INSTITUTE FOR CANCER RESEARCH ANNUAL REPORT 2016

Oslo University Hospital

HELSE SØR-ØST

UiO : University of Oslo

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Microscopy images of cells by
Vigdis Sørensen, Advanced Light
Microscopy Core Facility

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INTRODUCTION BY THE DIRECTOR

This is the third annual report from Institute for Cancer Research (ICR), and we can thank the institute's previous Director, Gunnar Sæter, for taking the initiative to publish such reports. In November 2016, Gunnar took over a new position as Research Director of the Cancer Division of Oslo University Hospital, but during his 3 1/2 years as institute director he managed to improve the institute's organisation in several ways. Under Gunnar's leadership the numbers of research groups and research departments were reduced, the focus on cancer research was strengthened, a new department for core facilities was established, a co-localisation of the core facilities for Genomics and Bioinformatics with the Section for Molecular Pathology at Oslo University Hospital was implemented, and an international scientific advisory board was appointed. On behalf of everyone at ICR I would like to thank Gunnar for his excellent achievements, and for leaving the institute in great shape.

Indeed, 2016 was a good year for ICR, with the number of publications reaching an all-time high, and research from the institute made the news headlines on several occasions as detailed elsewhere in this report. Most international attention was attracted by a *Science* paper published by PhD student Erlend Strønen and his co-workers in Johanna Olweus' group at Department of Cancer Immunology in which the authors employed a novel approach to "outsource" broad T-cell immune responses against tumours. This paper, which opens new avenues for T-cell-based cancer immunotherapy, was not only dedicated an editorial in ***Science*** but also a commentary in *New England Journal of Medicine*, the latter authored by ICR group leader Vessela Kristensen.

Currently, 2/3 of ICR's funding comes from external grants, and it is a goal for the institute to increase the amount of external funding further. In this respect, it is a positive sign that many of ICR's research groups were successful in obtaining substantial external funding from Norwegian and international sources in 2016. Kristian Berg (coordinator) and Theo Theodossiou at the Department of Radiation Biology obtained funding for a project under the extremely competitive Future Emerging Technology (FET) programme of the Horizon 2020 EU Framework for Research and Innovation. This project, called Lumiblast, aims at developing novel photon-based therapy of aggressive brain tumours. The success of Berg and Theodossiou provides an excellent example that ICR scientists can compete at the highest level in obtaining European grants, and hopefully this will inspire other ICR scientists to submit further proposals.

With several prominent ICR group leaders retiring during the last couple of years, it is reassuring that ICR has made several new group leader recruitments in 2016 that will contribute to fulfil the institute's ambitions of taking a leading role in European cancer research. Jorrit Enserink, new group leader at Department of Molecular Cell Biology, will strengthen molecular biology research at the institute and has exciting plans for identifying novel therapeutic targets in leukeumias. Another new group leader at the same department, Tor Erik Rusten, focuses on tumour-host interactions, and his group recently published a ***Nature*** paper on the importance of microenvironmental autophagy for tumour growth. Randi Syljuåsen at Department of Radiation Biology and Therese Sørlie at Department of Cancer Genetics have already led their own successful groups at ICR for several years, and in 2016 they were both offered permanent internally-funded contracts. A permanent Institute Director will be employed during 2017, as will a new Head of Department of Cancer Genetics and a new leader of the Sarcoma Biology group at Department of Tumour Biology.

The new Institute Director will certainly get an interesting and challenging job. In particular, it will be important to recruit and support the new generation of cancer researchers, secure increased external funding, increase national and international visibility of ICR's research, and improve collaborative efforts both within the different departments of ICR and between ICR and external research environments. The Cancer Division of Oslo University Hospital is making efforts to receive accreditation as a Comprehensive Cancer Centre (CCC), and ICR is a cornerstone in the Cancer Division's CCC concept. There is no doubt that the institute's excellent basic and translational cancer research has a great potential for clinical applications that still remains to be fully exploited.

Harald Stenmark
Acting Director

"CANCER RESEARCH OF INTERNATIONAL EXCELLENCE"

ORGANISATION

Head of Institute
Harald A. Stenmark

Administration Manager
Kari Aalrust Berger

- Administration
- Service Lab

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

Cancer Genetics
Gry Aarum Geitvik

- *Gry Aarum Geitvik* — Lab Technology
- *Åslaug Helland* — Translational Studies of Solid Tumors
- *Vessela N. Kristensen* — Cancer Genome Variation
- *Hege E. G. Russnes* — Molecular Biology of Breast Cancer
- *Therese Sørlie* — Breast Tumor Initiation

Cancer Immunology
Johanna Olweus

- *Johanna Olweus* — Experimental Immunotherapy
- *Karl Johan Malmberg* — NK Cell Biology and Cell Therapy
- *Mouldy Sioud* — Immunomodulation and Targeted Therapies
- *Erlend B. Smeland* — Lymphoma Biology

Molecular Cell Biology
Kirsten Sandvig

- *Kirsten Sandvig* — Intracellular Transport
- *Jorrit Enserink* — Cancer Molecular Medicine
- *Tor Erik Rusten* — Tumor-host Biology
- *Harald Stenmark* — Cellular Membrane Dynamics
- *Antoni Wiedlocha* — Protein Internalization and Signaling

Molecular Oncology
Ragnhild A. Lothe

- *Ragnhild A. Lothe* — Genetics
- *Guro Elisabeth Lind* — Epigenetics
- *Rolf I. Skotheim* — Genome Biology

Radiation Biology
Kristian Berg

- *Kristian Berg* — Photochemical Internalization
- *Heidi Lyng* — Clinical Radiation Biology
- *Einar Rofstad* — Radiation Biology and Tumor Physiology
- *Randi Syljuåsen* — Radiation Biology and DNA Damage Signaling

Tumor Biology
Gunhild M. Mælandsmo

- *Gunhild M. Mælandsmo* — Metastasis Biology and Experimental Therapeutics
- *Kjersti Flatmark* — Translational Cancer Therapy
- *Eivind Hovig* — Computational Cancer Genomics
- *Heidi M. Namløs* — Mesenchymal Cancer Biology

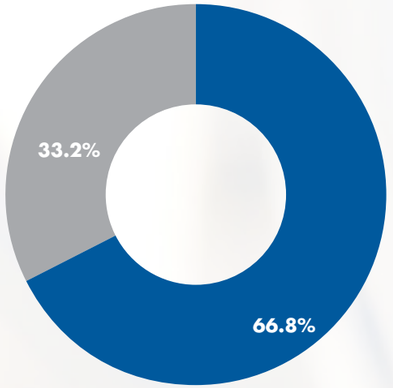
Core Facilities
Leonardo A.Meza-Zepeda

- *Leonardo A. Meza-Zepeda* — Genomics and Bioinformatics
- *Ellen Skarpen* — Advanced Microscopy
- *Trond Stokke* — Flow-Cytometry and Pre-Clinical Imaging

KEY FIGURES 2016

FUNDING

Percent

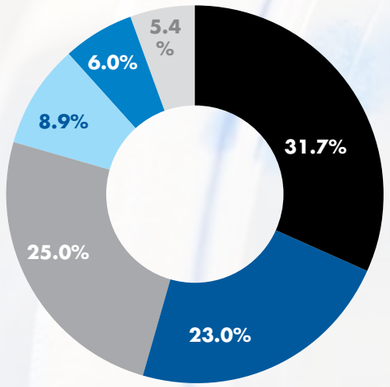


Actual Institute expenditure for 2016 by internal and external funding sources (total 297,8 MNOK = approx. 32,7 M€).

- Internal funding
- External funding

EXTERNAL FUNDING BY SOURCE

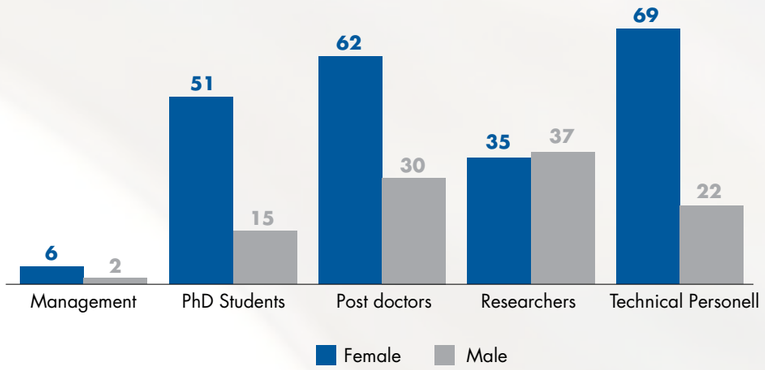
Percent



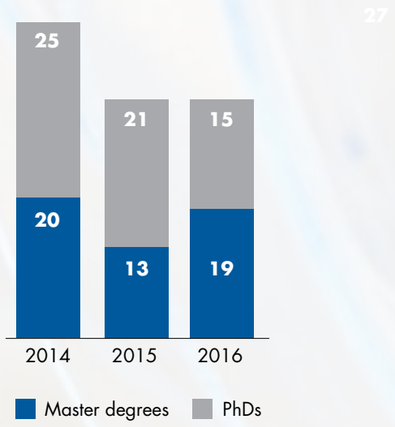
Sources of external competitive funding for 2016, based on actual expenditure (total 198,8 MNOK = approx. 21,8 M€)

- South-Eastern Norway Regional Health Authority
- The Research Council of Norway
- The Norwegian Cancer Society
- University of Oslo
- Other private sources
- International sources

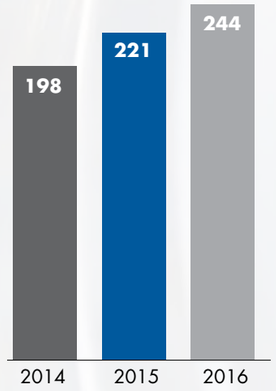
EMPLOYEES



COMPLETED PHDS AND MASTER DEGREES



ARTICLES PUBLISHED



IMPACT FACTOR

Mean	6.0	5.6	6.3
Median	4.1	4.4	5

ICR'S SCIENTIFIC ADVISORY BOARD

Professor Carl-Henrik Heldin, Ludwig Institute of Cancer Research, Uppsala (Chair)

Professor Eric Solary, Director of Research, Institut Gustave Roussy, Paris

Professor Per Eystein Lønning, Haukeland University Hospital, Bergen

Professor Josep Tabernero, Director,Vall d´Hebron Institute of Oncology, Barcelona

Professor Mef Nilbert, Head, Regional Cancer Centre South, Lund

Professor Odd Stokke Gabrielsen, University of Oslo

DEPARTMENTS AND RESEARCH GROUPS

DEPARTMENT OF

CANCER GENETICS

"Molecular classification to understand tumor progression, to improve prognosis and tailor treatment"

ACTING HEAD **GRY AARUM GEITVIK.** SCIENTIFIC ADVISOR: **THERESE SØRLIE**

Our vision is to perform integrated molecular and epidemiological studies to reduce risk, achieve early diagnosis, improve prognosis, and tailor treatment for individual patients with breast, lung, pancreatic and ovarian cancer. We are an interdisciplinary team of 50 members with MDs, molecular biologists, bioinformaticians and highly educated engineers organized in 4 research groups and one lab-technology unit. The engineers are allocated to specific research groups but also organized in a separate unit. The lab technology unit enhances the skills of "state of the art" technology, and improves exchange of knowledge across research groups and cancer types. This is a key asset leading to increased quality of the department's laboratory work and project management.

The research focus is on molecular classification, data integration, translation, and pan-cancer analyses, with a common goal of achieving deeper molecular understanding of inter- and intra-tumor heterogeneity between tumor entities and tumor subgroups, and within a single tumor. Mouse modelling of human cancers to understand cancer evolution, heterogeneity and therapy resistance is also part of the department's project portfolio.

We have established a pipeline for high-quality biobanking (>200 000 vials) and data handling of patient cohorts with long-term follow-up and perform multilevel molecular characterization down to single cell levels. Our database consists of > 3000 patients with analyses at 2-6 molecular levels, and include samples from, among others, the following trials:

- MetAction - Actionable targets in cancer metastasis. Targeted sequencing for selection of therapy in an N-of 1 Precision Oncology study
- NeoAva - Neoadjuvant chemotherapy in breast cancer with/without bevacizumab. Samples obtained before/ during and after treatment
- IBCT - Improved Breast Cancer Therapy in the neoadjuvant and metastatic setting
- EMIT - Establishment of Molecular profiling for Individual Treatment decisions in Early BC. Three-phase research study which includes a randomized intervention study
- TREM – Lung cancer patients with EGFR mutations and primary TKI-resistance
- ThoRaT - Lung cancer patients receiving radiotherapy
- NorPACT-1 - Neo-adjuvant chemotherapy for pancreatic cancer

We have extensive institutional, national and international collaborations and are partners in several networks and consortia; the Regional Network for Breast Cancer Research, the Regional Research Network on Extracellular Vesicles (RRNEV), Personalized Cancer Treatment and Metaflammation, International Cancer Genome Consortium (ICGC), EuroPDX, the Breast Cancer Association Consortium (BCAC); EU funded projects (EpiMark, Cancer-ID). We host The National Competence Center for Lung Cancer.

The total number of peer reviewed publications in 2016 was 57.

TRANSLATIONAL STUDIES IN SOLID TUMOURS

"With starting point in clinical studies and clinical questions, we do molecular analyses aiming at improving outcome for cancer patients"

GROUP LEADER: Åslaug Helland

ABOUT

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

The group has three project groups, with a total of 16 members (13 women). Six of these 16 are MDs, and India, Great Britain and Israel are represented. We are three researchers, three postdocs, five PhD-students, two master students, one study nurse and two engineers.

AIMS

The ultimate goal is to personalise cancer treatment, and improve prognosis.
Identification of biomarkers in blood samples, for diagnostics, follow-up and prognostication
Identification of tumour biomarkers for prediction of therapy response and for prognostication

PROJECTS

- Molecular characterisation of lung squamous cell carcinomas
- Molecular characterisation of pancreatic cancers
- MiRNA in ovarian cancer
- Improving radiotherapy in lung cancer
- Identification of biomarkers in colorectal cancers
- Protein (TMA) analyses in lung cancers
- Genome-wide detection of diagnostic plasma miRNAs in pancreatic cancer
- Exosome profiles of proteins and miRNAs in plasma of pancreatic cancer patients
- Serum N-glycans as prognostics markers in pancreatic and colorectal cancers
- Serum predictive markers for therapy response
- Elucidate mechanisms for therapy resistance

RECENT ACHIEVEMENTS

In 2016, the group was involved in several EU-applications, published 25 papers in peer-reviewed journals. We have had several talks at national and international meetings, and are PIs on >20 translational and clinical studies. Received funding for one PhD-student and one postdoc.

CANCER GENOME VARIATION

"Germ-line and somatic genetic and epigenetic variants in cancer and pharmacogenomics"

GROUP LEADER: Vessela N. Kristensen

ABOUT

The group at ICR: 2 research engineers, 6 postdocs, (1 postdoc with a career development grant, 2 of the postdocs 50% divided with other groups at the Department and Institute), 1 PhD student. Vessela Kristensen is a professor I at the Faculty of Medicine, UiO, and works towards active collaboration between KRF and University of Oslo, where she leads the group of Oncogenomics with a molecular branch consisting of 1 research engineer, 4 postdocs, 2 PhD students and 1 MSc student. Last summer a "Scientia fellows" postdoc from Italy as well as two Erasmus students from France joined the group. Both groups work closely together with a total of 6 male and 10 female members, half of them (9) from Norway, the rest from France, Italy, India, Pakistan, Sweden, Peru and Serbia. Kristensen was on the advisory committee of 3 graduate students at Princeton University, two of whom graduated in 2016.

AIMS

The Cancer Genome Variation group works to understand how genetic variation affects occurrence of somatic alterations, gene expression patterns and genome wide copy number alterations. We apply data integration towards identification of signaling pathways and integrated analysis of high resolution DNA methylation profiles, gene expression, germline genotypes and clinical end points in time-course studies of breast cancer patients under treatment. http://ous-research.no/kristensen/.

PROJECTS

- Genome variation; fine mapping characterization of susceptibility loci continues with in depth next generation re-sequencing analyses
- DNA methylation at specific CpGs affects the expression genome wide, pointing to signaling and effector pathways such as immune signaling. *Contribution to Nature. 2016. PMID: 27533040*
- Copy number alterations: commonalities between female cancers *BMC Cancer. 2016, PMID: 27876019, and implications in tumor dissemination. Genome Biol. 2016 PMID: 27931250*
- Non-canonical transcriptomes. Long non-coding RNAs in normal versus primary breast tumor tissues. *Defended PhD, Sunniva Bjørklund.*
- Immune signaling. Interleukin signaling in focus since our 2012 discovery of massive cytokine signaling. *Contributuion to Oncoimmunology. 2016. PMID: 28123884*
- Nano-dissection applied to identify multiple types of immune cells *in silico. Contribution to Cancer Res. PMID: 27406829*

RECENT ACHIEVEMENTS

Publication activity: 34 publications and 1 PhD dissertation, 2 Erasmus student theses in 2016.

DEPARTMENT OF **CANCER GENETICS**

MOLECULAR BIOLOGY OF BREAST CANCER

"Exploring inter- and intra-tumor heterogeneity at various molecular levels and perform integrated analyses to develop prognostic and predictive signatures for breast cancer"

ACTING GROUP LEADER: Hege G. Russnes

ABOUT

Focus of the group is to reach a more fundamental understanding of the biological dynamics of breast cancer through high-throughput molecular analyses of DNA, mRNA, miRNA and protein. It is organized into three project groups with a total of 4 scientists, 5 postdocs, 2 research engineers and one MD-PhD student. In addition, 1 oncologist, 1 study nurse and 1 professor in bioinformatics (UiO) are associated with the group (part-time).

As partners in several clinic trials we perform "state of the art" analyses of patient material, both on bulk tumors, single cells and liquid biopsies, at various stages of the disease. In July 2016 the former group leader, Prof. Anne-Lise Børresen-Dale, retired and project group leader Hege G. Russnes has been acting as Head of the group thereafter.

AIMS

Our group aims at defining, refining and implementing molecular classification and biomarker analyses to improve stratification of breast cancer patients into treatment relevant groups. We are addressing the impact of inter- and intra-tumor heterogeneity as well as host response on disease progression, response to therapy and patient outcome.

PROJECTS

- Somatic Genetics of Breast Cancer, from single genes to whole genome sequencing
- Single-level and multi-level data analyses of DNA/RNA/protein/metabolic alterations of primary tumors and metastases at various stages of the disease to improve classification of breast cancer
- Intra tumor heterogeneity
- Cell-free tumor DNA in blood
- Genomic and functional analysis of therapeutic targets in breast cancer
- Functional screens elucidating the role of miRNA's
- Glycans and miRNA as serum biomarkers

RECENT ACHIEVEMENTS

- 38 original publications in 2016 and 9 in press
- One PhD defense in 2016.
- The groupleader is appointed as "Young Associated Investigator" at NCMM (Centre for Molecular Medicine Norway).
- The group leader awarded "researcher of the month" (South-East Health Region, November)
- Hosting the International Symposium: PERSONALIZED CANCER CARE; Risk prediction, early diagnosis, progression and therapy, Oslo, May 18-20 2016

BREAST TUMOR INITIATION

"Understanding cell fate decisions in tumor progression"

GROUP LEADER: Therese Sørlie

ABOUT

The group counts 11 members (two men, 9 women) including one assistant professor (TS), one senior researcher, one scientist, four postdocs, two PhD students, one MD-PhD student and one master student. Two members are MD and one is DVM. Sørlie is an adjunct professor at CCBIO, University of Bergen. Our group studies aspects of breast tumor initiation and progression including the functional effect of known risk variants, the cell of origin of molecular subtypes and the specific pathways and processes that are deregulated and lead to invasion. We have a broad expertise in laboratory technologies which include high-throughput genomic technologies, *in vivo* lineage-tracing, in situ hybridization, confocal microscopy and FACS analysis. We use patient cohorts and mouse models (transgenic and patient-derived xenograft - PDX) in our studies. We also have expertise in bioinformatic and statistical methods and modeling.

AIMS

Our aim is to identify the cellular origins of breast tumors and the mechanisms behind tumor initiation and further development into the heterogeneous molecular subtypes. Through an increased understanding of how tumors progress to more advances stages, improved strategies for early intervention and more precise treatment can be developed.

PROJECTS

- Characterize the functional effect of breast cancer risk variants
- Characterize subtype-specific progression pathways of preinvasive lesions in the breast
- Identify and test potential molecular progression markers in large patient cohorts, and model their interactions
- Investigate the role of Hedgehog/GLI1 signaling in breast cancer progression
- Explore the tumorigenic potential of LGR5 expressing cells in the mammary gland
- Modeling the co-evolution of methylation and somatic aberrations in tumors
- Drivers of the BRCAness phenotype in basal-like tumors
- Investigate the role of FOXA1 in endocrine resistant breast cancer

RECENT ACHIEVEMENTS

- 12 publications in 2016
- One PhD defense
- Mørk Legacy Research prize to Therese Sørlie

DEPARTMENT OF

CANCER IMMUNOLOGY

HEADED BY **JOHANNA OLWEUS**

ABOUT

Department of Cancer Immunology (DCI) has 4 research groups. Among the PIs, 3 are full professors at UiO (MD, PhD), one is visiting professor at Univ of Tunis (DEA pharm, PhD), and one is also visiting professor at Karolinska Institute. Groups in the DCI are partners of: Center of Excellence for Cancer Biomedicine (CCB), two K.G. Jebsen Centers (Cancer Immunotherapy and Inflammation Research, and leader of the former) and OUH focus area for Cancer Immunotherapy. With emphasis on translation and extensive involvement in clinical trials, the DCI is the department with the highest number of MDs at the Institute. The DCI counts 48 members (60% women); 10 scientists, 15 postdocs, 10/2 PhD/Master students, and 11 technical staff. Recruited from Norway/abroad: 54/46%.

AIMS

Improve cancer diagnostics and therapy through cutting edge research on tumor immunology and lymphocyte biology.

PROJECTS

- Lymphocyte biology, by deciphering
  - ontogeny of B, T and NK cells
  - tumor heterogeneity (signaling and mutanome)
  - immune cell recognition elements (antigen discovery)
- Biomarkers, by profiling of
  - lymphocyte repertoires
  - the tumor and its microenvironment
  - T-cell receptors and humoral immunity
- Therapeutics, by
  - genetically engineered T and NK cells
  - immune priming with siRNA and antigen-targeting to DC
  - genetically engineered peptibodies
  - cell therapy across HLA barriers to overcome immune tolerance
  - clinical trials using experimental immunotherapy

RECENT ACHIEVEMENTS

In 2016, 18 publications (17 original) were published, of which 13 with first/last authors from DCI, with mean and median IF of 8.2 and 5.8, respectively. Two DOFIs/five patent applications were filed. One article in Science (first/last author from DCI) was subject of commentaries in Science and in New Engl J Med. A license and collaborative agreement with *Fate Therapeutics Inc.* concerning the development of a universal iPS-derived NK cell platform for cancer immunotherapy was signed.

"Our goal is to improve cancer diagnostics and therapy through cutting edge research on tumor immunology and lymphocyte biology"

DEPARTMENT OF **CANCER IMMUNOLOGY**

EXPERIMENTAL IMMUNOTHERAPY

"Our focus is to develop new strategies for T-cell based immunotherapy"

GROUP LEADER: Johanna Olweus

ABOUT

The group counts 13 members (67% women); 1 full professor (JO), 1 scientist, 4 postdocs, 4 PhD students and 2.5 engineers, and two associated clinicians. Three members have MD background. Ten members are recruited from abroad. The group is partner of two K.G. Jebsen Centers (2013-); "Cancer Immunotherapy (JCIT)" and "Inflammation Research (JIRC)", respectively. Olweus is Director of JCIT, which was awarded maximal prolongation in 2016 (two years), till 2020.

AIMS

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

PROJECTS

Strategy 1

- Identify cell-type specific T-cell epitopes from self-antigens and T-cell receptors reactive with such epitopes for future genetic transfer in adoptive cellular therapy *(OncoImmunology 2016, IF 7.6))*

Strategy 2

- Target neo-antigens neglected by patients *(Science 2016, IF 34.7)*
- Profile T-cell receptors as a tool to identify T-cell reactivities *(J Hepatol 2016, IF 10.6)*
- Identify neo-antigens and reactive T cells in biobanked material from patients responding to immunotherapy *(Lymvac I and II trials)*
- Identify auto-antibody targets by protein arrays and T cell biology in autoimmune disease (CVID) *(Clin Immunol 2016, IF 4)*

RECENT ACHIEVEMENTS

Four original articles published, with Olweus as senior author and group member as first author on three, including one in Science. This article was awarded one commentary article in Science and one in New Engl J Med, and was in the top 5% of all research outputs to media (internationally) as scored by Altmetric. Olweus is co-PI on one clinical trial testing new immunotherapy in lymphoma patients that started in 2016, and main inventor on one filed patent application.

NATURAL KILLER CELL BIOLOGY AND CELL THERAPY

"Our focus is to develop the next generation natural killer (NK) cell therapy"

GROUP LEADER: Karl-Johan Malmberg

ABOUT

The group counts 19 members (F/M: 7/12); 1 full professor (KJM), 2 scientists, 7 postdocs, 7 PhD students, 2 engineers. Six members have MD background. Malmberg is a visiting Professor at the Karolinska Institutet (KI) and the group is partner of the K.G. Jebsen Center for Cancer Immunotherapy (2013-). The main focus is to develop new strategies for cell-based immunotherapy based on insights into the molecular regulation of natural killer (NK) cells.

AIMS

The long-term goal of the laboratory is to advance our fundamental understanding of NK-cell development and function, and use this progress to design new immunotherapeutic approaches and clinical trials for patients with cancer. We focus on basic questions concerning 1) the formation of killer cell immunoglobulin-like receptor (KIR) repertoires and regulation of effector cell function, 2) translational questions of how NK cells may be function-enabled for anti-cancer activity and 3) clinical studies in the context of allogeneic stem cell transplantation (HSCT) and adoptive cell therapy.

PROJECTS

- Functional plasticity and diversification of human NK-cell repertoires in health and disease
- Metabolic reprogramming and NK-cell homeostasis
- Clinical trial program; harnessing adaptive NK cells in cancer therapy
- iPS-derived NK cells for off-the-shelf cancer immunotherapy. Collaborative partnership with Fate Therapeutics Inc.

RECENT ACHIEVEMENTS

Successful collaboration with the Muenz group at Zurich University and the Parham group at Stanford University to elucidate cellular and molecular mechanisms behind NK cell education (Journal of Clinical Investigation 2016 and Science Immunology 2016). Defined new drivers of adaptive NK cells (Liu et al, Cell Reports 2016). These advances laid the foundation for a license agreement with Fate Therapeutics Inc. to develop the next generation NK cell therapy.

DEPARTMENT OF **CANCER IMMUNOLOGY**

IMMUNO-MODULATION AND TARGETED THERAPIES

"Our goal is to develop cancer therapeutics and probe immune responses in cancer patients"

GROUP LEADER: Mouldy Sioud

ABOUT

The group has 7 members (66% women), including 1.5 postdocs, 2 research assistants, 2 master students and the group leader (DEA Pharm, PhD) with formal research experience in immunology, molecular/cell biology, proteomics and medicine. Sioud is visiting professor at University of Tunis (1997-). The group is part of the OUH focus area cancer immunotherapy and H2020 NANO-D-SIRE consortium. The main current focus is to develop anti-tumor antibodies and new cancer vaccine formulations based on recent advances in understanding the mechanisms regulating immune responses in patients.

Notably, some of our previous studies shed light on the underlying mechanisms regulating RNA sensing by the immune system, hematopoietic stem cell sensing of microbial products and gene regulation by endogenous antisense transcripts [e.g., Sioud & Sørensen, *Nature Biotech* 1998; Røsok & Sioud 2004 *Nature Biotech;* Sioud 2006 *Nature Biotech* (IF=41); Sioud 2004 *Trends Pharmacol Sci* (IF= 11.8); Sioud 2006 *Trends Mol. Med* (IF=10.1)].

AIMS

The main goal of the group is to develop new cancer-specific antibodies and dendritic cell-based vaccine formulations for cancer immunotherapy.

PROJECTS

- Enhancing immune responses by targeting antigens to APCs
- Engineering new therapeutic human mini-bodies
- Developing checkpoint-blocking siRNAs

RECENT ACHIEVEMENTS

- New peptide-Fc fusion proteins able to recruit innate immune effector cells and kill cancer cells *(Oncotarget-2016)*
- Combination immunotherapies to achieve optimal T-cell activation *(Case Rep Med- 2016)*
- New therapeutic targets by dissecting Wnt signaling pathway in neuroblastoma cells *(Oncotarget-2016)*
- Off-the-shelf universal anti-tumour mini-bodies (DOFI-16121, manuscript submitted)

The group has published 183 PubMed-indexed papers, including 3 original papers in 2016 with 1st and/or last authorship on 85% of the published papers. The work on therapeutic cancer antibodies resulted in a DOFI as well as a patent application (2016). Sioud participated as a steering committee member for the evaluation of research and teaching activities at the University of Tunis, Pasteur Institute.

LYMPHOMA BIOLOGY

"The Smeland/Myklebust lab is a translational research lab, focusing on identification of better prognostic markers and improved therapeutics for B-cell lymphoma"

GROUP LEADER: Erlend Bremertun Smeland/June Myklebust

ABOUT

The group consists of 13 members with research background in medicine, biology, biochemistry and biotechnology, and includes 1 professor (EBS), 1 assistant professor (JHM), 1 senior scientist (50% position), 5 postdocs, 4 PhD students and 1 technician. Four of the members are recruited from abroad (USA, China, Switzerland, Sweden). The group is part of the Centre for Cancer Biomedicine. Our studies focus on B-cell lymphoma, a heterogeneous group of malignancies originating from B cells of the immune system. Overall survival is steadily increasing and recent therapeutic advancements include novel targeted agents such as drugs targeting the B-cell receptor signaling pathway, as well as immunotherapy with chimeric antigen receptor (CAR) T cells and immune checkpoint blockade. The lab has a strong translational focus, and we use exome sequencing, high-dimensional flow cytometry and mass cytometry to identify tumor cell heterogeneity, and to characterize tumor microenvironment composition. The molecular biology expertise has been strengthened with establishment of CRISPR/Cas9 genome editing to create gene knockout models. Lymphoma xenograft mouse models have been established for testing of new drugs in vivo.

AIMS

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

PROJECTS

- Whole exome sequencing of diffuse large B-cell lymphoma biopsies to identify recurrent mutations associated with therapy relapse
- Whole exome sequencing of longitudinal tumor samples of follicular lymphoma patients to determine clonal evolution and disease progression
- Transcriptomics and proteomics characterization of tumor cells and tumor microenvironment in B-cell lymphoma
- Characterize recurrent driver mutations in B-cell lymphoma (CRISPR/Cas9 genomic manipulation and functional assays)
- Cancer sensitivity drug screen (in vitro) and in vivo testing of novel drugs (xenograft models)
- Identify abnormal cell signaling in lymphoma cells by phospho-specfic flow cytometry

RECENT ACHIEVEMENTS

Eight publications in 2016 with five as first author from the group, including Blood (IF 11.8).

DEPARTMENT OF

MOLECULAR CELL BIOLOGY

ACTING HEAD **KIRSTEN SANDVIG**

The department has a staff of about 75 and hosts 5 research groups (Enserink, Rusten, Sandvig, Stenmark, and Wiedlocha), 10 project groups, and a departmental service unit. Rusten was previously a project leader in Stenmark's group, and acquired status as group leader in the autumn 2016. The Enserink group moved to the department Nov. 1st, 2016. In 2015 the department acquired one new group (Skarstad group), and this group has in the autumn of 2016 moved to Dept. Microbiology, Laboratory Medicine, Oslo University Hospital.

Research in the department comprises various aspects of cancer relevant cell biology, including membrane traffic, receptor signaling and cell division. Also primary human cancer samples are studied.

Translational research on cancer cell-derived exosomes is a recent development in the department. A common goal for researchers in the department is to uncover novel molecular mechanisms that control cellular functions related to cancer. The department's research strategy is to combine molecular cell biology with biochemistry and advanced imaging in order to address relevant scientific questions. Recent key achievements from the department's scientists include studies on autophagy and tumor growth, growth factor signaling and intracellular transport, exosome secretion and biomarkers for prostate cancer.

In general, the department's groups have been successful in obtaining national and international external funding.

The groups of Stenmark, Sandvig, Wiedlocha and Rusten are associated with a Centre of Excellence, Centre for Cancer Biomedicine. In addition, Kirsten Sandvig heads a national project on Biodegradable Nanoparticles in Cancer Diagnosis and Therapy, and Harald Stenmark heads the Norwegian Advanced Light Microscopy Infrastructure Network.

"Uncovering the cellular basis of cancer development"

DEPARTMENT OF **MOLECULAR CELL BIOLOGY**

INTRACELLULAR TRANSPORT

"All the way from basic research to translation"

GROUP LEADER: Kirsten Sandvig

ABOUT

Sandvig's group, counting 18 members plus a master student, is interested in the mechanisms of endocytosis, intracellular transport and secretion. Uptake of receptors and ligands and correct intracellular sorting of endocytosed molecules are crucial for maintenance of a normal differentiated phenotype. In some studies we are using protein toxins such as ricin and Shiga toxin, which are well established as markers for studies of membrane traffic, and which can be used as agents in cancer diagnosis and therapy. Our expertise is also applied to investigate uptake of nanoparticles, and in 2013 we obtained a five year grant from the Norwegian Research Council to build national competence in nanomedicine. This project, "Biodegradable nanoparticles in cancer diagnosis and therapy", headed by Sandvig, involves collaboration with ten other Norwegian groups working in academia, research institutes, hospitals and industry. The Sandvig group is also involved in an INNO INDIGO granted project, which started April 2016. INNO INDIGO is an innovation-driven initiative for the development and integration of Indian and European research. We also characterize exosomes from prostate cancer cells and patients with the goal of detecting lipid and protein biomarkers. Our research spans all the way from basic to translational medicine, including innovation. The work published by the Sandvig group is well cited, and Sandvig's H-index is now 70 (more than 300 publications). The group has extensive national and international collaboration.

AIMS

The projects aim at increasing our knowledge about intracellular transport and biomarkers in order to provide a rational basis for diagnosis, treatment and prevention of disease.

PROJECTS

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

RECENT ACHIEVEMENTS

Characterization of the effect of glucose analogues and lipids (lysolipids and the drug Minerval) on cellular lipids, endocytosis and intracellular transport; description of exosomal lipid biomarker candidates for prostate cancer in urine; novel method to monitor turnover of glycosphingolipids. In 2016 the group published 16 articles, and one Ph.D. student and two master students finished their degrees. Concerning innovations, see separate paragraph.

CANCER MOLECULAR MEDICINE

"Identifying weak points in the molecular networks that drive cancer"

GROUP LEADER: Jorrit Enserink

ABOUT

The group, which started recently at the Institute for Cancer Research (November 2016), currently consists of one adjunct professor, one externally funded senior scientist, five post-docs, three PhD students and one Erasmus student. All but two of the group members are recruited from abroad, i.e. Ethiopia, France, the Netherlands, Spain and the UK. Research is mainly focused on basic cancer biology and personalized medicine, using a wide range of models such as budding yeast, fruit flies and zebrafish, human and mouse cell lines, and primary human cancer samples.

AIMS

Research is aimed at understanding cancer cell biology, with the ultimate goal of developing precise cancer treatments. The main focus is on hematopoietic cancers, including –but not limited to– Acute Myeloid Leukemia (AML).

PROJECTS

- High-throughput drug screens on primary AML blast cells to identify correlations between driver mutations and drug sensitivity profiles
- Development of a novel small-molecule immune checkpoint inhibitor
- Modeling of leukemia in fruit flies to better understand the genetic networks that drive AML
- Genome-wide CRISPR-Cas9 screens in CML cells to identify novel mechanisms of resistance to tyrosine kinase inhibitors
- Cellular responses to nutrient stress; particularly the role of Sumo in promoting cell proliferation, and identification of the upstream pathways that control the dynamics of autophagy

RECENT ACHIEVEMENTS

Four Erasmus-sponsored MSc degrees were completed. Major funding: Two grants from the Norwegian Research Council (FriMedBio and Biotek2021), one grant from the Norwegian Cancer Society, and three researcher grants from The South-Eastern Health Authorities. Innovation: One DOFI submitted. Awards: One article award from Oslo University Hospital. Finally, since the group's arrival at ICR in November 2017 two manuscripts were accepted for publication (PNAS and Oncotarget) with ICR as the new main affiliation.

DEPARTMENT OF **MOLECULAR CELL BIOLOGY**

TUMOR-HOST BIOLOGY

"Tumor-host interactions during cancer progression"

GROUP LEADER: Tor Erik Rusten

ABOUT

Our research group grew to count 6 members representing 6 nationalities in 2016 (Iran, Finland, Switzerland, India, Ireland and Norway): 1 group leader, 1 scientist, 2 post docs and 2 PhD students.

Cancer can be viewed as animal development derailed. Our overarching interest is to understand the mechanisms by which tumor and host cells mutually engage each other in reciprocal interactions to facilitate carcinogenesis. These interactions occur locally in the tumor microenvironment, but also systemically causing organ dysfunction such as in cancer cachexia - the catastrophic wasting of muscle and adipose tissue. We believe that by studying these processes we can uncover new ways to intercept carcinogenesis.

To this end, we investigate the molecular genetic mechanisms and cell biology of genetically defined experimental tumor-host interactions using a mix of human cell culture and the animal model system, the fruit fly Drosophila melanogaster. We collaborate with national and international experts in cell biology, electron microscopy, genetics, transcriptomics and metabolism to reach our goals.

AIMS

The principal aim is to understand tumor-host interactions that facilitate carcinogenesis in order to uncover novel ways to intercept cancer.

PROJECTS

- Oncogene-induced epithelial disintegration and invasion
- Cell signaling and autophagy function during tumor-microenvironment interactions
- Mechanisms of cancer cachexia

RECENT ACHIEVEMENTS

Discovery that malignant tumors induce a stress response in the tumor microenvironment that supports tumor growth through nutrient-generating autophagy (Katheder, N.S., et al, Nature 2017).

CELLULAR MEMBRANE DYNAMICS

"Diving into cellular membranes to find the keys of cancer"

GROUP LEADER: Harald Stenmark

ABOUT

The group studies the dynamics of cellular membranes and tries to understand their relevance to cancer. Cellular processes studied by the group include endocytosis, autophagy, and cell division. The group employs advanced molecular biology methods in combination with biochemistry and advanced light and electron microscopy technologies. As model systems the group uses cell cultures, organoid models, fruit flies and zebrafish.

The group is headed by Harald Stenmark (group leader) and Camilla Raiborg (assistant group leader). Its 5 project groups are led by Andreas Brech, Kaisa Haglund, Camilla Raiborg, Kay O. Schink and Eva Wenzel. The group consists of 6 men and 23 women, and 10 nationalities are represented. The staff consists of 1 group leader, 4 senior researchers, 2 researchers, 1 senior engineer, 9 postdocs, 5 PhD students, 4 technicians, 1 laboratory assistant and 2 visiting students.

AIMS

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

PROJECTS

- Interplay between membrane dynamics and cell signalling in carcinogenesis
- Phosphoinositides in regulation of membrane dynamics
- Centrosome dynamics in cancer
- Cytokinesis in development and carcinogenesis
- The β-catenin destruction complex in physiology and cancer
- Membrane dynamics in promotion of genome integrity

RECENT ACHIEVEMENTS

- Discovery that the ESCRT machinery mediates sealing of the newly formed nuclear envelope during mitotic exit, and that this mechanism is essential for genome integrity (Vietri et al., *Nature*, 2015).
- Identification of a novel mechanism for controlling intracellular positioning of late endosomes via their contacts with the endoplasmic reticulum, and demonstration that this mechanism promotes outgrowth of cellular protrusions (Raiborg et al., *Nature*, 2015).
- Characterization of ESCRT-mediated control of cytokinesis, the final stage of cell division (Christ et al., *J.Cell Biol.* 2016).
- One PhD student was graduated in 2016 (Tor Espen Thorvaldsen), and 19 papers were published by group members.
- In 2016, Marina Vietri received H.M. the King's Gold Medal for best PhD thesis.

DEPARTMENT OF **MOLECULAR CELL BIOLOGY**

PROTEIN INTERNALIZATION AND SIGNALING

"Searching for molecular targets in FGF-related malignancies"

GROUP LEADER: Antoni Wiedlocha

ABOUT

The group is composed of 6 members from 3 nationalities (1 group leader, 1 researcher, 3 postdocs, 1 Ph.D. student; 3 men, 3 women). Maintenance of tissue homeostasis depends on complex intercellular growth factor/growth factor receptors- mediated signaling networks that control basic cell functions. The fibroblast growth factor (FGF) signaling system represents one of the fundamental tools of such cell-to-cell communication. The signaling system exerts a powerful combination of biological effects during development and in maintaining a malignant phenotype. FGF/FGFR signaling is strongly oncogenic once the tight regulation on its physiological function is lost; it is enabled to be a central driver of tumor progression. FGFs as well as their receptors are frequently and abundantly expressed in various cancers and recognized as mediators of the epithelial-mesenchymal transition, tumor cell survival, migration/metastasis and neoangiogenesis, Therefore, the interest of FGF-induced signaling as a promising target for cancer therapy has systematically been increasing.

AIMS

The main goal of the research group is to elucidate differences in mechanisms of signaling induced by the FGF/FGFR axis in normal tissue and in progression of tumors.

PROJECTS

- Activation and downregulation of FGF/FGFR induced signaling
- Endocytosis, sorting and intracellular transport of FGF1 and FGFRs
- Mechanisms of FGF-induced malignant phenotype
- Targeted therapy for FGFR-expressing cancer – experimental approach

RECENT ACHIEVEMENTS

Using proteomic approaches, we found that FGFR4 uses clathrin-mediated endocytosis for internalization and that FGFR4 can recycle back to surface also through the trans-Golgi network (Haugsten E.M., et. al., J. Proteome Res., 2016). We have also elucidated that PTPRG, a membrane bound tyrosine phosphatase, is an important modulator of FGFR tyrosine kinase activity, by dephosphorylation of the activated FGFR1. Since PTPRG depletion elevated cell growth and negatively affected the efficacy of FGFR1 kinase inhibitors, the phosphatase may have future clinical relevance by being a predictor of outcome after FGFR inhibitor treatment (Kostas M., et al. under review).

DEPARTMENT OF

MOLECULAR ONCOLOGY

HEADED BY **RAGNHILD A. LOTHE**

The department of Molecular Oncology (MO) has 3 research groups and counts 41 employees. The group leaders are all professors at the University of Oslo, affiliated with the Institute for Biosciences, the Institute for Clinical Medicine, and the Institute for Informatics. The PIs are partners in the Centre of Excellence for Cancer Biomedicine (2007-17), the K.G. Jebsen Colorectal Cancer Research Centre (2014-18), and the OUH priority area for Colorectal Cancer (SMART- screening_management_research_translation - CRC 2014-18). The PIs are also partners in the Norwegian Cancer Genomics Consortium, the Global Testicular Cancer Research Consortium, European Network for the Study of Cholangiocarcinoma and Cooperation Studies on Inherited Susceptibility to Colorectal Cancer (COST action).

The employees have trans-disciplinary competence and hands-on experience in a broad range of technologies, including multilevel genomics, epigenetics, cell biology and pharmacogenomics. The MO research activity focuses on molecular biology of solid tumors and translation of biological knowledge to clinical use. Our main goal is to improve precision medicine and contribute to solve clinical challenges in colorectal and prostate cancer. The strategy for the next three to five years is to explore spatio-temporal tumor heterogeneity in colorectal and prostate cancer, and to combine the results with drug sensitivity testing and resistance patterns found by high throughput screening of cell cultures. This will be followed by translation of selected findings to clinical trials.

During the last 3 years, we have published 64 papers, with 1st and/or last authorships on more than half. The mean IF = 7.1 in the 3 ye period, including five papers with IF> 10. The MO total innovation activity (since 2007) includes 13 patent applications, several innovation grants, two signed license agreements and eight granted patents (covering four biomarkers in five countries)

In the period 2014-16, 11 PhDs and 10 MSc with supervisors from MO received their academic degrees.
Recently (2015-2016) we have established new technologies of mutual interest to the department groups, including a benchtop sequencer for deep sequencing of gene panels, digital PCR for exceptionally high-sensitivity detection of nucleic acid biomarkers in various clinical samples, CRISPR/Cas9 for knock-out experiments, and semi-automatic digital analysis of multiplexed in situ protein expression. Computational tools for interpretation of the respective high-throughput data are also established.

"Biological discoveries for precision cancer medicine"

GENETICS

"Genomics – irreversible mistakes in cancer and a source for clinical biomarkers"

GROUP LEADER: Ragnhild A. Lothe

ABOUT

Our group studies somatic genetic aberrations of solid tumors, with particular focus on colorectal cancer (CRC). We combine multi-level genomics, transcriptomics, multiplex immunohistochemistry, cell biology and drug screening to i) identify clinically useful biomarkers and novel treatment options in the context of tumor heterogeneity, and ii) better understand molecular mechanisms promoting cancer development and metastasis. The group has 24 employees (9 postdocs/scientists, 9 PhD students, 6 research assistants/engineers) plus currently 3 MSc students, including Dr. Edward Leithe's project group in Cell signaling.

AIMS

Our overarching goal is to translate novel biomedical knowledge to improved patient stratification and treatment of CRC.

PROJECTS

- Prognostic and predictive biomarkers (CRC and malignant peripheral nerve sheet tumors, MPNST)
- Modeling tumor heterogeneity and clonal evolution in primary and metastatic CRC
- miRNA expression - function and biomarker potential in CRC
- Pharmacogenomics: drug sensitivity screens of CRC and MPNST cells
- E3 ubiquitin ligases in intercellular communication and CRC pathogenesis

RECENT ACHIEVEMENTS

Tumor heterogeneity in CRC has important clinical implications. We discovered intra-patient heterogeneity among liver metastases to be a key determinant of patient survival and a stronger prognostic factor than known clinicopathological parameters for metastatic CRC (Sveen et al, PloS Genetics).

The power of large sample numbers to identify and assess high-precision clinical biomarkers calls for participation in international multi-center studies. We have contributed to a study of POLE mutations, found in 1% of >6500 CRCs and associated with increased lymphocyte infiltration and a low risk of recurrence (Domingo et al., Lancet Gastroenterology & Hepatology 2016), as well as a study of >8000 patients assessing the prognostic value of selected molecular markers, beyond clinicopathological staging (Dienstmann, Annals of Oncology, 2017).

We found that mitotic cells are able to form actin-based plasma membrane bridges, "mitotic nanotubes", with adjacent cells during rounding, identifying a novel mechanim of cell communication (Fykerud et al, Cell Cycle 2016).

Two comprehensive review papers about noncoding RNA in CRC and aberrant splicing in cancer (Cekaite et al, Oncotarget; Sveen et al, Oncogene) were published in 2016.

Multi-omics analyses and drug sensitivity testing (460 drugs) in a large series of CRC cell lines have recently been performed. Patient derived xenograft experiments validated in vivo effects and a support potential for clinical translation (unpublished).

EPIGENETICS

"Epigenomics – reversible changes in cancer and a source for clinical biomarkers"

GROUP LEADER: Guro E. Lind

ABOUT

In the group of Epigenetics we are studying DNA methylation alterations by integrating carefully selected methylome approaches with detailed candidate gene characterization. The research is performed across cancer types, with a main focus on colorectal cancer. In 2016 the group counted eight members, including two postdocs, two PhD students, two engineers, one MSc student and the group leader.

AIMS

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

PROJECTS

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

RECENT ACHIEVEMENTS

During 2016 our group has focused on methodology. In the literature, diverging methylation frequencies are often reported for the same locus in the same disease, underscoring the need for limiting variability. Based on more than 15.000 PCRs we provide guidelines for more robust and highly standardized DNA methylation analyses (Pharo et al, Sci Rep). We have also adapted the powerful ddPCR technology to standardized DNA methylation analyzes (manuscript). In 2016 Hege Marie Vedeld defended her PhD thesis, and demonstrated, among others, that the epigenetic phenotype CIMP has prognostic value and that it can stratify the poor prognostic group of MSS colorectal cancer patients with BRAF mutation (submitted).
Through a European network we have contributed to a consensus statement for cholangiocarcinoma (Banales et al, Nat Rev Gastroenterol Hepatol). In 2016 Lind led the Young Academy of Norway though it's first year. The vision of this national organization is becoming the clear voice of young researchers in the public arena.

DEPARTMENT OF **MOLECULAR ONCOLOGY**

GENOME BIOLOGY

"Transcriptomics – the expressed genome mistakes and a source for clinical biomarkers"

GROUP LEADER: Rolf I. Skotheim

ABOUT

The Genome Biology group studies how genomes and transcriptomes are altered in cancer cells by using both computational biology and wet-lab based approaches. Mutation analyses in cancer clearly benefit from knowing which genes and variants that are actually expressed. In this line, the group has particularly specialized in RNA-level analyses, and the projects focus on prostate cancer, although we are also involved with projects on testicular and colorectal cancers. An interdisciplinary set of competences is required to perform meaningful genome-scale cancer research. As such, personnel in the group have their basic education across the disciplines of biology, informatics, and medicine. We are a group of ten members, including three postdocs, two engineers, one PhD student, two MSc students, a study nurse and the group leader.

AIMS

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

PROJECTS

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

RECENT ACHIEVEMENTS

During 2016 we have continued to develop bioinformatics pipelines for high-throughput sequencing of DNA and RNA and utilized these in analyses of data from several cancer cohorts. For example, we identified the first fusion genes from testicular cancer, and found that several of these were recurrently expressed across tumours from a series of cancer patients (Hoff et al., Cancer Research). We also reported an in depth analysis and a review of the literature concerning alternative and aberrant splicing in cancer (Sveen et al., Oncogene). Altogether, we published five papers during 2016, including the two above mentioned papers with first and/or last authors from the research group. In 2016, Bjarne Johannessen defended his PhD theses, and Stian Lågstad and Jonas Meier Strømme completed their MSc degrees.

DEPARTMENT OF

RADIATION BIOLOGY

HEADED BY **KRISTIAN BERG**

The Department has more than 60 employees organized in 4 research groups and three project groups. The research at the department is focused on the biological responses to ionizing and non-ionizing radiation, including γ-radiation, ultraviolet radiation and visible light. Our department is actively engaged in revealing the mechanisms involved in DNA repair, cell-cycle regulation, genomic instability and immune responses after radiation, the impact of hypoxia on the radiation response and predictive markers for the outcome of radiotherapy of cancer patients. Another research area is the use of visible light to activate photosensitive compounds that are used for cancer detection and therapy. In that respect a technology has been developed, photochemical internalization (PCI), which may be utilized for site-directed intracellular delivery and activation of therapeutics into cancer cells. This technology induces reactive oxygen species that has similarities to the biological response to ionizing radiation. The department is also involved in revealing the impact of solar radiation on cancer development and protection by UV-induced vitamin D formation. Our vision is to develop a radiobiological understanding of response to ionizing and non-ionizing radiation on the molecular, cellular and physiological level, and to utilize this knowledge to design new strategies for the treatment of cancer. Our research strategy involves basic radiobiological research, translational and clinical studies.

OUR GOALS ARE

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

KEY ACHIEVEMENTS THE LAST 3-4 YEARS INCLUDE

- Novel patient-derived xenograft models of carcinoma of the uterine cervix showing functional intratumoral lymphatics have been established and characterized
- Increased knowledge about how Chk1 and Wee1 inhibitors work to kill cancer cells.
- PCI has been found efficient as a methodology to enhance antigen presentation during anti-cancer vaccination. Several new recombinant targeted protein toxins have been developed and are under preclinical evaluation. A phase I clinical trial documenting the safety and efficacy of PCI has been published in Lancer Oncology.
- A genomic hypoxia biomarker that can be visualized in diagnostic medical images has been developed for patients with cervical cancer.
- A G1-S checkpoint has been identified in fission yeast which is not only dependent on the DNA repair capacity of repair deficient cells, but also the nature of the repair deficiency.

"Our goal is to develop new predictive methods and treatment strategies for improved radiation therapy"

PHOTOCHEMICAL INTERNALIZATION

"Our goal is to develop and optimize the PCI technology for treatment of solid cancers"

GROUP LEADER: Kristian Berg

ABOUT

Group members: 16, including 5 researchers, 1 postdocs, 3 PhD students and 5 technical positions, including the project group of Asta Juzeniene.

Endocytic entrapment is a hurdle for therapeutic utilization of macromolecular therapeutics with intracellular targets. Photochemical internalisation (PCI) is a technology for release of endocytosed therapeutic macromolecules into the cells cytosol that has been development from experimental studies to clinical evaluation.
Project *Photobiophysics*: The project seeks to understand what a balanced level of sun exposure is needed to maintain an adequate level of vitamin D with a minimal risk for skin cancer. Senescent cells accumulate with age and after UV radiation. Preventing or eliminating senescent cells may be crucial for protection against skin cancer development.

AIMS

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

PROJECTS

- Design and development of recombinant immunotoxins for activation by PCI
- Reveal the potential of PCI for treatment of therapy resistant cancers, including cancer stem cells
- Utilize new vehicles for targeted delivery of small molecular drugs to endocytic vesicles for activation by PCI
- Evaluation of the vasculature as a target for PCI and further utilize these effects to reach a curative endpoint
- Develop PCI as a strategy for improving anti-cancer vaccines and utilize the anti-tumor immunity potential of the PCI technology
- Cutaneous vitamin D synthesis versus skin cancer development
- The role of UV radiation in melanoma development, progression and metastasis
- Targeting senescent cancer cells by photodynamic therapy

RECENT ACHIEVEMENTS

The first phase I clinical PCI trial published in Lancet Oncology. A unit for production of biomolecular drugs is established. No. of papers in 2016: 14 and 2 popular sciences articles
PhD thesis: 1
MSc thesis in 2016: 1
New grants in 2016:
Horizon 2020, (FET-OPEN): 'Lumiblast' (K. Berg and T. Theodosiou); EuroNanoMed II: 'NanoVax'; Several national grants.

CLINICAL RADIATION BIOLOGY

"Our goal is to discover biomarkers and molecular targets for combination therapies with radiation"

GROUP LEADER: Heidi Lyng

ABOUT

Group members: 9, including one researcher, three postdocs, two PhD Students, one master student and two technicians.

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

AIMS

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

PROJECTS

- Genetic alterations and chemo-radioresistance in cervical cancer
- Molecular hypoxia biomarkers in cervical and prostate cancer
- Combined molecular and imaging biomarkers in cervical and prostate cancer

RECENT ACHIEVEMENTS

Publications in 2016: 6
M.Sc thesis in 2016: 1 (Salberg)
We identified a biomarker for classifying patients according to tumor hypoxia in collaboration with colleagues at Oslo University Hospital and Aarhus University Hospital (Fjeldbo et al., Clin Cancer Res 2016). The study demonstrates a direct link between genomics and imaging that might facilitate implementation of a multifactorial tool for a more precise response prediction. We also published two more papers with first and last author from the group and three papers in collaboration projects.

RADIATION BIOLOGY AND TUMOR PHYSIOLOGY

"Our goal is to develop strategies for enhancing the radiocurability of tumors"

GROUP LEADER: Einar K. Rofstad

ABOUT

Group members: 9, including 2 researchers, 3 postdocs, 2 PhD students, and 2 technicians. The focus of the group is to reveal mechanisms causing tumor resistance to radiation therapy. The research is based on the hypothesis that radiation resistance is primarily a consequence of microenvironmental abnormalities in the tumor tissue. Xenografts of human cervical carcinoma, pancreatic carcinoma, and malignant melanoma are used as preclinical tumor models. In addition to standard molecular biology methods, important methods include intravital microscopy, MRI, and probe measurements of physiological parameters.

AIMS

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

- To develop MRI-based methods that can provide information on the physiological microenvironment and radiocurability of tumors.
- To develop antiangiogenesis-based treatment strategies for normalizing the physiological microenvironment and enhancing the radiocurability of tumors.

PROJECTS

- Mechanisms Governing the Microenvironment and Radiocurability of Tumors
- Interstitial Fluid Pressure and Hypoxia in Tumors: Causes and Consequences
- Preclinical and Clinical MRI
- Antiangiogenic Tumor Treatment

RECENT ACHIEVEMENTS

The group published 6 papers in 2016. In the following two papers, we report four novel PDX-models of cervix carcinoma and show that the tumors of two of the models can develop functional intratumoral lymphatics during growth:

Rofstad, E.K., Simonsen, T.G., Huang, R., Andersen, L.M.K., Galappathi, K., Ellingsen, C., et al.: Patient-derived xenograft models of squamous cell carcinoma of the uterine cervix. *Cancer Letters*, 373, 147–155, 2016.

Rofstad, E.K., Huang, R., Galappathi, K., Andersen, L.M.K., Wegner, C.S., Hauge, A., et al.: Functional intratumoral lymphatics in patient-derived xenograft models of squamous cell carcinoma of the uterine cervix: implications for lymph node metastasis. *Oncotarget*, 7, 56986–56997.

RADIATION BIOLOGY AND DNA DAMAGE SIGNALING

"Our goal is to obtain new knowledge about DNA damage signaling and utilize it to improve cancer therapy"

GROUP LEADER: Randi G. Syljuåsen

ABOUT

Group members: 17.9 including 4.5 researchers, 4 postdocs, 5 PhD students and 4.4 technicians/research assistants.

THEME

In radiotherapy ionizing radiation is used to cause DNA damage in cancer cells. The DNA damage is rapidly sensed and a network of intracellular DNA damage signaling cascades is activated. These signaling cascades influence whether the cells die or survive, through regulation of DNA repair, cell cycle checkpoint and cell death pathways.

Our group works on the border between basic and translational radiation research. We conduct basic projects to identify novel mechanisms of DNA damage checkpoint signaling, in addition to more applied projects to understand how inhibitors of checkpoint signaling can be used in an optimized manner for cancer treatment. From 2016 two project groups, headed by Beata Grallert and Trond Stokke, are members of our group.

AIMS

- Obtain new knowledge about DNA damage signaling, with focus on checkpoints and repair, and explore how such knowledge can be used to improve radiotherapy.

PROJECTS

- Pre-clinical exploration of the effects of checkpoint kinase (CHK1, WEE1, ATR) and PARP inhibitors
- The functional role of Protein phosphatase 1 (PP1) targeting subunits in DNA damage checkpoint signaling
- Identification of promising DNA damage combination treatments through flow cytometry-based large-scale compound screens
- Centrosomal and ciliary proteins in cell cycle regulation and genome integrity – roles and targets in cancer etiology, diagnostics and treatment
- The role of GCN2 in the cell cycle, translation and cellular stress

RECENT ACHIEVEMENTS

In 2016 the group published 6 articles. Members of the group were senior author on 4 of these (published in Molecular Oncology, Oncotarget, Cold Spring Harbor Protocols, Cell Cycle). Two master students graduated from our group in 2016.

DEPARTMENT OF

TUMOR BIOLOGY

"Preclinical and clinical efforts towards precision oncology"

HEADED BY **GUNHILD M. MÆLANDSMO**

The department has four research groups and 68 employees, with a common vision to better understand the biological mechanisms involved in cancer development, progression and metastasis, and to utilize this knowledge to improve cancer treatment. We are mainly performing translational research, and the main pillars in our research program are cancer genomics, computational science and investigations of biological mechanisms underlying resistence and metastatic progression. Our ambition is to identify candidate biomarkers and therapeutic targets, followed by validation in preclinical models and clinical trials. To foster high quality translational research we emphasize a close collaboration with clinical scientists, and have several researchers holding part-time clinical positions. Another prerequisite for the ongoing research is a huge collection of patient-derived tumor models established from different types of human cancer. The models are utilized for biological studies of disease progression, and for preclinical evaluation of novel drugs and drug combinations. We expect such patient-derived xenografts (PDX) to be crucial for clinical translation of precision oncology, an effort the department aims to actively participate in.

Key achievements over the last 3-4 years include project leader responsibilities in large collaborative projects in the area of precision oncology:

NCGC - The Norwegian Cancer Genomics Consortium, a national project aiming to sequence tumors across nine tumor types. Currently most of the exomes have been sequenced and are being analyzed.
NoSarC - Norwegian Sarcoma Consortium, a national project aiming to collect a prospective biobank and study disease development and treatment of sarcoma. Exome sequencing is ongoing and preclinical models are generated for studies of candidate drugs.
MetAction - Actionable targets in cancer metastasis. In 2016 we successfully established the diagnostic pipeline in this first clinical trial in Norway offering targeted treatment based on biomarker detection in metastatic lesions.
MOVEMBER - Identifying biomarkers distinguishing indolent and aggressive prostate cancer. Candidate biomarkers have been identified using Norwegian cohorts of serum, urine and tissue, and are currently undergoing validation in independent national and international cohorts.

Other clinical studies with substantial collateral research;
NeoAva: Bevacizumab in combination with neoadjuvant chemotherapy in breast cancer (patient inclusion ended)
I-BCT: DNA targeted chemotherapy to breast cancer patients with an aggressive phenotype
ImmunoPeCa: Immunotoxin in Peritoneal Carcinomatosis
Biobank Norway - a national initiative to coordinate biobank activities for research purposes

DEPARTMENT OF **TUMOR BIOLOGY**

METASTASIS BIOLOGY AND EXPERIMENTAL-THERAPEUTICS

Context-induced cellular plasticity - the route to resistance and metastasis

GROUP LEADER: Gunhild M. Mælandsmo

ABOUT

Employees: The group has 23 members with multidisciplinary background and experience (cell- and molecular biologists, medical doctors, physicists and animal technicians), including two MDs in shared clinical positions. Several of the technicians are trained in specialized technologies and constitute resources available for all groups in the department.
Research focus: Metastasis biology and identification of therapeutic targets/testing of experimental drugs.
Methodology: Molecular and functional analyses utilizing clinical samples, cell cultures and patient-derived in vivo models.

AIMS

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

PROJECTS

- Basic research revealing mechanisms causing metastasis or treatment resistance
  - Metastasis associated proteins and regulators, with special emphasis on tumor-stroma interactions and effects on cellular plasticity (invasion, metabolic reprogramming and immune responses)
- Preclinical research evaluating novel drugs and drug combinations
  - Efficacy and mechanistic studies in vitro and in vivo
  - Biomarker detection by molecular and functional techniques
  - Novel drug development in collaboration with commercial partners (Lytix Biopharma, Arctic Pharma/Biomolex, Oncoinvent, Smartfish)
- Clinical trials in precision medicine
  - NeoAva: bevacizumab in combination with neoadjuvant chemotherapy for patients with locally advanced breast cancer (patient inclusion closed, data processing ongoing)
  - I-BCT: extended DNA-targeted chemotherapy to breast cancer patients with an aggressive phenotype
  - MetAction: Actionable target identification in metastatic cancer for palliative targeted treatment

RECENT ACHIEVEMENTS

- Metrics: Group members were credited with 16 publications in 2016, of which seven with group members as first and/or last author; two PhD degrees completed and two others submitted for evaluation.
- Two clinical intervention trials open for inclusion (MetAction and I-BCT)

TRANSLATIONAL CANCER THERAPY

"New treatment for peritoneal metastases"

GROUP LEADER: Kjersti Flatmark

ABOUT

The Translational Cancer Therapy group comprises 18 members. Our strength is a broad variety of expertise, including students, basic biologists, translational scientists, and clinician-scientists. The approach to research is translational, encompassing methods from biochemistry and cell biology, preclinical drug testing in animal models, biomarker studies in clinical cohorts and interventional clinical trials. Extensive collaboration has been established within the Institute, with clinical departments, nationally and internationally.

AIMS

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

PROJECTS

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

RECENT ACHIEVEMENTS

- Group members were credited with 34 publications in 2016; 2 masters degrees completed.
- Funding was granted for the METIMMOX and the BIGMED projects, and funding for ACREDIT HSØ regional research network was extended for another 3 years
- Two clinical intervention trials are completed or ongoing, the ImmunoPeCa and MetAction trials, respectively.
- Extension of the Cure4PMP European Research Network

COMPUTATIONAL CANCER GENOMICS

"Systems solutions for precision medicine"

GROUP LEADER: Eivind Hovig

ABOUT

The 12-member group has strong interest in the development of computational approaches in cancer genomics in general, and in melanoma systems biology, with an emphasis on the MITF master switch of melanocytes. Currently, activity is centred on computational aspects of deep sequencing for cancer, with downstream analysis. The group has also facilitated precision cancer medicine towards the clinic, leveraging the participation in the BIGMED RCN-financed ICT lighthouse project.

The group collaborates with deCODE, Iceland, on the characterization of a familial cancer biobank, with 16000 genotyped samples, and where 2000 Norwegians have been whole genome sequenced. We pursue both the heritable cancer information from this effort, as well as a characterization of the ethnic Norwegian population genetics as a communal resource for Norway.

AIMS

We aim to

- apply and develop novel methodology for computational studies of cancer-related processes, including statistical genomics, immune informatics, 3-dimensional DNA conformation, drug prediction algorithms and mutational processes
- contribute insight on heritable cancer-predisposing DNA-variation in the Norwegian population
- characterize the geographical stratification aspects of the Norwegian population
- develop solutions for precision cancer medicine towards the clinic
- understand signaling processes in melanoma

PROJECTS

- Development of solutions for integrative cancer sequencing towards diagnostics, and participation in international efforts for development of best practice methods, including being computational leaders of the Norwegian Cancer Genomics Consortium, partner of the BIGMED ICT lighthouse and of Elixir Norway, and participates in the Center of Innovation Excellence Big Insight for the knowledge economy.
- Further development of statistical genomics based on our software, the Genomic HyperBrowser. This is an internationally used tool for multipurpose integrated statistical analysis of genomic data.
- Melanoma signalling perturbations for systems understanding, including MITF, BRAF and CDKN2A aberrations
- Understanding the consequences for modulation of immune responses in melanoma
- Familial cancer project, including a close collaboration with deCODE, Iceland

RECENT ACHIEVEMENTS

Publications: 14
BIGMED funding

MESENCHYMAL CANCER BIOLOGY

"Drug repurposed for orphan cancer"

ACTING GROUP LEADER: Heidi Maria Namløs

ABOUT

The 15-member group has a long standing interest in the biology of mesenchymal tumors (sarcomas). From September 2016, Heidi Maria Namløs has been the deputy group leader, as Ola Myklebost moved to Bergen and Haukeland University Hospital. The current focus is on precision medicine for sarcoma, and Ola Myklebost is head of the Norwegian Cancer Genomics Consortium (NCGC, www.kreftgenomikk.no) and Norwegian Sarcoma Consortium (NoSarC, www.nosarc.no).

AIMS

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

PROJECTS

- Norwegian Sarcoma Consortium (NoSarC) - Biobanking and genomic characterization of patient material of 2-3 national cohorts of sarcomas, estimated to at least 500 samples. The project will provide unique, population-based datasets including the many rare subtypes of sarcomas
- Preclinical investigation – Using in vitro and in vivo models to evaluate the therapeutic potential of drugs that target mutations identified in patient tumors
- Sarcoma biology – Gaining further understanding of mesenchymal biology, development and progression of osteo- and liposarcomas, and potentially identify biomarkers and novel drug targets
- Establishment of ex-vivo drug sensitivity/resistance screen for sarcoma primary tumors, and search for novel anti-sarcoma drugs using drug screen on panels of liposarcoma and osteosarcoma cell lines
- Implementation of sequencing in diagnostics
- Exploration of "liquid biopsies", the detection of tumor-derived DNA in blood, to monitor disease progression and therapeutic markers

RECENT ACHIEVEMENTS

Publications: 9 (and 1 in press)
PhDs completed: 1

DEPARTMENT OF

CORE FACILITIES

"Providing state-of-the-art technology and competence to excel research"

HEADED BY **LEONARDO A. MEZA-ZEPEDA**

The Department of Core Facilities runs seven regional and national technology platforms financed by the South-Eastern Regional Health Authorities and the Research Council of Norway, providing advanced services to regional, national and international users. The Department aims to deliver easy access to state-of-the-art advanced technologies, to improve research quality through assistance by experienced personnel and optimal choice of technology, and ultimately increase the scientific competitiveness of our users. The Department of Core facilities is organised in three units; Flow Cytometry and Pre-Clinical Imaging, Advanced Microscopy, and Genomics and Bioinformatics, with a total of 21 employees. In 2016, the Genomics and Bioinformatics Unit relocated to the new Oslo Cancer Cluster Innovation Park, colocalising its activities with the Section for Molecular Diagnostics at Oslo University Hospital. This strategic move aims to facilitate the implementation of sequencing-based molecular cancer diagnostics. From January 2017, the Genomics and Bioinformatics Unit is led by Susanne Lorenz. More information at: www.ous-research.no/corefacilities.

ADVANCED LIGHT MICROSCOPY

Ellen Skarpen

Facility staff: 2

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

ADVANCED ELECTRON MICROSCOPY

Ellen Skarpen

Facility staff: 1

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

BIOINFORMATICS

Leonardo A. Meza-Zepeda

Facility staff: 5

The Bioinformatics Core Facility (BCF) provides service, support and advice in the field of bioinformatics. By combining biology with computer science, statistics and mathematical modelling we offer support for analysis and interpretation of biological data including genomics, transcriptomics and proteomics for basic and translational research. The BCF has a specific focus on developing and providing solutions for precision medicine and cancer-related projects. Our service also includes support with data handling and storage by providing approved solutions for sensitive data. The operation of the BCF is aligned with the national and local Elixir bioinformatics infrastructure project, and also interacts with USIT, University of Oslo, to facilitate the use of high-performance computing resources.

FLOW CYTOMETRY

Trond Stokke

Facility staff: 4

The Flow Cytometry Core Facility (FCCF) provides analysis and sorting services for users within the South-Eastern Health Region of Norway. Flow cytometry analysis can be performed by users themselves, as well as assisted by core facility personnel. We have 2 analyzers and one sorter with 4 lasers each that may measure up to 17 fluorescence parameters simultaneously. Sorting experiments are either performed by core facility staff, or by the users in the recently acquired Sony SH100 sorter. The FCCF has possibilities for high-throughput screening, processing and staining of cells in 96- or 384-well plates, followed by automated analysis. We have installed a new "mass-spec flow cytometer", the CyTOF. This instrument can measure up to 50-60 parameters simultaneously at single cell resolution. The FCCF collaborates with facility nodes at the Rikshospitalet and Ullevål campuses of OUH.

GENOMICS HIGH-THROUGHPUT SEQUENCING AND MICROARRAYS

Leonardo A. Meza-Zepeda

Facility staff: 7

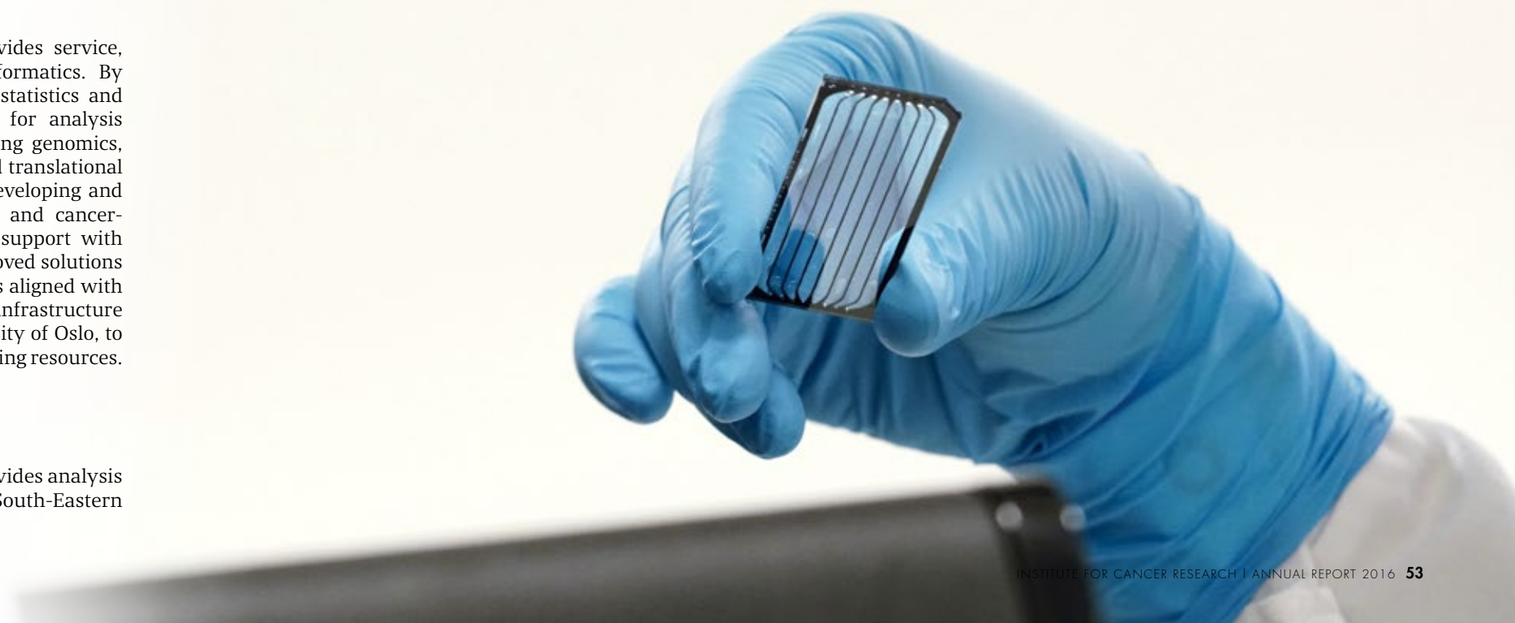
The Genomics Core Facility (GCF) provides state-of-the-art high-throughput genomic services to the Norwegian scientific community. The GCF offers an extensive portfolio of complex technologies to study genome structure, dynamics and function using high-throughput sequencing and different commercial microarray platforms. Our highly competent and experienced service personnel provide advanced support to clinical, translational and basic researchers. Our services include standard and custom solutions to study the transcriptome, genome and epigenome from multi-genes to genome wide level. The core facility collaborates with similar nodes at the Ullevål campus for sequencing and microarray services. The GCF is a member of the Norwegian Genomics Consortium, and the Norwegian Consortium for Sequencing and Personalised Medicine (NorSeq). The GCF provides the sequencing infrastructure and competence for the National Personalised Medicine initiative, and in 2016 has renewed its sequencing instrumentation by a large infrastructure grant financed by Research Council of Norway.

PRECLINICAL MAGNETIC RESONANCE IMAGING (MRI)

Trond Stokke

Facility staff: 2

The Preclinical MRI Core Facility provides access to a state-of-the-art 7T Bruker MRI system and all the necessary equipment for in vivo research on small animals or tissue/organ samples from larger animals or humans. A comprehensive library of standard off-the shelf protocols are available, and custom-protocols can be developed upon user request. The service offered by the core facility includes design, development and running of the MRI experiment, as well as post processing of the data in addition to instrument specific training. The core facility collaborates with the Preclinical MRI node at the Ullevål campus. In addition, an IVIS pre-clinical in vivo imaging service is available, suitable for whole body 2D imaging using fluorescence and luminescence.



RESEARCH CENTRES OF ICR

CENTRE OF EXCELLENCE

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

K. G. JEBSEN CENTRES

The K.G.Jebsen Foundation supports Centres for Medical Research of high international quality as part of its program for translational medicine. The centres are selected in collaboration with the Norwegian medical faculties and University Hospitals for a period of 4 years. The selected Centres receive 16 million NOK in basic funding from the Foundation and support from the host institutions, University of Oslo (Centre for Cancer Immunotherapy) or Oslo university Hospital (Colorectal Cancer Research Centre).

NORWEGIAN CANCER GENOMICS CONSORTIUM

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

CENTRE FOR CANCER BIOMEDICINE (CCB)

HEADED BY **HARALD STENMARK AND RAGNHILD A. LOTHE**

"Uniting basic and translational cancer research for the benefit of the patient"

ABOUT

CCB was inaugurated in September 2007 with the vision of joining cell biological research aimed at discovering new mechanisms in carcinogenesis and tumour suppression with translational cancer research focusing on discovery of novel molecular and phenotypic hallmarks of cancers that can be exploited in diagnostics, prognostics and therapy. Through collaboration with CCB's experts in biostatistics, this has indeed proven to be a fruitful strategy, and CCB scientists have made several discoveries and innovations that promise to be useful for future patients with lymphoma, colorectal cancer or prostate cancer.

AIMS

- Discovery of novel mechanisms in tumour suppression and cancer development
- Discovery of novel molecular and phenotypic hallmarks of cancers that can be exploited in cancer diagnostics, prognostics and therapy

PROJECTS

- Protein internalisation and signalling
- Cellular membrane dynamics
- Intracellular transport
- Cancer genetics
- Cancer epigenetics
- Cancer genomics
- Tumour heterogeneity and clonal expansion
- Cancer Biostatistics
- Advanced image analyses

RECENT ACHIEVEMENTS

CCB's interdisciplinary research strategy has continued to yield discoveries that will benefit the future cancer patient. A paper that received considerable attention came from PhD student Nadja Katheder in Tor Erik Rusten's CCB project group. Katheder, Rusten and their co-workers published in Nature that tumours instruct cells in their microenvironment to turn on autophagy, a cellular process that entails degradation of some of the cell's own proteins into amino acids. These amino acids are then transported back to the tumour as constituents of new cancer cell proteins. If this mechanism is inhibited, the tumour shrinks, which provides us with a new target for future cancer therapy. This findings were dedicated a commentary article in *Developmental Cell* and were covered by the news on national TV. Another CCB project leader, June Myklebust, has uncovered important differences between different subtypes of lymphomas in terms of signal transduction downstream of the B-cell receptor, and these differences may have consequences for choice of therapy. Researcher Anita Sveen in Ragnhild A. Lothe's group has demonstrated that genetic differences between metastases within the same colorectal cancer patient who has undergone liver surgery are key determinants for survival. The patients with the largest genetic heterogeneity have the worst prognosis. PhD student Andreas Hoff in Rolf I. Skotheim's group has identified 8 new fusion genes in testicular cancer that can potentially be used as biomarkers for diagnosing this disease. CCB's biostatisticians, headed by Knut Liestøl and Ole Chr. Lingjærde, have been important collaboration partners for several of the abovementioned projects, and cross-disciplinary cooperations continue to be a key to success in CCB. CCB congratulates Ragnhild A. Lothe with the "Toppforsk" grant from the Research Council with the project «Modeling tumor heterogeneity in colorectal cancer management» and Håvard E. Danielsen with the "Lighthouse" project under the Research Council, entitled "DoMore!". For the second year in a row, H.M. the King's gold medal for best PhD thesis was awarded to a PhD student from CCB, namely Marina Vietri in Harald Stenmark's group. CCB graduated 5 PhD candidates in 2016 and published 62 articles, several of these in leading journals.

CLINICAL TRANSLATION

Clinical associate Harald Holte was the senior author on a recent national population-based study of non-Hodgkin lymphoma (NHL) patients treated with autologous stem-cell transplantation (HDT-ASCT) in Norway between 1987 and 2008 (n = 578). NHL patients treated with HDT-ASCT were at increased risk of second cancer and premature death. The mortality was still elevated at 5 years, but after 10 years mortality equalled that of the general population (Smeland KB et al., Brit J Haematol 2016).

Clinical associate Arild Nesbakken was the senior author on a 10-year retrospective study reporting high clinical success rate in both the palliative and bridge to surgery setting for the controversial stent treatment of large bowel obstruction (Gleditsch D et al., J Gastrointest Surg 2016). Furthermore, Nesbakken and colleagues reported that frailty and old age is not a contraindication for CRC surgery but rather a significant quality of life score was present after surgery (Rønning B et al., Geriatr Oncol 2016).

In two clinicopathological studies of prostate cancer our clinical associate Karol Axcrona and colleagues showed the relevance of tumor stroma markers with prostate cancer specific death including lymphovascular invasion or perineural invasion combined with reactive stroma (Sæter T et al., Prostate 2016 a, b)

EXECUTIVE GROUP (IN 2016)

Harald Stenmark, director
Ragnhild A. Lothe, co-director
Håvard E. Danielsen
Knut Liestøl
Guro E. Lind
Kirsten Sandvig
Erlend B. Smeland

ASSOCIATE PIS

Sverre Heim
Rolf I. Skotheim
Antoni Wiedlocha

ASSOCIATE CLINICAL RESEARCHERS

Arild Nesbakken
Harald Holte
Karol Axcrona

K.G. JEBSEN CENTER FOR CANCER IMMUNOTHERAPY

HEADED BY **JOHANNA OLWEUS**

STIFTELSEN KGJ Kristian Gerhard Jebsen Foundation

"Our goal is to develop new therapeutic strategies that overcome immune tolerance to target cancer"

ABOUT

In the K.G. Jebsen Center for Cancer Immunotherapy (JCIT) hosted by the University of Oslo, five Norwegian and one Dutch research group have come together to find new immunotherapeutic strategies that overcome the major challenge of self-tolerance in cancer. JCIT was in 2016 awarded maximal prolongation following the first 4-year period, till 2020. This consortium of PIs is assembled based on highly complementary expertise in proteomics, cell signaling, T-cell receptor (TCR) and HLA-engineering and animal models, translational research and clinical trials in immunotherapy. Of the 53 center employees 55% are recruited from abroad (60/40 women/men). The center is part of OUH Focus Area for Cancer Immunotherapy, lead by partner Kolstad.

AIMS

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

PROJECTS

- Epitope discovery to identify targets for immunotherapy
- Identify immune cells expressing immune receptors that recognize and kill cells that express the identified targets
- Molecular cloning, genetic transfer and profiling of immune receptors
- Enhance cytotoxic lymphocyte function by overcoming inhibitory mechanisms
- In vivo evaluation of immune modulating therapies

RECENT ACHIEVEMENTS

- Identified molecular drivers of adaptive NK cell responses *(Liu et al., Cell Reports)*.
- Signed a license and collaborative agreement with *Fate Therapeutics Inc.* concerning the development of universal iPS-derived NK cells.
- Demonstrated that healthy donor T cells represent a rich source of T-cell receptors that can recognize cancer neo-antigens neglected by the patient T cells, with potential for new donor-derived immunotherapies *(Strønen et al, Science)*. The article was the focus of commentary articles in *Science* and *New Engl J Med.*
- Demonstrated that aspirin works as a secondary prevention, preventing relapse in patients treated for colorectal cancer in an unselected population-based study *(Bains et al, JCO)*
- Tools to compare large datasets of subcellular fractionation with those of modern mass spectrometry (MS) to generate detailed maps for the spatial organization of cellular proteins have been lacking. In an article published in *Nature Methods* by *Lund-Johansen et al,* user-friendly bioinformatics tools were applied to conduct the first meta-analysis of published data. The results form basis for a "consensus" map of subcellular proteomes and point to an urgent need for standardization of experimental protocols.

CLINICAL TRANSLATION

A key strength of the center is the ability to couple clinical trials testing new concepts for immunotherapy developed by the PIs, combined with penetrating mechanistic analyses:

- In 2016 a new clinical trial was started, Lymvac II. The trial builds on the successfully completed Lymvac I cancer immunotherapy trial, in which a novel local immunotherapeutic strategy was tested. Based on this successful study two follow-up studies were designed to i) identify T-cell targets (on-going) (supported by Roche), and ii) improve the local immunotherapy regime with addition of systemic anti-PD-1 in patients, supported by Merck. Three patients were enrolled.
- In 2016, a Swedish-Norwegian collaboration concerning NK-cell based cancer immunotherapy was launched and the second generation culture platform was validated in full-scale GMP at the Karolinska Institute and at Oslo University Hospital.

HOME PAGE

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

GROUP LEADERS/ STEERING COMMITTEE

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

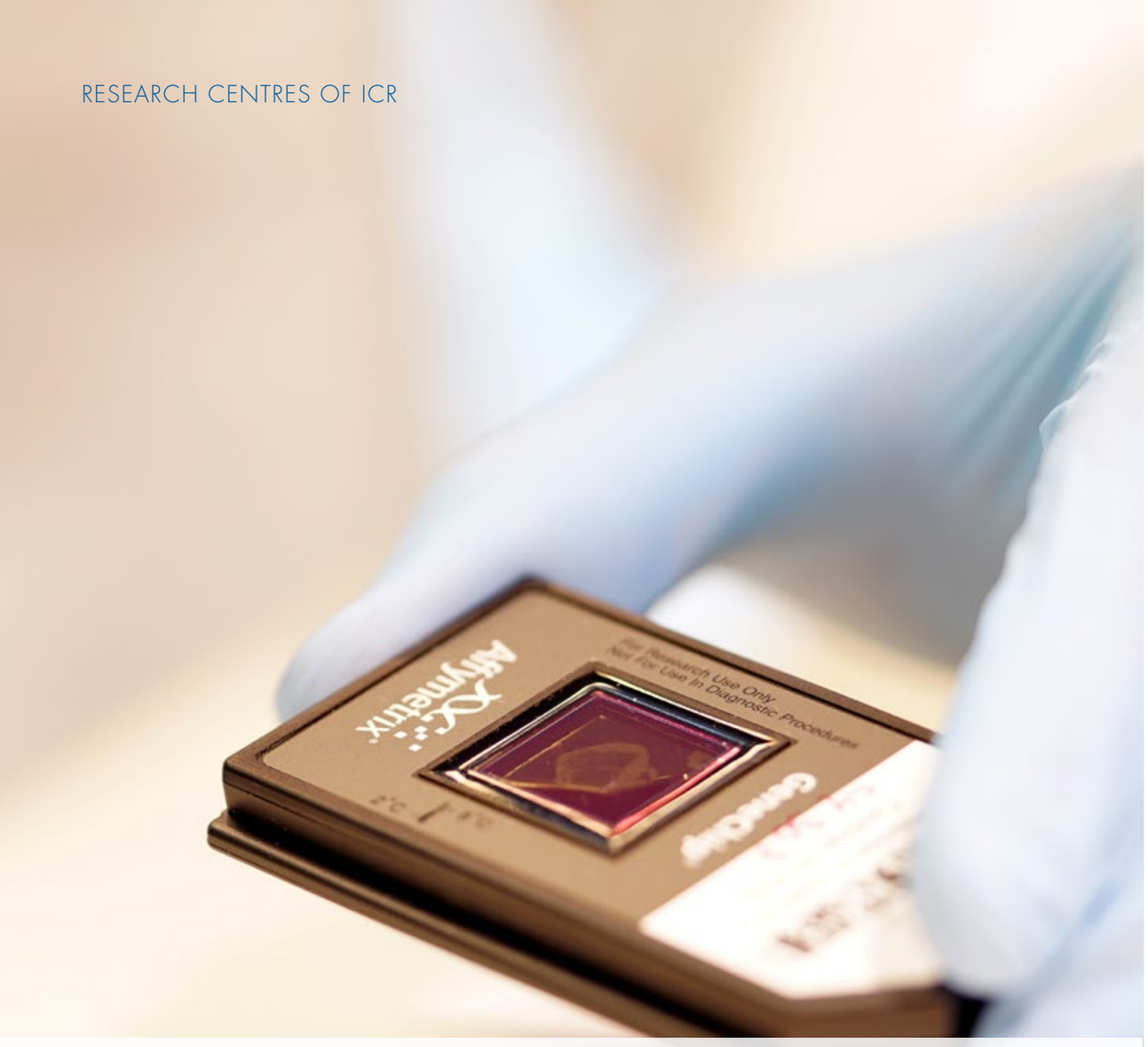
Karl Johan Malmberg (MD, PhD, deputy Director), Dept of Cancer Immunology, Institute for Cancer Research, OUH-Radiumhospitalet and UiO

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

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

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

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



K.G. JEBSEN COLORECTAL CANCER RESEARCH CENTRE

HEADED BY **RAGNHILD A. LOTHE**

STIFTELSEN KGJ Kristian Gerhard Jebsen Foundation

"High quality translational research for the benefit of colorectal cancer patients"

ABOUT

Colorectal cancer (CRC) is a major health burden, and the focus of our Centre is translational and clinical research to meet challenges in the management of the disease, including early detection and improved patient prognostication and treatment. The Centre is hosted by the Clinic for Cancer Medicine, Oslo University Hospital (OUH). The Centre PIs are also partners in the OUH SMART-Colorectal cancer priority area.

Home page: www.colorectalcancer.no

GROUP LEADERS/STEERING COMMITTEE OF THE CENTRE

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

AIMS

Translate biomedical knowledge to improve the prevention and treatment of CRC by uniting a translational multidisciplinary research environment with focus on high quality in all steps of the research process, following the patient through the course of the disease.

PROJECTS

- Effectiveness of screening and colonoscopy procedures
- Clinical and molecular biomarkers for improved risk stratification of patients
- Improved treatment efficacy from chemotherapy and/or targeted drugs by biologically guided treatment
- Model tumor heterogeneity and clonal evolution to monitor early relapse and treatment failure
- Identify of high risk precursor lesions and novel biomarkers in population-based screening studies

KEY ACHIEVEMENTS

In 2016, 37 peer reviewed papers related to CRC were published from the PI groups, including Ann Intern Med, Ann of Oncol, Brit Med J, GUT, JAMA Intern Med, Lancet Gastroenterology & Hepatology, Oncogene and PLoS Genet, and three PhDs were defended.

The Bretthauer group provided new insights in the effectiveness of CRC screening from long term trials, including 1) a low benefit of sigmoidoscopy for women older than 60, and alternative screening methods should be considered for these women (Holme Ø et al., Brit Med J 2017 Jan), and 2) screening colonoscopy have a modest benefit in preventing CRC in beneficiaries aged 70 to 74 years and a smaller benefit in older beneficiaries, and the risk for adverse events was low but greater among older persons (Garcia-Albeniz et al., Ann Intern Med 2017 Jan).

Tumor heterogeneity has important clinical implications. In 2016 we described substantial variation in the level of genomic heterogeneity among liver metastases from individual patients, (Sveen et al.,PLoS Genetics). We discovered inter-metastatic heterogeneity to be a key determinant of patient survival. Several studies related to the topic of heterogeneity are ongoing.

Collaborative studies among the Centre clinicians and other scientists report treatment improvements and management challenges of rectal cancer, related to survival end-points (Gledistch D et al., J Gastrointest Surg; Stornes T et al, Dis Colon Rectum; Glimelius B et al., Radiother Oncol 2016; Cameron MG et al., Acta Oncol 2016; Rønning et al. J Geriatr Oncol 2016; Labori et al., Colorectal Dis 2017).

The power of large patient series to identify and assess high-precision clinical biomarkers calls for participation in international multi-center studies. Two retrospective, pooled biomarker studies including several thousand patients were recently published (Domingo et al., Lancet Gastroenterology & Hepatology 2016; Dienstmann et al., Annals of Oncol 2017Feb)

We have continued to develop bioinformatics pipelines for high-throughput sequencing of DNA and RNA data and for pharmacogenomic analyses. By drug sensitivity analyses of preclinical models we have found several targeted drugs that in combination with chemotherapy are likely to achieve strong response in molecularly stratified patient subgroups (Sveen, Bruun et al., to be submitted March 2017).

PATIENT ADVISORY BOARD

User involvement in clinical research is a pronounced strategy from the Norwegian health authorities and our hospital. A patient advisory board was established in 2016 for our K.G.Jebsen Centre with the following members: Marianne Guriby (age 31), teacher, Lars Reed, (45), engineer, Thorvald Stoltenberg, (85), retired politician, Jack Waitz (71), athlete coach.

CLINICAL TRANSLATION

Efficient, inexpensive, clinical procedure: carbon dioxide rather than room air to distend the colon during endoscopy reduces post procedure discomfort (Bretthauer M et al., JAMA Intern Med 2016; Bretthauer et al., Ann Intern Medicine 2016).

A phase II intervention trial initiated in our KGJ Centre started patient recruitment in 2016: "Adjuvant chemotherapy in elderly with colon cancer stage III – geriatric assessment and prognostic gene signatures". PI Marianne Guren.

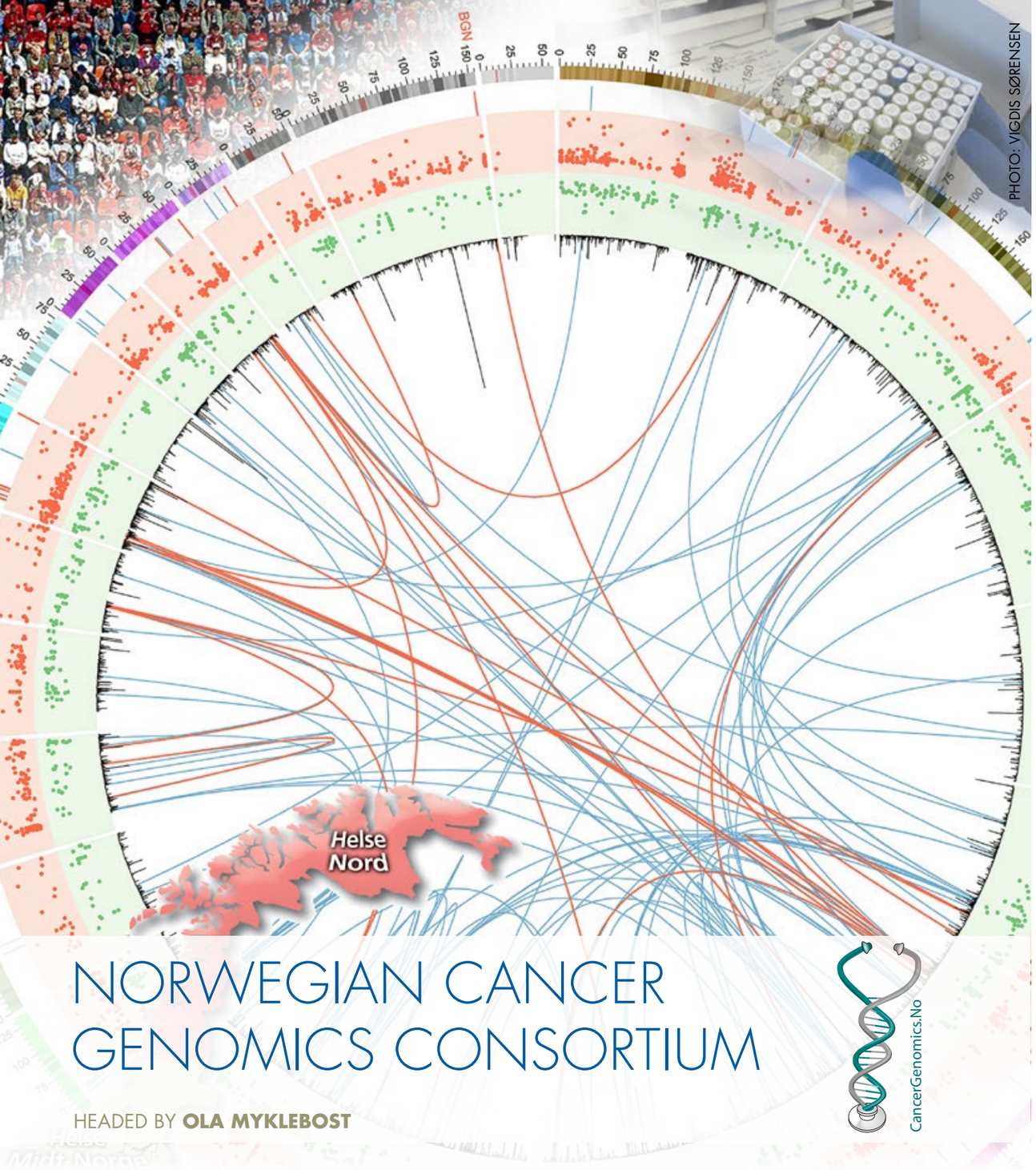


PHOTO: VIGDIS SØRENSEN

NORWEGIAN CANCER GENOMICS CONSORTIUM

HEADED BY **OLA MYKLEBOST**

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

ABOUT

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

AIMS

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

PROJECTS

- Exome sequencing and mutation profiling of nine selected cancer types
- Establishment and characterisation of relevant preclinical models
- Validation of novel targets in preclinical models
- Investigation of predisposing gene variants
- Establishing of national infrastructure for the storage and analysis of large-scale sensitive patient data
- Design of small-scale trials to identify potential of candidate drugs
- Develop decision support tools for pathologists and oncologists to better interpret genome diagnostic data for therapeutic interventions

The projects include the determination of the sequence of all genes in the patient and the tumour, identification of mutations that reveal mechanistic insights or can suggest specific treatments. Trial-derived biobanks from melanomas, leukemias, sarcomas, and breast cancers are being investigated for predictive biomarkers, as are biobanks containing colon, prostate, myeloma, and lymphoma samples from standard-ofcare treated patients. The leukemia trial investigated is from the first in man trial of an Axl inhibitor from BerGenBio. A prospective, population-based cohort of all Norwegian sarcoma patients for 3 years is being accrued (see NoSarC.no), and in addition to the 100 sample pairs exome sequenced by NCGC, about 200 additional pairs are being sequenced with additional funding. Up to now approximately 1800 samples from 630 patients have been sequenced. Promising targets for which drugs are available, but without documentation of effect in the cancers investigated, are tested pre-clinically in relevant cell and xenograft models. The intention is then to propose small, exploratory clinical trials to indicate activity in selected patients, and that promising results could lead to proper phase II studies. Several trials are in progress by the partners.

The main hub of NCGC is at the ICR and its core facility for genomics, and five of the co-principal investigators are from the ICR. The other main nodes are at the University of Oslo, Haukeland University Hospital (Bergen), St Olav University Hospital (Trondheim), University Hospital of Northern Norway (Tromsø), and the University of Tromsø.

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

RECENT ACHIEVEMENTS

The data from the sequenced samples are currently being deeply investigated, and a number of preclinical studies in cell lines are under way. A database has been generated at 1000genomes.no with all the SNPs detected in the germ lines, and the frequencies in the population. Other environments are preparing to add Norwegian SNP data, which will be a valuable resource for many types of genetic research and diagnosis.

CLINICAL TRANSLATION

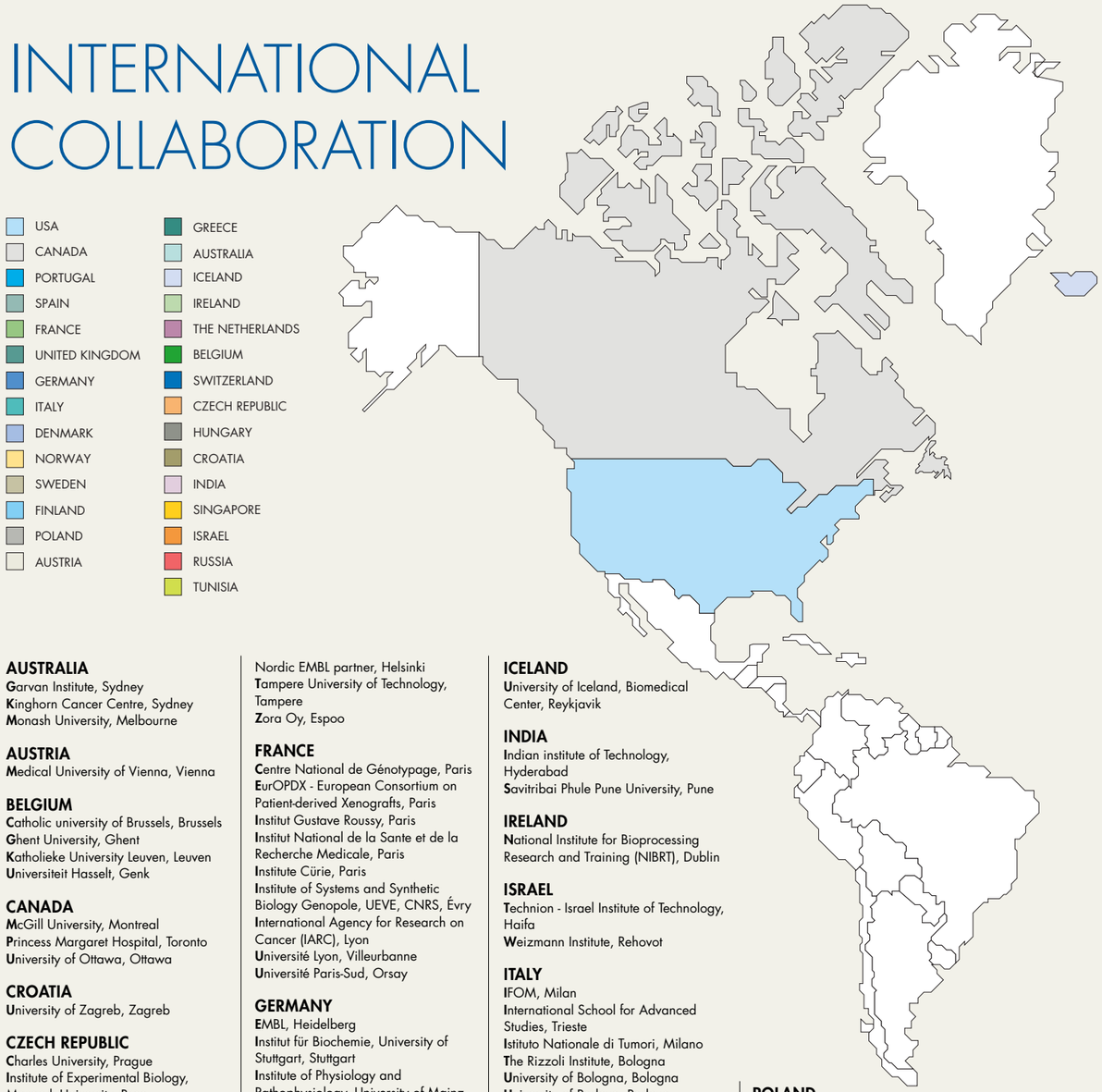
The project is investigating patient samples either prosepctively collected, or being part of clinical trials, with the aim to gain biologically based clinical insight. Oncologists are strong partners. The detection of novel therapeutic targets and their evaluation in pre-clinical studies may have immediate clinical value. The team maintains a systematic professional dialogue, with repeated discussions on the strategies and how they may be implemented in the clinic at institutional meetings, external conferences and public meetings.

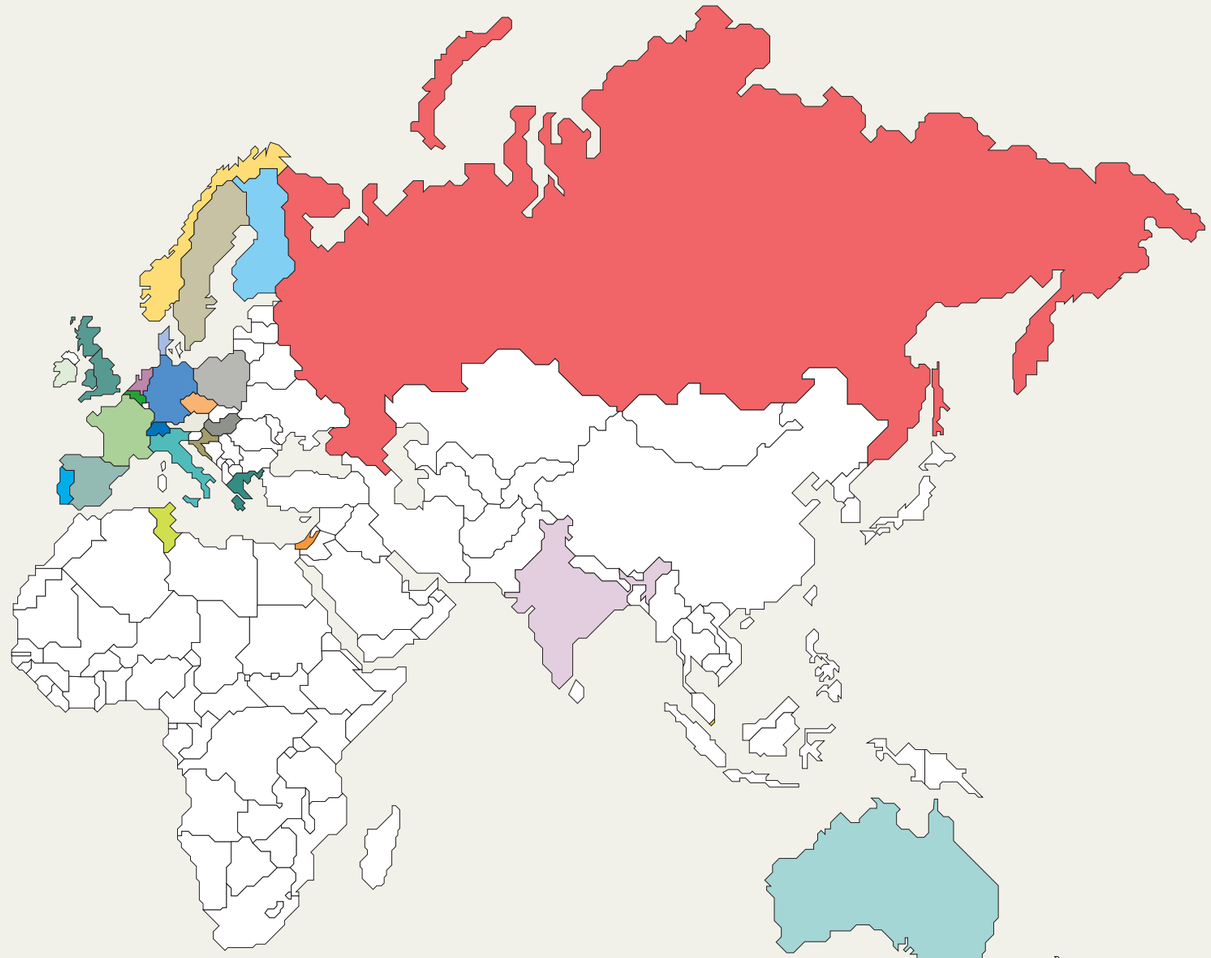
GROUP LEADERS/STEERING COMMITTEE

The project has a leader group consisting of Ola Myklebost (ICR, head), Ragnhild A Lothe (ICR), Harald Holte (KRE), Leonardo A Meza-Zepeda (ICR), Eivind Hovig (ICR), Per Eystein Lønning (HUS), Bjørn Tore Gjertsen (HUS), Anders Waage (St Olav US), Ole Morten Seternes (UiT), Tom Dønnem (UNN).
Our Board consists of Erlend Smeland (OUH, Head), Jónas Einarsson (RF), Edvin Johannessen (UiO), Knut Martin Torgersen (Pfizer), Bjørn Gustafsson (NTNU), Tove Flem Jakobsen (Inven2), Olav Mella (UiB), Anne Sameline Grinsgaard (UNN).

see http://CancerGenomics.No

INTERNATIONAL COLLABORATION





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Kinghorn Cancer Centre, Sydney
Monash University, Melbourne

AUSTRIA
Medical University of Vienna, Vienna

BELGIUM
Catholic university of Brussels, Brussels
Ghent University, Ghent
Katholieke University Leuven, Leuven
Universiteit Hasselt, Genk

CANADA
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Princess Margaret Hospital, Toronto
University of Ottawa, Ottawa

CROATIA
University of Zagreb, Zagreb

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Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague
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University of Oslo, Oslo

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Jagiellonian University, Kraków
University of Gdansk, Gdansk

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Portuguese Oncology Institute, Porto

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Institute of Cytology and Genetics, Novosibirsk

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University of Valencia, Valencia
Universitat Politècnica de València, Valencia
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University Medical Center, Groningen
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Hampshire Hospitals/Southampton University, Southampton
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Royal National Orthopaedic Hospital, Stanmore, Middlesex
The Beatson Institute for Cancer Research, Glasgow
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Fred Hutchinson Cancer Research Center, Seattle, Washington
Georgetown University, Washington DC
Harvard University, Boston, Massachusetts
Johns Hopkins Medicine, Baltimore, Maryland
Lawrence Berkeley National Laboratory, Berkeley, California
Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina
Masonic Cancer Center and University of Minnesota, Minneapolis
Massachusetts General Hospital, Boston, Massachusetts
MD Anderson Comprehensive Cancer Center, Houston, Texas
National Institutes of Health (NIH), Bethesda, Maryland
Oregon State University, Corvallis, Oregon
Princeton University, New Jersey
Rutgers Cancer Institute of New Jersey
Stanford University, California
The Mount Sinai Hospital, New York
The University of Kansas Hospital, Kansas
Tisch Cancer Institute, New York
UCSF, Helen Diller Family Cancer Centre, San Francisco, California
University of Albany, New York
University of California, Berkeley, California
University of Chicago, Illinois
University of Colorado, Denver, Colorado
University of Illinois, Champaign, Illinois
Washington University, St Louis, Missouri
Weill Medical College of Cornell University, New York

RECENT INNOVATIONS

Registered Declaration of Inventions (DOFIs), Patent Applications and Granted Patents

2014

GRANTED PATENTS

New markers for cancer (CNRIP1). Country: CN (and JP, GB, GE, FR in 2013). (R. Lothe, G. E. Lind, R. Skotheim)

2015

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Methods and biomarkers for detection and prognosis of cervical cancer (H. Lyng, C. H. Julin, M. Lando)

Urinary exosomal protein markers. (A. Llorente, T. Skotland, A. Øverbye, K. Sandvig)

Prostate cancer markers and uses thereof. (A. Llorente, T. Skotland, K. Sandvig)

Compositions and methods for targeting antigen-presenting cells (M. Sioud, G. Skorstad)

CTL peptide epitopes and antigen-specific T- cells, methods for their discovery, and uses thereof (J. Olweus, S. Kumari)

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2016

NO. OF DOFIs: 6

NO. OF UNPUBLISHED PATENT APPLICATIONS: 4

PUBLISHED PATENT APPLICATIONS

Modulation of function of immune effector cells (K-J. Malmberg, J. P. Goodridge)

Selective and controlled expansion of educated nk cells (K-J. Malmberg, V. Beziat)

Proteins in urinary exosomes as biomarkers for prostate cancer (A. Llorente, T. Skotland, K. Sandvig, A. Øverbye)

Methods and biomarkers for analyses of colorectal cancer. (R. A. Lothe, J. Bruun, M. Kolbreg, R. I. Skotheim, G. E. Lind, A. Nesbakken)

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