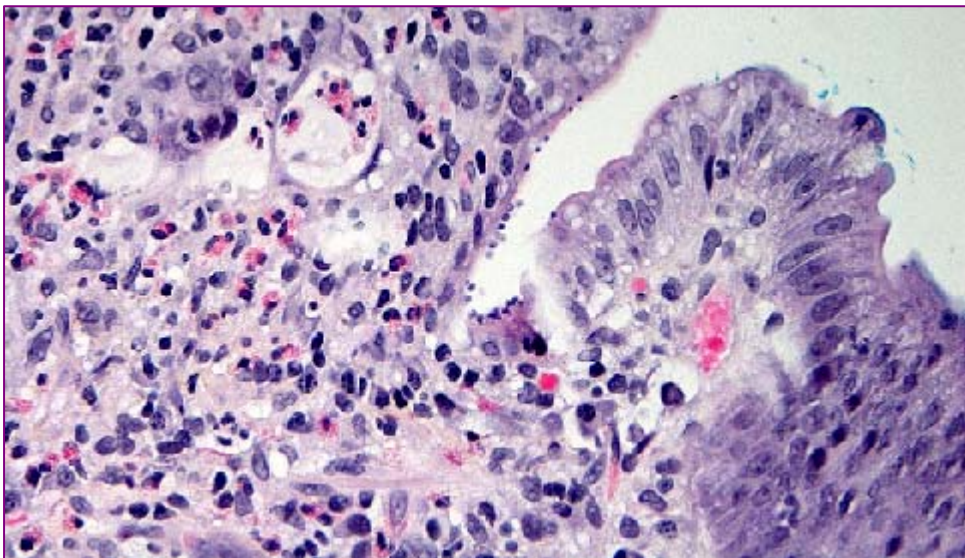


DEPARTMENT AND INSTITUTE OF PATHOLOGY  
Rikshospitalet-Radiumhospitalet Hf  
University of Oslo  
Oslo, Norway

# Annual Report 2006



# DEPARTMENT AND INSTITUTE OF PATHOLOGY

Rikshospitalet-Radiumhospitalet Hf

University of Oslo

Oslo, Norway

## ANNUAL REPORT 2006

### Contents

Contents.....	2
Introduction.....	4
Overview of the different research groups.....	5
<b>Laboratory for Electron Microscopy and Connective Tissue Research</b> .....	5
<b>The Micrometastasis Research Group</b> .....	7
<b>Laboratory for Immunohistochemistry and Immunopathology (LIIPAT)</b> .....	10
Section for Secretary Immunity and B Cells (SIB).....	10
Section for Vascular Endothelial Cells (VEC).....	11
Section for Immune Regulation and Allergy (IRA).....	12
<b>Laboratory for Toxicopathology</b> .....	14
<b>Research Group of Ovarian Carcinoma Biology</b> .....	16
<b>Laboratory for Experimental Pathology</b> .....	17
<b>Malignant Melanoma Laboratory</b> .....	20
<b>Laboratory for Molecular and Cellular Cancer Research</b> .....	23
<b>Research Group for Gastrointestinal and Skin Tumor Biology</b> .....	25
Section for Carcinogenesis.....	25
Section for Molecular Chemoresistance.....	25
<b>Hematopathology Research Group</b> .....	28
<b>Laboratory for Photodynamic Therapy</b> .....	29
<b>Tumour Stem Cell Research Group</b> .....	31
<b>Research Group on Experimental Forensic Medicine</b> .....	33
Diagnostic sections.....	37
<b>Diagnostic Section 1: Neuropathology</b> .....	37
<b>Diagnostic Section 2: Gastrointestinal/kidney/heart/lung/dermatology/perinatal</b> .....	38
<b>Diagnostic Section 3: Genitourinary pathology, bone and soft tissue pathology</b> .....	39
<b>Diagnostic Section 4: Hematopathology</b> .....	40
<b>Diagnostic Section 4: Hematopathology</b> .....	41
<b>Diagnostic Section 5: ENT and Paediatric Pathology</b> .....	43
<b>Diagnostic Section 6: Cytology</b> .....	45
Service sections.....	47
<b>Laboratory for Electron Microscopy (EM)</b> .....	47
<b>Diagnostic Immunohistochemical Laboratory</b> .....	48
<b>Laboratory for Molecular Pathology</b> .....	50
<b>Laboratory for Biopsy and Autopsy</b> .....	52

Administration and secretary services.....	53
Publications – Results of our research 2006 .....	54
<b>Acknowledgements</b> .....	54
<b>Doctoral Theses</b> .....	54
<b>Theses for Master of Science</b> .....	54
<b>Books, Book Chapters, Reviews and Commentaries</b> .....	54
<b>Publications (Papers in Peer Reviewed Journals)</b> .....	55
<b>Varia</b> .....	63

## Introduction

Welcome to our annual report for year 2006. Here you will find information about clinical activity, research projects and publications. Many thanks to Guttorm Haraldsen (Head Research: Department of Pathology) and Finn-Eirik Johansen (Head: Institute of Pathology) for collecting the material. Thanks to Hege Eliassen for editing the report.

In the course of the merger between Radiumhospitalet and Rikshospitalet in 2005, the two Departments of Pathology were merged to one Department and the clinical activity reorganized into six diagnostic sections: 1) Neuropathology, 2) Gastrointestinal/Cardiovascular/Skin pathology, 3) Genitourinary, Bone and Soft Tissue Pathology, 4) Hematopathology, 5) ENT and Pediatric Pathology and 6) Cytology.

The laboratory activity was likewise organized into five units: 1) Electron Microscopy, 2) Diagnostic Immunohistochemistry, 3) Molecular Pathology, 4) Biopsy and Autopsy and 5) Cytology.

In the summer 2006 the University of Oslo and Rikshospitalet-Radiumhospitalet Hf organized a common administrative structure that made Jahn M. Nesland the formal head of the Institute of Pathology as it was merged to the Department. The administration of the institute is supervised by the Head of the Faculty Division.

The research functions are carried out in several research groups that cover the areas connective tissue research, mucosal immunology, transplantation science, vascular biology, cancer biology including mitogenic signaling, carcinogenesis, phenotypic characterization, chemotherapeutic responsiveness and micrometastasis, cancer stem cells and photodynamic therapy.

Of particular interest, LIIPAT's (Head: Finn-Eirik Johansen) three sections were in 2006 partners in two applications that were finalist to become Norwegian Centre of Excellence (Research Council of Norway). One of these applications, *Centre for Immune Regulation*, was successful and the centre will be established in 2007.

Per Brandtzæg, LIIPAT/Pathology Clinic, received the following honors in 2006: Garnet Immunoglobulin Prize of the Czech Immunologic Society (Prague), and Commander of the Royal Norwegian Order of St. Olav.

Five doctoral theses were defended at the institute in 2006. Moreover, two theses were defended at foreign universities with main supervisors having affiliation with our Department.

We have extensive teaching functions in Clinical Pathology. This includes medical students, students in other fields such as biology, as well as at postgraduate levels. The present staff is comprised of approximately 240 persons, including medical doctors, scientists, research fellows, technicians and other personnel.

The department currently maintains an internal website that is launched daily upon login to the personal user account of each employee. In this fashion, general information on events, minutes from meetings etc. are efficiently broadcast.

*Jahn M. Nesland*

## Overview of the different research groups

### Laboratory for Electron Microscopy and Connective Tissue Research

GROUP LEADER: FINN P. REINHOLT, MD, PhD, PROFESSOR

#### GROUP DESCRIPTION

The projects are divided into two main lines of research: The first concerns technical development and the striving for optimum instrumentation and protocols in morphological research. The studies are particularly directed towards methods for studies of ultrastructure and molecular distribution in tissues samples. The main goal is to enable studies of tissues close to the native state. The second line of research includes the use of these methods to study the molecular composition and cell/matrix interactions in connective tissues, particularly bone and cartilage in animal models. A central hypothesis is that knowledge obtained in such studies will provide data of crucial importance for the understanding of serious chronic diseases of skeletal tissues, like osteoporosis (OP) and osteoarthritis. In the longer perspective, the data will form the basis for new treatment strategies and ultimately, effective preventive measures against the diseases. The research is conducted in two larger networks, the OSTEOGENE consortium supported by EU, and the Oslo Cartilage Research Group.

#### RESEARCH SUMMARY 2006

Using the know-how achieved during recent years of methodological development, we have investigated several aspects related to bone and cartilage structure and metabolism. A main line of interest has been on bone matrix proteins, their expression patterns and how they relate to micro architecture under normal and pathological conditions. In cartilage the focus has been on healing of articular cartilage injuries in animal models. Major achievements include:

- The laboratory for electron microscopy obtaining official status as Core facility at the Rikshospitalet-Radiumhospitalet Hf
- Implementation of updated specimen handling protocols for antigen retrieval in immuno-electron microscopical evaluation of bone samples
- The recognition of a sequence of events in enzyme secretion during osteoclast activation in bone resorption with potential for drug design targeting the enzyme cathepsin K
- The discovery of a bone phenotype in mice with deletion of the OP candidate gene osteoadherin with reduced tissue resorption, possibly due to interference with the mineralization process
- The discovery of a bone phenotype in mice with deletion of the OP candidate gene chondroadherin with reduced tissue resorption due to reduced function of clasts
- The identification of the relevance of the PTH-regulated transcription factor Sox4 in bone formation and osteoblast activity
- The recognition of new aspects on the bone phenotype of mice with deletion of the OP candidate gene osteopontin of particular relevance to OP
- Publishing an experimental study demonstrating the beneficial effect of bone marrow access in the healing of experimental cartilage injuries

## Overview of the different research groups

- The completion of a pilot and safety study in rabbits using mesenchymal stem cells in a 3-dimensional scaffold of polymerized hyaluronic acid to restore lost articular cartilage in an acute injury model

### GROUP MEMBERS 2006

Finn P. Reinholt (Group Leader)  
Sverre Henning Brorson (Senior Scientist)  
Aileen Murdoch Larsen (Bioengineer)  
Linda Trobe Dorg (Bioengineer)  
Lene B. Solberg (Medical Student)  
Gunhild Melhus (Medical Student)

### COLLABORATIONS 2006

#### National:

Prof Kaare M. Gautvik, Inst. of Biochemistry, University of Oslo.  
Senior Scientist Rune Jemtland, Dept. of Medicine, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Prof Lars Engebretsen, Orthopaedic Center, Ullevål University Hospital, Oslo.  
Senior Scientist Jan E. Brinchman, Inst. of Immunology, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Prof Lars Nordsletten, Inst. for Surgical Research, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Prof Ståle Petter Lyngstadås, Oral Research Laboratory, Inst. for Clinical Dentistry, University of Oslo.

#### International:

Prof Göran Andersson, Dept. of Pathology, Karolinska Institutet, Stockholm, Sweden.  
Prof Dick Heinegaard, Dept. of Molecular Biology, University of Lund, Sweden.  
Prof Serge Ferrari, Service of Bone Diseases, WHO Collaborating Center for Osteoporosis Prevention, Geneva University Hospital, Geneva, Switzerland.  
Prof Anna M. Teti, Dept. of Experimental Medicine, University of L'Aquila, L'Aquila, Italy.  
Prof Cathy S. Carlson, Dept. of Veterinary Diagnostic Medicine, College of Veterinary Medicine, University of Minnesota, St. Paul, USA.

## The Micrometastasis Research Group

GROUP LEADER: JAHN M. NESLAND

### GROUP DESCRIPTION

In this project we study the metastatic process and with special focus on circulating tumor cells in peripheral blood and bone marrow. It is a major collaboration between several research groups in Oncology clinic, Clinic for surgery, Inst. for Cancer Research and Pathology Laboratories.

By studying circulating tumor cells, we are studying cancer cells that have come half way in the metastatic process, and the clinical relevance has been demonstrated in many publications. The aims are:

- To continue with development of immunological methods for diagnostics and quantification of tumor cells in peripheral blood and bone marrow by use of monoclonal antibodies and immunomagnetic beads.
- To apply immunomagnetic beads for enrichment of tumor cells in peripheral blood and bone marrow and to do immunological and molecular characterization of the cells.
- Explore the possibility to develop specific PCR methods for detection and quantification of tumor cells in peripheral blood and bone marrow and further characterize these cells
- Characterize primary tumors and metastases from the same patients and compare expression profiles.

The micrometastasis laboratory (Head Anne Renolen) receives clinical material, prepare for primary diagnostics and store material for other analyses. A basic immunocytochemical method is applied for routine use, using AE1/AE3 as a marker for detection of cytokeratins. A clinical database provides information about the patients.

### RESEARCH SUMMARY 2006

#### **Breast cancer**

We do know that approximately 20% of stage 1 breast carcinoma patients later will develop metastases and die of the disease. Thus our approach has been to explore the impact of circulating tumor cells. In the larger Oslo breast cancer study (Head: Bjørn Naume) we collected 920 breast cancer patients from various hospitals in the Oslo region in the period 1995 to 1998. It was funded by The Norwegian Cancer Society. We continue with follow up of the patients. In the PhD thesis to Gro Wiedsvang and in several publications we have shown the clinical impact. In other studies of breast cancer patients with advanced disease, we have shown the possibility to use detection of circulating tumor cells as a predictor of treatment response.

We focus on optimizing mapping of tumor cells in early stage of the disease, so low risk patients can be saved for potentially toxic adjuvant therapy.

We also explore the possibilities to characterize single cells detected in peripheral blood and bone marrow and compare with expression profiles in primary tumors. In a series of 123

## Overview of the different research groups

tumors we have performed mRNA expression profiling of the primary tumors (collaboration Anne-Lise Børresen-Dale, Genetics and Stanford University), and could confirm the molecular classification system demonstrated in other breast cancer materials. Now we examine various profiles and relate to findings of tumor cells in the bone marrow. We also perform multicharacterization of the circulating tumor cells (Master Anne Renolen).

At the same time, cand med Elin Borgen, Pathology, will in June 2007 defend her thesis dealing with various techniques to detect these tumor cells, and international quality control programmes established.

When a reliable reproducible method for analyzing single cell expression profiles we will do so and compare with the primary tumors and metastases. We have a TMA with all 920 cases, for further testing of the clinical material. We collaborate with Applied Genomics and explore the benefit of using a limited number of antibodies raised against genes shown to be of importance. Cand med Hege G Russnes, Pathology is doing this as part of her Ph D programme and is showing that the molecular classification reported in the literature can be improved, by combining expression profiles with a few immunocytochemical markers.

We explore the impact of angiogenesis. Cand med Hari Dhakal, Pathology, is quantifying the vascular system and endothelial surface in primary tumors and relate to presence of tumor cells in the bone marrow. In a series of 450 cases, we did find a clinical impact of endothelial surface area, but no relation to the presence of circulating tumor cells. We explore further the mechanisms behind neovascularisation in this clinical material, and focus on VEGFR, VEGF, HIF1 alpha, EGR1 and others.

### Prostate cancer

In a series of 420 cases collected in collaboration with Ullevål University Hospital we did find 20% with tumor cells in the bone marrow at the time of diagnosis. In the main project run by Dr Med Wolfgang Lilleby, Oncology, the goal is to search for markers that can be use in a predictive setting and to develop immunotherapy for these patients (Dr Med Gustav Gaudernack and Gunnar Kvalheim).

### Other tumors

We also analyse ovarian cancer, adenoid cystic carcinoma, lung cancer, colorectal cancer, and osteosarcoma.

## GROUP MEMBERS 2006

Elin Borgen (Cand Med, Pathology)  
Hari Dhakal, (Cand Med, Pathology)  
Junbai Wang (Dr Philos, Pathology)  
Anne Renolen (Bioengineer, Pathology)  
Cecilie Schirmer (Bioengineer, Pathology)  
Maria Rypdal (Engineer, Pathology)  
Tove Anita Slyngstad (Engineer, Pathology)  
Annvei Thrane (Engineer, Pathology)  
Ida Hellerud (Bioengineer, Pathology)

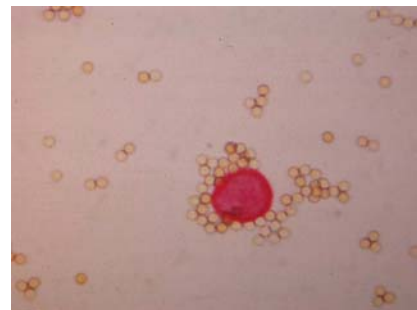


Figure: Tumor cell from bone marrow immunostained for cytokeratins and surrounded by magnetic beads linked to antibodies against an epithelial surface marker

## COLLABORATIONS 2006

### National:

Dr Med Bjørn Naume, Oncology  
Dr Med Gunnar Kvalheim, Oncology  
Cand Med Marit Synnestvedt, Oncology  
Dr Med Wolfgang Lilleby, Oncology  
Dr Philos Lars Baumbusch, Oncology  
Prof, Dr Med Øivind Bruland, Oncology  
Prof, Dr Med Karl Erik Giercksky, Surgery  
Prof, Dr Med Øystein Fodstad, Tumour Biology  
Cand real Arne Berg, Biophysics  
Prof, Dr Med Claes G Trope, Gynecology  
Prof, Dr Philos Anne-Lise Børresen-Dale, Genetics  
Cand Med Vilde Dragset, Genetics  
Dr Philos Terese Sørli, Genetics  
Dr Med Rolf Kåresen, Ullevål  
Dr Med Gro Wiedsvang, Ullevål  
Prof, Dr Med Ida Bukholm, Ahus

### International:

K Pantel, G Schlimoc, P Müller, W Janni, G Gebauer, Germany.  
J Hicks, USA.

### Companies:

AppliedGenomics  
Applied Imaging

### EU projects:

Mascot (JM Nesland)  
Dismal (B Naume)

## Laboratory for Immunohistochemistry and Immunopathology (LIIPAT)

GROUP LEADER: PER BRANDTZÆG, PhD (until 30/06-2006), FINN-EIRIK JOHANSEN, PhD (from 01/07-2006)

### GROUP DESCRIPTION

LIIPAT consists of 3 integrated sections which perform biomedical research on basic mechanisms in mucosal immunity, immune-mediated disorders and angiogenesis. The directly disease-oriented projects are primarily carried out in a collaborative network with several clinical departments at Gaustad hospital campus but also involve other national and international collaborators. In cooperation with 5 other laboratories, LIIPAT is also part of the basic research consortium, '*Centre for Vaccinology and Immunotherapy (CEVI)*' a thematic research group prioritized by the Faculty of Medicine.

In June 2006, Per Brandtzaeg's scientific career and 41 years as head of LIIPAT was celebrated with a symposium in his honor featuring distinguished European, American and Japanese speakers. LIIPAT's three sections were in 2006 partners in two applications that were finalist to become Norwegian Centre of Excellence (Research Council of Norway). One of these applications, Centre for Immune Regulation, was successful and the centre will be established in 2007.

### LIIPAT TECHNICIANS AND SUPPORT STAFF 2006

Aaste Aursjø (Technician)  
Hege Eliassen (Secretary, part time)  
Kathrine Hagelsten (Technician)  
Erik Kulø Hagen (Consultant, part time)  
Linda Kristiansen (Technician)  
Linda Solfjell (Technician)  
Vigdis Wendel (Technician)

## Section for Secretory Immunity and B Cells (SIB)

SECTION HEAD: FINN-EIRIK JOHANSEN, PhD

### RESEARCH SUMMARY 2006

Active polymeric Ig receptor (pIgR)-mediated epithelial transport of dimeric IgA and pentameric IgM, generates secretory IgA (SIgA) and SIgM antibodies, respectively. Such secretory antibodies provide immune exclusion of micro-organisms and are important for mucosal homeostasis. The section has continued its focus on regulation and function of secretory antibodies as well as the therapeutic potential of mucosal delivery of  $\beta$ -glucans as a modulator of immunity. A chemically induced colitis model was employed in our pIgR knockout mice, which lack secretory antibodies, and demonstrated that they were considerable more afflicted than wild type mice. We also demonstrated that oral feeding of  $\beta$ -glucan reduced the severity of organ injury in a rat model of endotoxin-mediated sepsis.

## Overview of the different research groups

Appropriate polymerization of IgA and its binding to the pIgR require incorporation of the small J-chain polypeptide. We have continued to analyze the direct role of J chain in this interaction and its phylogenetic conservation. Furthermore we demonstrated the presence of a functional pIgR in *Xenopus laevis*, the first amphibian and most distant pIgR to humans found to date.

### GROUP MEMBERS 2006

Finn-Eirik Johansen (PhD, Group Leader)  
Per Brandtzæg (PhD, Consultant)  
Ranveig Braathen (PhD Student – defended thesis in 2006)  
Alex Erofeev (MD, PhD Student)  
Anna Lång (BSc, PhD Student)  
Else Munthe (PhD, Postdoc)  
Anders Sandvik (BSc, PhD Student)  
Dag Henrik Reikvam (MD, PhD Student)

### COLLABORATIONS 2006

#### National:

Rolf Engstad, Biotec Pharmacon ASA, Tromsø.  
Inger Sandlie, Dept. of Molecular Biosciences, University of Oslo.  
Peter Gaustad, Inst. of Med. Microbiol., Rikshospitalet-Radiumhospitalet Hf.  
Dag Kvale, Dept. of Infectious Diseases, Ullevål University Hospital, University of Oslo.  
Jacob Wang, Inst. of Surgical Research, Rikshospitalet-Radiumhospitalet Hf.

#### International:

Richard S. Blumberg, Harvard Medical School, Boston, MA, USA.  
Nico Bos, University of Groningen, the Netherlands.  
Lars Eckmann, University of California, San Diego, CA, USA.  
Sven Hammerschmidt, University of Würzburg, Germany.  
Valerie Hohman, University of San Diego, CA, USA.  
Charlotte S. Kaetzel, University of Kentucky, KY, USA.  
Wayne Lencer, Harvard Medical School, Boston, MA, USA.  
Richard Strugnell, University of Melbourne, Australia.

## Section for Vascular Endothelial Cells (VEC)

SECTION HEAD: GUTTORM HARALDSEN, MD, PhD

### RESEARCH SUMMARY 2006

Much attention is currently focused on understanding the role of vascular endothelial cells in disease. The mechanisms that regulate the generation of new vessels and endothelial cell differentiation/activation are potential drug targets in several fields of medicine, because such targeting may enable control of cancer growth and metastasis, enhance the healing of ischemic lesions and modulate the leukocyte migration of inflammatory disorders including allograft rejection. VEC has focused on understanding the role of interleukin-33 in endothelial

## Overview of the different research groups

cell activation, revealing that it is most likely involved in the transition from one vascular phenotype to another. Moreover, studies designed at understanding how chemokines are targeted to compartments of regulated secretion and the role of such secretion *in vivo* are ongoing. Specifically, we have generated chimeras of interleukin-8 and IP-10 and shown that loop 2 of the tertiary structure contains aminoacids required for proper storage of IL-8 in Weibel-Palade bodies. A third line of experiments is focused at understanding the molecular *in vivo* actions of the angiogenesis inhibitor endostatin.

In collaboration with Diagnostic section 2, we have generated the first transcriptional profile of endothelial cells during experimental allograft rejection and identified more than 100 differentially expressed transcripts whose further verification and differentiation is ongoing.

### GROUP MEMBERS 2006

Johanna Balogh (Postdoc)  
Johanna Hol (PhD Student)  
Reidunn Jetne (PhD Student)  
Axel K uchler (Postdoc)  
Marlene Lundstr m (PhD Student)  
Bj rg Mikalsen (PhD Student)  
J rgen Pollheimer (Postdoc)



### COLLABORATIONS 2006

#### National:

P l Dag Line, Surgical Clinic, Rikshospitalet-Radiumhospitalet Hf.  
Dag R. S rensen, Comparative Medicine, Rikshospitalet-Radiumhospitalet Hf.

#### International:

Jean-Philippe Girard, CNRS, Toulouse.  
Robert Kastelein, Schering-Plough Research Inst., Palo Alto, USA.  
Robert Nibbs, Glasgow, Scotland.

## Section for Immune Regulation and Allergy (IRA)

SECTION HEAD: FRODE L. JAHNSEN, MD, PhD

### GROUP DESCRIPTION

We aim to identify and characterise mechanisms of immune dysregulation that are common to several allergic diseases: primary candidates are aberrant presentation of allergen to T cells by antigen-presenting cells, faulty interaction between T and B cells and dysfunction of a specific type of T cells, suppressive regulatory T cells (Tregs). These white blood cells (leukocytes) are the major players in acquired immunity. Thus, the primary goals of our research are 1) to characterise the mechanisms that underlie faulty interaction between T and B cells in allergy, with a special emphasis on T cells, and 2) to develop therapies.

## RESEARCH SUMMARY 2006

Dendritic cells are key regulators of T-cell function. Dendritic cells are therefore candidate targets for immunotherapeutic approaches related to improved vaccines as well as inflammatory disorders (e.g. allergy) as well as cancer. In the last year we have finalized several studies where we show: 1) how DCs traffick to mucosal sites in response to inflammatory signals (Jahnsen *et al.*, 2006, *J Immunol*); 2) how different dendritic cell subtypes show dramatically different effects on T-cell function (Kvale *et al.*, 2006 *Blood*; Farkas *et al.* 2006, *J Scand Immunol*; Kvale *et al.*, 2007, *Blood*); 3) identification of a unique dendritic cell population in the duodenal mucosa of patients with celiac disease (Raki *et al.*, 2006, *Gastroenterology*). We have furthermore shown that a specific subset of dendritic cells accumulate in the nasal mucosa of allergic rhinitis patients (Scheel *et al.* unpubl.) and that these cells are activated by a cytokine – TSLP – which is produced locally by nasal epithelial cells (Farkas and Scheel *et al.* unpubl). We have also characterized the population of antigen presenting cells in the bronchial mucosa of infants (Heier *et al.* submitted) and have ongoing studies both in humans and mice to explore the role for Tregs in allergy (Skrindo and Erofeev) and cancer (Heier). Finally, we have been examining the genetic defect of rare recessive autosomal skin disorder with an atopic phenotype (Khnykin).

## GROUP MEMBERS 2006

Frode Jahnsen (MD, PhD)  
Lorant Farkas (MD, PhD)  
Denis Khnykin (PhD)  
Ingvild Heier (MD)  
Cecilie Scheel (MD)  
Ingebjørg Skrindo (MD)  
Espen Ø. Kvale (Cand Pharm)

## COLLABORATIONS 2006

### National:

Ludvig Sollid, Inst. of Immunology, Rikshospitalet-Radiumhospitalet Hf.  
Tobias Gedde-Dahl jr, Dept. of Dermatology, Rikshospitalet-Radiumhospitalet Med. Center.  
Johanna Olweus and Fridtjof Lund-Johansen, Inst. of Immunology, Rikshospitalet-Radiumhospitalet Hf.  
Sheraz Yaqub and Ketil Tásken, Biotechnology Centre of Oslo, University of Oslo.

### International:

Kriistina Malmstrøm, Division of Allergy, Dept. of Medicine Helsinki University Central Hospital, Helsinki, Finland.  
Patrick Holt, Inst. of Child Health Research, Perth Australia.  
Niklas Dahl, Dept. of Pathology and Genetics, University of Uppsala.  
Bart Lambrecht, Erasmus University Hospital, Rotterdam, the Netherlands.  
Tara Hornell and Elisabeth Mellins, Dept. of Pediatrics, Stanford University School of Medicine.

### Laboratory for Toxicopathology

GROUP LEADER: HENRIK S. HUITFELDT, MD, PhD, PROFESSOR

#### GROUP DESCRIPTION

Our group aims at clarifying the initial steps of carcinogenesis; how some cells escape the mitoinhibitory effects of environmental carcinogens to become initiated cells, and thereafter expand to preneoplastic lesions. To study alterations in growth factor signalling and cell cycle regulation. We use an experimental rat liver carcinogenesis model, and have developed corresponding primary hepatocyte culture models, to reflect environmental carcinogens, the DNA-damaging polyaromatic hydrocarbon 2-acetylaminofluorene, is employed. In addition, prototype non-DNA damaging carcinogens (dioxin-like and non-dioxin-like polychlorinated biphenyls), are studied. In particular, EGF receptor activation of PI3K and MAPK pathways, and how these regulate Cdk2, Cdk4 and p53 during carcinogen exposure, are studied. We also maintain a core facility for advanced light microscopy for the Gaustad Campus. We offer training and provide access to confocal microscopy and image analysis. The Laboratory participates in Center for Cellular Stress Responses, one of the Thematic Research Areas at the Faculty of Medicine.

#### RESEARCH SUMMARY 2006

Carcinogens induce growth inhibition of normal cells, whereas initiated cells and preneoplastic lesions escape this effect and thus achieve a growth advantage. A model predicts that DNA-damaging carcinogens inhibit proliferation through induction of p53 and subsequently p21CIP. In previous research we have found that carcinogen exposure inhibits Erk1/2 nuclear translocation, but not phosphorylation. In addition, Cdk2 and Cdk4 became cytoplasmically arrested in carcinogen-exposed hepatocytes. Since p21CIP binding to Cdk2 and Cdk4 complexes were not increased, we hypothesized that p53 induction was not the mechanism of carcinogen mitoinhibition. To further clarify these mechanisms we sought a closer knowledge of the intracellular signalling transforming growth factor binding in the plasma membrane to transcriptional activation initiating DNA synthesis. We currently complete several studies:

- A manuscript showing that nuclear translocation of Erk1/2 is accomplished by MEK1, whereas MEK2 promotes cytoplasmic retention, has been submitted. Phosphorylations of MEK1 S292/S298 induce the release Erk1/2 from MEK1, and thus nuclear translocation. This phosphorylation depends upon Rac1-activation; probably reflecting integrin signalling.
- We now publish that p53 is growth factor induced, and plays an important role in the proliferation of normal hepatocytes. When p53 induction is inhibited, the cells become growth arrested, and Cdk2 and Cdk4 remain cytoplasmically arrested. These effects are counteracted by ectopic expression of p21CIP, which may provide a piggy-backing NLS signal to G1 Cdk complexes.
- Furthermore, we have submitted a manuscript showing that Cdk4 activation is necessary for subsequent Cdk2 nuclear translocation and proliferation.
- We currently publish that H-Ras and K-Ras are differentially involved in growth factor signalling of hepatocytes. Whereas H-Ras activates Erk1/2 and PI3K, thus

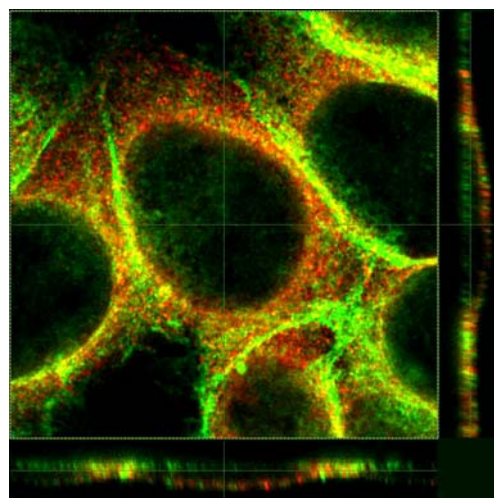
## Overview of the different research groups

promoting both proliferation and survival, K-Ras activation promotes survival through PI3K activation.

- Based on a grant from the Research Council of Norway we have initiated a study on the mechanisms of non-dioxin-like PCB toxicity. Initial studies show that PCB153 enhances the EGF-induced proliferation, possibly through shortened G1 phase. Involved mechanisms will be investigated in further studies.
- Two PhD students are in the final stages of their doctoral projects, and submitted their theses early 2007.
- Based on a grant from the Research Council of Norway, a confocal microscope configured for live cell imaging has been installed. The microscope has been made available for scientists at Gaustad campus through our core facility.

### GROUP MEMBERS 2006

Henrik S. Huitfeldt (Prof, MD, PhD)  
Ellen Skarpen (PhD, Postdoc)  
Morten Oksvold (PhD, Postdoc)  
Lene Wierød (PhD Student)  
Carola Rosseland (PhD Student)  
Helga Grøsvik (Bioengineer)  
Liv Ingrid Flinder (Medical Student)  
Svanhild Zirin Slåtto (Medical Student)



3D image of EGF receptor (green) and caveolin (red) in Hela cells

### COLLABORATIONS 2006

#### National:

Prof Anne Carine Østvold, Dept. of Biochemistry, Inst. of Basic Medical Sciences, University of Oslo.

Prof Bjørn Steen Skålhegg, Dept. of Nutrition, Inst. of Basic Medical Sciences, University of Oslo.

Prof Ragnhild E. Paulsen, Inst. of Pharmacy, University of Oslo.

Prof Philippe Collas, Dept. of Biochemistry, Inst. of Basic Medical Sciences, University of Oslo.

Chief Physician Terje Rootwelt, Clinic of Paediatrics, Rikshospitalet Hf.

Prof Jan Mæhlen, Dept. of Pathology, Ullevål University Hospital.

#### International:

Prof Wallace Langdon, Department of Pathology, University of Western Australia.

Dr Olga Timofeeva, Lombardi Comprehensive Cancer Center, Georgetown University, USA.

Dr Miriam Poirier, Laboratory for Chemical Carcinogenesis and Tumor Promotion, National Cancer Inst., USA.

## Research Group of Ovarian Carcinoma Biology

GROUP LEADER: BEN DAVIDSON, MD, PhD

### GROUP DESCRIPTION

Research group focusing on the characterization of ovarian carcinoma cells in effusions, with comparative models of breast carcinoma and malignant mesothelioma.

Focus on the following areas:

- Optimizing cancer diagnosis in effusions
- Mapping events mediating invasion and metastasis
- Studying genetic events and their clinical significance
- Identifying pro-survival molecules

### RESEARCH SUMMARY 2006

Focus on the above areas.

### GROUP MEMBERS 2006

Hiep Phuc Dong (Msc, PhD Student)

Lilach Kleinberg (PhD Student)

Arild Holth (Technician)

### COLLABORATIONS 2006

#### National:

Vivi Ann Flørenes, PhD (Senior Researcher), the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.

Prof Jahn M. Nesland, MD, PhD (Head of Clinic), the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.

Björn Risberg, MD, PhD (Method Chief, Pathology), the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.

Aasmund Berner, MD, PhD (Head, Cytopathology Section), the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.

Prof Claes G. Tropé, MD, PhD (Chief, Gynecologic Oncology), Gynecology Dept., the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.

Ilvars Silins, MD, PhD (Senior physician), Gynecology Dept., the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.

#### International:

Prof Ie-Ming Shih, MD, PhD (Pathologist, Lab Chief) and Prof Tian-Li Wang, PhD (Lab Chief), Johns Hopkins University Medical Institutions, Baltimore MD, Dept. of Pathology, Gynecology and Oncology.

Dr Elise C. Kohn, MD (Lab Chief), NCI/NIH, Bethesda MD, Molecular Signaling Section, Laboratory of Pathology.

Prof Reuven Reich (Lab Chief), Department of Pharmacology and Experimental Therapeutics, School of Pharmacy, Faculty of Medicine, the Hebrew University of Jerusalem Jerusalem 91120, Israel

### Laboratory for Experimental Pathology

GROUP LEADER: RUTH HOLM, PhD

#### GROUP DESCRIPTION

The research work of our group include gynaecological cancers and cell cycle-, apoptosis- and cell adhesion-markers, matrix metalloproteinases and HPV. In addition to our own projects we are doing research work for other departments at Rikshospitalet-Radiumhospitalet Hf (RRMC) as well as for other hospitals.

#### RESEARCH SUMMARY 2006

Malignant tumours of the female gynaecological 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 gynaecological 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 avoided 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 gynaecological cancers. Furthermore, we wanted to search for prognostic markers which may help the clinician to tailoring the treatment.

In our studies we found that p14, EphA2, EphrinA-1 and Zinc finger protein (ZNF652) abnormalities may be involved in the neoplastic process of vulvar cancers, but only p14 represents an independent prognostic predictor (Knopp et al., *Am J Clin Pathol* 2006; 126: 266-76; Holm et al., *J Clin Pathol*, Epub ahead of print Dec 8; Holm et al., *J Clin Pathol*, resubmitted). For the first time, we found correlations between human papillomavirus (HPV) infection and p14 and between p14 and p16 in vulvar carcinomas. This may be due to the association of HPV E7 oncoprotein with pRB, resulting in an increase of free E2F and up-regulation of p16 and p14, which are encoded by the same INK4a/ARF locus (Knopp et al., *Am J Clin Pathol* 2006; 126: 266-76). When comparing the cell cycle inhibitors p16, p21, p27 and the cyclins D1, D3, E and A in primary vulvar carcinomas and their corresponding lymph node metastases only p21 and cyclin D1 seems to have a role in the progression of vulvar squamous cell carcinoma (Knopp et al., *Histopathology* 2006; 49: 311-2).

In ovarian cancer stage III, Ki-67 represents as an independent prognostic predictor. We did not find p16, p14 and p57 to be useful as prognostic markers (Khouja et al., *Int J Gyn Pathol*, in press).

In cervical cancer we have compared gene expression (microarray analysis) and protein expression (immunohistochemistry) and found that for CKS2, CSTA and MSN there were a relationship between protein and gene expression. No correlation between gene and protein expression was found for MEF2A or HK2. Thirty-one genes differed in expression between patients with lymph node metastases and patients without lymph node metastases. Expression of eight of these genes (*MRPL11*, *CDS2*, *PDK2*, *MRPS23*, *MSN*, *TBX3*, *KLF3*, *LSM3*)

correlated with progression free survival. Multivariate analysis identified tumor volume and *PDK2* expression as independent prognostic variable (Lyng et al., *BMC Genomics* 2006; 7: 268-83). In cervical cancer we have compared the expression of HPV E6 and E7 mRNA with HPV DNA and integration of HPV DNA. There was a high association between HPV E6 and E7 mRNA, HPV DNA and integration of HPV DNA. Furthermore, we found that HPV infection among Norwegian women with cervical squamous cell carcinomas are limited mainly to the five-risk types, 16, 18, 31, 33 and 45 (Kraus et al., *J Clin Microbiol* 2006; 44: 1310-7).

In addition to our own projects we are doing research work for other departments at Rikshospitalet-Radiumhospitalet Hf (RRMC) as well as for other hospitals. We have done a high number of tests for immunohistochemistry (13088), *in situ* hybridization (650), H&E staining (4776), frozen sections for DNA/RNA extraction (73), tissue array (19), and electron microscopy (107). The number in brackets shows number of tests.

### GROUP MEMBERS 2006

Ruth Holm (Group Leader; Senior Scientist, PhD)  
Synne Knopp (PhD Student, MD)  
Zhihui Wang (PhD Student, MD)  
Ellen Hellesylt (Head Bioengineer)  
Vivi Bassøe (Bioengineer)  
Anne-Marie Becker (Bioengineer)  
Elisabeth Emilsen (Overengineer, MSc)  
Mette Førstund (Department Engineer)  
Liv Inger Håseth (Research Technician)  
Ann Larsen (Bioengineer)  
Mai Thi P. Nguyen (Bioengineer)  
Inger-Liv Nordli (Department Bioengineer)

### COLLABORATIONS 2006

#### National:

Prof Jahn M. Nesland (Dr Med), Dept. of Pathology, the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Prof Zhenhe Suo (Dr Med), Dept. of Pathology, the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Prof Claes Tropè (Dr Med), Dept. of Gynecologic Oncology, the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Gunnar Kristensen (Dr Med), Dept. of Gynecologic Oncology, the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Mark Baekelandt (Dr Med), Dept. of Gynecologic Oncology, the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Heidi Lyng (PhD), Dept. of Radiation Biology, the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Guro Lind (PhD), Dept. of Cancer Prevention, the Pathology Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Hanne Skomedal (PhD), NordChip AS.  
Irene Kraus (MSc), NorChip AS  
Tor Molden (PhD), NorChip AS

## Overview of the different research groups

### International:

Prof David Callen (Dr Med), University of Adelaide; Australia.

Prof M. Haysam Khouja (Dr Med), Aleppo University, Syria.

Gregg Van de Putte (Dr Med), Ziekenhuis Oost-Limburg Hospital, Belgium.

## Malignant Melanoma Laboratory

GROUP LEADER: VIVI ANN FLØRENES, PhD, SENIOR SCIENTIST

### GROUP DESCRIPTION

The group consists of one senior scientist, two PhD students and two technicians. The main objectives is to identify and study new biomarkers important for development and progression of malignant melanoma as well as the impact of cell-signaling, proliferation and cell death on anchorage-independent growth. In addition to the melanoma work the senior scientist and technicians have during the last year had the responsibility to build up a new laboratory and establishing an *in vitro* technique to test tumor response to chemotherapy. This has been successful and we have to date tested tumors from around 75 patients with ovarian cancer. We have, moreover, been involved in the work of Dr Ben Davidson and the group leader has functioned as a co-supervisor for the PhD student Lilach Kleinberg. The collaboration has resulted in 5 published papers (Kleinberg L et al., *Cancer* 2007; Davidson B et al., *Clin Cancer Res* 2006; Kleinberg L et al., *Virchows Arch* 2006; Davidson B et al., *Clin Cancer Res* 2006; Ødegaard E et al., *Gynecol Oncol* 2006).

### RESEARCH SUMMARY 2006

Malignant melanoma accounts for about 5% of all cancers and is one of the most rapidly increasing malignancies. Increased exposure to UV-radiation has been suggested to be the main reason for the pronounced rise in new incidences. Several subtypes exists of which the superficial spreading and nodular melanomas constitutes the majority of cases.

To study how deregulated gene/protein expression affect disease progression of, we use a well characterized panel consisting of paraffin embedded tissue from about 170 primary and 70 metastatic melanomas as well as 40 benign nevi.

Signaling pathways regulating cell proliferation and survival have been demonstrated to be abrogated in most cancer forms and have become attractive targets for anticancer strategies. In melanomas, mutations in B-raf or N-ras, both components in the MAPK/ERK1/2 pathway, have been found in the majority of cases. Furthermore, mutations and deletions in PTEN, known to inactivate the PI3K/Akt pathway, have been observed. We have shown that mutations in B-raf or N-ras are not always leading to increased MAPK/ERK1/2 activity. Furthermore, ERK1/2 activity was associated with increased proliferation, but not disease outcome in superficial spreading melanomas (Jørgensen et al., *Clin Cancer Res* 2003). Likewise, our results suggest that alterations in the PI3-kinase/PTEN pathway has limited prognostic impact in melanoma (Slipicevic et al., *Am J Clin Pathol* 2005). Whereas the MAPK/ERK1/2 and the PI3-kinase pathways have been associated with increased proliferation and survival, the MAPK/p38 and the JNK pathways are frequently associated with decreased proliferation and induction of apoptosis. We have shown that cytoplasmic localized activated JNK is associated with thicker primary superficial spreading melanomas and shorter disease-free survival (Jørgensen et al., *Mod Pathol* 2006).

Most normal cells are dependent on adhesion to extracellular matrix (ECM) for continued growth and survival. Upon detachment from the substratum, anchorage-dependent cells either

become arrested in the G1 phase of the cell cycle or trigger a death program referred to as anoikis. Resistance to anoikis is likely to play an important role in the three-dimensional growth of solid tumors allowing detached tumor cells to give rise to more aggressive and metastasizing tumors. To study anoikis we use a panel of human melanoma cell lines derived from different stages of the disease. From one of the cell lines, WM35, that die by anoikis when tried cultivated in suspension as multicellular aggregates (spheroids), we have created two anoikis resistant variants, one after repeated selection for ability to survive anchorage-independently (WM35sph6), the other by retroviral insertional mutagenesis (WM35-3.1). We have in particular studied the impact of the MAPK/ERK1/2, PI3K/Akt/PTEN pathways as well as protein kinase C (PKC).

Whereas normal melanocytes are dependent on the phorbol ester PMA (activator of PKC) for proliferation in monolayer culture, most malignant melanomas are growth inhibited by PMA. We have, however, shown that PKC activation increase proliferation and survival of melanoma cells cultivated as spheroids through a MEK-independent activation of ERK1/2 and inactivation of the pro-apoptotic proteins Bim and Bad (Jørgensen et al., *BBRC* 2003). As a follow up of this study, we have treated melanoma spheroids with PMA and/or the MEK inhibitor PD98059 and performed an Affymetrix microarray analysis. Among interesting gene products that were identified are several inactivators of the MAPK/ERK1/2 pathway (MKP3, Sprouty4). We are currently investigating their potential involvement in the MEK-independent activation of ERK1/2. Moreover, fatty acid-binding protein 7 (FABP7) was shown to be down regulated by PMA and PD98059. The encoded protein was recently suggested to play a role in tumorigenesis of melanomas. In addition to study the involvement of FABP7 in anoikis in *in vitro* models, we have in a pilot study shown that protein expression of FABP7 is reduced concomitant with increased melanoma aggressiveness. We are expanding this study and will by immunohistochemistry stain our melanoma panel with antibody against FABP7. Insulin-like growth factor binding protein (IGFBP3) and the orphan nuclear receptors NR4A1 and NR4A3 are other gene products we are studying further, the first in collaboration with Dr Mælandsmo at Dept of Tumor Biology, RR.

In attempt to identify gene products of importance for anchorage-independent survival we have also cultivated WM35, WM35sph6 and WM35-3.1 cells as spheroids for different time periods and analyzed the RNA by Affymetrix. The statistical analysis is ready and we are currently evaluating the results.

We have observed an upregulation of PTEN and p53 proteins when anoikis sensitive WM35, but not anoikis resistant WM35sph6 or WM239 cells are cultivated as spheroids. Moreover, loss of attachment did not effect constitutive activation of ERK1/2, but addition of PD98059 increased anoikis in WM35 and WM35sph6 cells. PD98059 treatment in these cells led to a marked increase in PTEN protein level and inactivation of ERK1/2. To study the impact of PTEN on anoikis we have transfected the cells with PTEN siRNA. WM239 cells, that do not express PTEN constitutively, were less sensitive to ERK1/2 inhibition. Interestingly, inhibition of the PI3K/Akt pathway following addition of LY294002 decreased anoikis in WM35 and WM35sph6 cells. LY294002 treatment led to a slight decrease in PTEN protein suggesting the possibility for a regulatory feedback loop. In WM239 cells, expressing high basal level of activated Akt due to lack of PTEN, LY294002 treatment provided no such protection and rather increased anoikis (Slipicevic et al., Manuscript in preparation). We are, moreover, in the progress of studying how PTEN is regulated by the MAPK/ERK1/2 pathway.

## GROUP MEMBERS 2006

Vivi Ann Flørenes (Senior Scientist, PhD)

Kjersti Jørgensen (Cand Scient, PhD student)

Ana Slipicevic (Cand Scient, PhD student)

Matina Skrede (Technician)

Marit Helgerud (Technician, from September 2006)

Lilach Kleinberg (Cand Pharm, PhD Student [co-supervised with Ben Davidson on the ovarian project])

## COLLABORATIONS 2006

### National:

Dr Med Ben Davidson, PhD, Patholgy Clinic, Rikshospitalet-Radiumhospitalet Hf, Oslo.

Dr Gunhild Mælandsmo, PhD, Dept of Tumor Biology, Rikshospitalet-Radiumhospitalet Hf, Oslo.

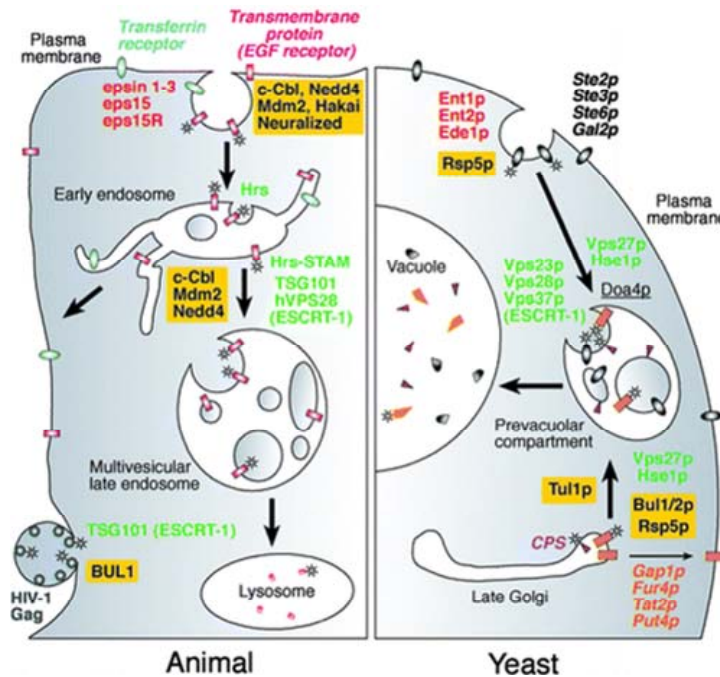
Dr Svein Ole Mikalsen, PhD, Dept. of Cancer Prevention, Rikshospitalet-Radiumhospitalet Hf, Oslo.

## Laboratory for Molecular and Cellular Cancer Research

GROUP LEADER: INGER HELENE MADSHUS, MD, PhD, PROFESSOR

### GROUP DESCRIPTION

The projects carried out in the group center around how EGFR family members can be downregulated physiologically and experimentally. Such studies are motivated by the fact that overexpression of these RTKs is driving oncogenesis in a number of epithelial cells. Potential ways of therapeutically downregulating these proteins is therefore of utmost importance in treatment of diseases like breast cancer, prostate cancer and glioblastomas. A prerequisite for designing mechanisms inducing therapeutic downregulation is more detailed knowledge on mechanisms normally controlling endocytosis and lysosomal degradation of the EGFR and of EGFR family members.



### RESEARCH SUMMARY 2006

We have pursued studies on how the EGFR is posttranslationally modified by ubiquitination. Lack of ubiquitination has previously been correlated with inefficient entry of the EGFR into clathrin coated pits and thereby with inefficient endocytosis (Stang, Johannessen, Kazazic, Bertelsen, Winther-Pedersen, Madshus). Also, lack of ubiquitination leads to inefficient sorting of the EGFR in early endosomes and thereby in blocked degradation (Longva, Myromslien, Grøvdal, Stang, Madshus). We have established that endocytosis of the EGFR is endocytosed clathrin-dependently only and have by FRAP demonstrated that caveolae are not mobilized when high concentrations of EGF are added to cells (Kazazic, Johannessen, Roepstorff, van Deurs, Stang, Madshus). Epsin has been demonstrated to be essential in

## Overview of the different research groups

clathrin-mediated endocytosis of ubiquitinated EGFR (Kazazic, Winther Pedersen, Vuong, Stang, Madshus). Activation of the EGFR was demonstrated to kinase- and Grb2-dependently induce formation of new clathrin coated pits in cells where preexisting coated pits had been removed (Johannessen, Pedersen, Winther Pedersen, Stang, Madshus).

### GROUP MEMBERS 2006

Inger Helene Madshus (Group Leader)  
Espen Stang (Scientist)  
Kamilla Breen (PhD Student)  
Ketil Winther Pedersen (Scientist)  
Lene Johannessen (Postdoc)  
Tram Thu Vuong (Postdoc)  
Lene M. Grøvdal (PhD Student)  
Vibeke Bertelsen (PhD Student)  
Nina Marie Pedersen (PhD Student)  
Maja Kazazic (PhD Student)  
Marianne Skeie Rødland (Technician)

### COLLABORATIONS 2006

#### National:

Prof Harald Stenmark, Dept. of Biochemistry, Rikshospitalet-Radiumhospitalet Hf, Oslo.  
Prof Kirsten Sandvig, Dept. of Biochemistry, Rikshospitalet-Radiumhospitalet Hf, Oslo.

#### International:

Prof Bo van Deurs, Panum Institutet, Københavns Universitet, Danmark.  
Prof Linton Traub, University of Pittsburgh School of Medicine, USA.

## Research Group for Gastrointestinal and Skin Tumor Biology

GROUP LEADER: OLE PETTER F. CLAUSEN, MD, PhD, PROFESSOR

### GROUP DESCRIPTION

The research group is composed of *two sections*:

- **Section for Carcinogenesis**, led by Ole Petter F. Clausen, MD, PhD
- **Section for Molecular Chemoresistance**, led by Paula M. De Angelis, PhD

### Section for Carcinogenesis

The main areas of interest for this section are investigations of cancers and their preneoplastic stages in the gastrointestinal tract, in squamous epithelium of the ENT region and in the skin. We try to better understand the different types of growth- and differentiation-related deregulations that might characterize a specific cancer type, and that often affect various signal transduction pathways for growth and cell death. The rationale behind these studies is to characterize aberrant genotypes and phenotypes that may be of importance for better classification of cancer subtypes, for detecting early and treatable disease, and to find prognostic markers that may be important for choice of treatment and follow up of patients. Such genetic aberrations have been shown to be of increasing importance in the development and evolution of many different types of human cancer. We have a special interest in studying the mechanisms for development of aneuploidy, which confers bad prognosis in colorectal cancer and in many other cancer types.

### Section for Molecular Chemoresistance

The chemotherapeutic drugs 5-fluorouracil (5-FU) and irinotecan, which are used to treat metastatic colorectal cancer, are DNA-damaging and apoptosis-inducing agents. However, resistance to these drugs is a major obstacle to successful therapy and may develop after a primary period of successful response. Elucidations of the complex biological mechanisms involved in development of resistance to 5-FU and irinotecan, in DNA damage checkpoint response, and in apoptosis induction, are essential steps in predicting treatment outcome or overcoming such resistance, and are the main areas of interest for this research section. Drug resistance in drug-sensitive and drug-resistant colorectal cancer cell lines is studied in order to elucidate the mechanisms underlying development of resistance and to identify biomarkers of drug response. Such knowledge will make it possible to counteract resistance development in the future, and to circumvent drug treatment of patients who will not derive any benefit of such treatment.

### RESEARCH SUMMARY 2006

- a) We studied genotypic and phenotypic alterations during colorectal carcinogenesis related to longstanding ulcerative colitis, as well as to sporadic colorectal cancer. By separately studying the diploid and aneuploid components of a series of aneuploid colorectal cancers by CGH, FISH, and mutation analysis, **we found that large scale aneuploidization in sporadic colorectal cancers was preceded by amplification of oncogene(s) on 20q13.2 and K-RAS mutations.** This work was just published recently (De Angelis PM et al., *Int. J Cancer* 120 (2007), 2734-2738).

We have developed methods for studying expression of the spindle checkpoint proteins Aurora A, B and C, Mad 2 and BUB1B by immunohistochemistry in formalin fixed tissues, and shown that some of these proteins are aberrantly expressed in malignant neoplasias (Borum-Auensen E et al., *J Histochem Cytochem* 55: 477-486, 2007). In particular, we have shown that Aurora A and BUB1B are aberrantly expressed in dysplastic mucosa during carcinogenesis in ulcerative colitis (Borum-Auensen E et al., *J Clin Pathol*, publ. online 230207) and that BUB1B is associated with aneuploidy in sporadic colorectal cancers. This may suggest that BUB1B has a role during aneuploidization and chromosome instability during colorectal carcinogenesis.

We compared genetic aberrations measured by CGH in a large series of keratoacanthomas with those in squamous cell carcinomas, concluding that these neoplasms probably develop through aberrations of different signaling pathways, and thus are separate entities (Clausen OP et al., *J Invest Dermatol* 2006; 126: 2308-15), contrary to the opinion of some authorities.

We have shown that biliary brush cytology from patients with primary sclerosing cholangitis is of great diagnostic value in diagnosing cholangiocarcinoma (Boberg KM et al., *J Hepatol* 2006; 45: 568-74).

- b) We published one article detailing the cellular response (cell cycle progression, apoptosis induction and associated gene expression changes) to 5-FU in 5-FU-resistant colon cancer cell lines during treatment and recovery (De Angelis PM et al., *Mol Cancer* 2006; 5:20). Another article, which is an invited review entitled 'Using pharmacogenomic tumor profiling to identify biomarkers of 5-fluorouracil response in colorectal cancer' has been accepted for publication in *Current Pharmacogenomics* (De Angelis PM). We have used siRNA-mediated knockdown of TP53 to investigate the function of the TP53 protein in mediating the cellular response to 5-FU. By assessing alterations in gene expression, we have identified potentially novel TP53 target genes that may play a role in mediating the 5-FU-induced cellular response in TP53 proficient cells. This work has recently been submitted for publication. Another article that has recently been submitted for publication describes the DNA damage response, cell cycle progression, and cell death during irinotecan treatment and recovery in 5-FU-sensitive and -refractory colon cancer cells.

During 2006 the research group published 5 scientific papers, and 4 others were accepted for publication.

## GROUP MEMBERS 2006

Ole Petter F. Clausen (MD, PhD, Prof, Leader)  
Paula M. De Angelis (PhD, Senior Scientist)  
Espen Burum-Auensen (PhD Student, The Norwegian Cancer Society)  
Birgitte Lid Adamsen (PhD Student, Stiftelsen UNI)  
Arne Westgaard (PhD Student, Dept. of Surgery, Rikshospitalet-Radiumhospitalet Hf)  
Aasa Schjølberg (Senior Research Technician University of Oslo (1/1))  
Liza Kravik (Research Technician, The Norwegian Cancer Society (1/1))  
Marzieh Beigi (Research Technician, The Norwegian Cancer Society (1/1))

## COLLABORATIONS 2006

### National:

Prof Morten Boysen (MD, PhD), ENT Dept., Rikshospitalet-Radiumhospitalet Hf.  
Ass Prof Ivar P. Gladhaug (MD, PhD), Dept. of Surgery, Rikshospitalet-Radiumhospitalet Hf.  
Prof Erik Schrumph (MD, PhD), Dept. of Medicine, Rikshospitalet-Radiumhospitalet Hf.  
Kirsten Muri Boberg (MD, PhD), Dept. of Medicine, Rikshospitalet-Radiumhospitalet Hf.  
Prof Torleiv O. Rognum (MD, PhD), Inst. of Forensic Medicine, University of Oslo  
Prof Magne Bryne (MD, PhD), Inst. of Oral Biology, University of Oslo.  
Senior Scientist Trond Stokke (PhD), Dept. of Radiation Biology, Inst. for Cancer Research, Rikshospitalet-Radiumhospitalet Hf.  
Prof Solveig N. Andersen (MD, PhD), Dept. of Pathology, Akershus University Hospital Hf.  
Odd Mjåland (MD, PhD), Dept. of Surgery, Sørlandet Hospital, Kristiansand S.

### International:

Prof Lars Bolund (MD, PhD), Inst. for Human Genetics, University of Aarhus, Denmark.  
Prof Steen Kølvraa (MD, PhD), Dept. of Clinical Genetics, Vejle Hospital, Vejle, Denmark.  
Charlotte M. Proby (MD, PhD), Centre for Cutaneous Research, Queen Mary's School of Medicine and Dentistry, University of London.  
Senior Scientist Ola Forslund (PhD), Dept. of Medical Microbiology, Malmö University Hospital, University of Lund, Malmö, Sweden.  
Loretta Mancinelli (PhD), University of Perugia, Italy.

## Hematopathology Research Group

GROUP LEADER: JAN DELABIE, MD, PhD

### GROUP DESCRIPTION

The group is involved with hematopathology research, both basic, applied and clinical research. We also deliver research services for clinical trials (molecular testing, flow cytometry and central pathology review).

### RESEARCH SUMMARY 2006

**The group has had several research projects in 2006:**

1. Notch2 mutation analysis in marginal zone lymphoma
2. SNP analysis in B-cell non-Hodgkin lymphoma
3. Marginal lymphoma antibody cloning for the detection of growth-stimulating antigens
4. Genome-wide gene expression analysis of lymphoma and development of a diagnostic lymphoma chip (co-investigator of an NIH-sponsored project)
5. Revision of primary testicular diffuse large B-cell lymphoma
6. Revision of all T-cell lymphomas and participation in the international T-cell lymphoma project (co-investigator of a University of Nebraska Medical Center sponsored project)
7. Revision of all primary small B-cell lymphomas of the bone-marrow
8. Pathology review for five clinical trials within the Nordic Lymphoma Group and the Nordic Pediatric Hematology/Oncology Group

### GROUP MEMBERS 2006

**Medical doctors**

Anne Tierens (MD, PhD)

Ida Ikonou (MD, PhD Candidate)

Ulla Randen (MD, PhD Candidate, maternity leave from Nov. 1, 2006)

**Scientists**

Gunhild Trøen (PhD)

Abdirashid Warsame (PhD Candidate)

### COLLABORATIONS 2006

**National:**

Hans Christian Åsheim and Erlend Smeland, Dept. of Immunology, the Norwegian Cancer Inst., the Norwegian Radium Hospital.

Harald Holte, Dept. of Oncology, the Norwegian Radium Hospital.

**International:**

Louis Staudt, Metabolism Branch, National Institutes of Health, Bethesda, USA.

John W Chan, Dept. of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, USA.

## Laboratory for Photodynamic Therapy

GROUP LEADER: QIAN PENG, Dr Med

### RESEARCH SUMMARY 2006

Photodynamic therapy (PDT) is a two-step therapeutic technique in which the topical or systemic delivery of a photosensitizing drug is followed by irradiation with visible light. The activated photosensitizer transfers energy to molecular oxygen, generating reactive oxygen species (ROS). The subsequent oxidation of lipids, amino-acids and proteins induces cell necrosis and apoptosis. This group has been working on the projects of PDT for more than 10 years. In 2006, research focused largely on mechanistic studies as follows:

PDT-induced tissue hypoxia as a result of vascular damage and photochemical oxygen consumption limits the efficacy of this modality. This may largely be due to hypoxia-mediated angiogenesis via hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), a major transcription factor involved in angiogenesis, hematopoiesis and anaerobic energy metabolism. High expression of HIF-1 $\alpha$  induced in vitro by cobalt chloride (CoCl<sub>2</sub>)-mediated chemical hypoxia mimic was seen in the Het-1A cell line. The CoCl<sub>2</sub>-treated cells were more resistant to PDT than those without CoCl<sub>2</sub> treatment. The photosensitivity of the cells to PDT decreased with increasing HIF-1 $\alpha$  expression by enhancing CoCl<sub>2</sub> concentrations. Moreover, transfection of the cells with anti-HIF-1 $\alpha$  short interfering RNA (siRNA) knocked down the HIF-1 $\alpha$  expression and restored the photosensitivity of the cells to PDT. The finding suggests that PDT in combination with anti-HIF-1 $\alpha$  treatment may enhance the PDT efficacy.

The mitochondrial permeability transition (PT) pore consists mainly of the mitochondrial outer membrane voltage-dependent anion channel and peripheral benzodiazepine receptor (PBR), and the mitochondrial inner membrane adenine nucleotide translocator (ANT). These mitochondrial proteins are responsible for the PT that leads to apoptosis. Since protoporphyrin IX (PpIX) is a known ligand for PBR, we hypothesized that PDT with PpIX targeted PBR causing apoptosis. PpIX-PDT induced apoptosis in tumor cells with high molecular weight (50 kbp) DNA fragmentation. Addition of PK11195 or Ro5-4864, two ligands of PBR, inhibited the induction of apoptosis by PDT. Bongkreic acid, a ligand for ANT, also reduced the PDT effect. Neither cytosolic translocation of mitochondrial cytochrome c, nor activation of caspase-9, caspase-3 and poly(ADP-ribose) polymerase were found. Furthermore, the potent inhibitor (Ac-DEVD-CMK) of caspases-3, -6, -7, -8 and -10 had no effect on the PDT-induced apoptosis. However, nuclear translocation of mitochondrial apoptosis-inducing factor (AIF) was demonstrated by both immunoblotting and immunocytochemistry. Since AIF is the sole one among all pro-apoptotic factors involved in caspase-dependent and caspase-independent pathways that induces the high molecular weight DNA fragmentation, we conclude that PpIX-PDT targets specifically the PT pore leading to an AIF-dependent pathway of apoptosis in the tumor cells. This study suggests the PT pore as a possible novel therapeutic target for PDT of cancer.

## GROUP MEMBERS 2006

Qian Peng (Senior Scientist)  
Jahn M. Nesland (Prof, Head of the Department)  
Beata Cunderlikova (Postdoc)  
Ingegerd E. Furre (PhD Student)  
Susan Shahzidi (PhD Student)  
Vlada Vasovic (Research Associate)

## COLLABORATIONS 2006

### National:

Groups of Karl-Erik Giercksky, Johan Moan and Kristian Berg at Rikshospitalet-Radiumhospitalet Hf.  
Group of Hans Prydz at the Biotechnology Center of Oslo.

### International:

Group of Jiyao Chen at Fudan University, Shanghai, China.  
Group of Henry Hirschberg at the Beckman Laser Inst., CA, USA.

## Tumour Stem Cell Research Group

GROUP LEADER: ZHENHE SUO, MD, PhD

### GROUP DESCRIPTION

In this group, we have two major projects towards tumour stem cell research: Application of curcumin and indirubin in treatment of cancer: A tumour stem cell targeting-based molecular and animal experimental study; Stemness-related factors in tumours and tumour stem cell identification.

### RESEARCH SUMMARY 2006

#### **Project 1:**

##### **Application of curcumin and indirubin in treatment of cancer: A tumour stem cell targeting-based molecular and animal experimental study**

Our idea or main goal of our present project is to extensively study different combinations of the effective ingredients/extract from selected TCM herbs or medical plants in our cell culture system, based on the principles of both western medicine and TCM, so as to explore new tumour remedy targeting tumour stem cells. Till now, we have chosen the following effective ingredients or medical plant, based on the fact that either the ingredient has been well documented to exert anticancer effect in vitro and in vivo (indirubin), or it is well-known edible herb/ medical plant with definite anticancer roles both proved in tradition and documented in laboratory work. We have already found in our molecular study that indirubin specifically inhibits FGFR, which may provide new modality targeting tumour stem cells since FGF/FGFR signaling is an important issue for tumour stem cells (Zhen et al, Oncogene, Inpress).

#### **Project 2:**

##### **Stemness-related factors in tumours and tumour stem cell identification**

There are several embryonic stem cells markers which are now discovered shown-up or reexpressed in tumour cells. Further studies indicate that these factors could also be detected in tumours developed from somatic tissues, with evidence indicating that these factors are tumour stem cell associated. Therefore, we coin these factors as tumour-associated embryonic stem cell marker. Through extensive literature analysis, we realized that there were a number of factors identified in different means in different cells. Since tumour stem cells must feature stemness, no matter how different from normal stem cells, study of stemness-related factors becomes very important for us. The purpose of this project is the systemically study all stemness-related factors, both in vitro materials (cell culture) and in vivo (clinical samples and animal experiments), in order to explore their clinicopathological correlations, and molecular mechanism (s) for tumour stem cell maintaining. This knowledge will help us to precisely identify and isolate tumour stem cells from a given tumour tissue.

### GROUP MEMBERS 2006

Zhenhe Suo (Group leader, MD PhD, Prof, Zhengzhou University, China, Assoc Prof, University of Oslo)

Zhen Yan (MD, PhD Candidate, University of Oslo (Suo is principal tutor)

Wei He (MD, PhD Candidate, University of Oslo and University of Zhengzhou (Suo is principal tutor)

Geng Li (MD, PhD Candidate, University of Zhengzhou (Suo is principal tutor)

Luo Suxia (MD, PhD Candidate, University of Zhengzhou (Suo is principal tutor)

Ping Wang (MD, PhD Candidate, University of Oslo (Suo is associate tutor for Ping)

Qinghua Wu (MD, PhD Candidate, University of Oslo (Suo is associate tutor for Qinghua)

Mariusz Goschinski (MD, PhD Candidate, University of Oslo (Suo is associate tutor for Mariusz)

### COLLABORATIONS 2006

#### National:

In collaboration with Dept. of Biochemistry, DNR, we ran the project related with indirubin (Oncogene, Inpress), with Depts. of Stem Cell Lab (Dr Gunnar Kvalheim), Tumour Biology (Prof Ola Myklebost, Gunnhild Mælandsmo), Immunology (Prof Gustav Gaudernack), we collaborated in the tumour stem cell research (The expressions of embryonic stem cell factors OCT4 and SOX2 in human esophagus cancer and their clinical significance (Wang et al, in preparation); the expressions of embryonic stem cell factors OCT4 and SOX2 in human urine bladder cancer and their clinical significance (Zhu et al., in preparation).

#### International:

We have been collaborating with Prof Chen (New York State University, Chen et al., 2006, Cancer Research) on Seprase project, with Prof Manuel Sobrinho in Porto and Prof Huixiang Li, Yongping Song, Xiaohang Zhao on tumour stem cells research.

## Research Group on Experimental Forensic Medicine

GROUP LEADER: TORLEIV OLE ROGNUM, MD, PhD, PROFESSOR

### GROUP DESCRIPTION

The group is focusing on the following topics: Epidemiological, genetic and immunological, studies of trigger- and death mechanisms in sudden unexpected deaths in infants and toddlers as well in stillbirths and in sudden adult deaths. Studies of mechanics in child abuse and maltreatment with emphasis on shaken baby syndrome, as well as follow up of survivors of child maltreatment. Development of better methods for time of death estimation. Furthermore investigation of cases reported to police for medical maltreatment, and finally immunological and biotechnological investigations of colorectal carcinoma and precancerous lesions.

### RESEARCH SUMMARY 2006

#### **Studies in sudden deaths in infants, toddlers and in stillbirths**

Institute of Forensic medicine have a large (400 cases) and well characterized Research Biobank, which is the basis for a wide range of national and international research projects:

*Long QT syndrome (LQTS) in Sudden infant deaths* (Marianne Arnestad, Peter J Schwartz, Alfred L George, Torleiv Ole Rognum). 201 SIDS cases + controls have been investigated with regard to mutations associated with LQTS. 9.5% of the SIDS cases had such mutations or functionally important polymorphisms. No mutations were found in the controls.

*Interleukins and SIDS* (Linda Ferrante, Siri H Opdal). Using multiplex analysis based on Sequenom platform we have analysed 25 SNPs located in 13 immunological genes to uncover any inconvenient genetic profile that can be associated with SIDS. The results of the genetic analysis are also compared to the individual environmental risk factor profile.

*Collectins and SIDS* (Arne Stray-Pedersen, Uffe Holmskov). Surfactant protein A (SP-A), Surfactant protein D (SP-D) and Mannose-binding lectin (MBL) are the constituents of a part of the innate immune system entitled collectins. In this project we investigate the role of the collectins in SIDS by immunohistochemical and genetic studies.

*Helicobacter pylori in newborn infants and SIDS* (Arne Stray-Pedersen, Peter Gaustad, Babill Stray-Pedersen, Kjetil Melbye, Torleiv Ole Rognum). *Helicobacter pylori* antigen has been detected in stool specimen from >50% of all newborns. A follow-up study is performed to investigate the transmission route.

*Serotonergic network and SIDS* (Siri H Opdal, Hannah Kinney, Ingvar Jon Rognum, Torleiv Ole Rognum). Dysregulation of the serotonergic network may be involved in some cases of SIDS. We investigate the gene encoding the serotonin transporter, 5-HTT (the bottle neck control protein), as well as the genes encoding the proteins tryptophan hydroxylase, monoamin oxidase, and serotonin receptors, with regard to SIDS. Brain sections from the SIDS cases and controls are investigated for cytokine expression.

## Overview of the different research groups

*G proteins and sudden infant death* (Siri H Opdal, Øyvind Melien). Many interleukin receptors are G-protein coupled, and we investigate the G-protein C825T polymorphism in cases of SIDS, infectious death and controls.

*Postmortem radiography compared to autopsy findings in unexpected deaths in infants and children* (Charlotte de Lange, Åshild Vege, Gunnar Stake). Virtual autopsy (Virtopsy) has become common in forensic pathology. This study compares skeletal and pulmonary findings in post-mortem radiology and conventional autopsy. Skeletal findings due to abuse often escape recognition at autopsy.

*Bacterial involvement in Sudden infant death* (Åshild Vege, Peter Gaustad). Half of our SIDS cases have elevated levels of IL-6 in the cerebrospinal fluid and several of them have pathogenic bacteria in pure culture in body fluids and tissues, although many lack symptoms before death. We investigate the correlation between immune response and the characteristics of the bacteria. Could for instance vaccination have prevented some deaths?

*Immune mechanisms and genetic risk factors for stillbirths* (Ingvild VK Lobmaier, Helge Scott, Åshild Vege, Peter Gaustad, Anne Tine Staff, Borghild Roald, Aage Erichsen, Torleiv Ole Rognum). Samples from stillbirths are gathered for the study of pathogenic mechanisms.

*The role of post-mortem time for microbiological investigations in sudden infant deaths* (Åshild Vege, Ingvild VK Lobmaier, Torleiv Ole Rognum, Peter Gaustad). In sudden infant deaths, blood- and CSF cultures as well as virus detection in nasopharynx aspirations are performed both at admittance in the pediatric departments and then for a second time at the autopsy. The significance of delay in sampling after death is investigated.

*Aquaporin 4 and sudden infant death* (Siri H Opdal, Mahmood Amiry-Moghaddam, Torleiv Ole Rognum). Aquaporin 4 is a water channel important for water homeostasis in the brain. This protein is investigated by electron microscopy in tissue sections from the brain. In addition are we investigating the gene encoding AQP4 in SIDS cases and controls.

### **Other projects in forensic medicine**

*Genetic studies in Sudden deaths in adults* (Trond P Leren, Knut Erik Berge, Marianne Arnestad, Torleiv Ole Rognum). We take part in a study on molecular genetic analysis of long syndrome in Norway. Samples from sudden unexplained deaths investigated at our institute are part of the study.

*Time of death estimation – TOD-kit* (Torleiv Ole Rognum, Siri Hauge Opdal, Musse A Musse, Ola Didrik Saugstad, Birkeland Inovasjon). A handhold instrument for measurement of hypoxanthine - with soft wear - for time of death estimation to be used on scene of crimes, has been developed and patented. The patent is currently being commercialized.

*Medical malpractice* (Åshild Vege, Torleiv Ole Rognum). 900 cases that have been investigated at the Institute of forensic medicine between 1997 and 2005 are studied with regard to type of malpractice as well as to the outcome of the police investigation and the investigation by the medical control system.

### **Immunological and genetic markers of large bowel carcinoma**

The research group dispose a large (500 cases) and well characterized Biobank with tissue- and blood samples as well as clinicopathological information about the patients operated on. The following project is currently going on:

*Colorectal cancer in the large bowel* (Tone Løvig, Ragnhild Lothe, Lars Akslen, Solveig Norheim Andersen, Gunn Iren Meling, Torleiv Ole Rognum). Carcinomas and precancerous lesions; adenomas and ulcerative colitis (UC) are investigated for genetic and protein changes known to be involved in initiation and progression of tumour growth. Results are related to clinicopathological data and patient survival. Main findings recent year: Microsatellite instability (MSI) is rare in UC-related neoplasia as well as non-neoplastic lesions, and does not contribute to the development of dysplasia. The angiogenesis marker GMP is analysed in 250 colorectal cancer.

### **GROUP MEMBERS 2006**

Torleiv Ole Rognum (Prof, MD, PhD, Group Leader)  
Åshild Vege (Prof, MD, PhD)  
Siri Hauge Opdal (PhD)  
Tone Løvig (PhD)  
Marianne Arnestad (MD, PhD, till August 2006)  
Arne Stray-Pedersen (MD, PhD student)  
Ingvild K. Lobmaier (MD, PhD Student, coop. with Prof Helge Scott)  
Linda Ferante (PhD student)

### **Technical Staff**

Musse Ahmed Musse (Cand Scient)  
Sara Moberg (Technician)  
Laila Kvendseth (Technician, birth leave)  
Anette Opstad (Technician)



## COLLABORATIONS 2006

### National:

Peter Gaustad, Inst. of Microbiology; Ola Didrik Saugstad, Dept. of Pediatric Research; Charlotte de Lange, Dept. of Radiology; Øyvind Melien, Dept. of Med. Biochem.; Trond P. Leren and Knut Erik Berge, Lab. for Med. Genetics; Ragnhild Lothe, Dept. of Cancer Prevention; Helge Scott and Ole Petter F. Clausen, Dept. of Pathology, Rikshospitalet-Radiumhospitalet.

Mahmood Amiry-Moghaddam, Center for Molecular Biology and Neuroscience, and Per Holck, Dept. of Anatomy, UiO.

Jens Grøgaard, Mother and Child Clinic; Lillian Nordbø Berge and Annetine Staff, Dept. of Obstetrics; Borghild Roald and Aage Erichsen, Dept. of Pathology, Ullevål University Hospital.

Christina Isaksen, Dept. of Pathology and Kirsti Myklestad, Dept. of Obstetrics, St. Olavs Hospital, Trondheim.

Anne Bødtker, Dept. of Obstetrics and Tonje Hajem, Dept. of Pathology, Buskerud Hospital, Drammen.

Annika M.D. Melinder, Inst. of Psychology, UiO.

Randi Reinertsen and Frode Strisland, SINTEF, NTNU.

Jørg Mørland, Norw. Inst. of Public Health, Forensic Toxicology and Drug Abuse.

Solveig Norheim Andersen, Dept. of Pathology and Gunn Iren Meling, Dept. of Surgery, AHUS.

Lars A. Akslen, Dept. of Pathology, Gades Institutt, University of Bergen.

### International:

Peter J. Schwartz, Dept. of Cardiology, Policlinico San Matteo IRCCS, Pavia, Italy.

Alfred L George, Dept. of Pharmacology and Medicine, Vanderbilt Univ, Nashville USA.

Hannah Kinney, Dept. of Pediatric Neuropathology, Childrens Hospital, Harvard Medical School, Mass., USA.

Uffe Holmskov, Inst. of Med Biology, University of Southern Denmark.

## Diagnostic sections

### Diagnostic Section 1: Neuropathology

SECTION HEAD: DAVID SCHEIE, MD

#### GROUP DESCRIPTION

##### **Diagnostic work**

The Neuropathology division conducts tissue diagnosis of diseases in brain, spinal cord and skeletal muscle.

We examine biopsies from the Neurosurgical Department (600 cases as well as 340 frozen sections), muscle biopsies (230 cases) and perform post mortem examination of the CNS (710 cases, including 400 cases from the Department of Forensic Medicine). We also perform electron microscopy of skeletal muscle and are involved in molecular genetic examination of brain tumors (oligodendrogliomas).

We organize meetings for clinicians from several hospital departments on a regular basis.

##### **Fellowship programs**

Currently we have one combined research and clinical fellowship program in neuropathology.

#### RESEARCH SUMMARY 2006

Currently our research activities are focused on pituitary tumors (investigation of different growth factors and immunohistochemical examination of somatostatin receptors) and oligodendroglial tumors (molecular genetic changes). We published 5 papers in 2006.

#### GROUP MEMBERS 2006

Kari Skullerud (Prof, Consultant)

David Scheie (Consultant)

Olivera Casar Borota (Assistant Physician)

## Diagnostic Section 2: Gastrointestinal/kidney/heart/lung/dermatology/perinatal

SECTION HEAD: FRODE L. JAHNSEN, MD, PhD

### GROUP DESCRIPTION

#### Diagnostic work

We perform clinically oriented surgical and biopsy pathology of gastrointestinal (>4,000 cases); liver and pancreas (>1,000 cases); kidney (>1,100 cases) heart and lung (>600 cases), and dermatological (~4,000 cases) material. The diagnostic section has responsibility for all transplantation pathology diagnostics in Norway. In addition to ordinary microscopic analysis we have diagnostic excellence in electron microscopic procedures. We offer consult service for renal diseases and immunofluorescence testing of dermatological disorders. We are also responsible for fetal and perinatal pathology at the hospital. In 2006 we performed more than 200 autopsies. We organize weekly meetings for clinicians from several hospital departments to discuss individual cases.

#### Fellowship programs

Currently we have one combined research and clinical fellowship program in transplantation pathology.

### RESEARCH SUMMARY 2006

Research activities are integrated with laboratories situated at the Institute of Pathology. These include basic and translational research programs within areas of gastrointestinal- and pancreas cancer, dermatopathology, transplantation pathology, mucosal immunology and bone and cartilage pathology (see various research sections above for details). We published more than 25 papers in 2006.

### GROUP MEMBERS 2006

Ole-Petter Clausen (Consultant, Prof)  
Tor Jac Eide (Consultant, Prof)  
Inger Nina Farstad (Consultant)  
Katrinn Fridrich (Consultant)  
Yousef Ghazi (Resident)  
Krzysztof Grzyb (Consultant)  
Clara Hammarstrøm (Resident)  
Erik Heyerdahl Strøm (Consultant)  
Guro Horni (Resident)  
Frode Jahnsen (Consultant, Section Leader)  
Alice Lund (Resident)  
Thu Nguyen (Pathology Assistant)  
Finn Reinholt (Consultant, Prof)  
Helge Scott (Consultant, Prof)



### Diagnostic Section 3: Genitourinary pathology, bone and soft tissue pathology

SECTION HEAD: VERA MARIA ABELER, MD, PhD

Group 3 is entirely localized to Montebello. The surgical specimens (biopsies and operation specimens) come from in-house and outpatient departments from the merged hospital Rikshospitalet-Radiumhospitalet Hf Gaustad and Montebello. We also receive surgical specimens from the county hospital in Aust-Agder and the community hospitals in Asker & Bærum and in Hamar. Frozen section service is given to Rikshospitalet-Radiumhospitalet Hf and Community hospital Asker&Bærum, and by telepathology to the county hospital in Aust-Agder and the community hospital in Hamar.

Referral specimens are provided by the departments of pathology throughout the country when a patient is admitted for treatment in our hospital.

Rikshospitalet-Radiumhospitalet Hf Montebello is a reference centre of gynaecological oncology, treatment of bone and soft tissue tumours and germ cell tumours. Our research focus is on gynaecological tumours (endometrial carcinoma, uterine sarcoma, ovarian carcinoma), post-irradiation induced sarcomas, testicular and ovarian germ cell tumours (in collaboration with the Department of Genetics), breast and prostate cancer. Our group has co-authored 38 peer-reviewed scientific publications in 2006.

#### Type and number of specimens performed 2006

	Analysis	Total number
<i>Number of specimens</i>	<i>90839 (mean 6.8 slides)</i>	<i>13376</i>
Referral cases		2707
Consultation cases		726
Frozen sections		427
Frozen sections – telepath		80
Deeper cutting	618	574
Additional sections		298
Alcian, PAS, etc.	717	551
Immunohistochemistry	9529	2230
Molecular pathology	45	30

#### Biopsy origin distribution

	<i>Inpatient</i>	<i>Outpatient</i>	<i>Total</i>
RR Hf Montebello	2016	4219	6235
RR Hf Gaustad	192	492	784
Aust Agder SH	657	1100	1756
Asker & Bærum SH	631	2561	3192
Hamar	146	294	440
	3642	8666	12407

GROUP MEMBERS 2006

**Consultants:**

Glenny Cecilie Alfsen (MD, PhD)  
Per Johannes Bøhler (MD)  
Bodil Bjerkehagen (MD)  
Ben Davidson (MD, PhD)  
Wenche Reed (MD, PhD)  
Ljiljana Vlatkovic (MD)

**Special Resident position:**

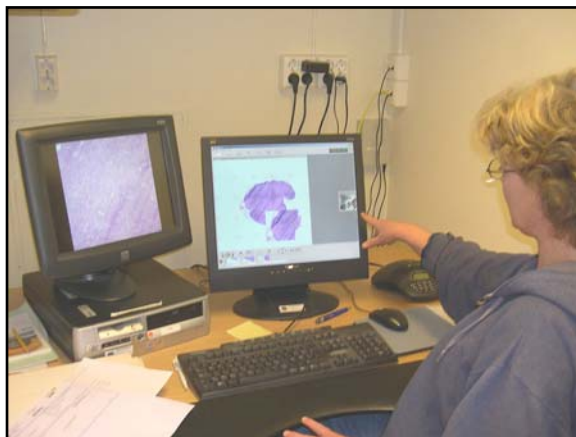
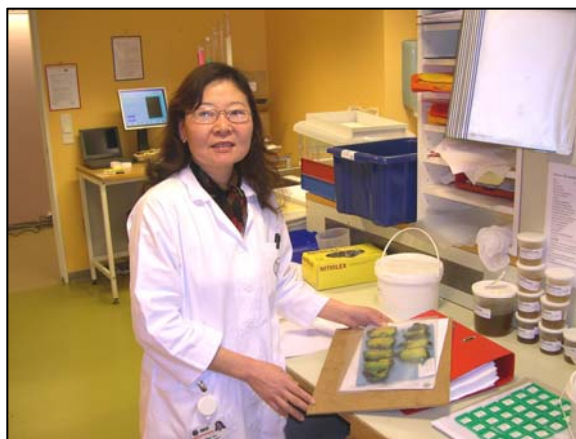
Maja Nenadovic (MD)

**Residents:**

Ellen-Ann Antal (MD, PhD)  
Bård Wiktorin Haavardsholm (MD)  
(Maternity leave: Sarita Joshi, MD; Stine Sivertsen, MD)

**Pathology assistant:**

Inger Cecilie Askildt (Maternity leave: Eva Hofstad)



## Diagnostic Section 4: Hematopathology

SECTION HEAD: JAN DELABIE, MD, PhD

Statistics 2006 (Montebello site)	
Biopsies	2842 (+25 % compared to 2005); consultations: 12 % of these samples
Smears	400 (+30 %)
Flow cytometry samples	1444 (+24 %)
Molecular pathology samples	1147 (+22 %)

### OTHER ACTIVITIES 2006

1. Research: see hematopathology research
2. Lectures (invited)
  - DAKO symposium
  - Norsk Hematologi Selskap
  - 3rd Hematologic Oncology Congress, Athens
3. Central Pathology review for 5 clinical studies
4. Member of the jury for a Ph.D. degree:
  - Xavier Sagaert, University of Leuven, Belgium
5. Supervision for Ph.D degree/master degree:
  - 2 Ph.D. candidates (I. Ikonomou, A. Warsame)
  - 1 master degree candidate (Kristin Udjus)
6. Grant review: Bergen research foundation
7. Review for journals 2006:
  - APMIS
  - Leukemia-lymphoma
  - Leukemia
  - J Pathology

### PLANS FOR 2007

- Expand the molecular testing (NPM mutasjoner)
- To expand the FISH testing
- To continue the gene expression array testing for clinical use (NCI-sponsored project)

### CHALLENGES FOR 2007

- Increased workload (+25%) and reduction of the number of consultant positions (3 positions have been lost during the last three years). Research activities have almost been abandoned as a consequence.
- New hematopathologists must be attracted, since Jan Delabie and Anne Tierens will resign 01-09-2007

### GROUP MEMBERS 2006

Anne Tierens (Senior Consultant): flow cytometry (laboratory leader), molecular pathology, smears

Ida Ikonomou (Senior Consultant): flow cytometry, biopsies

Ulla Randen (pregnancy leave 01.03.06-01.11.06): biopsies  
Joaquin Leal-Bermudez (Senior Consultant, temporary position from 01.11.06)  
Jan Delabie (Senior Consultant, Director of the Hematopathology Section): biopsies,  
molecular pathology (Laboratory Leader),  
Assia Bassarova (Consultant): biopsies, immunohistochemistry (Laboratory Leader)

## Diagnostic Section 5: ENT and Paediatric Pathology

SECTION HEAD: BJØRN HAGMAR, MD, PhD

### GROUP DESCRIPTION

We provide service for the ENT and the Paediatric Clinics in Rikshospitalet-Radiumhospitalet Hf. The service encompasses both biopsies and cytology and, in corresponding cases, autopsies. We have also an extensive service towards the Radiology Department, performing Fine Needle Aspiration Cytology (FNAC:s), where we form part of a team, investigating all sorts of deep-seated, non palpable lesions (mostly tumors), including ultrasound guided endoscopic FNAC:s.

In the ENT Department we have our own policlinic twice a week, investigating head-and-neck lesions with FNAC, with or without the help of ultrasound. Our service includes, where possible, an on-the-spot diagnosis after a Quickstain procedure on cytological material. We take part in oncology meetings 1-2 times a week and organs most commonly involved are lymph nodes, thyroid and salivary glands.

For the Pediatric clinic we primarily take part in the diagnostic work-up of solid tumours. The diagnosis of cancer in children is a very demanding procedure, where we form part of a diagnostic team. Time is always short for instituting the right type of treatment, which most often follows European protocols. Consequently, we belong to an extensive European network for consultation.

In the Department of Radiology, FNAC serves as a micromorphologic complement to CT and ultrasound investigation of chest and abdomen. New methods include trans-oesophageal and trans-bronchial Ultrasound guided cytology (EUS). This service is very time-consuming and demanding, but at the same time it allows a cost-saving shortening of investigation times, often with an instantaneous diagnosis.

In exfoliative cytology, we have since 2 years favoured the method of Liquid Based Cytology and monolayer preparation of gynaecological cytology and we have since long pioneered an effort to include HPV results in our report of low-grade cytological lesions. Molecular analysis of HPV is performed together with our Gene Diagnostic laboratory.

### Production statistics

<i>Cyt. Submitted</i>	<i>Cyt. Policlin.</i>	<i>Cyt. Ul-guided<sup>b</sup></i>	<i>Cyt. CT</i>	<i>Cyt. EUS<sup>a</sup></i>	<i>Cyt. EUS External</i>	<i>Cyt. Exfoliative</i>	<i>Vaginal</i>	<i>Biopsy</i>
666	635	241	46	55	23	868	10340	3439
<b>Total cytologi 2534</b>							<b>10340</b>	<b>3439</b>

<sup>a</sup>Endoscopic ultrasound-guided

<sup>b</sup>Ultrasound-guided

## RESEARCH SUMMARY 2006

Current projects for **Bjørn Hagmar** are related to HPV with development of a new method for detection and typing of HPV, based on nested, multiplex PCR (Skaug et al. manuscript). Poster at the 23<sup>rd</sup> International Human Papillomavirus Conference I, Praha, 2006. Participation in SWEDESCREEN, a Swedish study over primary screening by HPV detection and typing (Elfgren et al., 2005). In addition a regional HPV study in Värmland – Närke (Bjärre et al., submitted 2007) and in Stockholm (Muller et al., submitted 2007). Participation in a national Irish study on P16 expression in head and neck carcinoma (O’Leary et al., 2007, manuscript). In Norway, participation in national project over progression of cervical neoplasia in pregnant women (Nygaard et al. 2007) and advisory activity on screening policy in Norway (Skjeldestad et al., in print Norsk Lægetidsskrift, 2007).

**Klaus Beiske** has initiated a project which aims to identify new genetic prognostic markers in neuroblastoma. A new multiplex PCR method has been established and is currently validated by array CGH (Beiske et al. manuscript). As leader of the European Neuroblastoma Bone Marrow Special Committee, KB organises an ongoing prospective European multi-centre study on MRD, based on immunocytology (IC) and FISH, and investigates samples from Norway, Sweden, UK and Greece. Within the International Neuroblastoma Risk Grouping Committee, he has established consensus standard operating procedures between USA, Japan and Europe for MRD detection by IC and RT-PCR (Beiske et al., submitted). FISH is established as a core facility for solid tumours (Scheie et al., 2006, Scheie et al, submitted) and for haematological specimens (HOVON68 project). KB participates in a clinico-pathological study of B-cell proliferations in patients with cold agglutinin disease (CAD) (Berentsen et al., 2006, Berentsen et al, submitted).

**Peter Jebsen** is elected representative of the Norwegian society of Pathology in the national Lung Cancer Group. He is also actively working with the the miniinvasive diagnostic principles of endoscopic ultrasound (EUS) making fnac’s through the upper GI-tract and lower airways. Three years’ experience with EUS via the gastroscope was presented as a poster at the European cytology congress in October 2006. PJ is also working with a project on applying molecular methods for increased accuracy of brush cytology from D. choledochus with premalignant changes in PSC-patients (together with O.P. Claussen, P.A. Andresen and others).

**Lisa Walaas** has initiated a project on the follow-up of paediatric tumours with the aim of producing text-book in the Monographs in Clinical Cytology series.

**Katrin Fridrich** is working on a project “Clinical/radiological/pathological correlation of radiated carcinoma of the larynx with secondary laryngectomy. Manuscript on Granular tumor of the base of the skull (Meling et al., 2007). Working on course material for salivary gland Workshop, together with BH.

## GROUP MEMBERS 2006

Bjørn Hagmar (Prof, Consultant)  
 Lisa Walaas (Dr Med, Consultant)  
 Klaus Beiske (Dr Med, Scientific Consultant)  
 Peter Jebsen (Consultant)  
 Katrin Fridrich (Consultant)  
 Svetlana Tafjord (Consultant)  
 Marius Lund-Iversen (Resident)  
 Irene Kraus (PhD Student)



## Diagnostic Section 6: Cytology

SECTION HEADS: AASMUND BERNER MD, PhD, MIAC AND BENTE HELEN BORGE, CT (IAC)

### GROUP DESCRIPTION

The fused Department of Cytology is located to Rikshospitalet-Radiumhospitalet Hf, Montebello and Gaustad. The medical staff consists of 6 cytopathologists and 1 resident, and 16 medical technologists. The unit performs fine-needle aspiration cytology (FNAC) on in-house and referred patients and has a separate FNAC clinic at both locations (Montebello and Gaustad). Specimens submitted from local GPs and different community hospitals are also analysed. One cytopathologist participate in intervention FNAC at Asker & Bærum Community Hospital and Hedmark Central Hospital, the department is also responsible for cytology unit at "Laboratorium for Patologi AS" analysing more than 80000 papsmears per year.

The department's main task is to perform intervention FNAC to achieve early diagnosis of solid and non solid tumors and to monitor treatment response. Flow cytometry and DNA ploidy measurements on clinical and experimental specimens are ancillary techniques performed in separate laboratories in the department.



**Type of and number of specimens performed in 2006  
(M = Montebello, G = Gaustad):**

<i>Cervical smears:</i>	Conventional Pap smear G	6453
	ThinPrep G	3866
Lavage M		1124
exfoliative unspecified M		1700
exfoliative unspecified G		782
Bone marrow M		301
DNA-ploidy M		710
Clinical flow cytometry M		454
Experimental flow cytometry M		260
Experimental effusions M		195
Blood and bone marrow G		64

**FNAC Montebello:**

FNAC by cytopathologist	3162
FNAC referred	2303

*Place of examination:*

Breast center	729
Ultrasound laboratory	1058
Cytology out patient clinic	463
CT-lab	123
Asker & Bærum community hosp.	264
Hedmark Central hospital	320

**FNAC Gaustad:**

FNAC by cytopathologist	989
FNAC referred	561

*Place of examination*

ENT (ØNH) inhouse patients	216
EUS/EBUS inhouse patients	50
CT	45

**GROUP MEMBERS 2006**

## Service sections

### Laboratory for Electron Microscopy (EM)

SECTION HEAD: FINN P. REINHOLT, SENIOR CONSULTANT, PROFESSOR, MD

#### DIAGNOSTIC WORK

The laboratory for electron microscopy has 3.6 positions (head of the laboratory (0.2), two part-time consultants (0.4), 1 PhD (0.2) and 2.8 bioengineers). The laboratory is by far the largest diagnostic EM laboratory in the country performing analysis of in the order of 700 patient samples of a year. Among these are about 600 complete ultrastructural analyses. The samples are from in- and outpatients at Rikshospitalet-Radiumhospitalet Hf as well as from other hospitals in the health region. The laboratory shares equipment and premises with the University of Oslo/Rikshospitalet-Radiumhospitalet Core facility for EM and is located at the M-floor of the A-building at Gaustad. The premises include 7 laboratories/heavy equipment rooms and the equipment includes 2 electron microscopes with digital cameras, an automatic embedding devise, two ultratomes and 3 microtomes/tissue block trimmers along with other necessary smaller equipment units.

The laboratory is run according to GLP guidelines and international recommendations within the different diagnostic areas. Furthermore, work has started to obtain accreditation according to ISO 15189.

In addition to the diagnostic work, the laboratory is running quality assessment projects and methodological development. At present a larger inter-Nordic project is run in cooperation with laboratories in Stockholm, Gothenburg, Lund and Odense. The aim of the project is to work out a common procedure for measurements of glomerular basement membrane thickness and to define limits for normal values in the Nordic population.

#### Activity in 2006 and 2005 (for comparison)

Tissue	Total number of specimens		Complete ultrastructural analysis	
	2006	2005	2006	2005
Kidney	376	342	325	294
Skeletal muscle	188	191	141	151
Heart muscle	60	69	58	67
Cilia	47	51	31	35
Liver	24	24	23	20
Miscellaneous	21	27	20	24
All types of specimens	716	704	598	591



*Laboratory Leader Aileen Murdoch Larsen at work with one of our electron microscopes.*

## Diagnostic Immunohistochemical Laboratory

SECTION HEADS: ASSIA BASSAROVA MD, SAEED BEHDAD

### DIAGNOSTIC WORK

The diagnostic immunohistochemical stainings are performed in both places – Montebello and Gaustad.

The diagnostic panel consists of approximately 160 primary antibodies. Both places have some a little bit different panels, regarding the diagnostic diversity. In Montebello the lymphoma panel as well as breast panel are better presented while in Gaustad the primary antibody panel is oriented for the needs of gastro-intestinal pathology and neuropathology and diagnostics of muscle disorders.

1. In Montebello the Laboratory is equipped with 4 DAKO autostainers. As a detection system polymer based detection system – EnVision™ is used. For a small percentage of diagnostic antibodies – mostly antibodies against transcription factors – next generation polymer based detection system – Advanced™ is used.
  - a. The Laboratory is performing also diagnostic immunocytochemistry. The panel consists of approximately 30 antibodies. The stainings are performed manually.
  - b. RNA in situ hybridization with three probes – EBV, kappa and lambda light chains is performed in the Lab. The procedure is performed manually.
  - c. Since the last year the lab is involved in the routine FISH diagnostics. The FISH diagnostics is oriented to lymphoma diagnostics (two split probes – C-MYC and CyclinD1 translocation probes) and sarcoma diagnostics (EWS split probe).
2. In Gaustad the Laboratory is equipped with 2 NexES® IHC, 1 BenchMark® XT and 1 Discovery® XT Instrument. The detection system is streptavidin based – LSAB I View. The lab is in a process of shifting to a new polymer based detection system – UltraView detection system.
  - a. The Laboratory is performing also diagnostic immunocytochemistry. The panel consists of approximately 30 antibodies. The stainings are performed manually.
  - b. RNA in situ hybridization with three probes – EBV, HPV low risk and HPV high risk is performed in the Lab. The procedure is automated in Discovery® XT Instrument.

### RESEARCH ACTIVITIES

1. Montebello – three research projects:
  - a. D2-40 expression in effusions
  - b. MAF-B expression in bone marrow biopsies
  - c. Small cell lymphomas in the bone marrow trephine biopsies
2. Gaustad – one research project:
  - a. HPV infection in uterine cervix

### The diagnostic work (absolute numbers)

	<i>Number of cases</i>	<i>Number of stainings</i>
<b>Montebello</b>	29679	31409
	193 - FISH cases (C-Myc, EWS)	with 193 slides
	179 - EBV in situ cases	with 185 slides
	Immunocytochemistry	619 slides
<b>Gaustad</b>	5629	13500 from them:
		662 immunofluorescence stainings on kidney biopsies
		440 frozen section immunostainings on muscle biopsies
	EBV in situ cases	with 250 slides
	Immunocytochemistry	1447 slides
<b>Total</b>	<b>35308</b>	<b>45287</b>

### MEETINGS AND PRESENTATIONS

1. DAKO user meeting – two presentations:
  - a. QUALITY CONTROL IN A ROUTINE SETTING (Assia Bassarova)
  - b. ”ADVANCED” IN EVERYDAY PRACTICE (Grete Mykkelbost)

### EXTERNAL QUALITY CONTROL

The Lab is participating in two external quality control schemes:

1. NordicQC – with 4 test runs per year
2. UK Nequas – in three different test schemes
  - a. Montebello – General pathology, Cytopathology and HER-2 panel
  - b. Gaustad – General pathology, Cytopathology and Neuropathology

### GROUP MEMBERS 2006

Eva Gustavsen  
 Grete Mykkelbost Larssen  
 Torill Melby  
 Don Thrin  
 Anne Regina Galde  
 Nighat Shahzade (substitute position till August 2007)  
 Marit Karlsen  
 Anne-Gyrid Helland (50% position in Diagnostic Immunohistochemical Laboratory)  
 Marzieh Beigi (50% position in Diagnostic Immunohistochemical Laboratory till April 2007)  
 Jaklin Jelehanova (substitute position till August 2007)

## Laboratory for Molecular Pathology

SECTION HEAD: JAN DELABIE, MD

### DIAGNOSTICS 2006

#### Current tests

##### *Molecular analyses:*

##### Hematology

- Diagnosis of lymphoma/leukemia
- Mutations analysis for chronic lymphatic leukemia (centralized activity)
- Minimal residual disease detection for childhood leukemia (centralized activity)
- Minimal residual disease detection for chronic myelogenous leukemia (centralized activity)

##### Soft tissue tumor diagnostics

##### Cancer genetics (with emphasis on GI tract tumors)

##### Microbiology

- HPV typing
- Whipple's disease
- Polyoma virus testing

##### *Flow cytometry:*

- Diagnosis of lymphoma/leukemia/myelodysplasia
- Minimal residual disease detection for childhood leukemia (AML, ALL) (centralized function)

#### Statistics 01.01-31.12.06

Laboratory	Samples 2005	Samples 2006	Increase %
Molecular pathology (Montebello)	954	1157	21,2
Flow cytometry (Montebello)	1502	1898	26,3
Molecular Pathology (Gaustad)	1978	2228	12,6
<b>Total</b>	<b>4434</b>	<b>5283</b>	<b>19,1</b>

### RESEARCH AND DEVELOPMENT 2006

1. NCI-sponsored international collaboration for the testing of expression arrays for use in lymphoma diagnostics. Start of the project 2005, End of the project: 2008-2009.
2. Increased use and testing of flow cytometry for the follow-up of acute myeloid leukemia and myelodysplasia.
3. HPV analysis

## QUALITY ASSURANCE

The accreditation process is on-going.

## INVESTMENT PLAN FOR 2007

- All previous plans for the extension of the laboratory at the Montebello site have been stopped. We await further reorganisation in 2009, when more space will be made available. Some minor costs have to be expected due to a necessary minimal extension of the site for the storage of equipment and consumables.
- *Equipment*
  1. Investment plan for 2006 has been successfully accomplished (new flowcytometer, new real-time PCR utstyr, and software for flow).
  2. We need a pipetting robot for the Gaustad site (the application has been made).
- *Personal*

At the moment of writing (May 2007), a new position for an extra bioengineer has been created for the reception of samples. This person will be responsible for the Flow Cytometry Laboratory and the Molecular Pathology Laboratory. As we see a steep increase in the number of samples not only in 2006 but also in the first quarter of 2007, we need to closely follow-up the FTE requirements. It is expected that more FTE will be needed during the course of the year.

## GROUP MEMBERS 2006

Jan Delabie (Section Head, Clinical Manager, Montebello)

Per Arne Andresen (Clinical Manager, Gaustad)

Anne Tierens (Clinical Manager, Flow Cytometry, Montebello)

Ola Bjørang (Administrative Manager)

Sarah Ariansen (quality assurance manager with collaborators Trude Rognstad and Sigurd Borgen)

## Laboratory for Biopsy and Autopsy

SECTION HEAD: WENCHE REED, MD, PhD, JUNE THORVIG

### DIAGNOSTIC WORK

Laboratory for biopsy and autopsy provides the basic work for the pathology clinic. It produces stained histological sections for microscopical analysis and it assists in performing autopsies. The laboratory includes three units; one for preparing histological sections at both Montebello and Gaustad and one for autopsies at Gaustad.

The laboratory has during the end of 2006 purchased two instruments for rapid processing of tissue; the Sakura Tissue X-press and Milestone Pathos. Intensive testing and implementation of these instruments is planned for 2007.

### ACTIVITY 2006

Number of biotechnicians	30
Number of specimens	32 800
Number of blocks	136 000
Number of autopsies	249

## Administration and secretary services

SECTION HEAD: JAN-ROBERT LUND

This unit includes health- and general secretary services, personnel administration, economy and finances. The Head of administrative services serves the Hospital's central management office, external partners and IT-functions within the laboratory, and is a member of the Pathology Department management team.

The unit's tasks and functions are continuously changing as a consequence of the progress in technical concepts (IT-systems for dictation, speech recognition etc., electronic purchasing systems, electronic personal administration, finance systems etc.). These changes are meant to result in a "paper-less" hospital and imply that the character of the work for secretaries is altered over time.

At present the section comprises 14 persons.

## Publications – Results of our research 2006

### Acknowledgements

We are grateful to Rikshospitalet-Radiumhospitalet Medical Center, the University of Oslo, Southern Regional Health Authority (Helse Sør), the Research Council of Norway, the Norwegian Cancer Society, and other volunteer organizations. Without their continuous financial support, our research activity would not be possible.

### Doctoral Theses

**Braathen R.** *Structural Motifs for the Formation of Secretory IgA and Binding of Non-Ig Ligands by the Polymeric Ig Receptor*. Ph.D (ISBN 82-8072-675-6, No. 382), Faculty of Medicine, University of Oslo, 2006.

**Ji Z.** *Molecular mechanisms of photodynamic therapy efficiency in early cancer and precancerous lesions of the esophagus*, Zhengzhou University, China, 2006.

**Myromslien FD.** *Endocytosis and Downregulation of the Epidermal Growth Factor Receptor in Control of Growth Factor Signaling*. Ph.D. (ISBN 82-8072-686-1, No. 431), Faculty of Medicine, University of Oslo, 2006.

**Olaussen RW.** *Cytokines in Coeliac Disease: An Epithelial Perspective. Focusing on interferon-gamma, interleukin-15, and chemokine receptor 9*. Dr Med./Ph.D. (ISBN 82-8072-676-4, No. 409), Faculty of Medicine, University of Oslo, 2006.

**Skovseth DK.** *Adoptive Transfer of Human Endothelial Cells – An In Vivo Model of Angiogenesis and Vascular Phenotype Regulation*. Ph.D. (ISBN 82-8072-839-2, No. 372), Faculty of Medicine, University of Oslo, 2006.

**Zhang M.** *Seprase and DPPIV in ovarian carcinomas*, Zhengzhou University, China, 2006.

**Øynebråten I.** *Regulated Secretion and Surface Presentation of Endothelial Cell-Derived Chemokines*. Ph.D. (ISBN 82-8072-740-6, No. 386), Faculty of Medicine, University of Oslo, 2006.

### Theses for Master of Science

**Melhus G, Solberg LB.** Experimental studies on bone metabolism. Forskerlinje-eksamen, Universitetet i Oslo, 2006.

### Books, Book Chapters, Reviews and Commentaries

1. **Brandtzaeg P.** The innate and adaptive immune system of the intestinal epithelium. pp. 55-88. In: *Old Herborn University Seminar Monograph 19* (Defence Mechanisms of the Innate System: Influence of Microbes). (Eds.: Heidt PJ, Bienenstock J, Midtvedt T, Rusch V, van der Waaij D), Herborn Litterae, Herborn-Dill, 2006 (ISBN 3-923022-30-1).
2. **Brandtzaeg P.** Is coeliac disease an inflammatory condition? pp. 58-80. In: *Coeliac Disease, Proc. of the Eleventh International Symposium on Coeliac Disease, 2004* (Eds.: McMillan S, Feighery C, Watson P, O'Farrelly C), Belfast, 2006.
3. **Brandtzaeg P.** The changing immunological paradigm in coeliac disease. *Immunol Lett* 105: 127-39, 2006.
4. **Brandtzaeg P, Lefrancois L.** Lymphocyte homing: summary. *Mucosal Immunol Update* 14 (No. 1): 9-10, 2006.

5. **Davidson B, Risberg B, Berner A, Bedrossian CW, Reich R.** The biological differences between ovarian serous carcinoma and diffuse peritoneal malignant mesothelioma. *Semin Diagn Pathol* 23: 35-43, 2006.
6. **Haraldsen G, Rot A.** Coy decoy with a new ploy: interceptor controls the levels of homeostatic chemokines. *Eur J Immunol* 36: 1659-61, 2006.
7. **Heier I, Wathne K-O.** Atypiske mykobakterier – lymfadenitt. s. 109, Kapittel 3: Infeksjoner/vaksiner og undersøkelse av adoptivbarn. I: *Veileder i generell pediatri*, Norsk Barnelegeforening, 2006 (ISBN 9788280700404).
8. **Johansen F-E, Yen E, Dickinson B, Yoshida M, Claypool S, Blumberg RS, Lencer WI.** Biology of Gut Immunoglobulins, Ch. 43. In: *Physiology of the gastrointestinal tract* (Vol. 1-2), Fourth Edition (Ed.: Johnson L), Elsevier, 2006 (ISBN-13: 978-0-12-088394-3, ISBN-10: 0-12-088394-5).
9. **Michalek S, Russell M, Kaetzel C, Johansen F-E.** pIgR/IgA Sessions I and II: Summary. *Mucosal Immunol Update* 14 (No. 2): 8-9, 2006.
10. **Rognum TO.** Banalt og eksistensielt! Bokanmeldelse: Knokkelkvinnen (ISBN 82-92622-14-4). *Tidsskr Nor Lægeforen* 126: 2701, 2006.
11. **Rognum TO.** Bottom up! *Scand J Forens Sci* 12: 4, 2006.
12. **Skovseth DK, Küchler AM, Haraldsen G.** The HUVEC/Matrigel Assay: An in vivo assay of human angiogenesis suitable for drug validation. *Methods Mol Biol* 360: 253-68, 2006.

## Publications (Papers in Peer Reviewed Journals)

1. **Aamot HV, Tjønnfjord GE, Delabie J, Heim S.** Molecular cytogenetic analysis of leukemic mantle cell lymphoma with a cryptic t(11;14). *Cancer Genet Cytogenet* 165: 172-5, 2006.
2. **Aerts JG, Delahaye M, van der Kwast TH, Davidson B, Hoogsteden HC, van Meerbeeck JP.** 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: 523-7, 2006.
3. **Aghmesheh M, Suo Z, Friedlander M, Nesland JM, Kaern J, Stewart M, Kconfab, Dørum A, Tucker KM, Buckley MF.** Chromosome 2q24.2 is lost in sporadic but not in BRCA1-associated ovarian carcinomas. *Pathology* 38: 145-51, 2006.
4. **Aksnes LH, Hall KS, Folleraas G, Stenwig AE, Bjerkhagen B, Taksdal I, Winderen M, Bruland OS, Sæter G.** Management of high-grade bone sarcomas over two decades: the Norwegian Radium Hospital experience. *Acta Oncol* 45: 38-46, 2006.
5. **Amarzguioui M, Peng Q, Wiiger MT, Vasovic V, Babaie E, Holen T, Nesland JM, 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: 4055-61, 2006.
6. **Andersson S, Wangsa D, Flores-Staino C, Safari H, Mints M, Hjerpe A, Hagmar B, Johansson B.** Expression of p16(INK4a) in relation to histopathology and viral load of 'high-risk' HPV types in cervical neoplastic lesions. *Eur J Cancer* 42: 2815-20, 2006.
7. **Angell-Petersen E, Sørensen R, Warloe T, Soler AM, Moan J, Peng Q, Giercksky KE.** Porphyrin formation in actinic keratosis and basal cell carcinoma after topical application of methyl 5-aminolevulinate. *J Invest Dermatol* 126: 265-71, 2006.
8. **Angell-Petersen E, Spetalen S, Madsen SJ, Sun CH, Peng Q, Carper SW, Sioud M, Hirschberg H.** Influence of light fluence rate on the effects of photodynamic therapy in an orthotopic rat glioma model. *J Neurosurg* 104: 109-17, 2006.

9. **Armstrong RA, Kerty E, Skullerud K, Cairns NJ.** Neuropathological changes in ten cases of neuronal intermediate filament inclusion disease (NIFID): a study using alpha-interneixin immunohistochemistry and principal components analysis (PCA). *J Neural Transm* 113: 1207-15, 2006.
10. **Arøen A, Heir S, Løken S, Engebretsen L, Reinholdt FP.** Healing of articular cartilage defects. An experimental study of vascular and minimal vascular microenvironment. *J Orthop Res* 24: 1069-77, 2006.
11. **Banff Working Group; Demetris AJ, Adeyi O, Bellamy CO, Clouston A, Charlotte F, Czaja A, Daskal I, El-Monayeri MS, Fontes P, Fung J, Gridelli B, Guido M, Haga H, Hart J, Honsova E, Hubscher S, Itoh T, Jhala N, Jungmann P, Khettry U, Lassman C, Ligato S, Lunz JG 3rd, Marcos A, Minervini MI, Molne J, Nalesnik M, Nasser I, Neil D, Ochoa E, Pappo O, Randhawa P, Reinholdt FP, Ruiz P, Sebahg M, Spada M, Sonzogni A, Tsamandas AC, Wernerson A, Wu T, Yilmaz F.** Liver biopsy interpretation for causes of late liver allograft dysfunction. *Hepatology* 44: 489-501, 2006.
12. **Bassarova AV, Nesland JM, Davidson B.** D2-40 is not a specific marker for cells of mesothelial origin in serous effusions. *Am J Surg Pathol* 30: 878-82, 2006.
13. **Berentsen S, Ulvestad E, Langholm R, Beiske K, Hjorth-Hansen H, Ghanima W, Sørbo JH, Tjønnfjord GE.** Primary chronic cold agglutinin disease: a population based clinical study of 86 patients. *Haematologica* 91: 460-6, 2006.
14. **Berner A, Sigstad E, Pradhan M, Grøholt KK, Davidson B.** Fine-needle aspiration cytology of the thyroid gland: comparative analysis of experience at three hospitals. *Diagn Cytopathol* 34: 97-100, 2006.
15. **Boberg KM, Jebsen P, Clausen OP, Foss A, Aabakken L, Schrumph E.** Diagnostic benefit of biliary brush cytology in cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol* 45: 568-74, 2006.
16. **Bondi J, Bukholm G, Nesland JM, Bakka A, Bukholm IR.** An increase in the number of adhesion proteins with altered expression is associated with an increased risk of cancer death for colon carcinoma patients. *Int J Colorectal Dis* 21: 231-7, 2006.
17. **Borgen E, Pantel K, Schlimok G, Muller P, Otte M, Renolen A, Ehnle S, Coith C, Nesland JM, Naume B.** A European interlaboratory testing of three well-known procedures for immunocytochemical detection of epithelial cells in bone marrow. Results from analysis of normal bone marrow. *Cytometry B Clin Cytom* 70: 400-9, 2006.
18. **Borota OC, Scheie D, Bjerkhagen B, Jacobsen EA, Skullerud K.** Gliosarcoma with liposarcomatous component, bone infiltration and extracranial growth. *Clin Neuropathol* 25: 200-3, 2006.
19. **Braathén R, Sandvik A, Berntzen G, Hammerschmidt S, Fleckenstein B, Sandlie I, Brandtzaeg P, Johansen F-E, Lauvrak V.** Identification of a polymeric Ig receptor binding phage-displayed peptide that exploits epithelial transcytosis without dimeric IgA competition. *J Biol Chem* 281: 7075-81, 2006.
20. **Brandal P, Bjerkhagen B, Heim S.** Rearrangement of chromosomal region 8q11-13 in lipomatous tumours: correlation with lipoblastoma morphology. *J Pathol* 208: 388-94, 2006.
21. **Brandal P, Lie AK, Bassarova A, Svindland A, Risberg B, Danielsen H, Heim S.** Genomic aberrations in mucinous tubular and spindle cell renal cell carcinomas. *Mod Pathol* 19: 186-94, 2006.
22. **Brandtzaeg P, Carlsen HS, Halstensen TS.** The B-cell system in inflammatory bowel disease. In: *Immune Mechanisms in Inflammatory Bowel Disease* (Eds.: Blumberg RS, Neurath MF), Eurekah.com, Georgetown; Springer Science+Business Media, New York, 2006; *Adv Exp Med Biol* 579: 149-67.
23. **Brennhovd B, Johnsrud K, Berner A, Bogsrud T, Waehre H, Giercksky KE, Axerona K.** Sentinel node procedure in low-stage/low-grade penile carcinomas. *Scand J Urol Nephrol* 40: 204-7, 2006.
24. **Brorson O, Brorson SH.** An in vitro study of the activity of telithromycin against mobile and cystic forms of *Borrelia afzelii*. *Infection* 34: 26-8, 2006.

25. **Bukholm IR, Nesland JM, Bukholm G.** Expression of adhesion proteins E-cadherin, alpha-catenin, beta-catenin and gamma-catenin is different in T1 and T2 breast tumours. *Pathology* 38: 403-7, 2006.
26. **Carlsen HS, Yamanaka T, Scott H, Rugtveit J, Brandtzaeg P.** The proportion of CD40<sup>+</sup> mucosal macrophages is increased in inflammatory bowel disease whereas CD40 ligand (CD154)<sup>+</sup> T cells are relatively decreased, suggesting differential modulation of these costimulatory molecules in human gut lamina propria. *Inflamm Bowel Dis* 12: 1013-24, 2006.
27. **Casar Borota O, Jacobsen EA, Scheie D.** Bilateral atypical choroid plexus papillomas in cerebellopontine angles mimicking neurofibromatosis 2. *Acta Neuropathol (Berl)* 111: 500-2, 2006.
28. **Chen D, Kennedy A, Wang JY, Zeng W, Zhao Q, Pearl M, Zhang M, Suo Z, Nesland JM, Qiao Y, Ng AK, Hirashima N, Yamane T, Mori Y, Mitsumata M, Ghersi G, Chen WT.** Activation of EDTA-resistant gelatinases in malignant human tumors. *Cancer Res* 66: 9977-85, 2006.
29. **Chen J, Mak NK, Leung W, Cheung N, Peng Q.** Comparison of merocyanine 540-mediated photodynamic action on leukemia cells between pulsed and continuous wave light sources. *J Environ Pathol Toxicol Oncol* 25: 217-22, 2006.
30. **Clausen OP, Aass HC, Beigi M, Purdie KJ, Proby CM, Brown VL, Mattingsdal M, Micci F, Kølvråa S, Bolund L, DeAngelis PM.** Are keratoacanthomas variants of squamous cell carcinomas? A comparison of chromosomal aberrations by comparative genomic hybridization. *J Invest Dermatol* 126: 2308-15, 2006.
31. **Dave SS, Fu K, Wright GW, Lam LT, Kluin P, Boerma EJ, Greiner TC, Weisenburger DD, Rosenwald A, Ott G, Muller-Hermelink HK, Gascoyne RD, Delabie J, Rimsza LM, Braziel RM, Grogan TM, Campo E, Jaffe ES, Dave BJ, Sanger W, Bast M, Vose JM, Armitage JO, Connors JM, Smeland EB, Kvaløy S, Holte H, Fisher RI, Miller TP, Montserrat E, Wilson WH, Bahl M, Zhao H, Yang L, Powell J, Simon R, Chan WC, Staudt LM; Lymphoma/Leukemia Molecular Profiling Project.** Molecular diagnosis of Burkitt's lymphoma. *N Engl J Med* 354: 2431-42, 2006.
32. **Dauids BJ, Palm JE, Housley MP, Smith JR, Andersen YS, Martin MG, Hendrickson BA, Johansen F-E, Svard SG, Gillin FD, Eckmann L.** Polymeric immunoglobulin receptor in intestinal immune defense against the lumen-dwelling protozoan parasite Giardia. *J Immunol* 177: 6281-90, 2006.
33. **Davidson B, Espina V, Steinberg SM, Flørenes VA, Liotta LA, Kristensen GB, Tropé CG, Berner A, Kohn EC.** Proteomic analysis of malignant ovarian cancer effusions as a tool for biologic and prognostic profiling. *Clin Cancer Res* 12: 791-9, 2006.
34. **Davidson B, Konstantinovskiy S, Kleinberg L, Nguyen MT, Bassarova A, Kvalheim G, Nesland JM, Reich R.** The mitogen-activated protein kinases (MAPK) p38 and JNK are markers of tumor progression in breast carcinoma. *Gynecol Oncol* 102: 453-61, 2006.
35. **Davidson B, Tropé CG, Wang TL, Shih IeM.** Expression of the chromatin remodeling factor Rsf-1 is upregulated in ovarian carcinoma effusions and predicts poor survival. *Gynecol Oncol* 103: 814-9, 2006.
36. **Davidson B, Zhang Z, Kleinberg L, Li M, Flørenes VA, Wang TL, Shih IeM.** Gene expression signatures differentiate ovarian/peritoneal serous carcinoma from diffuse malignant peritoneal mesothelioma. *Clin Cancer Res* 12: 5944-50, 2006.
37. **De Angelis PM, Svendsrud DH, Kravik KL, Stokke T.** Cellular response to 5-fluorouracil (5-FU) in 5-FU-resistant colon cancer cell lines during treatment and recovery. *Mol Cancer* 5: 20, 2006.
38. **Dong HP, Elstrand MB, Holth A, Silins I, Berner A, Tropé CG, Davidson B, Risberg B.** NK- and B-cell infiltration correlates with worse outcome in metastatic ovarian carcinoma. *Am J Clin Pathol* 125: 451-8, 2006.
39. **Drageset V, Nesland JM, Erikstein B, Skovlund E, Sommer H, Anker G, Wist E, Lundgren S, Bergh J, Kvalheim G.** Monitoring of disseminated tumor cells in bone marrow in high-risk breast cancer patients treated with high-dose chemotherapy. *Int J Cancer* 118: 2877-81, 2006.

40. **Elloul S, Silins I, Tropé CG, Benshushan A, Davidson B, Reich R.** Expression of E-cadherin transcriptional regulators in ovarian carcinoma. *Virchows Arch* 449: 520-8, 2006.
41. **Farkas L, Kvale EØ, Lund-Johansen F, Jahnsen FL.** Plasmacytoid dendritic cells induce a distinct cytokine pattern in virus-specific CD4<sup>+</sup> memory T cells that is modulated by CpG oligodeoxynucleotides. *Scand J Immunol* 64: 404-11, 2006.
42. **Fehm T, Braun S, Muller V, Janni W, Gebauer G, Marth C, Schindlbeck C, Wallwiener D, Borgen E, Naume B, Pantel K, Solomayer E.** A concept for the standardized detection of disseminated tumor cells in bone marrow from patients with primary breast cancer and its clinical implementation. *Cancer* 107: 885-92, 2006.
43. **Frich L, Bjørnland K, Pettersen S, Clausen OP, Gladhaug IP.** Increased activity of matrix metalloproteinase 2 and 9 after hepatic radiofrequency ablation. *J Surg Res* 135: 297-304, 2006.
44. **Frich L, Hol PK, Roy S, Mala T, Edwin B, Clausen OP, Gladhaug IP.** Experimental hepatic radiofrequency ablation using wet electrodes: electrode-to-vessel distance is a significant predictor for delayed portal vein thrombosis. *Eur Radiol* 16: 1990-9, 2006.
45. **Furre IE, Møller MT, Shahzidi S, Nesland JM, Peng Q.** Involvement of both caspase-dependent and -independent pathways in apoptotic induction by hexaminolevulinic acid-mediated photodynamic therapy in human lymphoma cells. *Apoptosis* 11: 2031-42, 2006.
46. **Godal A, Nilsen NO, Klaveness J, Branden JE, Nesland JM, Peng Q.** New derivatives of 5-aminolevulinic acid for photodynamic therapy: chemical synthesis and porphyrin production in in vitro and in vivo biological systems. *J Environ Pathol Toxicol Oncol* 25: 109-26, 2006.
47. **Gorovetz M, ækelandt M, Berner A, Tropé CG, Davidson B, Reich R.** The clinical role of phospholipase A2 isoforms in advanced-stage ovarian carcinoma. *Gynecol Oncol* 103: 831-40, 2006.
48. **Granum S, Sundvold-Gjerstad V, Dai KZ, Kolltveit KM, Hildebrand K, Huitfeldt HS, Lea T, Spurkland A.** Structure function analysis of SH2D2A isoforms expressed in T cells reveals a crucial role for the proline rich region encoded by SH2D2A exon 7. *BMC Immunol* 7: 15, 2006.
49. **Gravning JA, Vege Å, Kjekshus J.** Unexpected sudden death after percutaneous coronary intervention. *Tidsskr Nor Lægeforen* 24: 2111-3, 2006.
50. **Greiner TC, Dasgupta C, Ho VV, Weisenburger DD, Smith LM, Lynch JC, Vose JM, Fu K, Armitage JO, Braziel RM, Campo E, Delabie J, Gascoyne RD, Jaffe ES, Muller-Hermelink HK, Ott G, Rosenwald A, Staudt LM, Im MY, Karaman MW, Pike BL, Chan WC, Hacia JG.** Mutation and genomic deletion status of ataxia telangiectasia mutated (ATM) and p53 confer specific gene expression profiles in mantle cell lymphoma. *Proc Natl Acad Sci USA* 103: 2352-7, 2006.
51. **Guarner F, Bourdet-Sicard R, Brandtzaeg P, Gill HS, McGuirk P, van Eden W, Versalovic J, Weinstock JV, Rook GAW.** Mechanisms of disease: the hygiene hypothesis revisited. *Nat Clin Pract Gastroenterol Hepatol* 3: 275-84, 2006.
52. **Gustavsen WR, Reinholt FP, Schlosser A.** Skin biopsy findings and results of neuropsychological testing in the first confirmed cases of CADASIL in Norway. *Eur J Neurol* 13: 359-62, 2006.
53. **Han LP, Dong ZM, Qiao YH, Nesland JM, Suo ZH.** Expressions of estrogen receptor subtypes in epithelial ovarian carcinomas. *Sichuan Da Xue Xue Bao Yi Xue Ban* 37: 606-10, 2006.
54. **Helland S, Johnsen H, Frøyland C, Landmark HB, Saetersdal AB, Holmen MM, Gjertsen T, Nesland JM, Ottestad W, Jeffrey SS, Ottestad LO, Rodningen OK, Sherlock G, Børresen-Dale AL.** Radiation-induced effects on gene expression: an in vivo study on breast cancer. *Radiother Oncol* 80: 230-5, 2006.

55. **Hirschberg H, Sørensen DR, Angell-Petersen E, Peng Q, Tromberg B, Sun CH, Spetalen S, Madsen S.** Repetitive photodynamic therapy of malignant brain tumors. *J Environ Pathol Toxicol Oncol* 25: 261-79, 2006.
56. **Holm AM, Tjønnfjord G, Yndestad A, Beiske K, Muller F, Aukrust P, Frøland SS.** Polyclonal expansion of large granular lymphocytes in common variable immunodeficiency – association with neutropenia. *Clin Exp Immunol* 144: 418-24, 2006.
57. **Hornell TM, Burster T, Jahnsen FL, Pashine A, Ochoa MT, Harding JJ, Macaubas C, Lee AW, Modlin RL, Mellins ED.** Human dendritic cell expression of HLA-DO is subset specific and regulated by maturation. *J Immunol* 176: 3536-47, 2006.
58. **Hvatum M, Kanerud L, Hällgren R, Brandtzaeg P.** The gut-joint axis: cross-reactive food antibodies in rheumatoid arthritis. *Gut* 55: 1240-7, 2006.
59. **Ikonomou IM, Tierens A, Troen G, Aamot HV, Heim S, Lauritzsen GF, Valerhaugen H, Delabie J.** Peripheral T-cell lymphoma with involvement of the expanded mantle zone. *Virchows Arch* 449: 78-87, 2006.
60. **Iqbal J, Neppalli VT, Wright G, Dave BJ, Horsman DE, Rosenwald A, Lynch J, Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Campo E, Ott G, Muller-Hermelink HK, Delabie J, Jaffe ES, Grogan TM, Connors JM, Vose JM, Armitage JO, Staudt LM, Chan WC.** BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. *J Clin Oncol* 24: 961-8, 2006.
61. **Jahnsen FL, Strickland DH, Thomas JA, Tobagus IT, Napoli S, Zosky GR, Turner DJ, Sly PD, Stumbles PA, Holt PG.** Accelerated antigen sampling and transport by airway mucosal dendritic cells following inhalation of a bacterial stimulus. *J Immunol* 177: 5861-7, 2006.
62. **Ji Z, Yang G, Shahzidi S, Tkacz-Stachowska K, Suo Z, Nesland JM, Peng Q.** Induction of hypoxia-inducible factor-1alpha overexpression by cobalt chloride enhances cellular resistance to photodynamic therapy. *Cancer Lett* 244: 182-9, 2006.
63. **Ji Z, Yang G, Suo Z, Nesland JM, Peng Q.** Effects of differentiatin of human esophageal carcinoma on producton of endogenous porphyrings. *World Chin J Digesto* 14: 6-11, 2006.
64. **Ji Z, Yang G, Vasovic V, Cunderlikova B, Suo Z, Nesland JM, Peng Q.** Subcellular localization pattern of protoporphyrin IX is an important determinant for its photodynamic efficiency of human carcinoma and normal cell lines. *J Photochem Photobiol B* 84: 213-20, 2006.
65. **Johannessen LE, Pedersen NM, Pedersen KW, Madshus IH, Stang E.** Activation of the epidermal growth factor (EGF) receptor induces formation of EGF receptor- and Grb2-containing clathrin-coated pits. *Mol Cell Biol* 26: 389-401, 2006.
66. **Jørgensen K, Davidson B, Flørenes VA.** Activation of c-jun N-terminal kinase is associated with cell proliferation and shorter relapse-free period in superficial spreading malignant melanoma. *Mod Pathol* 19: 1446-55, 2006.
67. **Kazacic M, Roepstorff K, Johannessen LE, Pedersen NM, van Deurs B, Stang E, Madshus IH.** EGF-induced activation of the EGF receptor does not trigger mobilization of caveolae. *Traffic* 7: 1518-27, 2006.
68. **Khnykin D, Troen G, Berner JM, Delabie J.** The expression of fibroblast growth factors and their receptors in Hodgkin's lymphoma. *J Pathol* 208: 431-8, 2006.
69. **Kleinberg L, Flørenes VA, Skrede M, Dong HP, Nielsen S, McMaster MT, Nesland JM, Shih IeM, Davidson B.** Expression of HLA-G in malignant mesothelioma and clinically aggressive breast carcinoma. *Virchows Arch* 449: 31-39, 2006.

70. **Knopp S, Holm R, Bjørge T, Tropé C, Nesland JM.** Cell cycle regulation in primary vulvar carcinomas and related lymph node metastases. *Histopathology* 49: 311-2, 2006.
71. **Knopp S, Nesland JM, Tropé C, Holm R.** p14ARF, a prognostic predictor in HPV-negative vulvar carcinoma. *Am J Clin Pathol* 126: 266-76, 2006.
72. **Kocjan G, Feichter G, Hagmar B, Kapila K, Kardum-Skelin I, Kloboves V, Kobayashi TK, Koutselini H, Majak B, Schenck U, Schmitt F, Tani E, Totch M, Onal B, Vass L, Vielh P, Weynand B, Herbert A.** Fine needle aspiration cytology: a survey of current European practice. *Cytopathology* 17: 219-26, 2006.
73. **Kraus I, Molden T, Holm R, Lie AK, Karlsen F, Kristensen GB, Skomedal H.** Presence of E6 and E7 mRNA from human papillomavirus types 16, 18, 31, 33, and 45 in the majority of cervical carcinomas. *J Clin Microbiol* 44: 1310-7, 2006.
74. **Kvale EO\*, Dalgaard J\*, Lund-Johansen F, Rollag H, Farkas L, Midtvedt K, Jahnsen FL, Brinchmann J, Olweus J.** CD11c<sup>+</sup> dendritic cells and plasmacytoid DCs are activated by human cytomegalovirus and retain efficient T cell-stimulatory capability upon infection. *Blood* 107: 2022-9, 2006.
75. **Lazarova P, Wu Q, Kvalheim G, Suo Z, Haakenstad KW, Metodiev K, Nesland JM.** Growth factor receptors in hematopoietic stem cells: EPH family expression in CD34<sup>+</sup> and CD133<sup>+</sup> cell populations from mobilized peripheral blood. *Int J Immunopathol Pharmacol* 19: 49-56, 2006.
76. **Lind GE, Kleivi K, Meling GI, Teixeira MR, Thiis-Evensen E, Rognum TO, Lothe RA.** ADAMTSL1, CRABP1, and NR3C1 identified as epigenetically deregulated genes in colorectal tumorigenesis. *Cellular Oncology* 28: 259-72, 2006.
77. **Lind GE, Skotheim RI, Fraga MF, Abeler VM, Esteller M, Lothe RA.** Novel epigenetically deregulated genes in testicular cancer include homeobox genes and SCGB3A1 (HIN-1). *J Pathol* 210: 441-9, 2006.
78. **Lloret I, Server A, Bjerkehagen B.** Primary spinal chondrosarcoma: radiologic findings with pathologic correlation. *Acta Radiol* 47: 77-84, 2006.
79. **Lyng H, Brovig RS, Svendsrud DH, Holm R, Kaalhus O, Knutstad K, Oksefjell H, Sundfor K, Kristensen GB, Stokke T.** Gene expressions and copy numbers associated with metastatic phenotypes of uterine cervical cancer. *BMC Genomics* 7: 268, 2006.
80. **Lyng K, Munkeby BH, Scheie D, Mallard C, Hagberg H, Stray-Pedersen B, Saugstad OD, Frøen JF.** Fetal brain injury in experimental intrauterine asphyxia and inflammation in Gottingen minipigs. *J Perinat Med* 34: 226-34, 2006.
81. **Madshus IH.** Ubiquitin binding in endocytosis – how tight should it be and where does it happen? *Traffic* 7: 258-61, 2006 (Erratum in: *Traffic* 7: 927, 2006).
82. **Mastroiani MA, Skjønberg H, Shi Y, Skinningsrud A, Blom GP, Barstad JE, Strøm EH.** En eldre mann med proteinuri og hyperkalsemi. *Tidsskr Nor Lægeforen* 126: 2665-7, 2006.
83. **Meza-Zepeda LA, Kresse SH, Barragan-Polania AH, Bjerkehagen B, Ohnstad HO, Namlos HM, Wang J, Kristiansen BE, Myklebost O.** Array comparative genomic hybridization reveals distinct DNA copy number differences between gastrointestinal stromal tumors and leiomyosarcomas. *Cancer Res* 66: 8984-93, 2006.
84. **Micci F, Panagopoulos I, Bjerkehagen B, Heim S.** Consistent rearrangement of chromosomal band 6p21 with generation of fusion genes JAZF1/PHF1 and EPC1/PHF1 in endometrial stromal sarcoma. *Cancer Res* 66: 107-12, 2006.
85. **Micci F, Panagopoulos I, Bjerkehagen B, Heim S.** Deregulation of HMGA2 in an aggressive angioyxoma with t(11;12)(q23;q15). *Virchows Arch* 448: 838-42, 2006.

86. **Molden T, Kraus I, Karlsen F, Skomedal H, Hagmar B.** Human papillomavirus E6/E7 mRNA expression in women younger than 30 years of age. *Gynecol Oncol* 100: 95-100, 2006.
87. **Myromslien FD, Grøvdal LM, Raiborg C, Stenmark H, Madshus IH, Stang E.** Both clathrin-positive and -negative coats are involved in endosomal sorting of the EGF receptor. *Exp Cell Res* 312: 3036-48, 2006.
88. **Nakayama K, Nakayama N, Davidson B, Katabuci H, Kurman RJ, Velculescu VE, Shih IeM, Wang TL.** Homozygous deletion of *MKK4* in ovarian serous carcinomas. *Cancer Biol Ther* 5: 630-4, 2006.
89. **Nakayama K, Nakayama N, Davidson B, Sheu J, Jinawath N, Santillan A, Salani R, Bristow RE, Morin PJ, Kurman RJ, Wang TL, Shih IeM.** A BTB/POZ protein, NAC-1, is related to tumor recurrence and is essential for tumor growth and survival. *Proc Natl Acad Sci USA* 103: 18739-44, 2006.
90. **Navarro S, Amann G, Beiske K, Cullinane CJ, d'Amore ES, Gambini C, Mosseri V, De Bernardi B, Michon J, Peuchmaur M; European Study Group 94.01 Trial and Protocol.** Prognostic value of International Neuroblastoma Pathology Classification in localized resectable peripheral neuroblastic tumors: a histopathologic study of localized neuroblastoma European Study Group 94.01 Trial and Protocol. *J Clin Oncol* 24: 695-9, 2006.
91. **Ødegaard E, Staff AC, Kaern J, Flørenes VA, Kopolovic J, Tropé CG, Abeler VM, Reich R, Davidson B.** The AP-2gamma transcription factor is upregulated in advanced-stage ovarian carcinoma. *Gynecol Oncol* 100: 462-8, 2006.
92. **Oldenburg J, Alfsen GC, Waehre H, Fosså SD.** Late recurrences of germ cell malignancies: a population-based experience over three decades. *Br J Cancer* 94: 820-7, 2006.
93. **Olsen GH, Andresen PA, Hilmarsen HT, Bjørang O, Scott H, Midtvedt K, Rinaldo CH.** Genetic variability in BK Virus regulatory regions in urine and kidney biopsies from renal-transplant patients. *J Med Virol* 78: 384-93, 2006.
94. **Opdal SH, Melien Ø, Rootwelt H, Vege Å, Arnestad M, Rognum TO.** The G protein  $\beta 3$  subunit 825C allele is associated with sudden infant death due to infection. *Acta Paediatr.* 95: 1129-32, 2006.
95. **Ørstavik KH, Kristiansen M, Knudsen GP, Storhaug K, Vege A, Eiklid K, Abrahamsen TG, Smahi A, Steen-Johnsen J.** Novel splicing mutation in the NEMO (IKK-gamma) gene with severe immunodeficiency and heterogeneity of X-chromosome inactivation. *Am J Med Genet A* 140: 31-39, 2006.
96. **Otterdal K, Smith C, Oie E, Pedersen TM, Yndestad A, Stang E, Endresen K, Solum NO, Aukrust P, Damas JK.** Platelet-derived LIGHT induces inflammatory responses in endothelial cells and monocytes. *Blood* 108: 928-35, 2006.
97. **Øyen O, Strøm EH, Midtvedt K, Bentsdal Ø, Hartmann A, Bergan S, Pfeffer P, Brekke IB.** Calcineurin inhibitor-free immunosuppression in renal allograft recipients with thrombotic microangiopathy/hemolytic uremic syndrome. *Am J Transplant* 6: 412-8, 2006.
98. **Park JT, Li M, Nakayama K, Mao TL, Davidson B, Zhang Z, Kurman RJ, Eberhart CG, Shih IeM, Wang TL.** Notch3 gene amplification in ovarian cancer. *Cancer Res* 66: 6312-8, 2006.
99. **Pascual V, Farkas L, Banchereau J.** Systemic lupus erythematosus: all roads lead to type I interferons. *Curr Opin Immunol* 18: 676-82, 2006.
100. **Peng Q.** Editorial: photodynamic therapy and detection. *J Environ Pathol Toxicol Oncol* 25: 1-5, 2006.
101. **Pradhan M, Abeler VM, Danielsen HE, Tropé CG, Risberg BA.** Image cytometry DNA ploidy correlates with histological subtypes in endometrial carcinomas. *Mod Pathol* 19: 1227-35, 2006.

102. **Ráki M, Tollefsen S, Molberg Ø, Lundin KEA, Sollid LM, Jahnsen FL.** A unique dendritic cell subset accumulates in the celiac lesion and efficiently activates gluten-reactive T cells. *Gastroenterology* 131: 428-38, 2006.
103. **Reis-Filho JS, Milanezi F, Steele D, Savage K, Simpson PT, Nesland JM, Pereira EM, Lakhani SR, Schmitt FC.** Metaplastic breast carcinomas are basal-like tumors. *Histopathology* 49: 10-21, 2006.
104. **Reseland JE, Reppe S, Larsen AM, Berner HS, Reinholt FP, Gautvik KM, Slaby I, Lyngstadaas SP.** The effect of enamel matrix derivative on gene expression in osteoblasts. *Eur J Oral Sci* 114 (Suppl 1): 205-11, 2006.
105. **Rimsza LM, Roberts RA, Campo E, Grogan TM, Bea S, Salaverria I, Zettl A, Rosenwald A, Ott G, Muller-Hermelink HK, Delabie J, Fisher RI, Unger JM, Leblanc M, Staudt LM, Jaffe ES, Gascoyne RD, Chan WC, Weisenburger DD, Greiner T, Braziel RM, Miller TP.** Loss of major histocompatibility class II expression in non-immune-privileged site diffuse large B-cell lymphoma is highly coordinated and not due to chromosomal deletions. *Blood* 107: 1101-7, 2006.
106. **Rocha AS, Risberg B, Magalhaes J, Trovisco V, de Castro IV, Lazarovici P, Soares P, Davidson B, Sobrinho-Simoes M.** The p75 neurotrophin receptor is widely expressed in conventional papillary thyroid carcinoma. *Hum Pathol* 37: 562-8, 2006.
107. **Rognum TO.** Norway to get a national board of forensic medicine? *Scand J Forens Sci* 12: 47, 2006.
108. **Saethre M, Lea T, Borgen MS, Fiane AE, Michaelsen TE, Thorsby E, Haraldsen G, Mollnes TE.** Human complement-activating immunoglobulin (Ig)G3 antibodies are essential for porcine endothelial cell activation. *Xenotransplantation* 13: 215-23, 2006.
109. **Scheie D, Andresen PA, Cvancarova M, Bø AS, Helseth E, Skullerud K, Beiske K.** Fluorescence in situ hybridization (FISH) on touch preparations: a reliable method for detecting loss of heterozygosity at 1p and 19q in oligodendroglial tumors. *Am J Surg Pathol* 30: 828-37, 2006.
110. **Sert B, Abeler VM, Dørum A, Tropé CG.** A new approach to treatment of early-stage cervical carcinoma: entire laparoscopic abdominal radical hysterectomy with bilateral pelvic lymphadenectomy without vaginal cuff closure – case reports. *Eur J Gynaecol Oncol* 27: 513-8, 2006.
111. **Sert BM, Abeler VM.** Robotic-assisted laparoscopic radical hysterectomy (Piver type III) with pelvic node dissection – case report. *Eur J Gynaecol Oncol* 27: 531-3, 2006.
112. **Shahzidi S, Stokke T, Soltani H, Nesland JM, Peng Q.** Induction of apoptosis by hexaminolevulinate-mediated photodynamic therapy in human colon carcinoma cell line 320DM. *J Environ Pathol Toxicol Oncol* 25: 159-71, 2006.
113. **Sivertsen S, Berner A, Michael CW, Bedrossian C, Davidson B.** Cadherin expression in ovarian carcinoma and malignant mesothelioma cell effusions. *Acta Cytol* 50: 603-7, 2006.
114. **Sivertsen S, Hadar R, Elloul S, Vintman L, Bedrossian C, Reich R, Davidson B.** Expression of Snail, Slug and Sip1 in malignant mesothelioma effusions is associated with matrix metalloproteinase, but not with cadherin expression. *Lung Cancer* 54: 309-17, 2006.
115. **Solberg LB, Melhus G, Brorson SH, Wendel M, Reinholt FP.** Heat-induced retrieval of immunogold labeling for nucleobindin and osteoadherin from Lowicryl sections of bone. *Micron* 37: 347-54, 2006.
116. **Southard TE, Franciscus RG, Fridrich KL, Nieves MA, Keller JC, Holton NE, Krizan KE, Reimer SB, Marshall SD.** Restricting facial bone growth with skeletal fixation: a preliminary study. *Am J Orthod Dentofacial Orthop* 130: 218-23, 2006.
117. **Steffensen IL, Schut HA, Nesland JM, Tanaka K, Alexander J.** Role of nucleotide excision repair deficiency in intestinal tumorigenesis in multiple intestinal neoplasia (Min) mice. *Mutat Res* 611: 71-82, 2006.

118. **Steigen SE, Eide TJ.** Trends in incidence and survival of mesenchymal neoplasm of the digestive tract within a defined population of northern Norway. *APMIS* 114: 192-200, 2006.
119. **Stray-Pedersen A, Rognum TO.** Shaken baby syndrome: commentary on current debate. *Scand J Forensic Sci* 12: 79-83, 2006.
120. **Swerts K, De Moerloose B, Dhooge C, Vandesompele J, Hoyoux C, Beiske K, Benoit Y, Laureys G, Philippe J.** Potential application of ELAVL4 real-time quantitative reverse transcription-PCR for detection of disseminated neuroblastoma cells. *Clin Chem* 52: 438-45, 2006.
121. **Torlakovic E, Slipicevic A, Robinson C, DeCoteau JF, Alfsen GC, Vyberg M, Chibbar R, Flørenes VA.** Pax-5 expression in nonhematopoietic tissues. *Am J Clin Pathol* 126: 798-804, 2006.
122. **Wang YY, Dahle MK, Agren J, Myhre AE, Reinholt FP, Foster SJ, Collins JL, Thiemermann C, Aasen AO, Wang JE.** Activation of the liver X receptor protects against hepatic injury in endotoxemia by suppressing Kupffer cell activation. *Shock* 25: 141-6, 2006.
123. **Waterhouse KE, Haugan T, Kommisrud E, Tverdal A, Flatberg G, Farstad W, Evenson DP, De Angelis PM.** Sperm DNA damage is related to field fertility of semen from young Norwegian Red bulls. *Reprod Fertil Dev* 18: 781-8, 2006.
124. **Wiedswang G, Borgen E, Schirmer C, Kåresen R, Kvalheim G, Nesland JM, Naume B.** Comparison of the clinical significance of occult tumor cells in blood and bone marrow in breast cancer. *Int J Cancer* 118: 2013-9, 2006.
125. **Wijburg OL, Uren TK, Simpfendorfer K, Johansen F-E, Brandtzaeg P, Strugnell RA.** Innate secretory antibodies protect against natural *Salmonella typhimurium* infection. *J Exp Med* 203: 21-6, 2006.
126. **Wu Q, Suo Z, Kristensen GB, Baekelandt M, Nesland JM.** The prognostic impact of EphB2/B4 expression on patients with advanced ovarian carcinoma. *Gynecol Oncol* 102: 15-21, 2006.
127. **Xie X, Clausen OP, Boysen M.** Correlation of numerical aberrations of chromosomes X and 11 and poor prognosis in squamous cell carcinomas of the head and neck. *Arch Otolaryngol Head Neck Surg* 132: 511-5, 2006.

## Varia

1. **Blumberg RS, Brandtzaeg P.** Inflammatory mechanisms in coeliac disease: Introduction and summary. pp. 48-49. In: *Coeliac Disease*, Proc. of the Eleventh International Symposium on Coeliac Disease, 2004 (Eds.: McMillan S, Feighery C, Watson P, O'Farrelly C), Belfast, 2006.
2. **Brandtzaeg P.** Oljefondet og verdiskaping. *Aftenposten* (Økonomidebatt), 30. januar, s. 7, 2006.
3. **Brandtzaeg P.** Forskning som utviklingshjelp. *VG Replikk*, 31. januar, s. 31, 2006.
4. **Brandtzaeg P.** Hvorfor jukser forskere? *VG Debatt*, 1. februar, s. 31, 2006.
5. **Brandtzaeg P.** Trenger vi kontroll av forskere? *Kronikk, Dagbladet*, 13. februar, s. 56, 2006.
6. **Brandtzaeg P.** Ingen forskning uten tillit. *Debatt, Aftenposten* (Kultur), 13. februar, s. 5, 2006.
7. **Brandtzaeg P.** Forstår Waage forskning? *Debatt, Aftenposten* (Kultur), 2. mars, s. 5, 2006.
8. **Brandtzaeg P.** Villedende (Forskning og medforfatterskap). *Debatt, Morgenbladet* (3.-9. mars), 3. mars, s. 17, 2006.
9. **Brandtzaeg P.** Avsluttende om medforfatterskap. *Debatt, Morgenbladet* (17.-23. mars), 17. mars, s. 23, 2006.

10. **Brandtzæg P.** Ingen tvil i Torgersen-saken. Debatt, *Aftenposten* (Kultur), 9. april, s. 5, 2006.
11. **Brandtzæg P.** Olje blir kunnskap i Qatar. Kronikk, *Aftenposten* (Kultur), 3. juli, s. 4, 2006.
12. **Brandtzæg P.** Stoltenbergs uklare løfter. *Aftenposten* (Økonomidebatt), 24. august, s. 11, 2006.
13. **Brandtzæg P.** Ikke drep entusiasmen. Debatt, *Aftenposten* (Kultur), 8. oktober, s. 5, 2006.
14. **Brandtzæg P.** Torgersen er dømt på feil premisser (svar til Torbjørn Guldseth). *Nor Tannlegeforen Tid* (Norw Dent J) 116: 739-40, 2006.
15. **Brandtzæg P.** Feil om fusk i forskningen. Debatt, *Aftenposten* (Kultur), 22. oktober, s. 5, 2006.
16. **Brandtzæg P.** Avsluttende tilsvar til Torbjørn Guldseth. *Nor Tannlegeforen Tid* (Norw Dent J) 116: 867, 2006.
17. **Brandtzæg P.** En foreldet og farlig jus. Kronikk, *Aftenposten*, 15. desember, s. 4, 2006.
18. **Brandtzæg P.**, **Norum KR.** Hvileskjær gir ingen vinner. Kronikk, *Aftenposten* (Kultur), 21. november, s. 4, 2006.
19. **Brandtzæg P.**, **Norum KR.** Skuffende forskningspolitikk. Debatt, *Aftenposten* (Kultur), 1. desember, s. 5, 2006.
20. **Heier I.** Barn vaskes syke. Replikk, *Aftenposten* (Kommentar), 27. april, s. 3, 2006.
21. **Heier I.** Lindstad og verdensreligion. *Klassekampen*, 4. oktober, 2006.
22. **Heier I.** Vetlesens analogi: Islamfrykt og antisemittisme. *Morgenbladet*, 15. september, 2006.
23. **Heier I.** Vel plassert om ære. Replikk, *Aftenposten* (Kommentar), 10. oktober, s. 3, 2006.
24. **Heier I.** Lindstads statsbærende religioner. *Klassekampen*, 12. oktober, 2006.
25. **Heier I.** Rana forsvarer det bestående. Debatt, *Aftenposten* (Kommentar), 13. oktober, s. 5, 2006.
26. **Heier I.** Familiens ære. Debatt, *Aftenposten*, 26. oktober, s. 5, 2006.
27. **Heier I.** Pakistanske studenter uten opprør. Debatt, *Aftenposten*, 12. november, s. 5, 2006.
28. **Heier I.** Hvervens naivitet. *Klassekampen*, 18. november, 2006.
29. **Heier I.** Å forme morgendagens kultur. Debatt, *Aftenposten*, 22. november, s. 5, 2006.
30. **Oksvold MP.** Miljøkrise med politisk velsignelse. Kronikk, *Dagbladet*, 17. oktober, s. 53, 2006.
31. **Oksvold MP.**, **Aass HCD.** Kunnskapsnasjon eller militærstat? Kronikk, *Dagbladet*, 5. januar, s. 52, 2006.
32. **Rognum TO.** Kamp mot spilleautomater. *OP Magasin* (Organ for Oslo Politidistrikt) 44: 20-21, 2006.
33. **Rognum TO.** SIDS, hjerneødem og AQP4. *Oss foreldre imellom* 4: 29, 2006.
34. **Rognum TO.** Samsoving og nikotinpåvirkning. *Oss foreldre imellom* 4: 29, 2006.
35. **Rognum TO.** SIDS – diagnostiske kriterier. *Oss foreldre imellom* 4: 29, 2006.
36. **Stray-Pedersen A.** Er det farlig å sove sammen med spedbarn? *Tidsskrift for jordmødre* 5: 11-13, 2006.