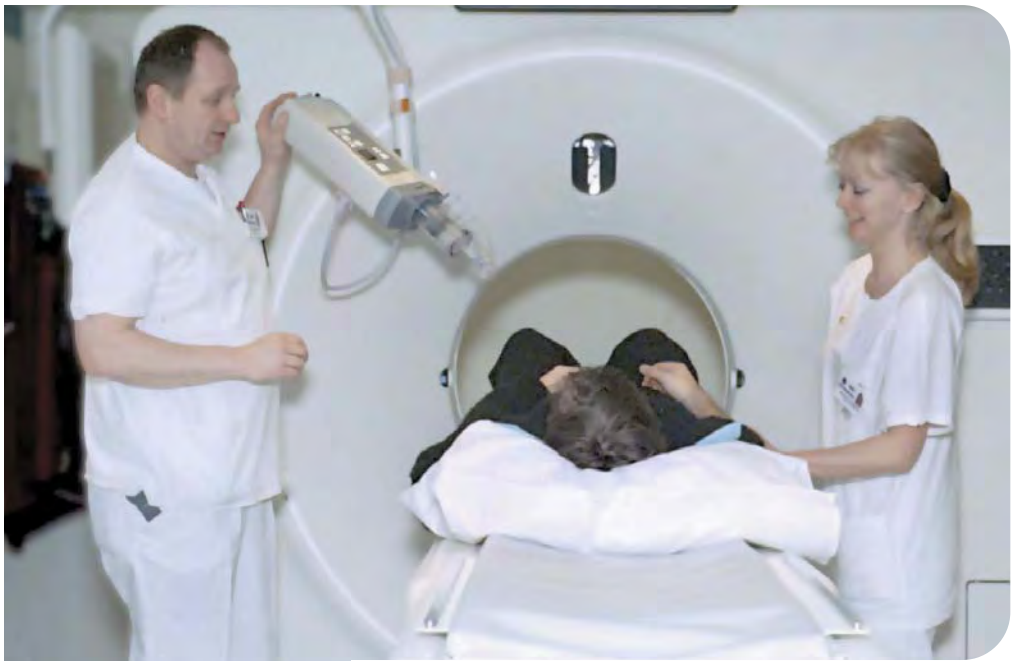
Research projects:

- Immunomagnetic isolation of tumor cells present in peripheral blood and bone marrow aspirates in osteosarcoma patients (leader **Øyvind S. Bruland**)

Co-protocol to Euroboss I: European Osteosarcoma Surveillance Study
(Aims to systematically indentify incident osteosarcoma cases in the European countries)

ISG/SSG III: An Italian – Scandinavian treatment protocol for nonmetastatic Ewing's family tumors. From 1999-2007, 296 patients have been included in the protocol, 53 from SSG. With a median follow-up of 37 months, 5 years overall and event free survival were 74% and 66 %, respectively. Compared with the former Ewing protocol for SSG –SSG IV- which showed 5years overall survival 46% and EFS 43%, the results seem encouring. Patients with poor response receiving high-dose chemotherapy with steem cell rescue had similar outcome with good responders (5 year event free survival of 70%). Poor responders with no HD had 5 years EFS 35%. The high-dose strategy for poor responders seems to improve their prognosis. Longer follow-up is needed to confirm its efficacy. The preliminary results were reported at the ASCO annual meeting June 2007.

ISG/SSG IV: An Italian – Scandinavian treatment protocol for high-risk Ewing's family tumors (metastatic disease).



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• Soft tissue sarcoma

SSG XX (Soft-tissue-sarcoma): A Scandinavian Sarcoma Group multicenter study for adult patients with non-metastastic high-risk soft tissue sarcoma of the extremities and trunk wall. The study was activated Oct 1, 2007. SSG adopts an inclusion decision algoritm for defining high-risk based on the following criteria: 1. vascular invasion or 2.presence of at least two of the risk factors: tumor size >=8cm, necrosis or infiltrative growth. The system was based on studies by Engellau et al 2007 (see reference list). Primary end point is metastasis-free survival. European centres are invited to participate.

Research project:

- A translation research part with tumor biology and pharmacogenetic studies with the aim of improved prognostic and treatment predicitive factors. (leader: **Kirsten Sundby Hall**)

XVIII (SSG/Germany, GIST): Short (12months) versus long (36m) duration of adjuvant treatment with imatinib of operable gastrointestinal stromal tumor (GIST) with a high risk for recurrence. The target number of 340 patients will soon be reached and there is discussions ongoing regarding expansion of the study.

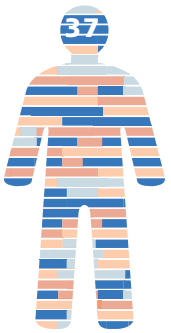
Research project:

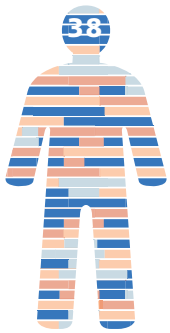
- Mutation analyses, various biochemical parameters for correlation to prognosis and effect of imatinib.

Sutent: A treatment protocol for patients with gastrointestinal stromal tumor who are ineligible for participation in other SU011248 protocols and are refractory to or intolerant of imatinib mesylate (The protocol has just been closed for inclusion of new patients)

MAIN CLINICAL RESEARCH PROJECTS

Almost all sarcoma patients are included in international clinical studies. In these protocols various research projects are included. The data of all patients are registered in a database in which 748 bone sarcomas, 2785 soft tissue sarcoma and 6172 benign/other cancer /uncertain have been entered since 1980. Complete registration of diagnosis, treatment and follow-up gives an unique possibility for clinical research. There are ongoing studies on diagnostics, treatment and follow-up. Most of the re-





search activities by the sarcoma programme are done in co-operation with many departments within the hospital (translation projects):

Department of Tumor Biology, Institute for Cancer Research

* By DNA microarray gene expression and chromosome structure are studied. The research focuses on discovering new classifications, to predict chemotherapy effect and resistance mechanisms.
* Microscopic disease in ostosarcoma: Immunomagnetic isolation of tumor cells present in peripheral blood and bone marrow aspirates in osteosarcoma patients, useful as diagnostic and prognostic tool in the management of osteosarcoma.

Department of Cancer Prevention, Institute for Cancer Research

*Translation research relevant for malignant peripheral nerve sheath tumour with or without nevrofibromatosis I

Division of Pathology

* Studies of pathology, radiology and clinical history in patients with radiation induced sarcoma

Department of Genetics, Institute for Cancer Research

*Cytogenetic analyses serve as diagnostic markers for many subtypes of sarcoma and translocation studies are ongoing

Department of Nuclear Medicine, Division of Medical Imaging and Intervention

*Targeted internal radionuclide treatment employing 153-Samarium-EDTMP for advanced bone sarcoma

Other

* Quality of life and long term morbidity among survivors after multimodal treatment for Ewing`s sarcoma and osteosarcoma (mainly a clinical research project in collaboration with other SSG centres)
* A study of prognostic factors in osteosarcoma
* Genetic factors determining chemosensitivity and – resistance in bone and soft tissue sarcoma
* Biologically adapted therapy against mesenchymal tumors * Studies of pharmacokinetics and markers indicating toxic effect of methotrexat in osteosarcoma patients
* Radiotherapy of soft tissue sarcoma: the impact on local recurrence and prognosis (mainly a clinical research project in collaboration with Haukeland University Hospital and other centres in SSG
* Photochemical internalization (PCI) An animal study: Photochemical Internalisation as a treatment modality for soft tissue sarcomas- A collaborative project between Dept of Radiation Biology and Dept.of Surgery for the development of PCI for treatment of soft-tissue sarcomas

NATIONAL/REGIONAL FUNCTIONS

Sarcoma patients are treated at four central hospitals in Norway, but the majority is treated at this hospital. The hospital has a status as a National Center of Competence for this group of patients. For many years there has been close collaboration between the Health Regions East and South). Sarcoma patients from the Region East are routinely been referred for treatment at Rikshospitalet. There is a close collaboration with the paediatricians in the Division of Pediatrics on the treatment of children with sarcomas. Our hospital is **National Centre for Treatment with Isolated Limb Perfusion** using TNF alfa and melphalan.

Research programs

Øystein Fodstad and his group at the Department of Tumor Biology, Institute for Cancer Research, study:

I) THE DETECTION AND CHARACTERIZATION OF MICRO-METASTATIC CANCER CELLS

The metastatic process is inefficient, as only a small fraction of the cells detached from the primary tumor has the capacity to form a secondary tumor. Little is known about the fate of the tumor cells in the circulation, and of the characteristics that determine whether such cells will die, stay dormant or form a metastasis. We have developed methods for detection of such disseminated tumor cells, and are engaged in several projects where we characterize the selected cells. Antibody-coated magnetic particles are used for positive selection of disseminated tumor cells, and the method can be used for screening of cancer cells in peripheral blood, bone marrow, ascites, pleura fluid, urine, CSF, fine needle aspirates and lymph nodes. In clinical studies statistically significant relationships have been observed between the presence of tumor cells in the bone marrow and survival of patients with malignant melanoma or osteosarcoma, and with clinical stage in colorectal, ovarian and lung carcinoma. The selected cells can be characterized for expression of surface markers by incubating the cells with fluorescent latex particles coated with antibodies directed against tumor markers or clinical relevant target molecules (e.g.: EGFR, erbB2, PSA). For further molecular analysis we use a micromanipulator to pick pure fractions of selected tumor cells. In several of the studies it has been possible to perform repeated bone marrow sampling during therapy and a change in the presence of micrometastatic cells occurred before clinically detectable effects was observed, making it of interest to use the approach as an early indicator of response. Such a surrogate marker of response is highly needed, e.g. in adjuvant and immune therapy trials, and detection of micrometastatic disease is used as a surrogate marker in an ongoing clinical phase I trial utilizing immunotoxins for treatment of carcinomas.

II) MOLECULAR PROFILING AND POSSIBILITY FOR PREDICTION OF THERAPY RESPONSE IN OSTEOSARCOMA XENOGRAFTS

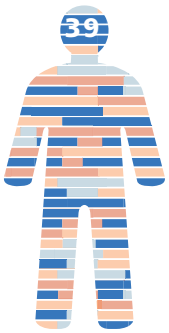
Osteosarcoma prognosis has improved markedly with the advent of effective chemotherapy, but there has been little improvement in outcome recently despite intensification of effective chemotherapy and introduction of new drugs. Consequently, many patients are likely over-treated with significant morbidity and even mortality, whereas many would require alternatives to current chemotherapy regimens. Identifying which patients would fall into which group is currently impossible. Therefore, identification of molecular markers that could do so would be a potentially major advance in the management of these patients.

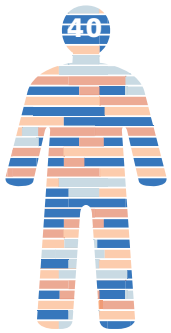
Multimodal treatment regimens usually involve neo-adjuvant and adjuvant chemotherapy with high-dose methotrexate, doxorubicin, cisplatin, and more recently ifosfamide. For patients diagnosed without overt metastasis the most powerful prognostic indicators today is the degree of necrosis in the primary tumor induced by preoperative chemotherapy. We have obtained microarray gene expression profiles from our panel of osteosarcoma xenografts. By correlating these with response of the xenografts to doxorubicin, cisplatin and ifosfamide we identified subset of genes that are differentially expressed among xenografts poorly or highly sensitive to these three drugs. The results have been validated technically with quantitative PCR. We are now in the process of picking candidate genes for further validation by: A) Functional studies in vitro, using siRNA knock down of putatively novel resistance genes and B) Expression studies of candidate genes in OS patient samples to investigate whether the identified marker genes are differentially expressed among primary osteosarcomas with poor or good histological response to preoperative chemotherapy. Recently, we have identified candidate mi-RNA presumably regulating the expression os such genes.

Ragnhild A. Lothe and her group, in the Department of Cancer Prevention, Institute for Cancer Research, study MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MPNST). MPNST is a rare cancer disease in the general population, and is typically found among patients with the hereditary disorder neurofibromatosis type 1.This malignancy arises in Schwann cells and are believed to develop through a benign neurofibroma precursor stage. The disease is typically found among young adults, the patients have a poor prognosis, and no consensus for therapy, except surgery, exists. We have previously identified Topoisomerase IIa and Survivin as target genes for 17q amplification in MPNST and shown that increased expression was associated with poor clinical outcome. Several new biomarkers identified from the functional genomics studies are currently being analysed for in situ expression using a tissue microarray including neurofibromas and MPNST from about one hundred Norwegian and Swedish patients. Furthermore, ongoing large scale genomics and transcriptomics of MPNST stratified by knowledge on hereditary predisposition will provide new insights to this agressive disease. This is a collaborative study between Mertens lab., Lund University hospital and the Lothe lab., as well as active partners in the clinic, Sigbjørn Smeland and Kirsten Sundbye Hall.

Ola Myklebost and his group, at the Department of Tumor Biology, Institute for Cancer Research, study

I) FUNCTIONAL GENOMICS ON THE SARCOMA SYSTEMS BIOLOGY





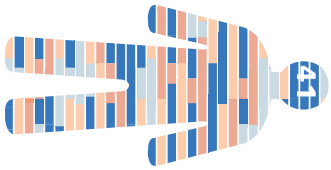
Based on our genome-scale analysis of clinical samples and cell lines, we aim to understand how various levels of genomic programming and aberrations determine the properties of cancer cells. This work is based on our involvement in the National Microarray Platform, and is a prerequisite for mainttaining and developing the competence needed to provide advanced genomic services to the scientific community (see microarray.rikshospitalet.no). As part of the European Network of Excellence on Bone Tumors, we are now focussing on osteosarcoma, and participate in the expression profiling of about 150 clinical samples from clinical trials, and are doing the genomic profiling here. We have established an extensive panel of cell and xenograft lines that, based on expression and genomic profiles reflecting important clinical groups, will be used as models for biological and preclinical studies. These lines will also be profiled for microRNA expression and epigenomic programming, and used to approach a system biology understanding of this type of cancer.

II) MESENCHYMAL STEM CELL BIOLOGY

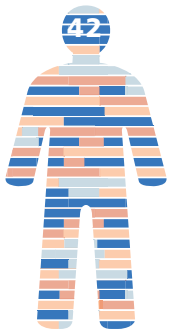
The group is part of the Norwegian Stem Cell Network. Together with other groups we have characterised mesenchymal stem-like cells from bone marrow and adipose tissue, and we have made a set of model multipotent mesenchymal cell lines immortalised by telomerase transduction. We are using these cells also to study the interaction of mesenchymal bone marrow cells with leukaemia stem cells, in collaboration with the Rian group. These projects led us to a focus on the involvement of stem-like cells and stem cell properties in cancer, and to the successful application for a Centre for Research-based Innvoation focussing on Cancer Stem Cells (CAST, see cancerstemcell.no), for which Ola Myklebost is assistant managing director. In CAST we will use various strategies to identify stem-like cells in sarcoma cell or xenograft lines, as well as primary tumour samples. If such cells are identified, as suggested by our preliminary results, they will be characterised and we will attempt to identify markers that can be used for diagnosis or therapy.

III) MESENCHYMAL STEM CELL BIOLOGY AND ONCOGENESIS

Our main aim is to understand the biology of mesenchymal cancer, i.e. malignant tumors of bone and connective or supportive tissues, so called sarcomas. We use genomic technologies to identify recurrent chromosomal aberrations in these tumors and to investigate candidate genes and regulatory pathways that may be involved in sarcoma development and progression. The most interesting genes are cloned and transferred to model cell cultures to study the function of their encoded protein. Since stem cell functions are inherently linked to cancer, we are also involved in studies of mesenchymal stem-like cells, both as a model system for candidate genes, and to compare their properties with those of sarcoma cells. The aim of the studies is to increase our biological understanding to be able to identify new targets for therapy or diagnostic criterias that can be used for improved therapy selection (kreftforskning.no/myklebost).



Sarcoma



Thyroid and endocrine cancer

Treatment program

Trine Bjøro is head of the thyroid and endocrine treatment program. In Norway about 200 patients with thyroid cancer are diagnosed every year, however, the prevalence of nodules in the thyroid is high (5% have palpable tumors and as much as 70% have tumors detectable with ultrasonography). Today a large number of diagnostic hemithyroidectomies are performed. Better pre-operative methods are needed to select both patients who need surgery. Even though the survival for differentiated thyroid cancer (DTC) is high (>95% 5 years survival), lymph node metastasis is common (20-70%) and also distant metastases is a clinical problem. Since most patients are low-risk patients after primary treatment (surgery and radioactive iodine), it is important to find those patients at risk for more aggressive disease. A subgroup has extremly high mortality and/or morbidity and more extensive treatment.

PATIENT GROUPS

About two hundred patients are referred to Rikshospitalet University Hospital for either primary diagnostic of thyroid tumors or secondary investigation. Patients with thyroid cancer are referred both to primary surgery, complementary surgery, radioactive iodine treatment and extrenal radiation. Patients who are primary treated and/or with advanced disease are followed life-long.

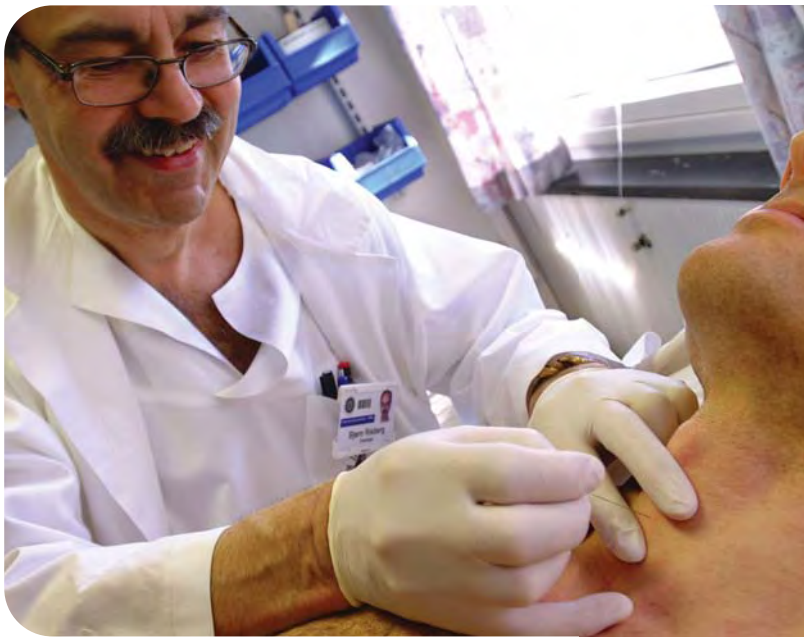
The treatment modalities are surgery, radioactive iodine, external radiation, percutaneous ethanol injection and for the anaplastic thyroid cancer chemoradiation. To date no patients are treated in protocols, however all patients are treated according to The Norwegian guidelines.

MAIN CLINICAL RESEARCH PROJECTS

- Improved diagnosis of metastasis to regional lymph nodes - the usefullness of FNA-Tg in papillary thyroid cancer (PTC) metastasis to regional lymph nodes. Ultrasonography with fine needle aspiration (FNA) is the most important method used to identify metastasis. Measurements of both serum and FNA-thyroglobulin (Tg) are important in follow-up after treatment. FNA-Tg is a valuable supplement to cytology in samples from suspicious lymph nodes.

- PET: Retrospective studies the determine the value of FDG PET/CT in the management of patients with suspected residual or recurrent well differentiated thyroid cancer, medullary thyroid cancer and anaplastic thyroid carcinoma. Further, retrospective studies to evaluate the clinical significance of diffusely increased and focally increased FDG uptake in the thyroid gland as an incidental finding on whole-body PET/CT.

- Percutaneous ethanol injection (PEIT) in lymph node metastasis: In spite of a total or near-total thyroidectomy with excision of regional lymph node metastasis, followed by 131-iodine therapy in PTC patients, new or previously undiagnosed lymph node metastasis are often found in the follow-up. Repeated neck explorations are a difficult task because of fibrous connective tissues. PEIT has been used with great success in benign cystic lessions. Good results have also been repoted in malignat tumor, especially in hepatomas. US-guided PEIT in cervical lymph node metastasis from PTC seems to be a possible alternative to repeat surgery. The thyroid cancer team started in 2004 a pilot project using PEIT in cervical lymph node metastasis, preliminary results are published as abstract.



REGIONAL FUNCTIONS

All patients with thyroid cancer in Health Region South and more than 80% of those in Health Region East are treated ether primary or only with radioactive iodine at Rikshospitalet University Hospital.

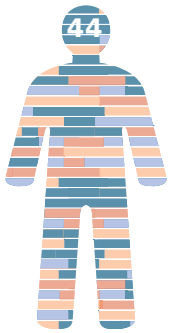
Research program

Trine Bjøro and her group are working on

IMPROVED DIAGNOSTICS AND TREATMENT OF THYROID CANCER

The focus is the development of new and better markers for diagnostics and follow -up. Thus, our aim is to improve existing methods and to make new methods which enable discrimination between thyroid carcinoma and adenoma. We have established an immunological method for determination of thyroglobulin (Tg) in serum, with a sensitivity of 0.1 µg/l. The clinical use of this sensitive method reduces the use of whole body scans of the patients. Another application is Tg measurements in fine needle biopsies (Tg-FNAB), which has proved to be important for detecting cystic metastases when cytology is not conclusive. In order to increase the diagnostic sensitivity, methods for determination of mRNA for thyroid specific proteins (Tg, TSH receptor) are under development. This approach may also be useful for determination of Tg expression and secretion into blood, particularly for patients with auto-antibodies against Tg. There is a need for markers to discriminate between thyroid carcinomas and adenomas. Some candidate antigens have been described (ITM1, Clorf24, DDIT3 and ARGII), but few reagents are available for these markers. We have therefore started to develop antibodies to these promising proteins. Rabbits have been immunized with peptides from two antigens (ITM1 and Clorf24) conjugated to a carrier protein. The rabbits have responded very well to the peptides, and we are ready to investigate their performance in immuno histochemistry. For production of monoclonal antibodies mice have been immunized with all four peptide conjugates. Several responders have been identified and fusion is planned in order to select monoclonal antibody-producing hybridomas.

II Basic/translational research

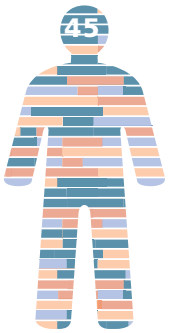


Cancer genetics

Sverre Heim (head of the faculty divisjon of the Radium Hospital) and head of the Section of cytogenetics, Division of Laboratory Medicine, and his group study
GENE MUTATIONS
The focus is on acquired gene mutations in cancer cells and the genetical epidemiology in familial cancer.

The project of ***Eivind Hovig*** and his group, at the Department of Tumor Biology, Institute for Cancer research, is
HIGH-THROUGHPUT SNP GENOTYPING FOR DETERMINATION OF INHERITED CANCER-DISPOSING GENES
With the development of microarray techniques for both expression profiling and more recently genotyping of DNA variation, a very efficient set of tools are now available. In this project, we have established laboratory protocols and analytical pipelines in order to examine inherited cancer families in Norway, through the utilization of genetic linkage analysis of single nucleotide polymorphisms (SNPs). This enables identification of DNA regions that cosegregate with the putative causative gene alteration to be the minimal region not having experienced cross-over events in the family. With this method, we havef irmly identified a chromosomal region for a family with papillary thyroid cancer, and are now pursuing the candidate gene, using tumor material from the family, by identifying potentially smaller events on the remaining normal allele. This strategy will be pursued further for a large number of Norwegian families with inherited cancers in collaboration with ***Pål Møller*** and ***Louise Mæhle,*** the Section of Genetic Counselling, Division of Laboratory Medicine. The project may also be seen as translational, in that positive identification of genes will potentially impact genetic counselling, and may thus be clinically important, for instance in monitoring of disease.

Vessela N. Kristensen and her group, from the Department of Genetics, Institute for Cancer Research, study
WHOLE GENOME MICROARRAY BASED ANALYSIS OF SNPS WITH RELEVANCE TO INTRATUMORAL MRNA EXPRESSION AND GENETIC INSTABILITY
The gene expression in each tissue, healthy or malignant, may have its inherited genetic component which differs from individual to individual. One of the earliest evidence for this was brought by us in recent publications. Candidate SNPs were analyzed for associations to an unselected whole genome pool of tumor ~3000 mRNA transcripts in unrelated patients with breast cancer. We have developed a general statistical framework for the simultaneous analysis of gene expression data and genotype data. Our analysis revealed significant associations between subsets of SNPs and transcripts, shedding light on the underlying biology. The project aims to analyse blood and tumor DNA pairs from the same patient for 109 000SNPs (lab work is finalised) in order to cover a whole spectrum of SNP profiles of breast carcinoma, both germline and somatic, as well as the allele specific aspect of mRNA expression. In this case we take a different (whole genome) approach rather than the candidate gene/pathway approach of part I, where we have a known metabolic pathway to follow. Studying these profiles will hopefully give us more profound insight into the origin of deregulation of mRNA expression, which occurs genome wide and the genetic events at early stages of malignancy, i.e. the somatic alterations, which may originate on a certain background and specifically from certain naturally occurring genotypes. Accumulating evidence points to the impact of haplotypes studied here.



Cancer informatics

Anne-Lise Børresen-Dale and her coworkers, from the Department of Genetics, Institute for Cancer Research, study GENOME-WIDE MOLECULAR PROFILING AND PREDICTION OF CANCER PATIENT SURVIVAL: STATISTICAL METHODOLOGY AND APPLICATIONS.

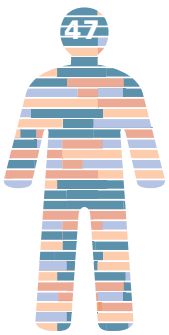
A major challenge in cancer patient therapy is that patients typically respond very differently to a particular treatment. It is therefore of vital importance to develop prognostic tools that predict patient response (including tumor response, risk of metastasis, and side effects) on the basis of information available at the time of diagnosis. The aim of the project is to enhance current statistical methodology for prediction of clinical endpoints on the basis of genome-wide molecular profiles. Genome-wide molecular profiling offers potentially great benefits over traditional methods for identification of molecular targets for diagnosis, prognostication, prediction and therapy intervention. First, by the very nature of such studies, the molecular targets are unknown and high genomic coverage is a key premise for successful target identification. Second, changes in the molecular profile may need to be understood and analyzed at a global level to be useful in prediction of the specific form of the disease and the patient's prognosis. Examples of profiles include measurements of gene expressions (expression arrays), genotypes SNP arrays) and copy number alterations (CGH arrays). Although many classical prognostic markers exist, new markers may be found that are independently better than the classical ones in prognostics as well as in prediction of benefit from treatment. In this project new biostatistical methodology will be developed for predicting clinical outcome based on genome-wide molecular profiles, with particular focus on the incorporation of existing sets in the literature, and apply this methodology to data from cancer studies in Norway and abroad. The project will be part of and contribute to the already existing close collaboration between the Department of Genetics and the Institute of Informatics at the University of Oslo.

Eivind Hovig and his group, from the Department of Tumor Biology, Institute for Cancer Research, are working on INFORMATICS MODELLING OF THE PHYSICAL ASPECTS OF DNA

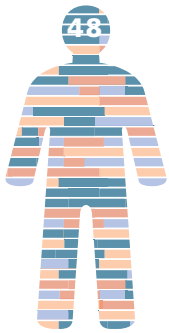
A number of proteins contribute to the physical structure of DNA, as does indeed the DNA itself. Chromatin may be defined as the complex of DNA and proteins in the nucleus of cells. As is evidenced from for instance from imaging of chromatin of cancer cells, the chromatin undergoes changes in cancer. This multidisciplinary bioinformatics project builds on our research on the human genomic melting map, and aims to develop improved algorithms for this aspect of the physical behavior of DNA, mainly termed stitch profiles. A stitch profile will capture the segments of DNA that will tend to denature locally, and incorporate information on the various simultaneous configurations that any DNA segment will have. Further, this project is being expanded with various other physical aspects of DNA, including information on nucleosome positioning, DNA matrix attachment regions, DNA curvature tendencies and similar aspects to build a model of how the physical structure of DNA acts also as an informational premise in addition to the pure DNA sequence. The overriding goal will be to develop a model for chromatin behavior. A further extension to this will be to correlate these models with the vast number of other features known for

human DNA, in order elucidate the informational influence. This project involves the Statistics for Innovation SFI, and other collaborators include Christoph Bock and Thomas Lengauer at Max Planck Institute in Saarbrucken and Kristian Vlahovicek at the University of Zagreb.

Vessela N. Kristensen and her group, from the Department of Genetics, Institute for Cancer Research, study
MICRORNA REGULATION OF TRANSCRIPTION
Many of the SNP-expression associations described above were in trans and the potential mechanism of the observed regulation of mRNA expression by intronic SNPs remains unclear. Recently a new class of ~500 regulatory genes, termed microRNAs (miRNA) has been identified in humans. These are non-coding, meaning that they do not encode for proteins. They are shown to inhibit translation via complementary RNA-RNA binding, most commonly at the 3´-UTR of the target genes, but can also guide mRNA cleavage and degradation. We have launched a project on the genotyping and expression analyses of microRNAs and have summarized their structural and functional organization in a recent review. Both in vitro and in vivo experiments have shown that miRNA are capable to down regulate the mRNA level of genes that have a complementary target sequence in their UTRs. They have been linked to numerous biological processes, including cell proliferation and cell death during development, stress resistance, and fat metabolism. Furthermore, human miRNAs are frequently located at fragile sites and genomic regions involved in cancers and are deregulated in many cancers. This part of the project involves 1) the studies on the expression of miRNA and its correlation (anti-correlation) to the expression of mRNA. 2) The studies on miRNA in silico binding sites, their experimental validation and 3) the effect of SNPs on this binding. We have recently completed the study of genotyping of 89SNPs in putative miRNA binding sites. We have started a collaboration with Eirik Frengen, from Ulleval University Hospital to functionally characterize these binding sites. This will include functional studies of target predictions from the miRNA analysis and miRNA expression profiling and elucidating regulatory loops, signals and short pulses.



Cancer prevention

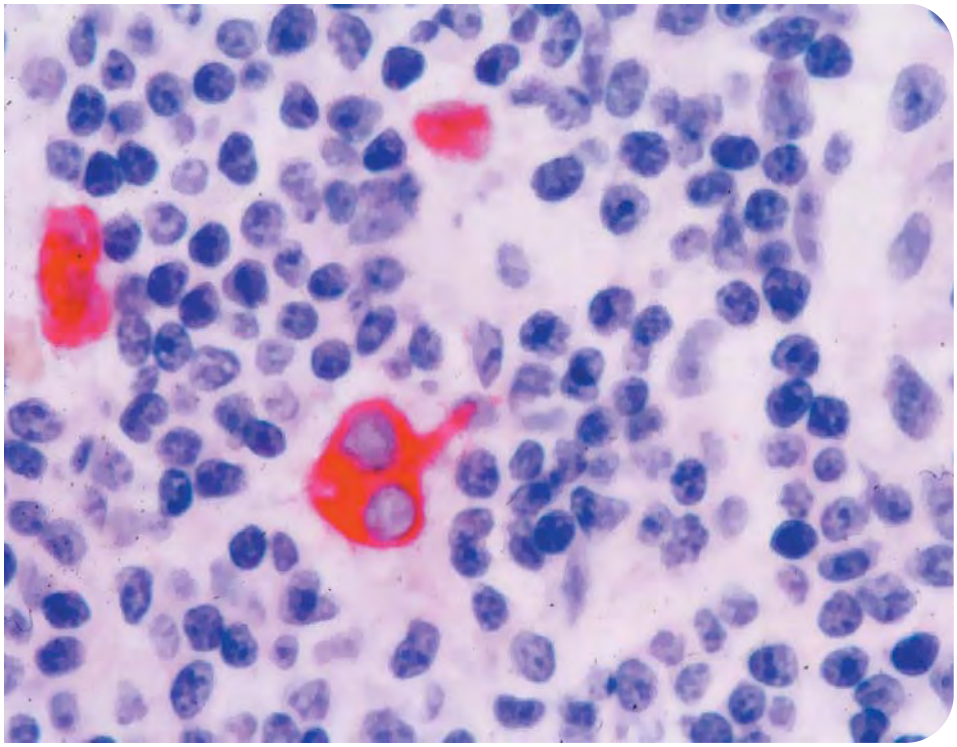


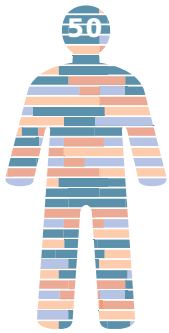
Ragnhild A. Lothe and her group, in the Department of Cancer Prevention, Institute for Cancer Research, study
THE DEVELOPMENTAL BIOLOGY OF SOLID TUMORS
with the aim to transfer such knowledge into novel theragnostics. Our focus is secondary and tertiary cancer prevention, through research that will aid in development of novel diagnostics for molecular predictive oncology. Full-blown malignancies contain different combinations of a variety of molecular alterations, including those important for the disease initiation and progression. Insights to the affected molecular pathways and signalling networks in the cells are hidden within the complex tumour genomes. We seek to identify and understand the mechanisms behind the key changes during the dynamic process of tumour development by combining the global views of functional genomics with detailed molecular biology. For this purpose we study the various developmental stages of three cancer diseases: colorectal cancer, testicular cancer and tumors of the peripheral nerves.The influence of epigenetic mechanisms affecting the activity of this and other central pathways are currently being investigated in all cancer models. Novel epigenetic markers are under investigation for their suitablility as non-invasive biomarkers. The developmental lineages of testicular germ cell tumors mimic the early embryogenesis and the transcriptomes can be looked upon as a caricature of the complete human programming. The ongoing comparative studies of embryonal stem cells in culture and embryonal carcinomas may identify key malignancy associated pluripotency markers, and are performed as partner of the Cancer Stem Cells Innovation Centre.The ongoing cancer-omics (genome, transcriptome, epigenome) studies in combination with detailed biology identify novel biomarkers for these diseases, which are analysed for clinical relevance in ongoing translational projects. This research group is partner in the CoE-Centre for Cancer Biomedicine.

Cancer stem cells

Gunhild Mælandsmo and her group, at the Department of Tumor Biology, Institute for Cancer Research, study CANCER STEM CELLS.

Traditionally, cancer has been assumed to develop through expansion of cell clones harbouring a number of genetic changes giving the particular clone a selective growth advantage. An alternative hypothesis is that cancer arises due to critical mutations in the stem cell population, thus forming a cancer-initiating cell, or a cancer stem cell (CSC). CSC should have two intrinsic characteristics; the ability to self-renew and differentiate, meaning that a small population of CSC can initiate and sustain a heterogeneous tumor. If such small sub-populations are the driving force in cancer development, targeting and eradicating these slow cycling and treatment resistance cells will be essential for successful treatment. Based on this hypothesis, The Cancer Stem Cell Innovation Center (CAST) was established as a Center for Research-based Innovation. The focus of CAST is to investigate the CSC population within different type of cancer with the aim to develop novel anticancer therapies. We are participating in CAST and our contribution is studies on the existence and further characterization of CSC from malignant melanoma and breast cancer. Research on CSC is challenging due to the lack of established protocols and assays, and also the fact that fresh/live tumor material is the optimal starting point. In our breast cancer studies we are utilizing orthoptopic xenograft models representing the luminal A and the basal-like subtypes of breast cancer. We aim to investigate whether the different subtypes of breast cancer develop from different stem-and progenitor cells in the stem cell hierarcy. In the case of malignant melanoma several new cell lines and in vivo metastasis models have been established from patient biopsies. The different cell clones demonstrate specific metastasis pattern in animals and the aim of the project is to elucidate whether the stem cell population are of importance for homing and tissue-preferred metastasis formation.





Cell kinetics

Erik Boye and his group, at the Department of Cell Biology, Institute for Cancer Research, study

MOLECULAR MECHANISMS REGULATING DNA REPLICATION IN EUKARYOTES In this project we shall further study and characterise a novel checkpoint that we have recently discovered. Checkpoints are important regulators of the cell cycle. Cancer development is frequently associated with the lack of checkpoints and the checkpoint proteins represent possible targets for cancer treatment. Our goal is to map the novel pathway, from initiation to the final target molecule(s). We have shown that the onset of DNA replication is delayed by ultraviolet light in a process dependent upon the Gcn2 protein kinase, which means that it represents a totally novel form of checkpoint. Therefore, we wish to identify all proteins that interact with Gcn2, both upstream and downstream. This kinase is known to phosphorylate the translation initiation factor eIF2a in response to nutrient limitation, and we wish to find out whethe eIF2a-phosphorylation is part of the checkpoint response. Furthermore, we have evidence that the classic checkpoint proteins Rad3 (the equivalent to human ATR) and Rad26 (ATRIP) are involved in the checkpoint, and we shall verify and study this involvement. The strategy for identification of targets for the different proteins involved in the pathway will involve proteomics. We shall tag the respective proteins (Gcn2, Rad3, eIF2a) and try to identify their interaction partners by immunoprecipitation followed by mass spectrometry. This analysis will also involve the mapping of the actual phosphorylation sites.We are also doing a site-specific mutagenesis of the gcn2 gene, in order to study its function and its substrates further.

Kirsten Skarstad and her group, at the Department of Cell Biology, Institute for Cancer Research, study

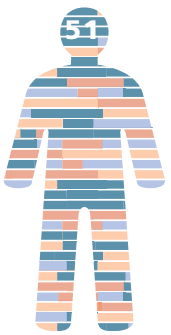
I) CELL CYCLE REGULATION IN ESCHERICHIA COLI

Cancer cells are characterized by loss of regulation, allowing them to go through the cell cycle in an uncontrolled fashion. The goal of this project is to understand the molecular mechanisms behind regulation of DNA replication in a simple model organism, the bacterium E. coli. We have shown that DNA replication is tightly coupled to cell growth in wild type E. coli cells. Initiation of replication occurs precisely at the same point in the cell cycle, generation after generation. The molecular mechanisms behind the precise timing of initiation of replication are not yet understood. We have characterized gene products that are important for maintenance of correct initiation frequency. The DnaA protein is the main actor in the initiation process. It recognizes the origin, separates the strands of the double helix and recruits the replication machinery. At the time of initiation there is a danger of immediate reinitiation. Reinitiation at new origins is prevented by two different control systems. First, a process called sequestration makes newly formed origins unavailable to the initiation apparatus. The sequestration process involves membrane components, SeqA protein and DNA adenine methylation at GATC sites. Second, the DnaA protein is inactivated by a process termed regulatory inactivation of

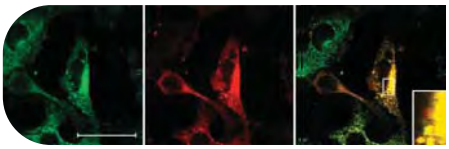
DnaA (RIDA). The RIDA mechanism is dependent on the Hda protein and the beta clamp of an actively replicating polymerase. We have found that pairs of replication forks are co-localized in the cell and that SeqA forms a left-handed helical structure that may contribute to sister chromosome cohesion. Currently we focus on how the SeqA protein is involved in sister chromosome pairing or anchoring, and also the transport of sister molecules to opposite halves of the cell. We are also investigating how the RIDA mechanism works through characterization of the mechanism of action of the Hda protein and the beta clamp.

II) NOVEL CELL CYCLE INHIBITORS

The main aim of the project is to discover new types of antibacterial and anticancer drugs. Knowledge about the mechanisms of action of replication proteins will be used to design screens for drugs that specifically target the replication machinery. A conditional mutant of the Escherichia coli initiator protein, DnaA, has been characterized. The mutant grows with normal growth rate at 42°C, but dies at 30°C due to excess initiation (overinitiation). In this strain, there is too much activity of DnaA. Such a strain is exploited in the search for new antibacterial agents. A potential drug targeting DnaA activity will reduce overinitiation and cause the strain to survive at low temperature. The strain has been improved and made amenable for high-throughput screening by providing an alternative initiation pathway which does not depend on DnaA activity. The strain still shows lethal overinitiation at 30°C, but will not die if DnaA is knocked out. When a potential drug inhibits DnaA activity and overinitiation occurs in a screen (detected by recovery of growth at low temperature), it will not be missed if added in a concentration that completely inactivates DnaA. The strain is the basis of an exceptionally robust screen and the method is already licenced by several companies. The phenomenon of lethal overactivity is rarely found in nature and is ideal in a positive screen. An effort is made to transfer the technology to eukaryotic cells in order to develop a screen for novel anticancer drugs. High throughput screening for compounds that interrupt specific protein-protein interactions is being developed by yeast two-hybrid technology. Strains will be constructed which will only survive if the given protein-protein interaction is disrupted. Also protein-protein interactions important to replication and regulation of the cell cycle of mammalian cells have been selected as targets.



Cellular signaling/ cellular transport



Characterisation of the intracellular routing of endocytosed FGF1: Cellular colocalisation (yellow) betewen FGF (in red) and intracallular structures (in green).

Paula M. De Angelis at the Division of Pathology is involved in functional studies to determine whether identified signature genes actually play a role in 5-FU response/resistance (RNA interference and cellular phenotype studies).

Inger Helene Madshus and her group, at the Institute of Pathology, Division of Pathology, study:

I) CONTROL OF SUBCELLULAR LOCALIZATION OF EGFR, ERBB2 AND ERBB3, IMPACT OF GLYCOSYLATION

ErbB2 is endocytosis-deficient and negatively impacts on endocytic down-regulation of EGFR (Haslekås et al., 2005) and ErbB3 (unpublished). ErbB localizes to cellular protrusions rich in cholesterol and gangliosides. We will investigate how raft-localization of ErbB2 inhibits its endocytosis by excluding ErbB2 from clathrin coated pits.

II) MECHANISMS INVOLVED IN FORMATION OF CLATHRIN COATED PITS

Activation of the EGFR initiates signaling responsible for formation of clathrin coated pits. These pits are qualitatively different from the coated pits that are enriched in transferrin receptors (TfR). We are characterizing signal transduction responsible for formation of clathrin coated pits. This will largely be performed by proteomics approaches.

III) ENDOCYTOSIS OF ErbB3.

ErbB3 has deficient kinase activity and depends on heterodimerization to be phoshorylated on tyrosines. ErbB3 has been described to be endocytosis deficient. However, our unpublished data demonstrate that ErbB3 is efficiently endocytosed from clathrin coated pits. While heterodimers of EGFR and ErbB3 are endocytosed, heterodimers of ErbB2 and ErbB3 are endocytosis-deficient. We will characterize the coat proteins responsible for regulation of endocytosis of ErbB3.

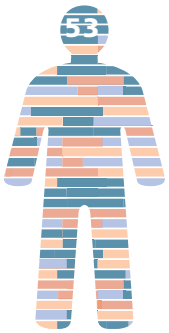
The research group led by ***Edgar Rivedal,*** at the Department of Cancer Prevention, Institute for Cancer Research, is studying THE ROLE OF ABROGATED INTERCELLULAR COMMUNICATION IN CANCER DEVELOPMENT, WITH FOCUS ON GAP JUNCTIONS

Gap junctions are plasma membrane domains enriched in intercellular channels that provide direct cell-cell communication between the cytoplasms of neighboring cells. The gap junction channels are made of a family of transmembrane proteins called connexins. Connexins are expressed in almost all mammalian cell types, and play important roles in the regulation of cellular growth, differentiation, and homeostasis. In normal cells, gap junctions are highly expressed, and their functions are tightly regulated. In contrast, most cancer cells have reduced or abolished intercellular communication via gap junctions. Reestablishment of gap junction function in cancer cells has been shown to reverse their malignant development. Connexins are therefore potential biomarkers of cancer and possible future targets in cancer chemoprevention. A major aim of our studies is to obtain a better understanding of the mechanisms involved in the loss of gap junction intercellular communication in cancer. We are focusing on how gap junctions are regulated by intracellular signalling pathways. We are particularly interested in elucidating how connexin phosphorylation and ubiquitination affect functional gap junction communication, and how these post-translational modifications are dysregulated in carcinogenesis. Another major aim in our research group is to elucidate the molecular mechanisms by which connexins act as tumor suppressors. We are analyzing the expression profiles of connexins in normal and cancer colon tissue and cell lines, and are currently investigating whether the tumour suppressor activities can be linked to specific members of the connexin family.

Kirsten Sandvig and her group, at the Department of Cell Biology, Institute for Cancer Research, study cellular signalling/cellular transport:

I) ENTRY OF PROTEIN TOXINS INTO CELLS

Errors in intracellular transport and signalling are associated with cancer. This project aims at increasing our knowledge about these processes to provide a rational basis for treatment and prevention of disease. Protein toxins from plants and bacteria are used as tools to obtain increased knowledge about basic transport mechanisms and signalling, and importantly, the toxins can be used in targeted drug delivery and as vehicles to bring in other proteins and even genes into cells. When the toxins are used for vaccination purposes or in connection with gene therapy only the nontoxic part or modified nontoxic versions of the proteins are used, and their ability to go all the way from the surface of the cell to the interior of the cell is being exploited. The toxins here investigated act by first binding to cell surface receptors, then they are endocytosed and transported retrogradely to the Golgi apparatus and to the endoplasmic reticulum, and finally they are translocated to the cytosol. These toxins have proven valuable to study all the transport steps along their pathway. A number of important findings have been published during the years. In conclusion, studies of protein toxins are important not only to increase our knowledge about basic processes in cell bio-



logy and the errors created in cancer cells, but also to develop new therapeutic strategies.

II) ENTRY OF NANOPARTICLES INTO CELLS Research on nanoparticles have evolved into biological applications with large expectations for the use of magnetic iron oxide nanoparticles and fluorescent Quantum dots in different imaging techniques both for tumor targeting and drug delivery in humans and as probes at the cellular level. In this research project we addresses several questions concerning the fate of these nanoparticles after binding to the cells that need to be answered in connection with their use in cell biological studies and certainly before applying them in humans: To which extent are they internalized? Can they be recycled out again, or are they degraded by the cell? If they accumulate in the cells, to which extent do they disturb trafficking of natural ligands, and do they have a cytotoxic effect? An important question is whether the answer to the questions above is dependent on the type and size of the nanoparticles. Thus, this project aims at gaining more knowledge about the endocytic mechanisms and intracellular pathways followed by various nanoparticles in cells, and the role of size and composition of nanoparticles for the compartments reached and for clearance from the cells.

Per Seglen and his group, at the Department of Cell Biology, Institute for Cancer Research, study
AUTOPHAGY
Autophagy is a fundamental intracellular degradation mechanism used by cells for nonspecific digestion of their own cytoplasm under starvation conditions (macroautophagy), or for the selective degradation of damaged organelles (mitophagy, pexophagy, reticulophagy), toxic protein aggregates (aggrephagy) or infectious organisms (xenophagy). Although a basic level of autophagy is essential for the cleansing and long-term survival of cells, excessive autophagy can be lethal and is sometimes used as an instrument of programmed cell death. Many cancer cell types thus tend to dispose of inducible macroautophagy in order to improve their growth and survival, whereas an insufficient basal autophagy/aggrephagy is a major cause of neurodegenerative disease. The project has a long-standing record of providing central facts, methods and concepts within the autophagy field, and is currently concentrating on understanding the molecular structure and functional dynamics of the organelles involved in autophagy (phagophores, autophagosomes, amphisomes and autolysosomes). We have, by using proteomic methods, identified approximately 40 proteins that are selectively associated with autophagosomal membranes. Many of these are novel (truncated or modified) protein variants that are now being characterized individually. Most of the autophagic membrane-associated proteins are derived from full-length precursors involved in antioxidant defense, chaperoning, drug metabolism or protein methylation, suggesting that they may function as receptors for the autophagic scavenging of denatured proteins. By using some of these proteins as antigenic markers of autophagic membranes, we are presently studying the subcellular localization and movements of the earliest autophagic organelles (phagopores and their precursor vesicles) in isolated hepatocytes under various conditions and treatments known to modulate the autophagic activity of these cells.

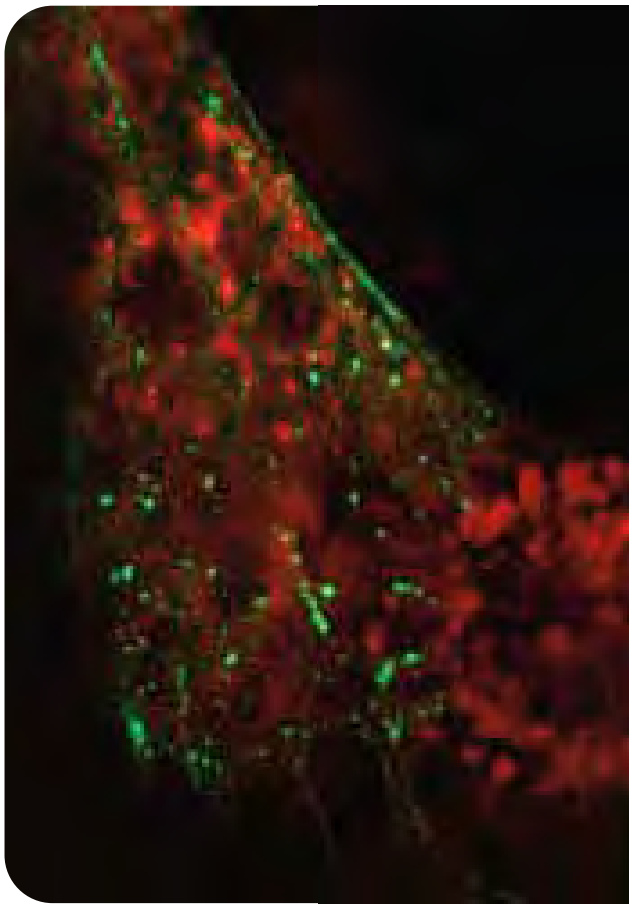
Harald Stenmark and his group, at the Department of Biochemistry, Institute for Cancer Research, research on
LIGAND-INDUCED UBIQUITINATION
Ligand-induced ubiquitination is a dominant signal for downregulation of growth factor receptors. We have been elucidating the molecular mechanisms of ubiquitin recognition and sorting at the endosome membrane. The endosomal sorting complexes required for transport (ESCRTs) constitute the core machinery for these events. In collaboration with Soichi Wakatsuki's lab we solved the structure of the ubiquitin-interacting motif (UIM) of the ESCRT-0 subunit Hrs in complex with ubiquitin. Hrs is kept in restricted microdomains of the endosome membrane through binding the coat protein clathrin. In collaboration with Ivan Dikic' lab we showed that Hrs is autoinhibited by mono-ubiquitination. While previous studies have shown that ESCRT-0 and –I are required for downregulation of epidermal growth factor receptors (EGFRs), we now showed that ESCRT-II and –III are also required. We previously identified the phosphoinositide- and ubiquitin-binding GLUE domain in ESCRT-II, and with Soichi Wakatsuki's group we now solved the crystal structure of the GLUE-ubiquitin complex. The Rab7-interacting lysosomal protein, RILP, was recently found to bind ESCRT-II, and we showed that RILP is required for EGFR downregulation. Ubiquitination of receptors is a key event in their downregulation, and we demonstrated that the PI 3-kinase-activated protein kinase CISK regulates the activity of the ubiquitin ligase AIP4 which mediates ubiquitination and downregulation of the metastatic chemokine receptor AIP4. Finally, using a Drosophila model we found that ESCRTs are not only important to mediate receptor downregulation but also to mediate autophagic clearance of toxic protein aggregates, thus having a neuroprotective function.

Functional genomics

Jan Brinchmann and his group, at the Institute of Immunology, Division of Laboratory Medicine, study
DIFFERENTIATION PATHWAYS IN HUMAN STEM CELLS
Human stem cells may be divided into two main categories: the pluripotent embryonal stem cells (hESC), and the pluripotent adult stem cells (hASC). For the purpose of cell therapy, the hASC have the advantages that they can be obtained from the patient him/herself, they do not form teratomas, and they do not involve difficult ethical considerations. Although they are considered to be more restricted in their differentiation potential than the hESC, recent data showing how insertion of genes encoding a combination of transcrition factors may grossly enhance the differentiation capability of end-differentiated human cells suggest that the therapeutic potential of hASC may be greater than exåected. In the present project, we have two objectives: to change multipotent human mesenchymal stem cells (hMSC) to pluripotent hESC-like cells by insertion of 1 – 2 masterswitch genes, and to develop hematopoietic stem cells (hHSC) from hMSC by insertion of other masterswitch genes. We have now obtained, or cloned ourselves, the relevant genes. We have established a retroviral transduction strategy, and have obtained 50% transduction efficiency. We are now in the process of establishing read-out assays to determine the biological effect of these genetic modifications. This project may impact within the field of cancer in two ways: first, by contributing to our understanding of the normal differentiation pathways in stem cells we may further our understanding also of cancer stem cells, and second, if we should be able to make hHSC from hMSC, such cells may be used to treat patients in need of hHSC with autologous cells.

Anne-Lise Børresen-Dale and her group, at the Department of Genetics, Institute for Cancer Research, are doing a
FUNCTIONAL STUDY OF NOVEL THERAPEUTIC TARGETS IN BREAST CANCER in collaboration with O.Kallioniemi's group VTT, Finland. Breast cancer is considered to be a genetic disease, and is one of the most common causes of cancer related deaths among women in the Western world. In the past decades, the use of different highthroughput genomewide profiling techniques has identified several novel molecular genetic events in breast cancer, as well as the validation of their biological and clinical impact. The current challenge is to transfer this new knowledge into the clinics. The aim of our project is to facilitate this transition, and the mainfocus is to identify novel therapeutic targets by combining largescale genomewide and functional studies. The project described in this application will be carried out by. The project is divided into three steps:
1. Identification of novel genes that are important in the breast cancer development and progression by using a combined analysis of gene expression and array based comparative genomic hybridisation (CGH).
2. Analysis and validation of the impact of the novel target genes identified in the first step based on several clinical parameters, including survival.
3) Follow up of the selected therapeutic targets from the second step with functional studies, RNA interference, and drug screening.

Paula M. De Angelis at the Division of Pathology focuses on
I) IDENTIFICATION OF SIGNATURE GENES AND CELLULAR PATHWAYS ASSOCIATED WITH 5-FU RESISTANCE IN COLORECTAL CANCER (GENE EXPRESSION AND CELLULAR PHENOTYPE STUDIES):
Poor patient response to 5-fluorouracil (5-FU) and irinotecan (CPT-11), chemotherapeutic drugs used in the treatment of metastatic colorectal cancer (CRC), is due to drug resistance. To be able to predict an individual patient's response to these drugs would lead to more optimal treatment management. Pharmacogenomic studies of drug-treated cancers are currently providing valuable information as to how variability on a genome-



Coas2-protein tagged with green fluorescent protein, counterstained with a lysosomal marker.

wide scale influences drug response. These investigations are facilitated by high throughput technologies such as genomic and expression microarrays and single nucleotide polymorphism (SNP) assays which have revolutionized investigations of drug response and drug resistance. Our approach to investigations of 5-FU resistance mechanisms in CRC is an in vitro pharmacogenomic approach which utilizes established colorectal cancer cell lines and two different 5-FU treatment protocols to generate 5-FU-resistant derivatives. One treatment protocol simulates clinical bolus regimens and used clinically achievable 5-FU levels to generate Bolus treatment derivatives. The other protocol uses continuous exposure of 5-FU-sensitive cell lines to increasing doses of 5-FU over a specific time-course in order to generate Continuous treatment resistant derivatives.

II) IDENTIFICATION OF SIGNATURE GENES AND CELLULAR PATHWAYS ASSOCIATED WITH TRANSIENT RESPONSE TO 5-FU IN CRC (GENE EXPRESSION, RNA INTERFERENCE, AND CELLULAR PHENOTYPE STUDIES):

The identification of novel biomarkers of 5-FU and CPT-11 response would facilitate more optimal treatment management, since there is much conflicting data concerning currently-used biomarkers of drug response. Drug response and resistance development are complex processes resulting from multiple genomic/genetic variations that in turn affect important cellular pathways such as cell growth signaling, apoptosis, DNA damage response, DNA repair, senescence development, and others. Understanding the molecular mechanisms involved in drug response is an essential step towards identifying robust biomarkers that may predict treatment outcome and/or the development of drug resistance.

Vivi Ann Flørenes and her group at the Division of Pathology study

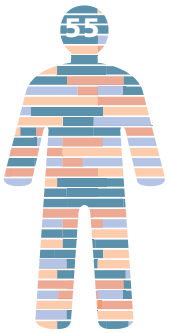
ANCHORAGE-INDEPENDENT GROWTH OF MELANOMA CELLS

One of the hallmarks of cancer cells are their ability to survive anchorage-independently. We are studying anchorage-independent growth of melanoma cells using several approaches. In one project we have shown that activation of protein kinase C (PKC) activates the MAPK (ERK) signaling pathway through an ERK-independent mechanism and protects anchorage-dependent cells against suspension-induced death. To identify additional factors involved in this process, we have performed an Affymetrix microarray analysis, comparing mRNA expression profiles in monolayer and suspension grown cells as well as after treatment with the PKC activator PMA and the MAPK-inhibitor PD980459. Four of the most differently expressed genes (FABP7, IGFBP3, NR4A1 and NR4A3) were chosen to study in more detail. From an early stage derived melanoma cell line known to be anchorage-dependent, two anchorage-independent variants have been created. An Affymetrix microarray analysis has been performed to identify genes differentially expressed in the three sublines. Verification of the results is ongoing.The Akt/PI3-kinase signaling pathway plays an important role in protecting cells against suspension mediated death. We have shown that expression of the phosphatase PTEN, known to inactivate PI3-kinase, is induced when anchorage-dependent cells are cultivated in suspension. By using siRNA to knock down expression of PTEN, we will clarify whether PTEN is directly involved in this process. We have shown that PTEN is mainly regulated at the transcriptional level in melanomas. By using PTEN promoter constructs we aim to identify factors involved in this regulation.

Vessela N. Kristensen and her group, at the Department of Genetics, Institute for Cancer Research, are working on

A FUNCTIONAL CHARACTERIZATION OF REGULATORY AND CODING SNPS AND HAPLOTYPE STRUCTURES AND ON DNA METHYLATION

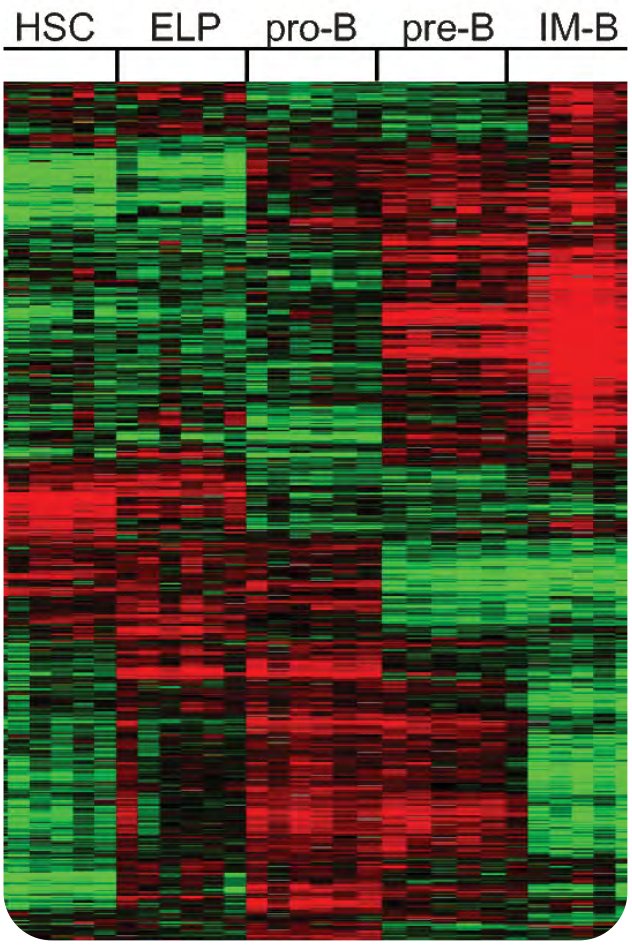
The goal of this project is to investigate the role of regulatory SNPs in relation to DNA methylation and promoter activity. Our initial analyses suggest that there is a possible association between the genetic structure of a haplotype and the extent of methylation in its neighbouring CpG islands. We analyzed the impact of the most frequent haplotype structure of the GSTP1 promoter in relation to the extent of methylation and a correlation was observed (p-value 0.008) suggesting that haplotype structures can affect de novo methylation of adjacent sequences. We have established a very fruitful collaboration with the group of Jörg Tost in the Centre National de Gènotypage, France for the quantitative analysis of a panel of CpG islands in pivotal genes for the carcinogenesis using pyrosequencing. Further, Jo Anders Ronneberg is working in collaboration with Leonardo Meza Zepeda and Ola Myklebost on the use of whole genome tiling arrays for methylation and ChIP (chromatin immunoprecipitation analysis). . It is essential to show the biological ground of the function of SNPs observed by association to be either susceptibility or response markers. Two isoforms of the c-Myb gene were indeed shown to induce different gene expression of GSTM1 possibly through a Myb binding site in the gene. We found a putative c-Myb response element (MRE) cgccagttCgctg in the promoter region of GSTP1. We were able to show that c-Myb indeed binds to GSTP1 but this binding element is considerably weakened by two polymorphisms using EMSA, siRNA analysis and lucipherase reporters.



Immunobiology

Trine Bjøro and her group, at the Division of Laboratory Medicine, are involved in THE IMMUNOBIOLOGY OF MALIGNANT MELANOMA. We are testing the measurement of the tumor marker S100 in serum and in bone marrow plasma from patients with malignant melanoma. S100B is a marker frequently used in melanoma trials, and will now be included in the follow up as marker for progression of metastatic melanoma.

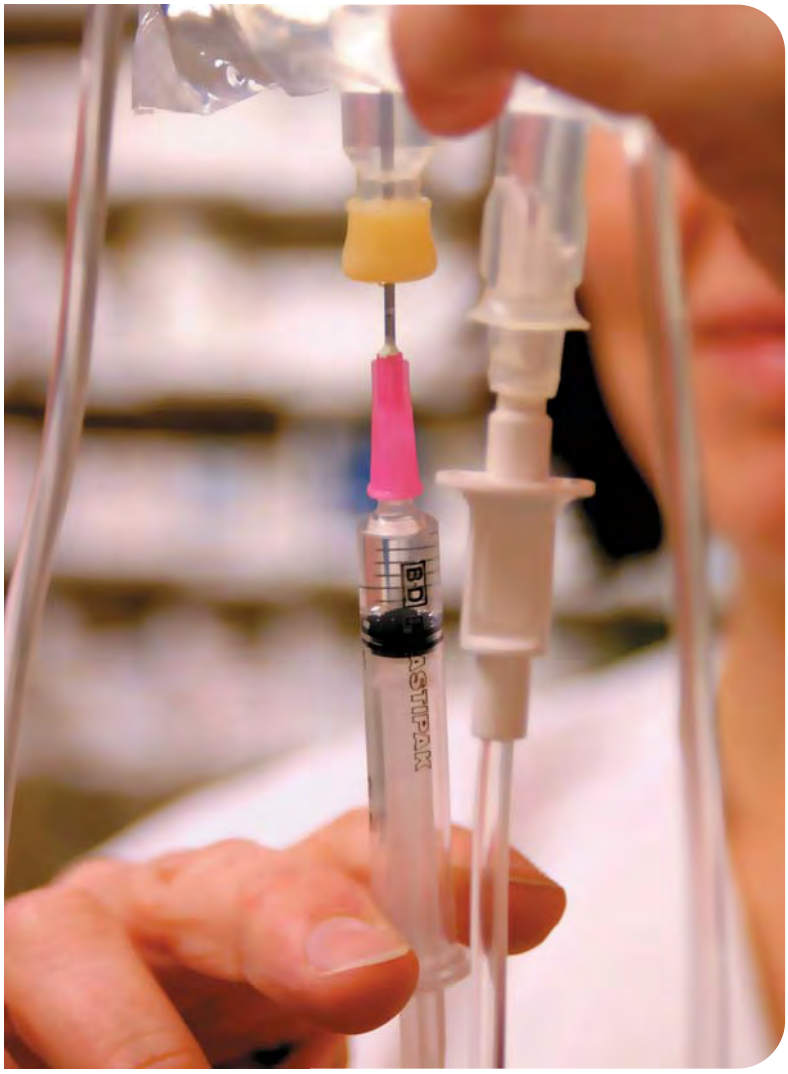
John Torgils Vaage, head of the Division of Laboratory Medicine, and his group are working on
THE IMMUNOBIOLOGY OF NK – CELLS
NK cells respond to certain MHC class I-mismatches by efficiently lysing the allogeneic mismatched cells. This NK cell alloreactivity can be exploited therapeutically in transplantation, to mediate a graft-vs-leukemia (GvL) effect, or to reduce GvH or HvG responses by elimination of antigen presenting cells (APC) from the host or donor, respectively. These NK-mediated effects are mediated, at least in part, by a broad repertoire of inhibitory and activating recognition molecules (receptors) for MHC class I molecules. For this function, rodents NK cells primarily use members of the Ly49 multigene family of receptors, which can be viewed as functional homologues of the KIR receptors in human. One main focus has been to characterize members of the Ly49 multigene family of lectin-like receptors in rats, some of which mediate rejection of leukocyte and stem cell allografts. The rat contains more than 30 Ly49 genes, most of which are expressed in a unique subset of rat NK cells (Ly49s3+). The complementary Ly49-low NK subset expresses a tolerizing NK receptor (NKR-P1C) for a non-MHC ligand. A heterologous reporter system for ligand identification has allowed us to identify novel ligands for several lectin-like receptors. Receptor function is studied in vivo, in rat models for allogeneic stem cell transplantation, in acute myelogeneic leukemia (AML), and in an infection model using the intracellular bacterium Listeria monocytogenes.It is hoped that these studies will improve our understanding of the roles played by the various activating and inhibitory NK receptors in the immune defense against certain cancerous and infected cells, and in experimental stem cell allotransplantation.



Expression profiling of human B cell development Hierarchical cluster analysis identified a gene expression pattern that clearly separated five consecutive B-cell populations isolated by cell sorting from human bone marrow.

Immunotherapy/ gene therapy

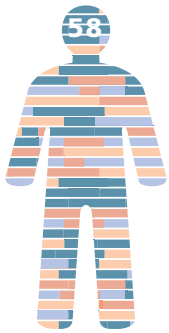
Kristian Berg and his group, at the Department of Radiation Biology, Institute for Cancer Research, study
PHOTOCHEMICAL INTERNALIZATION (PCI)
The PCI-group develops the PCI technology to enhance the therapeutic efficacy of adenoviral-based gene therapy as well as peptide nucleic acid (PNA)-based down regulation of target genes. Delivery of genes and oligonucleotides to target cells is limited by cellular membrane hindering transfer of these macromolecules into the cytosol. Photochemical internalisation (PCI) is a novel technology for the release of endocytosed macromolecules, including genes and oligonucleotides, into the cytosol. PCI has been shown to enhance the transfer of genes delivered by both non-viral and viral (adenoviral and adeno-associated viral) vectors into the cytosol and thereby enhance transgene activation. The group is presently developing methods for retargeting the adenovirus to cellular uptake through the epidermal growth factor receptor (EGFR) in order to improve the specificity of the adenoviral vector for the cancer cells. The PCI-group has also documented the enhanced delivery of PNA against telomerase (hTERT mRNA) by PCI. The treatment effect has been further improved by utilizing a chimeric PNA molecule, made by conjugation of PNA to HIV-Tat internalizing peptide. The technology is under development for in vivo documentation. The PCI of PNA project is performed in collaboration with Drs. Nadia Zaffaroni and Marco Folini at the Insituto Nationale Tumori, Milano.



At the institute of immunology, Division of Laboratory Medicine, *Bjarne Bogen* and his group are working on several projects:
I) IMMUNOTHERAPY/GENE THERAPY
We have developed a novel type of vaccine molecule called Vaccibodies that may be of use in treatment of lymphoma and multiple myeloma but also in other forms of cancer. Vaccibodies are currently being tested in mouse tumor models but we plan to develop them for human cancers.

II) IMMUNOBIOLOGY
The role of Id-specific CD4+ T cells in rejection of multiple myeloma and B cell lymphoma. These experiments are conducted in a T cell receptor transgenic mouse model system developed over many years in Bogen lab. Current experiments focus on the cellular and molecular mechanisms by which Id-specific CD4+ T cells eliminate cancer cells. 2. Development of novel Id vaccines (vaccibodies). Vaccibodies are homodimers containing scFV from B cell tumors and that are targeted to MHC class II molecules and other targets on antigen presenting cells for induction of strong anti-Id immune responses. 3. A new mechanism for lymphomagenesis. Recent work in Bogen lab has demonstrated that B cells that chronically proliferate in response to helper Th2 cells can accumulate mutations and undergo malignant transformation. The genetic and molecular mechanisms for lymphoma development will be studied.

III) TUMOR IMAGING
We label mouse myeloma and lymphoma cells with Luciferase /DsRed/mCherry and detect thei location and growth in vivo with an IVIS Spectrum instrument.



Jan Brinchmann, at the Institute of Immunology, Division of Laboratory Medicine, and his group's objective are

TO ESTABLISH SUICIDE GENE TRANSDUCED, DONOR DERIVED T CELLS FOR TREATMENT OF PATIENTS WITH LEUKEMIA

Today, the only curative treatment for patients with chronic myelogenous leukemia is transplantation of allogeneic bone marrow. The possibility of a cure seems to reside within the transplanted T cells, which may kill allogeneic leukemia cells (graft versus leukemia effect, GVL). Unfortunately, these cells may also carry serious side effects, called graft versus host disease (GVHD). One way to control GVHD would be to transduce donor T cells with a drug responsive suicide gene. That way, if GVHD becomes too severe, one may give the appropriate drug which in turn will induce death in all donor T cells. To this end we have optimalized a T-cell activation protocol, which ensured that some of the most important T-cell specificities are represented among the activated T cells. Using this T-cell activation protocol, we then optimalized the suicide gene transduction protocol. We used a retrovirus transduction strategy, and obtained 30 – 50% transduction efficiency. Using tetramer staining technology and T-cell receptor BV CDR3 length analysis, we observed that important T cell specificities are represented among the transduced T cells. This strategy might be useful in the clinic for treatment of patients with hematological malignancies.

The focus of **Eivind Hovig** and his group, Department of Tumor Biology, Institute for Cancer Research, is

GENE SILENCING USING PHOTOCHEMICAL INTERNALIZATION (PCI) WITH PEPTIDE NUCLEIC ACIDS AND SIRNAS TARGETED AGAINST MITF IN MELANOMA

Building on inventions of photodynamic therapy and the related principles of membrane permeabilization (called PCI), we have developed protocols for in vitro gene silencing with both peptide nucleic acids (PNAs) in chimeras with charged peptides, and also for short interfering RNA (siRNA). These types of molecules are among the most potent gene silencers, and the PCI technology opens for specific targeting to relevant body locations. We are currently developing this technology further, and are now starting animal studies, in order to optimize treatment for in vivo use. We have selected the gene MITF as a target molecule for silencing, as this is considered a "master switch" of melanogenesis, and thus in a central reghulatory molecule for the deadly melanoma type of tumor. The control systems involving MITF are very complex, and as part of our work we are also developing in silico systems biology models for this, as well as monitoring of gene changes following silencing, and we also pursue an understanding of the alternate MITF splicing forms and their effects, in order to obtain specific and targeted down-regulation. This project includes collaboration with the inventor of PNA molecules, Peter Eigil Nielsen, University of Copenhagen, and the company PCI Biotech.

Gunhild Mælandsmo and her group, Department of Tumor Biology, Institute for Cancer Research, study

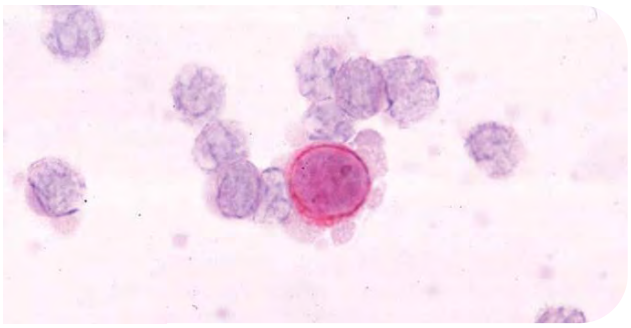
I) IMMUNOTHERAPY / GENE THERAPY IN MALIGNANT MELANOMA

Essential questions in cancer gene therapy are how to target the right cells and which gene/pathway to deliver/target. In our gene therapy projects we are working with different targeting strategies for delivery of recombinant adenoviral vectors for use in cancer therapy. The vectors can enhance their selectivity towards tumor cells through i) transcriptional targeting by limiting the expression of the transgene to the target cells, ii) transductional targeting by redirecting the vectors to bind only target cells and iii) physical targeting, such as the PCI-technology, which enhance the efficiency of the vectors to infect exposed areas. For malignant melanoma, more efficient treatment alternatives are needed. We have constructed an adenoviral vector in which the expression of the transgene is directed by the human tyrosinase promoter, which controls the rate-limiting enzyme in the biosynthesis of melanin. The vector possesses efficient and tissue-specific expression in melanoma compared to non-pigmented cells, and we have confirmed that this vector may be used for tissue specific delivery of therapeutic genes (eg: PAI-1). To increase the therapeutic efficacy further, we have investigated the efficacy of combining Ad-delivered TRAIL with conventional chemotherapy, and found that the combination therapy may be better than either alone.

II) COMBINED PHOTOCHEMICAL INTERNALIZATION (PCI) AND ADENOVIRAL INFECTION

The group have obtained a significant enhancement in transgene expression in illuminated areas. By combining PCI and Ad-TRAIL we demonstrated promising effects in vivo using colorectal cancer models. At present we are characterizing a panel of melanoma and breast cancer cell lines for expression of apoptosis inhibitors with the aim of constructing siRNA molecules against such inhibitors, and use adenoviral or other delivery principles, possibly in combination with PCI and/or conventional treatment, for the therapy of the respective tumor types.

Metastasis and micrometastasis biology



Gunhild Mælandsmo and her group, at Department of Tumor Biology, Institute for Cancer Research, study

MOLECULAR AND THERAPEUTIC ASPECTS OF THE METASTATIC PROCESS

Our goal is to extend the knowledge about how the individual steps in the process are regulated, and subsequently use this information for identification of potential target molecules that can be utilized in cancer therapy. We are mainly focusing on malignant melanoma and breast cancer and are utilizing cell lines, in vivo model systems and patient material. Available model systems representative for human cancer are of great importance for studies of biological factors involved in the metastatic process, and also for evaluation of compounds with possible therapeutic benefit. Such model systems are also utilized for investigations on the existence of cancer stem cells. At present the main focus for our basic research is functional studies of the metastasis-promoting protein S100A4. S100A4 is a multifunctional protein, and our hypothesis is that the protein has specific functions according to where it is localized (cell nucleus, cytoplasm or in the extracellular space), and that several of these functions might have impact on the metastatic potential. S100A4 is supposed, by interacting with cytoskeletal proteins, to have impact on the motility of cancer cells, but the protein can also be secreted and may be involved in activation of proteases (MMPs and plasmin activators). In therapy related projects we are focusing on principles for targeted therapy and we have ongoing projects including the use of antibodies (by means of immunotoxins or function blocking Ab) or molecular targeting (by means of HDACI or small molecule inhibitors) in combination with radiation therapy, chemotherapy and also gene therapy.

Øystein Fodstad and his group, at Department of Tumor Biology, Institute for Cancer Research study

METASTASIS MECHANISMS, MODELS, DETECTION AND TREATMENT

Cancer metastasis is a complex process composed of many individual steps, and at each step there is a finely tuned interplay between the cancer cells and multiple host factors. Thus, cancer metastasis is an in vivo process and the microenvironment plays a fundamental role. We have therefore put considerable effort into development of animal models representative for human cancer growth and metastatsis, and have several ortothopic and experimental metastasis models available which form the basis for several of the ongoing research projects. One example is our models for human breast cancer and malignant melanoma that, in agreement with the metastasis patterns observed in patients, metastesize to specific organs. The model systems are used for molecular profiling and investigation of factors of importance for tissue-preferred metastasis formation, also to brain. The in vivo models are also continuously used in preclinical evaluation of chemotherapeutic drugs and different principles for targeted therapy. Development and preclinical evaluation of immunotoxins has been a prioritized area, and has resulted in one ongoing phase I clinical trial. We are at present investigating the mechanisms of action, and are also performing preclinical evaluation of immunotoxins in combination with immunosuppressive agents, a combination that have shown synergistic anti-tumour effects. Our method for detection of disseminated cancer cells (micrometastases), where we select live cancer cells with immunomagnetic beads, make us capable to selectively pick the cells by a micromanipulator and thus isolate a pure fraction of micrometastatic cells. We are in the process of using such cell fractions for molecular characterization, and our goal is to compare primary, micrometastatic and metastatic material from the same patient. Since we isolate live cells we can also examine the growth potential of the isolated micrometastatic cells.

Einar K. Rofstad and his group, at Department of Radiation Biology, Institute for Cancer Research, study

RADIATION- AND MICROENVIRONMENT-INDUCED METASTASIS

The main aim of the project is to identify molecular and cellular mechanisms of radiation-and/or microenvironment-induced metastasis. Our hypothesis is that angiogenic factors and proteolytic enzymes may play important roles, whether the metastasis is caused by the tumor microenvironment, radiation therapy, or alterations in the tumor microenvironment induced by radiation therapy. Human melanomas xenografted into BALB/c-nu/nu mice are used as preclinical models of human cancer. Molecular mechanisms are studied by using cDNA microarrays and conventional methods (immunohistochemistry, Western blotting, Northern blotting). Oxygen electrodes, hypoxia markers (pimonidazole), interstitial fluid pressure (IFP) electrodes, pH electrodes, and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) are used to characterize the tumor microenvironment.

Molecular pathology

Anne-Lise Børresen-Dale and her group, at the Department of Genetics, Institute for Cancer Research, focus on
MUTANT TP53 IN CANCER
The project is EU funded with 15 partners and 26 WPs.
The objectives for the WPs we are responsible for are:

1. Identify and validate differentially expressed genes in wild type vs. mutant tumours and in cell lines with wt vs. different type of TP53 mutations,
2. Identify genes differentially expressed in TP53 wt tumours with very high or very low wt TP53 expression.
3. Use information in 2) to identify tumours with a p53 altered pathway and identify genes/gene-alterations responsible.
4. Characterization of TP53 mutations and the haplotype background they reside on in patients with breast and ovarian cancers with long-term follow-up.
5. Evaluation of the impact of the mutation, alone and in combination with the haplotype background, on clinical outcome.

Vivi Ann Flørenes, from the Division of Pathology, focuses on
CELL CYCLE REGULATION
Malignant melanoma accounts for about 5% of all cancers, the incidence of which is one of the most rapidly increasing tumor forms. Furthermore, to date, few treatment alternatives exists for patients with advanced disease. The overall aim of the project is to increase the understanding for which genetic and phenotypic alterations are involved in development and progression of malignant melanoma. Such knowledge may have potential to improve the opportunity to better predict clinical outcome and lead to new and improved therapeutic strategies. We use a panel of paraffin-mbedded tissue from different stages of melanoma progression (nevi, primary, metastases) to study, by immunohistochemistry, the impact of specific protein expression on clinical outcome. In particular, we focus on proteins known to play a role in cell cycle regulation and cell signaling. Interesting findings are studied further using human melanoma cell lines derived from different stages of the disease.

Guttorm Haraldsen and his group, from the Institute of Pathology, Division of Pathology, study:
ROLE OF NUCLEAR IL-33 IN ANGIOGENESIS AND THE MOLECULAR REQUIREMENTS OF ENDOSTATIN ACTION ON ANGIOGENESIS IN VIVO We propose to explore the actions of the angiogenesis inhibitor endostatin, a cleavage fragment of collagen XVIII. To this end, we shall take advantage of a surrogate in vivo model for human angio¬genesis developed in our lab and analyze the global endothelial cell transcription profiles during primitive tube formation and recruitment of perivascular cells while exposing them to endostatin. A second aim is to define the functional, angiostatic domains of endostatin by means of mutated endostatin variants. The proposed studies should expand our understanding of the complex mechanisms regulating endothelial cell function during angiogenesis.

Palliative cancer research

Nina Aass heads a group with their main focus on palliative cancer research. In 2002 WHO defined palliative care in the following way: "Palliative care is an approach which improves quality of life of patients and their families facing life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual". Thus, palliative medicine is an important aspect for optimal treatment and care of patients with advanced disease. However, the principles are relevant for all cancer patients independent of treatment intention and also for patients cured of their disease but suffering from longterm side effects.

The main projects are:

1. European Pharmacogenetic Opioid Study (EPOS).

The unit participates in this European multicenter study that obtains data on clinical characteristics, measures serum concentrations of opioids and collect biological material for pharmacogenetic studies from 3000 patients using opioids for cancer pain. Recruitment of 230 patients from our institution was finalised in May 2006.

2. European Palliative Care Research Collaborative (EPCRC).

The unit participates in this multicenter study which is part of the 6th framework program within EU.The project is led by professor Stein Kaasa, Faculty of medicine, NTNU. The focus of the project is pain, depression and cachexia/fatigue which are common symptoms in patients with advanced cancer. The project has several objectives including identification of genes and genetic variation relevant for pain, opiod response and cachexia, improvement of classification and assessment, development of evidence based guidelines and establishment of a longlasting European colllaborative in palliative care cancer research.

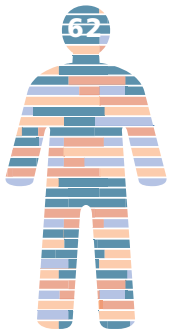
3. Patients with brain metastases.

In a descriptive project, clinical, medical and treatment characteristics, longitudinal quality of life and treatment outcome and survival is prospectively collected in patients with brain metastases from lung cancer or malignant melanoma treated at the Norwegian Radium Hospital.Target sample size is 100 patients.

The palliative care unit at the Rikshospitalet is one of five regional palliative care units in Norway and is serving the Southern part of the country.

The four main objectives for the regional unit are:

1. Research, focusing on clinical aspects and quality of life of cancer patients in a palliative setting
2. Clinical work
3. Teaching
4. Work related to facilitate palliative care both in hospitals and in general practice in the Southern part of Norway.



Proteomics

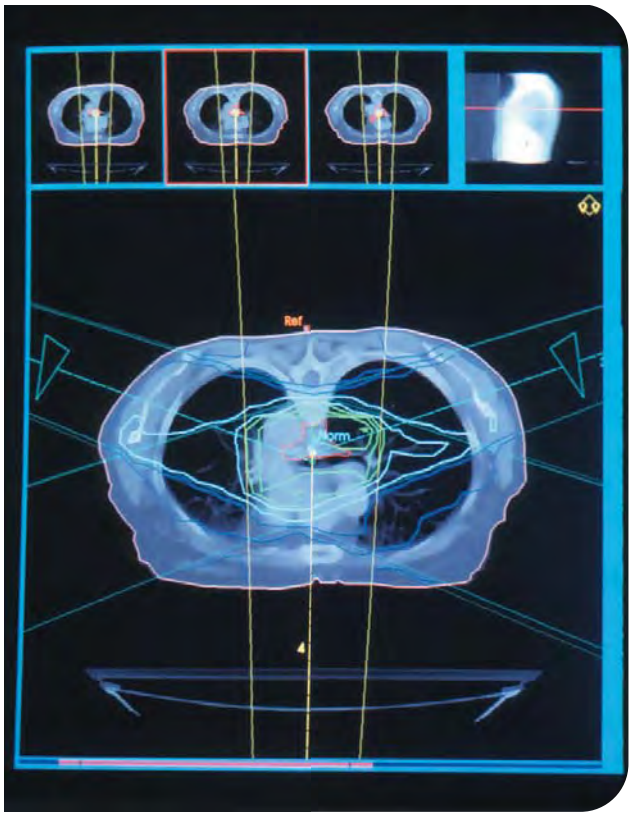
Together with a research group at Department of Pharmaceutical Chemistry, University, Oslo, ***Trine Bjøro*** and her group, from the Division of Laboratory Medicine, study

HOW CANCER MARKERS IN SERUM CAN BE DETECTED BY COMBINED LIQUID CHROMATOGRAPHY AND MASS SPECTROMETRY, LC-MS

Preparing protein samples for LS-MS involves cutting the proteins with trypsin into smaller peptides, and using at least two different separation techniques on the resulting mixture. Peptides are then fragmented in the process of tandem mass spectrometry and the resulting pieces are used to identify specific peptides. ProGRP has been chosen as a marker to investigate the potential of this method. The results are quite promising and we will continue the collaboration to improve the assays. This methodology has the potential of multiple measurements, thus generating results for many markers simultaneously.

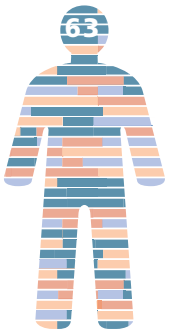
Radiation biology

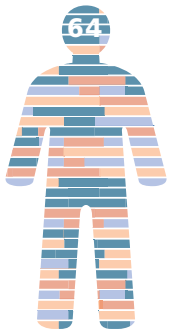
Kristian Berg and his group at the Department of Radiation Biology, Institute for Cancer Research, study:
THE UTILISATION OF MACROMOLECULES IN THE THERAPY OF CANCER AND OTHER DISEASES
Recent advances in molecular biology and biotechnology have made it possible to improve the targeting and design of cytotoxic agents, DNA complexes and other macromolecules for clinical applications. In most cases the targets of macromolecular therapeutics are intracellular. However, degradation of macromolecules in endocytic vesicles after uptake by endocytosis is a major intracellular barrier for the therapeutic application of macromolecules having intracellular targets of action.
Photochemical internalisation (PCI) is a novel technology for the release of endocytosed macromolecules into the cytosol. The



technology is based on the activation by light of photosensitizing compounds (photosensitizers) located in endocytic vesicles to induce the release of macromolecules from these compartments. Thereby, endocytosed molecules can be released to reach their target of action before being degraded in the lysosomes. PCI has been shown to stimulate intracellular delivery of a large variety of macromolecules and other molecules that do not readily penetrate the plasma membrane, including type I ribosome-inactivating proteins (RIPs), RIP-based immunotoxins, DNA delivered as gene-encoding plasmids or by means of adenoviruses or adeno-associated viruses, peptide-nucleic acids and chemotherapeutic agents such as bleomycin. The efficacy and specificity of PCI of macromolecular therapeutic agents has been improved by combining the macromolecules with targeting moieties, such as the epidermal growth factor and antibodies. Several animal models have been used for in vivo documentation of the PCI principle. Recent results also indicate that PCI may reverse doxorubicin resistance or be utilized to circumvent multidrug resistance. In general, PCI can induce efficient light-directed delivery of macromolecules into the cytosol, indicating that it may have a variety of useful applications for site-specific drug delivery, as for example, in gene therapy, vaccination and cancer treatment. PCI is under development for clinical utilization. The first clinical trial is scheduled for the autumn of 2008.

Johan Moan and his group, at the Department of Radiation Biology, Institute for Cancer Research, study
PHOTODYNAMIC THERAPY OF CANCER
Worldwide, experimental and clinical photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) and its esters has become more important during the last decade. However, still only 2 mm thick tumours can be treated with ALA-PDT. Further studies are needed to optimize the delivery vehicle and to ALA derivatives with larger penetration depths and better protoporphyrin IX (PpIX) production. Experiments will be designed to investigate new ALA-derivatives and their delivery vehicles, to increase PpIX production by different methods and to further document the influence of ALA-PDT on cell adhesion and metastasis. The major side-effect of ALA-PDT is pain experienced during treatment. Pain relief by local anaesthetics, cooling, etc. may change tissue oxygenation, production of singlet oxygen, optical penetration into tissue, tissue pH and temperature, all factors which have large influence on PDT outcome. Different approaches to reduce pain and their possible impact on the therapeutic effectiveness will be investigated. In spite of increasing clinical application, there is a lack of reliable and non-invasive methods to evaluate physiological parameters of relevance for the therapy, such as oxygen level, vasoconstriction, vasodilatation and erythema. We have found that non-invasive reflectance spectroscopy provides useful information about blood volume and oxygen changes, and even skin pigmentation. We will quantify blood, oxygen and melanin distribution changes during and after PDT from reflectance spectra using a bio-optical algorithm for calculation of these parameters in tissues. Our preliminary studies have shown an increased production of endogenous PpIX in the presence of folic acid. Our work indicates that folate is degraded both in patients treated with PDT and in folate solutions exposed to visible light in the presence of a photosensitizer. The effect of PDT on folate degradation will be investigated.





Qian Peng, at the Division of Pathology, studies

I) MITOCHONDRIAL BENZODIAZEPINE RECEPTOR AS A NOVEL THERAPEUTIC TARGET FOR 5-AMINOLEVULINIC ACID-MEDIATED PHOTODYNAMIC THERAPY OF CANCER

Photodynamic Therapy (PDT) with protoporphyrin IX (PpIX) induced from 5-aminolevulinic acid (ALA) has been established for the treatment of several types of cancer. Apoptosis, or cell suicide, is a form of cell death that is morphologically and biochemically distinct from necrosis. Three main processes are involved in the mechanisms of apoptosis: mitochondrial permeability transition (PT) that initiates early events; translocation of mitochondrial pro-apoptotic factors and caspase activation that execute the apoptosis; and Bcl-2 family proteins that regulate the apoptotic process. Mitochondrial benzodiazepine receptor (MBR) comprises a complex of three proteins that includes an 18-kDa receptor protein, the 32-kDa voltage-dependent anion channel and the 30-kDa adenine nucleotide translocator. MBR is involved in the formation of mitochondrial PT pore. Most importantly, MBR utilizes PpIX as an endogenous ligand and is thus expected to be the primary target for PDT when ALA is used. We hypothesize that the damage to MBR complex by ALA-PDT may induce PT, open the PT pore and rupture mitochondrial membranes to trigger apoptotic process by disruption of transmembrane potential and/or release of pro-apoptotic factors. Several pathways for the apoptotic induction will be identified. The main aims of this project are to investigate the mechanisms and correlations of MBR and Bcl-2 family proteins with the apoptotic induction by ALA-PDT and to explore possible therapeutic intervention strategies.

II) 5-AMINOLEVULINIC ACID HEXYLESTER-MEDIATED PHOTODYNAMIC THERAPY FOR THE EX VIVO PURGING OF HEMATOPOIETIC STEM CELLS GRAFTS: A PRECLINICAL STUDY IN ANIMAL TUMOR MODELS

High doses of chemotherapy and/or radiation therapy in combination with autologous bone marrow or more recent mobilized peripheral-blood stem cell transplantation are used for the treatment of a number of hematologic malignancies and selected solid neoplasms. In contrast to allografts, however, autografts may harbor residual occult malignant cells that can cause a tumor relapse. Various 'purging' methods to eradicate tumor cells from the autograft have thus been recently developed. Unfortunately, none of the techniques have so far provided complete and definite clinical and cytogenetic remissions. Photodynamic therapy (PDT) involves administration of a tumor-localizing photosensitizer and its subsequent activation by light. Although several photosensitizers have been tested as agents for the purging purpose, all the exogenous dyes have a limited selective accumulation in neoplastic cells. The aim of the present project is to explore the possibility of using ALA hexylester-induced endogenous PpIX-based PDT in a much more selective manner for the purging of tumor cells from autologous bone marrow grafts in animal leukemia and solid tumor models. Three murine tumor models (L1210 leukemia, 4T1 mammary carcinoma and B16 melanoma) in immuno-competent syngeneic mice (DBA/2 for L1210, Balb/c for 4T1 and C57B/6 for B16) will be utilized to study animal survival rates (leukemia model) and lung metastasis (4T1 and B16) following a lethal dose of total body irradiation and ex vivo ALA hexylester-mediated photodynamic purging. Mechanisms of photodynamic action such as apoptosis and immunologic effects will also be studied.

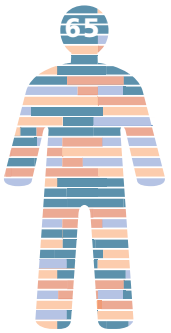
Einar K. Rofstad and his group, at the Department of Radiation Biology, Institute for Cancer Research, study

COMBINED RADIATION AND ANTIANGIOGENIC THERAPY

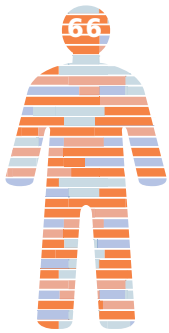
Angiogenesis is a necessary prerequisite for tumor growth and metastasis. The main aim of the project is to investigate the potential usefulness of combined radiation and antiangiogenic therapy in the treatment of metastatic cancer. Human melanomas xenografted intradermally into BALB/c-nu/nu mice are used as preclinical models of human cancer. Melanoma cells transfected with green fluorescence protein are transplanted to dorsal window chambers and studied by vital microscopy. Molecular mechanisms are studied by using cDNA microarrays and conventional methods (immunohistochemistry, Western blotting, Northern blotting).

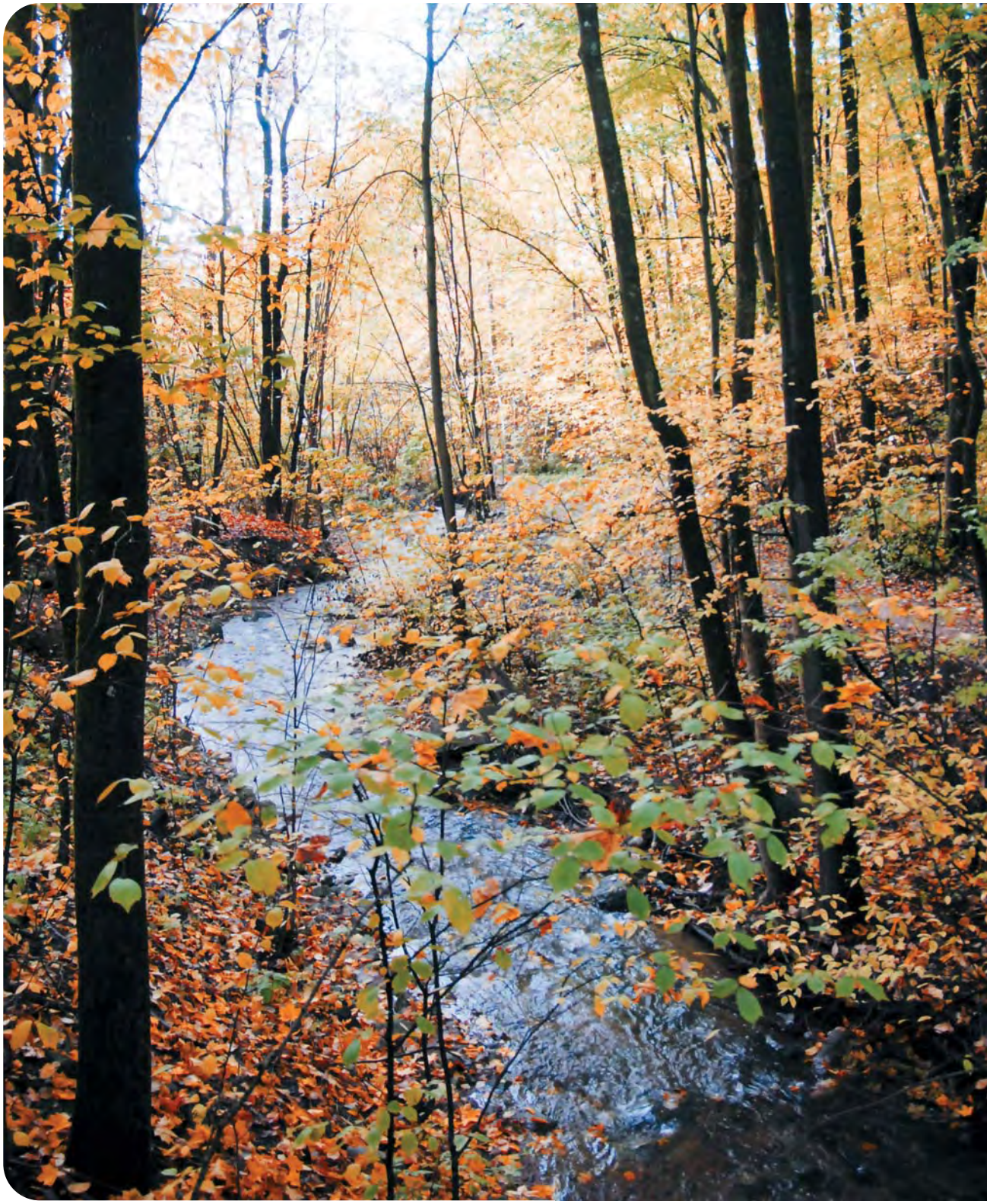
Vitamin D

Johan Moan and his group, at the the Department of Radiation Biology, Institute for Cancer Research, study IMPROVEMENT OF CANCER PROGNOSIS BY VITAMIN D: INVESTIGATIONS OF MECHANISM OF ACTION AND CLINICAL RELEVANCE Vitamin D and its role in calcium metabolism has been in focus for decades. Only recently vitamin D deficiency was linked to risk and prognosis of several cancer types and other chronic diseases. Potential molecular and genetic mechanisms of these actions have been identified and characterized throug experimental studies. Humans have two main sources of vitamin D: solar ultraviolet radiation and intake from food and supplements. Studies suggest that higher vitamin D levels, beyond current recommendations, may be needed to obtain protection against cancer. From this perspective, a large fraction of the population is at high risk of vitamin D deficiency. Other factors with increasing prevalence in the population (obesity, metabolic syndrome) may add to the increased risk of vitamin D deficiency. The present project is a proposal of observational and experimental studies aimed at elucidating important mechanisms of vitamin D photobiology and metabolism and their cancer relevance. Moreover, we want to test our epidemiologic hypothesis that the non-calcaemic vitamin D derivative, calcidiol, is an active anti-cancer agent. We will : 1) Compare vitamin D levels achieved by exposure to controlled UV doses and by oral intake of the vitamin; 2) Determine the vitamin D levels at the time of diagnosis in patients with head-neck cancer and sarcomas; 3) Evaluate the main predictors and vitamin D status in overweight and obese patients; 4) Study vitamin D synthesis and metabolism in a rat model of androgen and estrogen deprivation, respectively; 5) Study tumor development, growth and differentiation under calcidiol administration in rats under various hormone conditions; 6) Study anticancer potential of calcidiol in combination with standard chemotherapeutic agents. We hope that our results will form the basis for an interventional study of vitamin D for cancer patients.



III Other CCC-related research





Centres for Research – Based Innovation

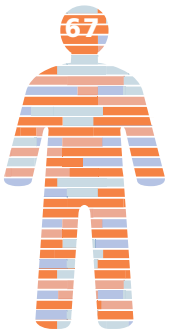
The Norwegian Research Council selected in 2006 14 centres for research – based innovation. The main objective is to enhance the capability of the business sector to innovate by focusing on long – term research based on forging close alliances between research – intensive enterprises and prominent research groups. Rikshospitalet University Hospital is heavily involved in two of these.

I) Statistics for innovation

Eivind Hovig from the Department of Tumor Biology, Institute for Cancer Research, is involved in this project. Statistics is an essential tool for integrating, processing and analyzing data. Optimizing the data will have impact on future research and patient treatment.

II) Stem cell based tumor therapy (SENIT)

Stefan Krauss is coordinator of this centre. The overall aim of this project is to shift the focus in cancer research and cancer treatment from the tumor as a whole to the entity called tumor stem cell. It is the firm belief of the consortium that this will change the way we understand and treat cancer in the near future. The main goals will be to characterize tumor stem cells and provide methods for identifying, visualizing, isolating and targeting tumor stem cells. We aim to create a concerted action between key players of the Norwegian biotechnology industry and academic researchers to used gained knowledge for advancing tumor cell based therapy and treatment.



Centre of Cancer Biomedicine

Centre of cancer Biomedicine (CBB) was funded Centre of excellence by the Norwegian Research Council in 2007. The centre is headed by ***Harald Stenmark*** and located to the Institute for Cancer Research. The centre is affiliated to the University of Oslo and constitutes seven independent research groups, six are localized at Rikshospitalet University Hospital. Cancer is a complex invasive – cell disease. To combat it efficiently, integration of cancer – related biological information occurring at multiple levels is needed. Complex analysis, known as systems biology, is based on the team approach to advance the work of individual scientist from different disciplines.

Out of the seven groups, three are well established within basic cell biology research. Multiple aspects of cell signaling, growth regulation and intracellular transport are studied by the groups of ***Kirsten Sandvig, Harald Stenmark*** and ***Sjur Olsnes.*** The groups of ***Erlend Smeland*** and ***Ragnhild A. Lothe*** characterize molecular status, genetics and epigenetics of tumor and cancer cells by large – scale and detailed biology research, high – throughput analyses generate large amounts of data that need careful evaluation to enable valid interpretation.

Together, the efforts of the centre aim towards a better understanding of the complex dynamics of cancer evolution, more accurate prediction of cancer prognosis and response to treatment, more powerful molecular based treatment – for the future benefit of the individual cancer patient.

Centre for Shared Decision Making and Nursing Research

Cornelia Ruland is head of the Centre for Shared Decision Making and Nursing Research. Her group's research program focus on

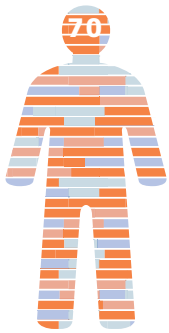
DEVELOPING AND TESTING ELECTRONIC INTERVENTIONS TO SUPPORT PATIENT-PROVIDER COMMUNICATION AND SHARED DECISION MAKING (SDM)

The electronic interventions are tested in illness /symptom management for cancer patients, and providing patients with individually tailored self-management support through the Internet. Research activities also include theoretical, methodological and informatics- related questions, cognitive and behavioral aspects associated with decision making and communication, as well as questions associated with streamlining and adapting SDM systems into clinical practice. Our current applications include: (1) The Choice application that allows patients to elicit and share their symptoms and illness experiences with their care providers to support communication and shared care planning and where patients' self-reported data are integrated into the electronic health record (EHR) in five of Rikshospitalets cancer units. (2) SISOM is a tool for pediatric oncology, that uses a graphical user interface to help the children with cancer communicate their symptoms/problems in a child-friendly, age-adjusted manner to support indivually tailored patient care. (3) WebChoice, an Internet-based support system that allows patients to monitor symptoms over time; access evidence-based, reliable options for self-management tailored specifically to their reported symptoms, and use e-mail and a communication forum to ask questions to a clinical nurse specialist in cancer care and exchange experiences with other cancer patients. (4) Connect, a shared EHR for cancer patients and their care providers. So far these applications have repeatedly shown to significantly increase congruence between patients' reported symptoms and patient care, increased number and precision of patients' reported symptoms, and high user satisfaction and perceived usefulness.

The cancer patient groups are lymphoma, sarcoma, leukemia, breast cancer and prostate cancer.

The main projects are:

- A clinical trial to measure the effect of Choice on patient provider communication, stress and anxiety, documented patient care, and patient satisfaction in outpatient consultations (with physicians) and inpatient admission interviews (with nurses), before and after the Choice application is implemented routinely into Rikshospitalets hematological and lymphoma units.
- A clinical trial to measure effects of SISOM in children with cancer age 7-12, on communication in outpatient consultations between children, parents and physician, documented patient care, anxiety, coping style, locus of control, and patient satisfaction.
- A randomized clinical trial to measure effects of WebChoice on symptom distress, symptom patterns over time, self-efficacy, social support, depression and health service use in 324 breast and prostate cancer patients from all over Norway who are followed with repeated measures over one year. Further, to investigate usage patterns, patients' experiences of Web-CHOICE's



usefulness and ease of use; patients' ability to comprehend information and their knowledge gained about the disease and self- management; and the patterns and content of patients' communication with the cancer nurse and other patients.

Our research team is interdisciplinary and includes nurses, physicians, informaticians, computer scientists, psychologists, social workers, librarians and others.

Tone Rustøen is part of the Centre for Shared Decision Making and Nursing Research. Her group study

I) CANCER PATIENT'S ATTITUDES TO PAIN TREATMENT AND WHAT BARRIERS PATIENTS AND THEIR FAMILIES HAVE TO PAIN REGIME.

There is a turn from treatment and care in hospitals to community and outpatient care settings. This challenge demands increased knowledge about how patients and their family cope with the situation. The study is cross-sectional and describes patient related factors like barriers to pain treatment, compliance with pain regime, report of pain, side-effects of pain treatment, patients' self-efficacy to pain treatment, and patients' anxiety and depression. Family member are also included. Patients were screened in the outpatient oncology clinic for the presence of pain and/or analgesic use. Those who reported pain or the use of analgesics were invited to participate in the study. A total of 1790 patients were eligible and 1549 completed the screening questionnaire. Of these 1549, 332 patients reported having pain and/or using analgesics and 21.4% reported pain or used analgesics. Of the 217 patients who completed the study questionnaires, 53% had only cancer pain (pain due to cancer and/or treatment), 25.3% had non-cancer pain, and 21.7% had both cancer and non-cancer pain. The findings suggest that outpatients with a combination of cancer and non-cancer pain may be at greater risk for under-treatment of pain. This study also describes patients' level of adherence to an analgesic regimen; examining variables that are related to adherence, determining the relationship between adherence and specific pain characteristics and patients' level of self efficacy, and evaluating the effects of demographic variables, specific pain characteristics and self-efficacy for pain management on adherence to pain medication.

II) PALLIATIVE CANCER RESEARCH

Hope and coping is considered an important factor in patients' personal adjustments during times of loss, uncertainty, and suffering. The study is cross-sectional and describes the relationship between hope, coping and pain in hospitalized oncology patients. Hospitalized cancer patients were included as they would be on a regularly scheduled opioid treatment for their cancer pain for at least 3 days. Following enrollment, patients were asked to complete the study questionnaires. Patients filled in questionnaires measuring hope, coping, pain charactersitics, and self-assessed health. To better understand the levels of hope reported by these oncology inpatients with pain, their responses were compared to data from the general Norwegian population. This study is part of a larger multisite European Pharmacogenetic Opioid Study, in collaboration with ***Pål Klepstad,*** St. Olavs Hospital, Trondheim University Hospital.

National Competence Centre for Neuroendocrine Tumors

Espen Thiis-Evensen is the head of the National Competence Center for Neuroendocrine Tumors. As The Rikshospitalet University Hospital is the National Competence Center for Neuroendocrine Tumors, a large percentage of patients in Norway with NETs are evaluated and treated at the Department of Medicine, Division of Gastroenterology, giving us a unique opportunity to study these rare cancers. Since 1994 all patients with NETs evaluated at our hospital have been entered into a database. All of the journals for these patients will be reviewed and diverse data of interest (eg. symptom presentation, date of diagnosis, biopsy results, treatment and response for each admission, etc.) will be entered into the expanded database. This database will be used to evaluate the various epidemiological features of interest as well as treatment response.The database is now completed (as of November 15, 2007) with a total of 483 patients reviewed and the data are currently being evaluated with statistical analysis.The group is currently studying:

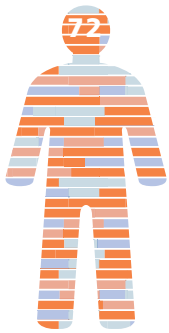
I) FIBROSIS IN NEUROENDOCRINE GASTROINTESTINAL TUMORS

A poorly understood feature of neuroendocrine gastrointestinal tumors, more specifically mid-gut carcinoid tumors, is their propensity to develop marked fibrosis. These tumors can result in intraabdominal fibrosis resulting in pain and intestinal obstruction. In addition, patients with these tumors can develop cardiac fibrosis (carcinoid heart disease). The mechanism behind the development of fibrosis in these patients is poorly understood. Growth factors are being studied ever more intensely with regard to their role in other fibrotic diseases. There currently exists no method to discover the changes of fibrosis at an early, possibly treatable stage. The aim of this study is to show a difference in fibrosis markers (including growth factors) among mid-gut carcinoid patients with and without carcinoid heart disease. It is hypothesized that patients with fibrosis have higher levels of fibrosis markers, including growth factors. This study involves the inclusion of patients with histologically verified mid-gut carcinoid. Each patient will undergo echocardiography to determine if they meet the criteria for the presence of carcinoid heart disease. Blood samples will be taken and stored at the time of inclusion. In addition, biopsies taken at the time of diagnosis will be examined for fibrosis markers as well. The study also involves inclusion of healthy control persons for comparison. 93 patients with mid-gut carcinoid are included as well as 20 healthy volunteers in the control group. The collected blood samples are currently being analyzed for the fibrosis markers of interest with ELISA. Biopsies for a selected group of patients will be evaluated with immunohistochemistry in January 2008.

II) CHANGE IN KI 67 OVER TIME IN PATIENTS WITH NEUROENDOCRINE TUMORS

One of the most important prognostic markers for patients with NETs is the proliferation index Ki 67. Ki 67 is a protein expressed in all phases of the cell-cycle except for Go. To calculate the Ki 67 for a tumor, one uses a mouse monoclonal antibody against this antigen to determine what percentage of cells in the biopsi are positive for Ki 67 and therefore, undergoing division. The higher

the Ki 67 value, the more aggressive the tumor is. Patients with NETs with lav Ki 67 have increased survival compared with those with higher Ki 67. The Ki 67 value can be different between the primary tumor and metastases in the same patient. Clinicians use the Ki 67 value to help determine which treatment is best for patients with NETs. Tumors with a higher Ki 67 respond better to chemotherapy, while those with low Ki 67 have a better response to "biological" agents such as interferon. It is unknown whether Ki 67 values change in the same tumor over time. It is important to answer this question as it can help clinicians give the most appropriate treatment.
From the database completed in project 1, we have determined that 134 patients have had multiple biopsies taken during the course of their illness. We have obtained consent where appropriate and will determine the Ki 67 value in each biopsy.



III) RISK OF SECOND PRIMARY CANCER AMONG PATIENTS WITH NEUROENDOCRINE TUMORS

It has been observed that patients with neuroendocrine tumors have an increased risk of second cancers. In one series including over 13,000 patients with neuroendocrine tumors, 22% had a second primary cancer. This is in contrast to the reported 5% of patients with cancer in general that develop a second primary tumor. However, there has been uncertainty regarding whether patients with NETs are truly at higher risk for second cancers, with conflicting results in studies looking at this question. The aim of this study is to evaluate the occurrence of second primary cancers in Norwegian patients with neuroendocrine tumors diagnosed between 1980 and 2005. This information will be obtained via the Norwegian Cancer Registry. The data will be analyzed using standardized incidence ratios to determine if there truly exists a significant risk or if the observed rates of second cancers are expected based on known rates in the Norwegian population. This is important to determine as it could lead to increased screening for second cancers. In addition, clinicians need to be aware of this risk as symptoms resulting from a second, more aggressive tumor, might be attributed to the patient's neuroendocrine tumor leading to inadequate treatment and/or treatment delays. We are currently waiting for the data from the Norwegian Cancer Registry regarding the percentage of patients with neuroendocrine tumors diagnosed between 1980 and 2005 with a second primary cancer. Once this data is available, we will analyze the data using standardized incidence ratios.

IV) EPIDEMIOLOGICAL CHARACTERISTICS AND TREATMENT RESPONSE OF NEUROENDOCRINE TUMORS

The aim of this study is to analyze epidemiological characteristics of patients with neuroendocrine tumors as well as their response to conventional treatment. Characteristics of interest include distribution of the different types of neuroendocrine tumors, age at diagnosis, sex distribution and survival. In addition, the study will look at the response to the diverse treatments used in these tumors.

V) QUALITY OF LIFE

To obtain increased understanding and knowledge concerning quality of life for patients with NET and establish an educational programme based on health promotion behaviours due to the multidisciplinary cognitive theory including the concept of self-efficacy. The main objectives of the study are:
-to investigate the patient's health-related quality due to sociodemographic and disease-related variables compared to the general population -to evaluate psycho-sociological predictors of quality of life-to explore, in a quasi-experimental trial, the change in health-related quality of life due to an educational programme based on the principles of Banduras cognitive theory and the concept of self-efficacy-to explore the usefulness of Bandura's concept of self-efficacy due to a patient educating programme.Method: A group is pre-tested and post-tested with a follow-up for six months. The study will need an estimated sample of 73 persons from three health regions in Norway. So far 40 participants have undergone the educational program. The main aim with the patient educational program is to promote the patient to change health-related behavior by 12 education lectures, weekly supervised individual telephone dialogue and supervised group dialogue every fourth week for a period of six months. The main goals are to generate knowledge about the disease and relevant challenges and to focus on the connection between how to exercise some control over potential stressors and health-related behaviour in everyday life. Validated questionnaires are used to evaluate different aspects of quality of life.

National Resource Centre for Studies on Long-term Effects after Cancer

Sophie D. Fosså is head of National Resource Centre for Studies on Long-term Effects after Cancer. Today 60% of cancer patients survive for at least 5 years and have to live with eventual long-term effects after cancer. Therefore the field of long-term survivorship after cancer has become an increasingly important field of clinical oncology. The Nordic countries have excellent conditions for long-term follow-up research of cancer survivors by clinical or epidemiological methods (unique person number, population-based registries). On this background the National Centre was established in 2005 by the Directorate of Health and Social Affairs. The Centre`s research focuses on somatic and psychosocial effects after cancer with 2 main objectives.

1. Research: A) Achievement of new knowledge by clinical examinations of cancer survivors with collection of biological material for translational research, by questionnaires and/or by linkage studies between registries. Particular interest is put on gonadal and cardiovascular toxicity, fatigue, anxiety/depression, sexuality, "living with cancer" and adaptation to the labor force. B) In addition, and the Centre offers support to health care professionals from the own hospital or from other institutions with clinical cancer research projects in general or in relation to the aims of the Centre.
2. Information: Information with health care professionals concerning long-term effects after cancer with the aim to induce adjustments of current treatment strategies for reduction of future adverse long-term effects, and to diagnose eventual health-threatening morbidity at an early stage.

Patient groups that are studied are:
1. Childhood cancer survey: Referred patients with long-term toxicity.
2. Long-acting testosterone substitution in anorchid Testicular Cancer Survivors: Intervention study (Nebido®, Schering) focusing on biochemical and quality of life parameters (40 patients).
3. Testosterone substitution in hypogonadal survivors after malignant lymphoma (70 patients).

We have multiple ongoing projects:

- Testicular cancer (TC):

1. Late effects: A national study (1453 patients).
2. Prospective evaluation of cognitive function.
3. Androgen substitution in hypogonadal long-term survivors.
4. Polymorphisms.

- Breast cancer stage II/III:

Treatment-related clinical, psychosocial, radiobiological and genetic parameters after breast cancer (415 patients).

- Malignant lymphoma (ML):

Fatigue, gonadal function and psychological well-being (ca.700 patients).

- Childhood cancer:

1. Multi-disciplinary survey of 220 long-term survivors after ML and TC including research on polymorphisms.
2. Nordic survey of long-term survivors after Wilm`s tumor, astrocytoma and myelogenous leukemia (398 survivors and 152 parents).

- Prostate cancer:

Prospective and cross-sectional studies of treatment-related side-effects and psychological distress (400-2400 patients).

- Cancer in general:

Linkage between the Hospital`s registry, Cancer Registry (CRN) and Medical Birth Registry of Norway (MBRN) and National Health Insurance.
1. Post-cancer fertility. 2. Adaptation to the labor force. 3. Physical activity as palliative treatment.

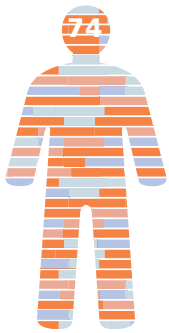
- Depression in cancer:

EU-funded study on assessment and classification of depression in palliative cancer patients.

- Translational research is established with the Institute for Cancer Research (Anne-Lise Børresen – Dale and Ragnhild A.Lothe) and the International Testicular Cancer Linkage Consortium (NCI), ICR laboratory for Genetic Epidemiology, Leeds. Cooperation exists with the Department of Radiation Biology (Dag-Rune Olsen), the Medical Division and Oslo University.

- International studies

1. Cooperation with Nordic co-workers (childhood cancer), researchers at NCI (Second cancer; Genetics in Testicular Cancer) and M.D. Anderson Hospital (Gonadal function). ICR laboratory for Genetic Epidemiology, Leeds.



2. European Palliative Research Cooperative (EPCRC)

• Other national studies

1. Testicular cancer follow-up: Emphasis is put on cardiovascular long-term effects.
2. Childhood cancer follow-up: Clinical survey started in 2007.
3. Long-term side effects in prostate cancer: Hospital-based data are analysed, the national study is to be started in 2008.
4. Registry-based fertility studies (CRN/MBRN): The aim is to explore cancer patients` possibility for post-treatment parenthood.

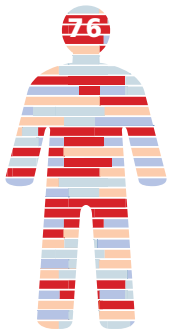
• Regional studies (extramural co-operation in Norway)

1. Ullevål University Hospital, Dep. of Oncology
2. University Hospital Tromsø, Dep. of Oncology
3. Haukeland University Hospital, Dep. of Oncology
4. Sørlandet Hospital, Kristiansand / Arendal, Depts. of Gynecology
5. University of Oslo, Laboratory of Genetics (Trine Haugen)
6. University of Science and Technology, Dep. of Molecular Medicine and Cancer Research (Line Oldervold)
7. Department of Biological & Medical Psychology, Faculty of Psychology, University of Bergen

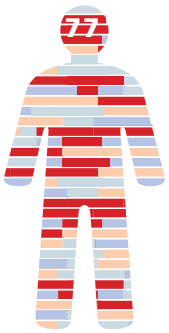
National Resource Centre for Studies
on Long-term Effects after Cancer

IV The Cancer Registry of Norway

Summary



The Cancer Registry of Norway



Head: Frøydis Langmark, professor PhD

The Cancer Registry of Norway, (Institute of Population-based Cancer Research) was established as early as 1951, thus being one of the oldest institutes of its kind in the world. Frøydis Langmark has been its Director through the last 25 years.

Reporting of all cancer cases and most precancerous conditions to the Cancer Registry is mandatory in Norway according to Regulation on the collection and processing of personal health data in the Cancer Registry of Norway.

The Institute is an independent research institute, with its own board, within the Rikshospitalet Medical Centre. It is, however, mainly funded through its own chapter in the Norwegian National budget.

The Cancer Registry of Norway provides its services to all four health regions of Norway, as well as research groups, nationally and internationally. Its core activities are research on causes of cancer, screening-based research, and population-based clinical research.

The Cancer Registry of Norway currently employs 150, organized in three research divisions, one administrative and one IT department. The research takes place within the:

1. Department of Etiological Research - focusing on the influence of heredity, hormones, life style, nutrition, environmental and occupational factors on cancer. This department is also responsible for exposure databases.

2. Department of Screening-based Research – runs the screening programmes for cervical and breast cancer and the colorectal cancer screening project, as well as screening-based research projects as a whole. The department is responsible for invitation databases, cytology, biopsy and radiology databases.

3. Department of Clinical and Register-based Research – its focus is on information and research based on the main database and all the special clinical registries for the different sites (breast, colorectal etc.). Its responsibility is coding and registration of tumor data and clinical data.
The Cancer Registry of Norway is extending its work, and its aim in the future is to provide data from the quality registries for all major cancer forms. These new databases will be important sources for clinical and translational research as well as for health care authorities in their work to monitor the delivery of and evaluate the quality of cancer care.

These new, organ-specific registries currently running or planned function in close collaboration with the clinical cancer communities.
Registries have already been established for the following diagnoses;
- Colorectal cancer
- Prostate cancer
- Lung cancer
- Hereditary cancer (especially polyposis)
- Pediatric solid tumors
- Ovarian cancer

Special registries on breast cancer, malignant melanoma, lymphoma and chronic lymphatic leukemia are soon to be established.
The Cancer Registry is in charge of the national screening programmes for breast and cervical cancer. This work involves IT-logistics, management as well as the continuous effort to ensure high quality of procedures and data, through evaluation of the results. The screening-based research focus on data on incidence, tumor growth and mortality, and on vaccination studies to prevent HPV-infection.

The Norwegian Cancer Registry is an attractive scientific partner in international research, as the National Cancer Institute (NCI) and MD Anderson Cancer Centre in the United States and the International Agency for Research on Cancer (IARC) in Lyon.

In 2007, the institute initiated and/or participated in a wide range of different research projects. Many projects are conducted in collaboration with international partners within cancer research as the Nordic Cancer Registries, as well as the abovementioned IARC and NCI. They focus on causes of cancer and patients' prognosis.

The researchers at the Registry published in 2007 75 scientific papers (per 15th October) and 5 dissertations took place. For information we refer to the annual report from the Cancer Registry of Norway "Cancer in Norway 2006."

Department of Etiological Research

Head: Steinar Tretli, professor PhD

The department's main focal points are on biological and environmental mechanisms in the development of cancer. This is reflected in the broad range of research topics such as occupation, environmental factors, hormones, nutrition, smoking, physical activity and heredity.

Many of these studies are initiated within the institution itself, but the department is also involved in various other national and international research projects. These have resulted in a number of publications in high impact international journals.

The Department of Etiological Research is deeply involved in the training of new researchers, in collaboration with the universities in Norway. In 2007, eight PhD students were supervised by at least one senior researcher from the department. The PhD projects have resulted in dissertations with opponents from both national and international scientific communities. The senior researchers also supervise students from other research institutions.

In 2007, its two main priorities were biological mechanisms and occupation and environmental factors. **Steinar Tretli** focuses, in his work, among other things, on cancer in relation to vitamin D or hormones. He also supervises PhD students dealing with a wide range of topics such as life after a cancer diagnosis and statistical simulation of breast cancer biology. Currently there are 5 PhD students at the department.

Tom Grotmol is studying different risk factors for testicular cancer whereas **Trude Eid Robsahm** is currrently working with physical activity and cancer in a large cohort of Norwegian elite athletes. **Elisabete Weiderpass Vainio** is primarily working on female cancer types and is actively involved in several international collaboration studies, especially in Uganda. **Kristina Kjærheim** and **Tom Grimsrud** are the main senior researcher within the field of occupational and environmental factors. **Anette Hjartåker** is working on nutrition and cancer. All senior researchers are actively involved in supervising PhD students.

Wider collaboration studies, nationally and internationally, are often vital in the search for scientific results. In 2006, the department participated in Nordic studies like NOCCA (occupational cancer), European studies like ARCAGE (ear/nose/throat, tobacco/alcohol and genetic) and RACE (effects of cardiovascular mortality and radiotherapy), and international studies like WECARE 2 (on breast cancer) and CCPRB (serum bank studies).

The department also has the responsibility for the Janus Serum Bank, project leader **Tom Grimsrud** (from September 2007 **Hilde Langseth**). It was transferred from the Cancer Society to the Cancer Registry in May 2004. It was established in 1973, thus being one of the oldest bio banks in the world. The objective of the Janus Serum Bank is to provide material for cancer research. In April 2005, the employees at the bank moved from Rikshospitalet to the Cancer Registry. The Cancer Registry is responsible for the data from the bank and the licensure from the Data Inspectorate, which was renewed in 2005. The storage facilities are not satisfactory, but the Cancer Registry is working with the establishment of new routines.

The Cancer Registry is responsible for the Janus Serum Bank, established in 1973. More than 470 000 blood samples from 330 000 individuals are currently stored in the bank. Among these, more than 40 000 of those have developed premalignant lesions or cancer.

All in all, research based on the Janus material has resulted in over 100 scientific publications.

Dissertations published in 2007 from Department of Etiological Research;

Langseth, Hilde: Risk of cancer and non-malignant mortality among women in the Norwegian pulp and paper industry: A focus on ovarian cancer and exposure to asbestos and other dust. University of Oslo 2007

Lie, Jenny Sigstad: Cancer risk among Norwegian nurses. University of Oslo 2007.

Department of Screening-based Research

Head: Rita Steen, MD PhD

Department objectives

The Screening Department administers two programmes for early detection of cancer and premalignant disease, the Breast Cancer Screening Programme and the Cervical Cancer Screening Programme.

Since 1993, the Cervical Cancer Screening Programme has recommended women aged 25-69 years to undergo a PAP smear every third year. The Breast Cancer Screening Programme started in 1995 in 4 counties, and since 2004 all 20 counties are included in the programme, and through this programme all women aged 50-69 years are offered mammography every two years.

The Cervical Cancer Screening Programme mails a personal letter to women who have had not had a PAP test in the last three years, with a recommendation to get tested. Invitation to mammography screening is mailed to all eligible women, together with a prespecified date of examination.

The Screening Department monitors the programmes' effectiveness and efficacy by examining early quality indicators (e.g. coverage/attendance, detection rate, tumor stage for mamma cancer, and grade of premalignant lesions of the cervix), as well as changes in rates of incidence and mortality of the diseases. The main objective of the Norwegian Breast Cancer Screening Programme is to reduce mortality by 30% among women invited to mammography screening. For the Cervical Cancer Screening Programme, the main objective is to achieve a reduction of 50% in the incidence and mortality rates of cervical cancer compared to the rates prior to the programme launch. The most important factor determining the success of these screening programmes is high coverage. In 2005, the coverage was 79% in the Cervical Cancer Screening Programme, and the attendance rate was 76% in the Breast Cancer Screening Programme, raising expectations that the programmes will accomplish their objectives.

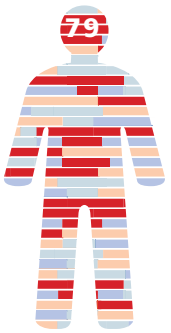
Current Research Priorities

The current research priorities of the Cervical Cancer Screening Programme are:

1) Evaluation of the CIN (cervical intraepithelial neoplasia) register, a follow-up register with data on treatment, established in 1997.
2) Study of the impact of HPV-testing in triage after PAP smear screening on CIN 2+.
3) Study of the impact of changing the screening interval and screening age range.
4) Studies of the efficacy and effectiveness of screening in women aged 25-69 years.
5) Study of the screening history of women diagnosed with cervical cancer before reaching the age of 25, including a re-examination of their PAP tests, pathological tissue and samples.
6) Study of the screening history of women aged over 70 years diagnosed with cervical cancer.
7) Investigate the need for a more individual-orientated approach to Cervical Cancer Screening Programme, dependent on vaccination status.
8) Investigate non-attendance in the cervical cancer screening program
9) Long-term follow-up after HPV vaccination of women participating in the vaccine trials. Study of HPV prevalence among women 18-45 years, both in the general population and in those with premalignant disease and cervical cancer.

The current research priorities of the Breast Cancer Screening Programme are:

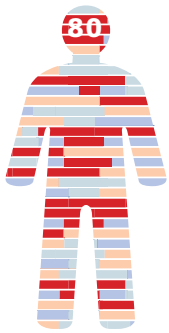
1) Further investigation of early (process) indicators and tumor characteristics in screening.
2) Study of the effectiveness of the programme in relation to breast cancer survival and mortality.
3) Study of overdiagnosis associated with the Breast Cancer Screening Programme.
4) Analysis of attendance by socio-economic factors and of attendance pattern.
5) Moments in connection to an expansion of the programme to cover age groups outside of 50-69 years.
6) Comparison of breast cancer screening in Norway and Vermont (USA)
7) Hormone therapy and risk of breast cancer



Department of Screening-based Research

For the Breast Cancer Screening Programme, one PhD student is currently studying socio-demographic differences in attendance and mortality between attendees and non-attendees in the programme and investigating effects of mammography screening on breast cancer survival. Another PhD student is evaluating the Norwegian Breast Cancer Screening Program on DCIS (Ductal Carcinoma in Situ), overdiagnosis and implementation of new technology. As for the Cervical Cancer Screening Programme, one PhD student is doing a population based follow-up study on women diagnosed with severe cervical dysplasia in Norway.

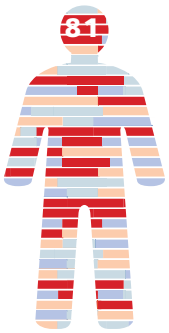
In 2007 the department participated in national collaboration studies like NORCCAP (on colorectal cancer screening), lead by **Geir Hoff**.



Dissertations published in 2007 from the Department of Screening-based Research;

Paulsen, Torbjørn: Epithelial ovarian cancer. A clinical epidemiological approach on diagnosis and treatment. University of Oslo 2007

Department of Clinical and Register-based Research



Head: Bjørn Møller PhD

Tom Børge Johannesen is the Assistant Head of Department and responsible for the quality of the medical data in the registry.

The Statutory Regulations for the Cancer Registry of Norway include the registration of treatment and follow-up of Norwegian cancer patients. By establishing special registries – comprehensive registration schemes dedicated to specific cancers – the Registry supplements its current cancer registry record with more detailed information on diagnostic measures, therapy, and follow-up. By fostering strong collaborative links with the clinical community of Norway, the aims are to provide an empirical basis for scientific studies regarding prognostic factors and treatment outcomes and evaluation of quality of cancer care. ***Jan F. Nygård*** is the head of the section organizing special organ related registries.

Special registries have been established for childhood cancer, polyposis, and cancers of the lung, ovarian, rectum and prostate. They are all underpinned by a reference group, a panel of multi-disciplinary experts drawn from the clinical community in Norway. The activity in the Colo-Rectal Cancer Registry is co-ordinated by ***Maria Gaard,*** and research projects include effects of clinical parameters like operational technique, circumferential resection margin and radiotherapy. The Prostate Cancer Registry is co-ordinated by ***Rune Kvåle.*** Some main areas of research include regional variations in radical treatment, quality of Gleason score at biopsy and evaluation of bone scintigraphy.

Christine Mellem is head of section for registration and she is responsible for the coding of the incidence cases.

Hans Rostad is studying patients operated for lung cancer. The aim is to optimize handling of lung cancer. Under Rostads supervision, ***Trond Eirik Strand*** will defend his thesis in the near future. Very few countries apart from Norway have access to complete population based data regarding incidence, mortality, histological subtypes, results of surgery and final outcome. Data from the main data base in the Cancer Registry and data on all patients treated with surgery are extracted from clinical case records, and are included in a comprehensive data base in the Cancer Registry. The results of surgery on various subgroups and age groups compared with other treatment modalities have been analysed with resulting-percentage of patients operated upon in each region in Norway, complications of surgery and outcome.

The department also publishes the annual report Cancer in Norway, with the most recent published in December 2006 describing cancer patterns for the year 2005 and including predictions for the year 2020. Cancer in Norway 2006 will be published towards the end of 2007, together with a Critical Evaluation of the Quality of the Registry data. Each annual publication will include a special topic, the first ones being Predictions and Quality Evaluation respectively.

The report is the responsibility of the data research section and its leader ***Freddie Bray.*** Two main areas of priority of the research activities in the department are:

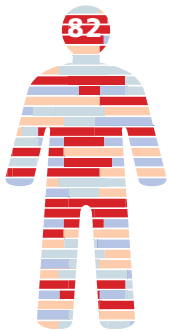
1) Clinical surveillance including the comparative evaluation of population-based and cancer-specific survival,
2) Routine surveillance including the analysis and interpretation of geographical and temporal variability of cancer incidence and mortality rates within Norway.

The department is actively involved in a number of Nordic and international collaborations that cover both types of activity. ***Tom Børge Johannesen*** is responsible for the section of quality control with regard to completeness and detailedness of the data.

Dissertations published in 2007 from the Department of Clinical and Register-based research;

Larsen, Inger Kristin: Colorectal Cancer Screening By Flexible Sigmoidoscopy: Acceptance of screening, risk factors for neoplasia, and impact of screening on future health behaviour. University of Oslo 2007

Eriksen, Morten Tandberg: Prognosis after surgery for rectal cancer - focus on complications and high-risk patients, University of Oslo 2007



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3. Alvik A, Haldorsen T, Lindemann R. Alcohol consumption, smoking and breastfeeding in the first six months after delivery. Acta Paediatr 2006; 95(6):686-693.

4. Alvik A, Heyerdahl S, Haldorsen T, Lindemann R. Alcohol use before and during pregnancy: a population-based study. Acta Obstet Gynecol Scand 2006; 85(11):1292-1298.

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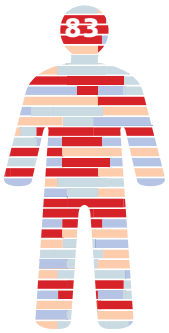

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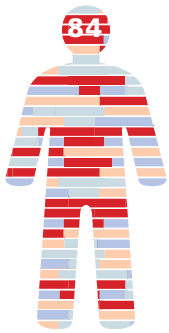

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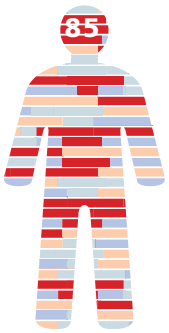

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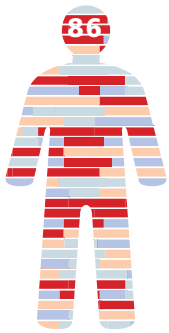

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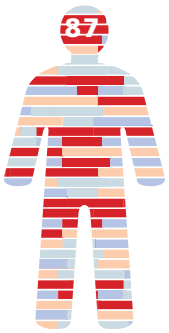

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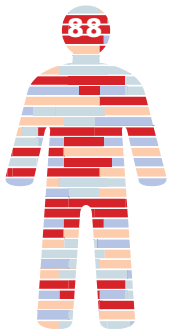

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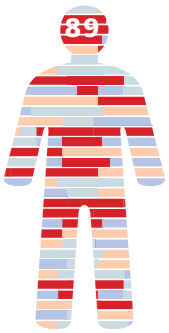

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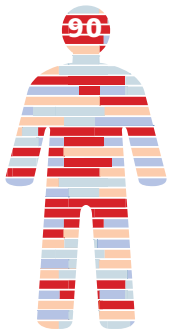

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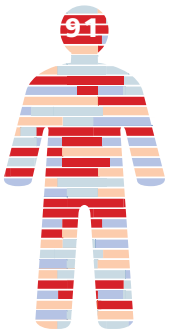

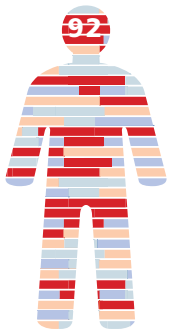

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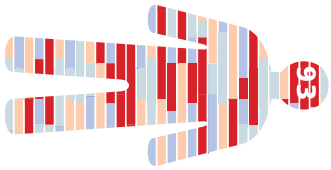

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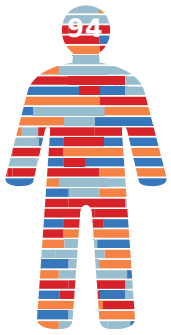
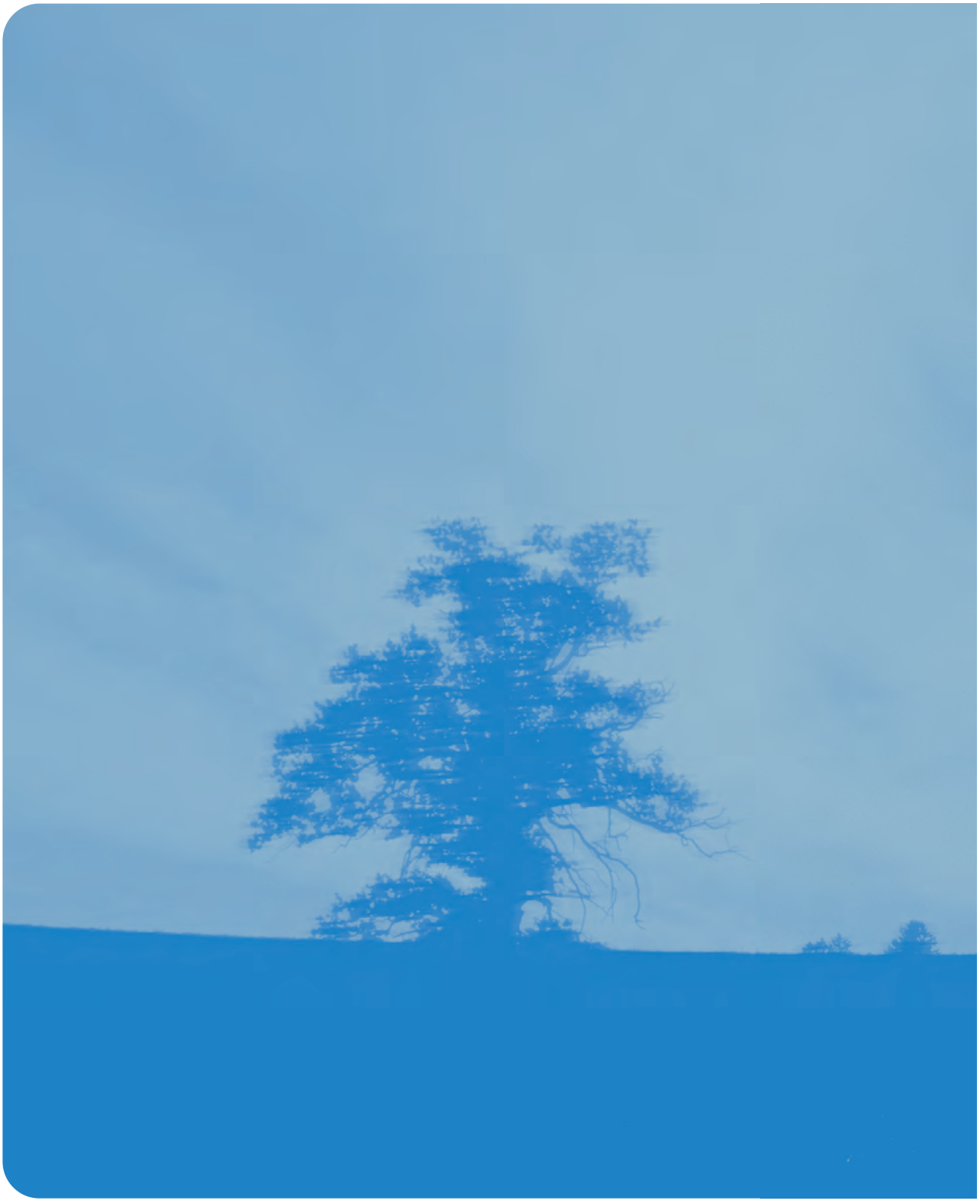
V Appendix





Members of the CCC-council

Fodstad, Øystein (head)	Institute for Cancer Research
Bjøro, Kristian	Medical Division
Børresen-Dale, Anne-Lise	Institute for Cancer Research
Danielsen, Håvard	Institute for Medical Informatics
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Heim, Sverre	Division of Laboratory Medicine
Helseth, Eirik	Neuro Clinic
Holte, Harald Jr	Division of Cancer Medicine and Radiotherapy
Jakobsen, Jarl	Division of Medical Imaging and Intervention
Kongerud, Johny	Division of Cardiovascular and Respiratory Medicine and Surgery
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Kaastad, Trine Sand	Division of ENT, Plastic and Orthopaedic Surgery
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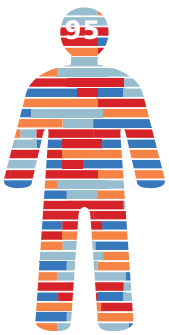

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Head of the clinical divisions:

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Bjøro, Kristian	Medical Division
Hysing, Einar	Division of Anaestesiology and Intensive Care Medicine
Gierscksky, Karl-Erik	Divison of Surgery
Jakobsen, Jarl	Division of Medical Imaging and Intervention
Jakobsen, Jørn	Hospital for Rehabilitation
Kaastad, Trine Sand	Division of ENT, Plastic and Orthopaedic Surgery
Nesland, Jahn	Division of Pathology
Rootwelt, Terje	Division of Pediatrics
Røste, Geir Ketil	Division of Clinical Neuroscience
Smeland, Sigbjørn	Division of Cancer Medicine and Radiotherapy
Smiseth, Otto A.	Division of Cardiovascular and Respiratory Medicine and Surgery
Sverstad, Marit	Department of Operating Theatres (3)
Vaage, Torgils J	Division of Laboratory Medicine
Åbyholm, Thomas	Division of Obstetrics and Gynaecology

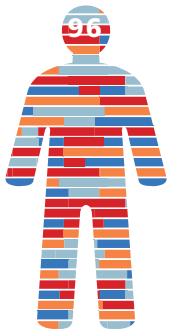
Head of the research divisions:

Danielsen, Håvard	Institute for Medical Informatics
Fosse, Erik	The Interventional Centre
Gogstad, Geir	Department of Research Services
Ruland, Cornelia	Centre for Shared Decision Making and Nursing Research
Smeland, Erlend B	Institute for Cancer Research
Sørensen, Dag	Centre for Comparative Medicine
Aasen, Ansgar	Institute for Surgical Research

Cancer Registry of Norway, Institute of population-based cancer research:

Langmark, Frøydis (head)

Møller, Bjørn	Departement of Clinical Registry-based Research
Steen, Rita	Department of Screening-based Research
Tretli, Steinar	Department of Etiological Research



Organization of clinical programs and research groups

Treatment programs

Brain tumor:

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Bogsrud, Trond	Division of Medical Imaging and Intervention
Bollerslev, Jens	Medical Division
Hald, John	Division of Medical Imaging and Intervention
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Helseth, Eirik	Division of Clinical Neuroscience
Johannesen, Tom B.	The Cancer Registry of Norway
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Wesenberg, Finn	Division of Pediatrics

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Bjørndal, Hilde	Division of Medical Imaging and I ntervention
Bogsrud, Trond	Division of Medical Imaging and Intervention
Borgen, Elin	Division of Pathology
Bøhler, Per	Division of Pathology
Børresen-Dale, Anne Lise	Institute for Cancer Research
Danielsen, Turi fysiker	Division of Cancer Medicine and Radiotherapy
Engebråten, Olav	Division of Cancer Medicine and Radiotherapy
Fangberget, Anne	Division of Medical Imaging and Intervention
Fodstad, Øystein	Institute for Cancer Research
Fosså, Sophie	Division of Cancer Medicine and Radiotherapy
Heim, Sverre	Division of Laboratory Medicine
Helland, Åslaug	Institute for Cancer Research
Hoelstad, Cathrine	Division of Cancer Medicine and Radiotherapy
Holmen, Marit	Division of Medical Imaging and Intervention
Gjertsen, Turid	Division of Cancer Medicine and Radiotherapy
Kvalheim, Gunnar	Division of Cancer Medicine and Radiotherapy
Løkkevik, Erik	Division of Cancer Medicine and Radiotherapy
Mæhle, Lovise	Division of Laboratory Medicine
Mælandsmo, Gunhild	Institute for Cancer Research
Møller, Pål	Division of Laboratory Medicine
Nesland, Jahn M.	Division of Pathology
Olsen, Dag Rune	Institute for Cancer Research
Skjerven, Helle	Division of Surgery
Skjønsberg, Gudbrand	Division of Surgery
Sætersdal, Anna	Division of Cancer Medicine and Radiotherapy
Sørlie, Therese forsker	Institute for Cancer Research

Colorectal cancer and oesophagus cancer:

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Bjordal, Kristin	Division of Cancer Medicine and Radiotherapy
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Flatmark, Kjersti	Division of Surgery
Giercksky, Karl-Erik	Division of Surgery
Grøholt, Krystyna K.	Division of Pathology
Hjortland, Geir O.	Division of Cancer Medicine and Radiotherapy
Hole, Knut H.	Division of Medical Imaging and Intervention

Jacobsen, Anne-Birgitte	Division of Cancer Medicine and Radiotherapy
Karlsen, Karl O.	Division of Surgery
Larsen, Stein G.	Division of Surgery
Rønning, Geir	Division of Surgery
Stoldt, Stephan	Division of Surgery
Sørensen, Olaf	Division of Surgery
Tausjø, Johan	Division of Cancer Medicine and Radiotherapy
Vetrhus, Turid	Division of Medical Imaging and Intervention
Wanderås, Eva H.	Division of Cancer Medicine and Radiotherapy
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Børresen-Dale, Anne-Lise	Institute for Cancer Research
Danielsen, Håvard	Institute for Medical Informatics
Davidson, Ben	Division of Pathology
Dong, Hiep Phuc	Division of Pathology
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Flørenes, Vivi A.	Division of Pathology
Gaudernack, Gustav	Institute for Cancer Research
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Heim, Sverre	Division of Laboratory Medicine
Helland, Åslaug	Division of Cancer Medicine and Radiotherapy
Holm, Ruth	Division of Pathology
Huitfeldt, Henrik	Division of Pathology
Kleinberg, Lilach	Division of Pathology
Knutstad, Kjetil	Division of Medical Imaging and Intervention
Kristensen, Gunnar B.	Division of Obstretrics and Gynaecology
Kærn, Janne	Division of Obstretrics and Gynaecology
Langmark, Frøydis	The Cancer Registry of Norway
Larsen, Stein	Division of Surgery
Lothe, Ragnhild A.	Institute for Cancer Research
Lyng, Heidi	Institute for Cancer Research
Nesland, Jahn M	Division of Pathology
Oksefjell, Halldis	Division of Obstretrics and Gynaecology
Paulsen, Torbjørn	The Cancer Registry of Norway
Pradhan, Monohar	Division of Pathology
Rofstad, Einar	Institute for Cancer Research
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Sandstad, Berit	Department of Research Services
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Sert, Bilal	Division of Obstretrics and Gynaecology
Silins, Ilvars	Division of Obstretrics and Gynaecology
Skeie-Jensen, Tone	Division of Obstretrics and Gynaecology
Sundfør, Kolbein	Division of Obstretrics and Gynaecology
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Stensager, PerA.	Division of Obstretrics and Gynaecology
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Boysen, Morten	Division of ENT, Plastic and Orthopaedic Surgery
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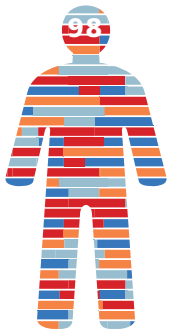
Eilertsen, Karsten	Division of Cancer Medicine and Radiotherapy
Furre, Torbjørn	Division of Cancer Medicine and Radiotherapy
Helland, Åslaug	Division of Cancer Medicine and Radiotherapy
Hole, Knut H.	Division of Medical Imaging and Intervention



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Lyng, Heidi	Institute for Cancer Research
Mork, Jon	Division of ENT, Plastic and Orthopaedic Surgery
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Rennemo, Erlend	Division of ENT, Plastic and Orthopaedic Surgery
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Kolstad, Arne	Division of Cancer Medicine and Radiotherapy
Lauritzsen, Grete F.	Division of Cancer Medicine and Radiotherapy
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Olweus, Johanna	Institute for Cancer Research
Randen, Ulla	Division of Pathology
Rødal, Jan	Division of Cancer Medicine and Radiotherapy
Smeland, Erlend	Institute for Cancer Research
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Tierens, Anne	Division of Pathology

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Glosli, Heidi	Division of Pediatrics
Greve-Isdahl, Margrethe	Division of Laboratory Medicine
Monclair, Tom	Division of Surgery
Ruud, Ellen	Division of Pediatrics
Smevik, Bjarne	Division of Medical Imaging and Intervention
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Zeller, Bernward	Division of Pediatrics

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Lehne, Gustav	Division of Cancer Medicine and Radiotherapy
Lie, A. Kathrine	Division of Pathology
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Lothe, Ragnhild A.	Institute for Cancer Research
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Olsen, Dag Rune	Institute for Cancer Research
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Tafjord, Gunnar	Division of Cancer Medicine and Radiotherapy
Vlatkovic, Ljiljana	Division of Pathology
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Fodstad, Øystein	Institute for Cancer Research
Follerås, Gunnar	Division of Surgery
Heim, Sverre	Division of Laboratory Medicine
Jørgensen, Lars	Division of Cardiovascular and Respiratory Medicine
Kristensen, Gunnar	Division of Obstretrics and Gynaecology
Lloret, Isabel	Division of Medical Imaging and Intervention
Lothe, Ragnhild A.	Institute for Cancer Research
Myklebost, Ola	Institute for Cancer Research
Nenadovic, Maja	Division of Pathology
Norum, Ole J.	Division of Surgery
Poulsen, Jan P.	Division of Cancer Medicine and Radiotherapy
Skjeldal, Sigmund	Division of Surgery
Zaikova, Olga	Division of Surgery
Helgerud, Per	Division of Surgery
Solberg, Steinar	Division of Cardiovascular and Respiratory Medicine
Stoldt, Stephan	Division of Surgery
Taksdal, Ingeborg	Division of Medical Imaging and Intervention
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Thyroid and endocrine cancer:

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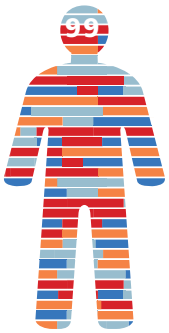
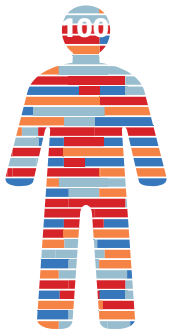
Babovic, Almira	Division of Medical Imaging and Intervention
Bach-Gansmo, Tore	Division of Medical Imaging and Intervention
Bjerner, Johan	Division of Laboratory Medicine
Bogsrud, Trond V.	Division of Medical Imaging and Intervention
Cappelen, Tone	Division of Medical Imaging and Intervention
Grøholt, Krystyna K.	Division of Pathology
Heilo, Arne	Division of Medical Imaging and Intervention
Holgersen, Kristin	Division of Medical Imaging and Intervention
Jebsen, Peter	Division of Pathology
Jetlund, Olav	Division of ENT, Plastic and Orthopaedic Surgery
Jørgensen, Lars H.	Division of Cardiovascular and Respiratory Medicine
Nustad, Kjell	Division of Laboratory Medicine
Osnes, Terje	Division of ENT, Plastic and Orthopaedic Surgery
Paus, Elisabeth	Division of Laboratory Medicine
Sigstad, Eva	Division of Pathology
Skjerven, Helle	Division of Surgery
Solheim, Hanne	Division of Medical Imaging and Intervention





Research groups

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Fredriksen, Agnete	post doc
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Schjetne, Karoline	post doc
Tunheim, Gro	post doc
Øynebråten, Inger	post doc
Frøyland, Marianne	PhD student
Grødeland, Gunnveig	PhD student
Jakobsen, Johanne	PhD student
Os, Audun	PhD student
Ruffini, Pier	PhD student
Haga, Jon Magnus	student
Løvås, Tom Ole	student
Røsje, Egil	student
Zangani, Miriam	student
Hegge, Beate	engineer
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Omholt, Hilde	engineer
Vikse, Elisabeth	engineer

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Langerød, Anita	post doc
Bergamaschi, Anna	PhD student
Drageset, Vilde	PhD student
Landmark, Hege	PhD student
Mohammed, Hyat	PhD student
Muggerud, Aslaug	PhD student
Vollan, Hans Kristian	PhD student
Aarø, Jørgen	PhD student
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Due, Eldri U.	med. technol.
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Jansen, Laila	med. technol.
Johnsen, Hilde	med. technol.
Vu, Phoung	med. technol.
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P, Ivan	student
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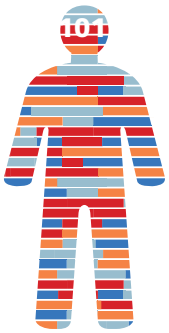
Kravik, Liza	research technician



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Tekle, Christina	PhD student
Tveito, Siri	PhD student
Høifødt, Hanne	Lab manager
Dybsjord, Indrejit	engineer
Juell, Siri	engineer
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Gehrken, Hege	technician
Svendsen, Hege	technician

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Loge, Jon Håvard	professor
Cvancarova, Milada	statistician
Hess, Siri Lothe	study nurse
Opperud, Vigdis	research associate

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Pollheimer, Juergen	post doc
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Haysam, Khouja	guest scientist
Wang, Zhihui	PhD Student
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Bassøe, Vivi	bioengineer
Becker, Anne-Marie	bioengineer
Larsen, Ann	bioengineer
Moripen, Leni T.	bioengineer
Nguyen, Mai Thi P.	bioengineer
Emilsen, Elisabeth	senior engineer
Førsund, Mette	dept. engineer
Håseth, Liv Inger	research technician

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Tøstesen, Eivind	post doc
Cekaite, Lina	PhD
Liu, Fang	PhD
Bøe, Sigurd	PhD student
Clancy, Trevor	PhD student
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Longva, Ane Sager	engineer

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Nordgard, Silje	post doc
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Lind, Guro E.	post doc
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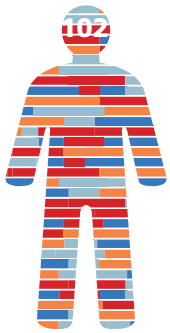
Berg, Marianne	PhD student
Brekke, Helge R.	PhD student
Danielsen, Stine Aske	PhD student
Merok, Marianne	PhD student
Sveen, Anita	PhD student
Ågesen, Trude	PhD student



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Hektoen, Merete	dept. medical technol
Løvig, Tone	dept.medical technol

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Honne, Hilde	student
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Kresse, Stine H.	PhD student
Müller, Christoph	PhD student
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Skårn, Magne	PhD student
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Engesæter, Birgit	post doc
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Torgersen, Maria L.	post doc
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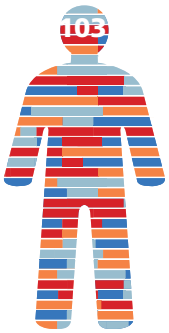
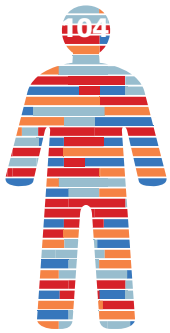




Dissertations at Rikshospitalet University Hospital 2006/2007

1. **Angell-Petersen Even Ph. D. 10.08.2007:** Dept. of Radiation Biology, Institute for Cancer Research and Division of Surgery. "Light and drug dosimetry considerations in porphyrin precursor based photodynamic therapy". Main supervisor: Harald B. Steen

2. **Bach Trond Dr. Philos 24.02.2006:** Dept. of Cell Biology, Institute for Cancer Research. Sequestration of newly replicated origins in Escherichia coli. Main supervisor: Kirsten Skarstad

3. **Bonsted Anette Dr. Philos 17.03.2006:** Dept. of Radiation Biology, Institute for Cancer Research. Evaluation of photochemical internalization (PCI) as a method for enhancing adenovirus based gene theraphy. Main supervisor: Kristian Berg

4. **Borgen Elin Faye Dr. Med 26.06.2007:** Division of Pathology. Detection of disseminated tumour cells in the bone marrow of breast carcinoma patients Main supervisor: Jahn M. Nesland

5. **Boye Kjetil Ph. D. 22.06.2007:** Dept. of Tumor Biology, Institute for Cancer Research. The metastasis promoting protein S100A4; expression, regulation and biological function. Main supervisor: Gunhild M. Mælandsmo

6. **Brandal Petter Ph. D. 16.06.2006:** Dept. of Medical Genetics, Division of Laboratory Medicine. Analysis of Archival and Fresh Solid Tumor Samples. Main supervisor: Sverre Heim

7. **Cekaite Lina Ph. D. 09.11.2007:** Dept. of Tumor Biology, Institute for Cancer Research. Microarrays on macromolecules: implication of high throughput methods in cancer screening. Main supervisor: Eivind Hovig

8. **Dietze Andreas Ph. D. 09.06.2006:** Dept. of Radiation Biology, Institute for Cancer Research. Preclinical evaluation of photochemical treatment on rheumatoid arthritis and soft tissue sarcomas. Main supervisor: Kristian Berg

9. **Edvardsen Hege Dr. Philos 09.05.2007:** Dept. of Genetics, Institute for Cancer Research. Genetic variation and response to radio and chemotherapy and adverse side effects in cancer patients. Main supervisor: Vessela N. Kristensen

10. **Engesæter Birgit Dr. Med. 20.06.2006:** Dept. of Tumor Biology, Institute for Cancer Research. Enhanced Gene Transfer to Cancer Cells Using Photochemically Mediated Delivery of Adenoviral Vectors. Main supervisor:Gunhild M. Mælandsmo

11. **Fossum Solveig Ph. D. 23.08.2007:** Dept. of Cell Biology, Institute for Cancer Research. Timing and coordination of DNA replication in Escerichia coli. Main supervisor: Kirsten Skarstad

12. **Fredriksen Agnete Brunsvik Dr. Philos 12.06.2007:** Institute of Immunology, Division of Laboratory Medicine. Targeting vaccines to antigen presenting cells. Main supervisor: Bjarne Bogen

13. **Frøyland Marianne Ph. D. 22.02.2007:** Institute of Immunology, Division of Laboratory Medicine. Immunoglobulin variable regions as tumor markers and vaccine targets in B cell malignancies. Main supervisor: Bjarne Bogen

14. **Geirdal Amy Kristin Østertun Dr. Philos 13.06.2007:** Dept. of Medical Genetics, Division of Laboratory Medicine. Psychological distress quality of life, personality and coping in women with a family history of cancer with unidentified mutation. Main supervisor: Alv A. Dahl

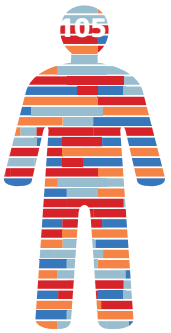
15. **Grov Ellen Karine Dr. Polit 18.09.2006:** Dept. of Oncological Nursing. Primary caregivers of cancer patients in late palliative phase aspects of their quality of life and caregiver reaction. Main supervisor: Sofie Fosså

16. **Grøvdal Lene Melsæther Ph. D. 15.06.2007:** Institute of Pathology, Division of Pathology. Proteins and mechanisms involved in the endosomal sorting of the epidermal growth factor receptor. Main supervisor: Espen Stang

17. **Gudbergson Sævar B. Ph. D. 26.10.2007:** Dept. of Clinical Cancer Research, Division of Cancer Medicine and Radiotherapy. Life after Cancer: work experiences, living conditions and impact of cancer in tumour free cancer survivors. Main supervisor: Sophie D. Fosså

18. **Gulliksen Anja Dr. Sci. 11.06.2007:** Dept. of Molecular Biosciences. Microchips for isothermal amplification of RNA. Development of microsystems for analysis of bacteria, virii and cells. Main supervisor: Reidun Sirevåg

19. **Juzeniene Asta Dr. Philos 12.01.2007:** Dept. of Radiation Biology, Institute for Cancer. Research Photodynamic therapy and fluorescence diagnosis based on 5 aminolevulinic acid: Roads towards optimization. Main supervisor: Johan Moan



20. Kazazic Maja Ph. D. 04.05.2007: Institute of Pathology, Division of Pathology. Mechanisms involved in ligand induced downregulation of the epidermal growth factor receptor from the plasma membrane. Main supervisor: Inger Helene Madshus

21. Kersten Christian Ph. D. 16.02.2007: Dept. of Immunology, Institute for Cancer Research. Studies of tumor associated antigens and BMP 6 signalling in normal and neoplastic B cells. Main supervisor: Erlend B. Smeland

22. Khnykin Denis Ph. D. 21.04.2006: Dept. of Biochemistry, Institute for Cancer Research. Fibroblast growth factor receptors: Role in intracellular trafficking and in diseases. Main supervisor: Sjur Olsnes

23. Kleivi Kristine Dr. Philos 24.03.2006: Dept. of Genetics, Institute for Cancer Research. Genome and transcriptome profiles of primary and advanced colorectal carcinomas. Main supervisor: Ragnhild A. Lothe

24. Knopp Synne Dr. Med 15.05.2007: Institute of Pathology, Division of Pathology and Section for Gynaecology, Division of Obstetrics and Gynaecology. Prognostic studies in vulvar squamous cell carcinoma. Main supervisor: Jahn M. Nesland

25. Kristensen Annette Torgunrud Ph. D. 22.06.2007: Dept. of Surgical Oncology, Division of Surgery. Capillary electrophresis in analysis of DNA variations in rectal cancer. Main supervisor: Per Olaf Ekstrøm

26. Kyte Jon Amund Dr. Med 13.02.2007: Dept. of Immunology, Institute for Cancer Research. Immuno gene therapy of cancer with tumor mRNA transfected dendritic cells. Main supervisor:Gustav Gaudernack

27. Laurak Silje U. Dr. Philos 26.04.2006: Dept. of Biochemistry, Institute for Cancer Research. Endocytosis and intracellular transport of ricin and Shiga toxin. Main supervisor: Kirsten Sandvig

28. Leithe Edward Ph. D 09.06.2006: Dept. of Cancer Prevention, Instiute for Cancer Research. Regulation of the gap junction protein connexin43 by phosphorylation and ubiquitination. Main supervisor: Edgar Rivedal

29. Lillehammer Trine Ph. D. 04.12.2007: Dept. of Tumor Biology, Institute for Cancer Research. Adenovirus mediated gene transfer to melanoma and glioma cells a study of transcriptional targeting and candidate therapeutic genes. Main supervisor: Olav Engebråten

30. Lindmo Karine Ph. D. 07.12.2007: Dept. of Biochemistry, Institute for Cancer Research. Regulation and function of autophagy in Drosophila melanogaster. Main supervisor: Harald Stenmark

31. Liu Fang Dr. Med 22.05.2007: Dept. of Tumor Biology, Institute for Cancer Research. Large scale bioinformatic studies of DNA denaturation and transcriptome profiling technologies. Main supervisor: Eivind Hovig

32. Molden Tor Egil Faksvaag Dr. Philos 19.01.2007: Institute of Pathology, Division of Pathology. Detection of Human Papillomavirus mRNA or DNA in Screening for Cervical Cancer. Main supervisor: Bjørn Hagmar

33. Mu Li Jun Ph. D. 20.01.2006: Dept. of Immunology, Institute for Cancer Research. Immuno Gene Therapy in Cancer Patients. Main supervisor: Gustav Gaudernack.

34. Myromslien Frøydis Deinboll Dr.Philos 13.10.2009: Institute of Pathology, Division of Pathology. Endocytosis and downregulation of the epidermal growth factor receptor in control of growth factor signaling. Main supervisor: Bjarne Bogen

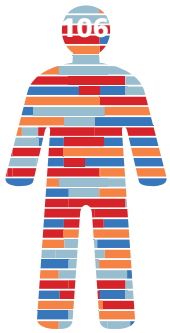
35. Nilsen Trine Ph. D. 22.06.2007: Dept. of Biochemistry, Institute for Cancer Research. Intracellular interactions and nucleocytoplasmic trafficking of exogenous FGF 1. Main supervisor: Sjur Olsnes

36. Nygaard Vigdis Dr. Philos 13.12.2006: Dept. of Tumor Biology, Institute for Cancer Research. Microarray Technology: Approaches to define application sensitivity limits. Main supervisor: Eivind Hovig

37. Otterdal Kari Dr. Philos 15.06.2007: Internal Medicine, Medical Division. Platelet mediated inflammation: Involvement of the tumor necrosis factor superfamily ligands CD40L and LIGHT. Main supervisor: Frank Brosstad

38. Patzke Sebastian Ph. D. 11.03.2006: Dept. of immunologi, Institute for Cancer Research. Identification and Characterization of Novel Genes Expressed in Neoplastic Human B Cells. Main supervisor: Erlend B. Smeland

39. Paulsen Torbjørn Dr. Med 30.11.2007: Section for Gyneacology, Division of Obstetrics and Gynaecology. Epithelial ovarian cancer. A clinical epidemiological approach on diagnosis and treatmen.t Main supervisor: Janne Kærn



40. Pedersen Nina Marie Ph. D. 27.04.2007: Institute of Pathology, Division of Pathology. Endocytic Downregulation of the Receptor Tyrosine Kinases EGFR and ErbB2. M ain supervisor: Inger Helene Madshus

41. Ruud Ellen Karine Dr. Med. 10.11.2006: Division of Pediatrics. Central line associated venous thromboembolism in children with cancer – prevalence, prevention and outcome. Main supervisor: Finn Wesenberg

42. Shahdadfar Aboulghassem Ph.d. 21.12.2007: Institute of Immunology, Division of Laboratory Medicine. Human somatic cells in regenerative medicine. In vitro characterization of mesenchymal stem cells and chondrocytes. Main supervisor: Jan E. Brinchmann

43. Sivertsen Einar Andreas Dr. Med 26.04.2007: Dept. of Immunology, Institute for Cancer Research. Characterization of signaling pathways in normal and malignant hematopoietic cells by microarray technologies. Main supervisor: Erlend B. Smeland

44. Skovseth Dag Kristian Ph. D. 20.01.2006: Institute of Pathology, Division of Pathology. Adoptive transfer of human endothelial cells an in vivo model of angiogenesis and vascular phenotype regulation. Main supervisor: Guttorm Haraldsen

45. Spilsberg Bjørn Dr. Philos 13.01.2006: Dept. of Biochemistry, Institute for Cancer Research. Regulation of Protein Toxin Trafficking by Sphingolipids. Main supervisor: Kirsten Sandvig

46. Søvik Åste Ph. D. 15.06.2007: Dept. of Radiation Biology, Institute for Cancer Research and Department of Oncology, Division of Cancer Medicine and Radiotherapy. Biologically adapted radiotherapy and evaluation of non uniform dose distributions. Main supervisor: Dag Rune Olsen

47. Torgersen Maria Lyngaas Dr. Philos 30.03.2007: Dept. of Biochemistry, Institute for Cancer Research. Endocytosis and retrograde transport of Shiga toxin and cholera toxin. Main supervisor: Kirsten Sandvig

48. Tunheim Gro Dr. Philos 24.05.2006: Institute of Immunology, Division of Laboratory Medicine. Recombinant antibody based vaccines. Main supervisor: Bjarne Bogen

49. Tvegård Tonje Ph. D. 20.12.2007: Dept. of Cell Biology, Institute for Cancer Research. Effects of UV light on cell cycle regulation in fission yeast. Main supervisor: Erik Boye

50. Van De Putte Gregg Dr. Med. 03.11.2006: National Resource Centre for Gynaecological Oncology, Division of Obstetrics and Gynaecology. DNR Prognostic factors in early stage squamous cell cervical carcinoma.a Main supervisor: Gunnar B. Kristensen

51. Vangstein Aamot Hege Ph. D. 25.11.2006: Dept. of Medical Genetics, Division of Laboratory Medicine. Molecular cytogenetic analyses of primary and secondary chromosome abnormalities in B cell non Hodgkin lymphoma. Main supervisor: Sverre Heim

52. Øverbye Anders Ph. D. 18.12.2007: Dept. of Cell Biology, Institute for Cancer Research. Proteomic studies of hepatocytic autophagosomes. Main supervisor: Per O. Seglen

53. Aagård Hedfors Ida Ph. D. 09.05.2007: Institute of Immunology, Division of Laboratory Medicine. Activation and gene transduction of human T cells. Main supervisor: Jan E. Brinchmann

Publications at Rikshospitalet University Hospital 2006/2007

1. Abildgaard, L., Ellebaek, E., Gustafsson, G., Abrahamsson, J., Hovi, L., Jonmundsson, G., Zeller, B., and Hasle, H., Optimal treatment intensity in children with Down syndrome and myeloid leukaemia: data from 56 children treated on NOPHO-AML protocols and a review of the literature, Ann Hematol, 85, 275 (2006).

2. Abrahamsson, J., Clausen, N., Gustafsson, G., Hovi, L., Jonmundsson, G., Zeller, B., Forestier, E., Heldrup, J., and Hasle, H., Improved outcome after relapse in children with acute myeloid leukaemia, Br J Haematol, 136, 229 (2007).

3. Adamsen, B. L., Kravik, K. L., Clausen, O. P., and De Angelis, P. M., Apoptosis, cell cycle progression and gene expression in TP53-depleted HCT116 colon cancer cells in response to short-term 5-fluorouracil treatment, Int J Oncol, 31, 1491 (2007).

4. Aerts, J. G., Delahaye, M., van der Kwast, T. H., Davidson, B., Hoogsteden, H. C., and van Meerbeeck, J. P., The high post-test probability of a cytological examination renders further investigations to establish a diagnosis of epithelial malignant pleural mesothelioma redundant, Diagn Cytopathol, 34, 523 (2006).

5. Aghmesheh, M., Suo, Z., Friedlander, M., Nesland, J. M., Kaern, J., Stewart, M., Kconfab, Dorum, A., Tucker, K. M., and Buckley, M. F., Chromosome 2q24.2 is lost in sporadic but not in BRCA1-associated ovarian carcinomas, Pathology, 38, 145 (2006).

6. Akkok, C. A., Brinch, L., Lauritzsen, G. F., Solheim, B. G., and Kjeldsen-Kragh, J., Clinical effect of buffy-coat vs. apheresis platelet concentrates in patients with severe thrombocytopenia after intensive chemotherapy, Vox Sang, 93, 42 (2007).

7. Aksnes, L. H., and Bruland, O. S., Some musculo-skeletal sequelae in cancer survivors, Acta Oncol, 46, 490 (2007).

8. Aksnes, L. H., Hall, K. S., Folleraas, G., Stenwig, A. E., Bjerkehagen, B., Taksdal, I., Winderen, M., Bruland, O. S., and Saeter, G., Management of high-grade bone sarcomas over two decades: the Norwegian Radium Hospital experience, Acta Oncol, 45, 38 (2006).

9. Aksnes, L. H., Hall, K. S., Jebsen, N., Fossa, S. D., and Dahl, A. A., Young survivors of malignant bone tumours in the extremities: a comparative study of quality of life, fatigue and mental distress, Support Care Cancer (2007).

10. Almstrup, K., Leffers, H., Lothe, R. A., Skakkebaek, N. E., Sonne, S. B., Nielsen, J. E., Meyts, E. R., and Skotheim, R. I., Improved gene expression signature of testicular carcinoma in situ, Int J Androl, 30, 292 (2007).

11. Amarzguioui, M., Peng, Q., Wiiger, M. T., Vasovic, V., Babaie, E., Holen, T., Nesland, J. M., and Prydz, H., Ex vivo and In vivo Delivery of Anti-Tissue Factor Short Interfering RNA Inhibits Mouse Pulmonary Metastasis of B16 Melanoma Cells, Clin Cancer Res, 12, 4055 (2006).

12. Andersen, A., Warren, D. J., Brunsvig, P. F., Aamdal, S., Kristensen, G. B., and Olsen, H., High sensitivity assays for docetaxel and paclitaxel in plasma using solid-phase extraction and high-performance liquid chromatography with UV detection, BMC Clin Pharmacol, 6, 2 (2006).

13. Andersson, Y., Le, H., Juell, S., and Fodstad, O., AMP-activated protein kinase protects against anti-epidermal growth factor receptor-Pseudomonas exotoxin A immunotoxin-induced MA11 breast cancer cell death, Mol Cancer Ther, 5, 1050 (2006).

14. Anensen, N., Skavland, J., Stapnes, C., Ryningen, A., Borresen-Dale, A. L., Gjertsen, B. T., and Bruserud, O., Acute myelogenous leukemia in a patient with Li-Fraumeni syndrome treated with valproic acid, theophyllamine and all-trans retinoic acid: a case report, Leukemia, 20, 734 (2006).

15. Angell-Petersen, E., Christensen, C., Muller, C. R., and Warloe, T., Phototoxic reaction and porphyrin fluorescence in skin after topical application of methyl aminolaevulinate, Br J Dermatol, 156, 301 (2007).

16. Angell-Petersen, E., Sorensen, R., Warloe, T., Soler, A. M., Moan, J., Peng, Q., and Giercksky, K. E., Porphyrin formation in actinic keratosis and basal cell carcinoma after topical application of methyl 5-aminolevulinate, J Invest Dermatol, 126, 265 (2006).

17. Angell-Petersen, E., Spetalen, S., Madsen, S. J., Sun, C. H., Peng, Q., Carper, S. W., Sioud, M., and Hirschberg, H., Influence of light fluence rate on the effects of photodynamic therapy in an orthotopic rat glioma model, J Neurosurg, 104, 109 (2006).

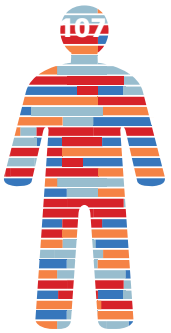
18. Annunziata, C. M., Kleinberg, L., Davidson, B., Berner, A., Gius, D., Tchabo, N., Steinberg, S. M., and Kohn, E. C., BAG-4/SODD and associated antiapoptotic proteins are linked to aggressiveness of epithelial ovarian cancer, Clin Cancer Res, 13, 6585 (2007).

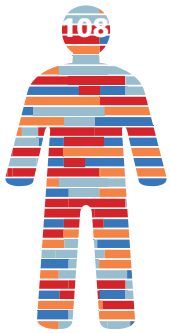
19. Arraras, J. I., Kuljanic-Vlasic, K., Bjordal, K., Yun, Y. H., Efficace, F., Holzner, B., Mills, J., Greimel, E., Krauss, O., and Velikova, G., EORTC QLQ-INFO26: a questionnaire to assess information given to cancer patients a preliminary analysis in eight countries, Psychooncology, 16, 249 (2007).

20. Axcrona, K., Brennhovd, B., Alfsen, G. C., Giercksky, K. E., and Warloe, T., Photodynamic therapy with methyl aminolevulinate for atypia/carcinoma in situ of the penis, Scand J Urol Nephrol, 1 (2007).

21. Bache, K. G., Stuffers, S., Malerod, L., Slagsvold, T., Raiborg, C., Lechardeur, D., Walchli, S., Lukacs, G. L., Brech, A., and Stenmark, H., The ESCRT-III subunit hVps24 is required for degradation but not silencing of the epidermal growth factor receptor, Mol Biol Cell, 17, 2513 (2006).

22. Bach-Gansmo, T., Danielsson, R., Saracco, A., Wilczek, B., Bogsrud, T. V., Fangberget, A., Tangerud, A., and Tobin, D., Integrin receptor imaging of breast cancer: a proof-of-concept study to evaluate 99mTc-NC100692, J Nucl Med, 47, 1434 (2006).





23. Barsnes, H., Mikalsen, S. O., and Eidhammer, I., MassSorter: a tool for administrating and analyzing data from mass spectrometry experiments on proteins with known amino acid sequences, BMC Bioinformatics, 7, 42 (2006).

24. Bassarova, A. V., Nesland, J. M., and Davidson, B., D2-40 is Not a Specific Marker for Cells of Mesothelial Origin in Serous Effusions, Am J Surg Pathol, 30, 878 (2006).

25. Bauer, N. N., Chen, Y. W., Samant, R. S., Shevde, L. A., and Fodstad, O., Rac1 activity regulates proliferation of aggressive metastatic melanoma, Exp Cell Res, 313, 3832 (2007).

26. Baumbusch, L. O., Myhre, S., Langerod, A., Bergamaschi, A., Geisler, S. B., Lonning, P. E., Deppert, W., Dornreiter, I., and Borresen-Dale, A. L., Expression of full-length p53 and its isoform deltap53 in breast carcinomas in relation to mutation status and clinical parameters, Mol Cancer, 5, 47 (2006).

27. Beiner, M. E., Finch, A., Rosen, B., Lubinski, J., Moller, P., Ghadirian, P., Lynch, H. T., Friedman, E., Sun, P., and Narod, S. A., The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study, Gynecol Oncol, 104, 7 (2007).

28. Ben-Dor, A., Lipson, D., Tsalenko, A., Reimers, M., Baumbusch, L. O., Barrett, M. T., Weinstein, J. N., Børresen-Dale, A.-L., and Yakhini, Z., Framework for identifying common aberrations in DNA copy number data, in Lecture Notes in Computer Science, Vol. 4453, Springer Berlin/ Heidelberg, pp. 122 (2007).

29. Benjaminsen, I. C., Brurberg, K. G., Ruud, E. B., and Rofstad, E. K., Assessment of extravascular extracellular space fraction in human melanoma xenografts by DCE-MRI and kinetic modeling, Magn Reson Imaging (2007).

30. Benson, M., Hov, D. A., Clancy, T., Hovig, E., Rudemo, M., and Cardell, L. O., Connectivity can be used to identify key genes in DNA microarray data: a study based on gene expression in nasal polyps before and after treatment with glucocorticoids, Acta Otolaryngol, 1 (2007).

31. Berentsen, S., Beiske, K., and Tjonnfjord, G. E., Primary chronic cold agglutinin disease: an update on pathogenesis, clinical features and therapy, Hematology., 12, 361 (2007).

32. Berentsen, S., Ulvestad, E., Langholm, R., Beiske, K., Hjorth-Hansen, H., Ghanima, W., Sorbo, J. H., and Tjonnfjord, G. E., Primary chronic cold agglutinin disease: a population based clinical study of 86 patients, Haematologica, 91, 460 (2006).

33. Berentsen, S., Ulvestad, E., and Tjonnfjord, G. E., B-lymphocytes as Targets for Therapy in Chronic Cold Agglutinin Disease, Cardiovasc.Hematol.Disord.Drug Targets., 7, 219 (2007).

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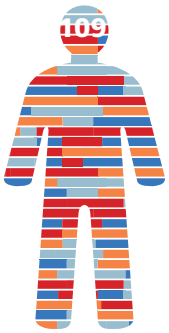

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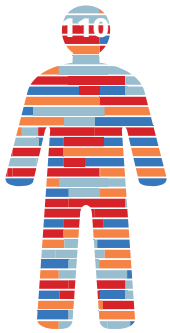

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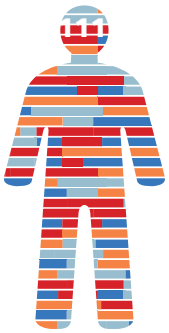

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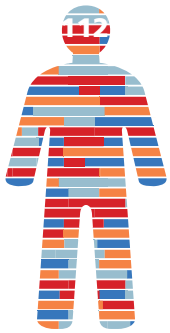

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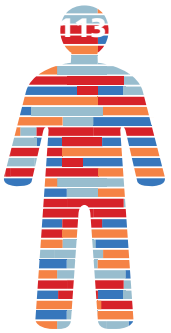

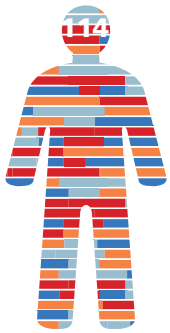

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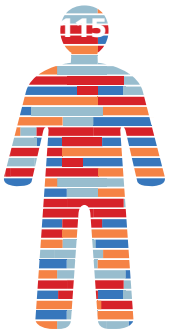

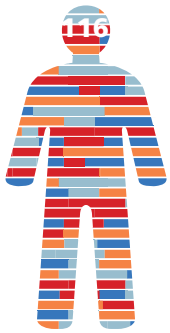

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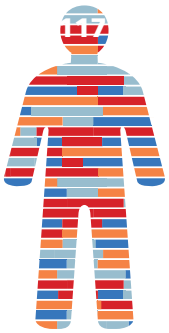

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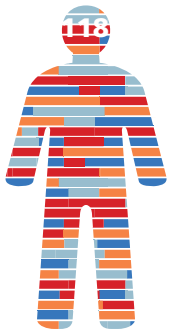

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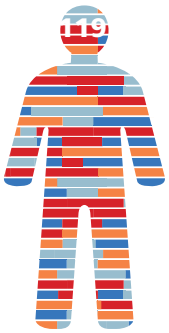

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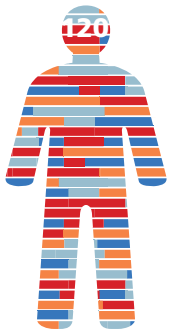

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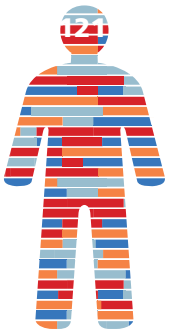

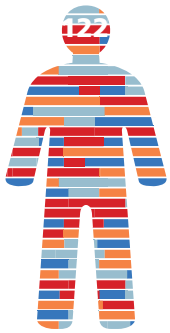

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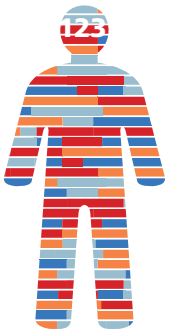

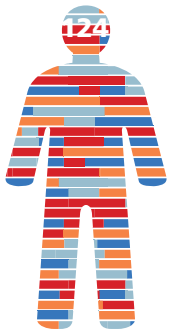

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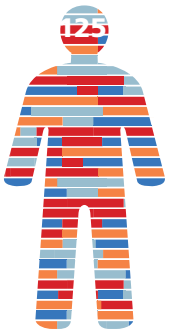

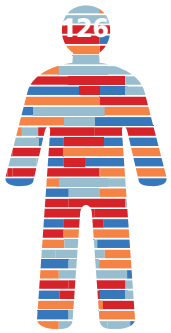

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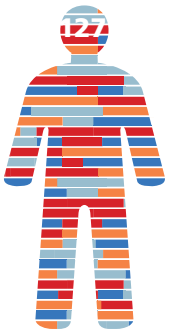

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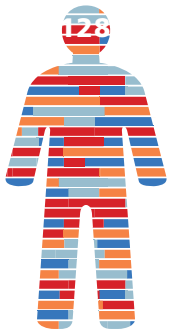

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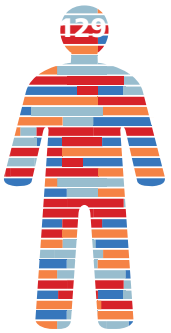

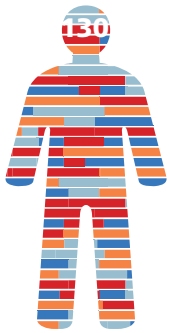

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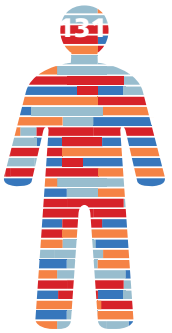

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