INSTITUTE FOR CANCER RESEARCH

Annual Report 2018

Oslo University Hospital

HELSE SØR-ØST

UiO : University of Oslo

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The photographic theme of this year's Annual Report is *Humans at ICR*.
- The most important part of ICR is by far its human resources and our collective competence.

FRONT PAGE:
Light, protons and neutrons are utilised to activate photosensitizers for cancer therapy. This is funded by two new EU Horizon2020 Future Emerging Technologies (FET-OPEN) grants to Department of Radiation Biology (Theo Theodossiou and Kristian Berg) along with support from HSØ. Here: Diode laser-based PCI treatment.

PAPER: 150/300 Profimatt
CIRCULATION: 800

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Introduction by the Director

The Institute for Cancer Research (ICR) is an institution with approximately 350 employees plus students organised in 24 research groups complemented with cutting-edge core facilities. The ICR is a premier institution in basic and translational cancer research on a national and international arena and has a strong prior track record in translation and innovation. It was therefore with a great deal of humility and respect that I came to the position as Head and Director of the Institute of Cancer Research (ICR) at Oslo University Hospital (OUH) from January 2018.

From the start of 2018 we set out as a long-term goal, in agreement between the ICR Leadership group and the Head of the Division for Cancer Medicine, that rather than increasing the scientific output in terms of number of papers, we would like to see a further increase in quality of the output. Against this backdrop, it is interesting to see that already now, the median impact factor of the papers produced is up from 4.1 in 2017 to 5 in 2018. The fact that we have still produced 186 papers (and more than 50 in the two first months of 2019) is also excellent, particularly as almost half of the production also has first and/or senior authors from ICR.

More than 2/3rds of the total ICR funding in 2018 (310 MNOK) came from extramural grants. ICR scientists have also been able to obtain substantial new funding and secured major new grants from the Norwegian Cancer Society, the Research Council of Norway, and the South-Eastern Norway Regional Health Authority as well as private and international sources.

We celebrate our victories at the ICR, and in 2018 we have marked the fact that both Karl-Johan Malmberg and Tor Erik Rusten won very prestigious 5-year "Toppforsk" grants from the Research Council and the University of Oslo. We have also had the official opening of a new KG Jebsen Centre for B Cell Malignancies where ICR scientists participate (and with June Myklebust as Deputy Director). In the fall, we celebrated the award of a highly prestigious ERC Advanced Grant to Harald Stenmark (one of very few that has been granted an ERC AdG for the second time!). We have marked the fact that Kristian Berg and Theo Theodossis have won two prestigious Horizon2020 Future Emerging Technologies (FET-OPEN) grants for research on how light, neutrons and protons can be combined with photosensitizers for drug delivery and cancer therapy and that Guro Lind won a large KLINBEFORSK grant for a multi-centre trial to document a biomarker for bladder cancer recurrence. Newly appointed Assoc. Prof. Anita Sveen won a Young talent grant from the RCN. And we have celebrated internally the award of King Olav Vs Prize for Cancer Research by the Norwegian Cancer Society to Vessela Kristensen, the award of the UiO Research Prize to Harald Stenmark, the Ragnar Mørk's Prize for Outstanding Research to Kaisa Haglund and the election of Johanna Olweus to the Norwegian Academy of Science and Letters. Also, OUH awarded prizes in their bi-annual assessment of best papers to ICR researchers Fergal O'Farrell and Tor-Erik Rusten (May 2018) and Tord Hompland and Heidi Lyng (Nov 2018).

2018 marked the end of the Norwegian Cancer Genomics Consortium project (NCGC, headed by Ola Myklebust) where numerous patients with nine different cancers have been sequenced and mutational analysis conducted. A special report has now been published that summarizes the extent of the accomplishments made and shows how this may form a solid research fundament for future development of precision cancer medicine in Norway.[1]In addition to the above highlights, numerous other research discoveries and clinical trials report on major scientific advances at ICR and represent good news for future cancer patients, as exemplified elsewhere in this report.

In the Department of Cancer Immunology, June Myklebust has been appointed Group Leader for the Lymphoma Biology Group and succeeds Erlend Smeland who continues to support the group as a senior member and co-lead in addition to his job as OUH Director of Research and Innovation. ICR's strong standing in Norwegian research is also illustrated by the fact that members of the institute lead a Centre of Excellence (CoE) Centre for Cancer Cell Reprogramming (CanCell, Director Harald Stenmark) and the three K.G. Jebsen centres for Cancer Immunotherapy (Director Johanna Olweus), Colorectal Cancer Research (Director Ragnhild A. Lothe), both in the extension phase, and for B Cell Malignancies (new, Deputy Director June Myklebust), all with strong participation from ICR groups.

The ICR sets out to maintain the excellent science and outstanding production and to further build excellence by organising more collaborative efforts at all levels to deal with grand challenges in cancer medicine and to position the ICR in national and international alliances and consortia (see following section on ICR into the future). We aim to be a significant partner for the clinical activities in the Division of Cancer Medicine and the OUS OECI-accredited Comprehensive Cancer Centre (CCC). We continue feeding results into a translational research path and to have **patient benefit** in mind in all aspects of research and innovation.

March, 2019,
Kjetil Taskén, Head of the ICR

[1] The NCGC Report can be downloaded at: https://kreftgenomikk.no/files/2019/01/NCGC-Rapport.pdf

“Research and innovation with patient benefit in mind”

The Institute for Cancer Research

Into the future!

In 2018 the new ICR leadership team consisting of Department Heads Therese Sørlie, Johanna Olweus, Harald A. Stenmark, Ragnhild A. Lothe, Kristian Berg, Gunhild M. Mælandsmo and Leonardo A. Meza-Zepeda, ICR Chief Administrative Officer Kari Aalrust Berger and ICR Director Kjetil Taskén have worked to find our complementarities and create basis for future collaboration and cohesion.

VISION, VALUES AND OBJECTIVES

In a leadership development programme with the assistance of Tone Ringstad in Culturengine, we have mapped our individual values and work culture. We have worked on how we want the ICR as a whole to stand out with its vision, objectives and values. We have analysed what work culture we need and where the gaps are that we need to fill. The draft ICR Objectives for 2019-20 and the ICR vision and values have next been discussed in an ICR leadership meeting in February 2019 and at an all-day ICR Group Leader meeting on March 4, 2019. The finalized ICR vision, values and objectives 2019-2020 were then approved by the ICR Leadership in a meeting on March 20, 2019 and represent our joint view on where the ICR as a whole is going.

OBJECTIVES 2019-2020

With basis in the research goals of the Division for Cancer Medicine and OUH and our internal ambitions, the ICR shall:

1. **Strengthen translational research.** Hereunder:
a) Establish an advisory board or team for translational research projects drawing on our internal competencies to help projects forward;
b) Define and inform the Division for Cancer Medicine (DCM) what we aim to accomplish and where we are heading with ICR (translational) research, our strengths and needs; and
c) Find the opportunity space in DCM and OUH for developing projects.

2. **Strengthen contact, coordination and collaboration with clinicians and diagnostic staff in OUH CCC.** Hereunder:
a) Take forward and make an overview of basic, translational and clinical studies that ICR groups conduct or are involved in *;
b) Invite and meet N4-leaders on the clinical /diagnostic side in CCC (DCM and other divisions) for discussion on coordination and collaboration (ICR group- and project leaders); and
c) Use this as a starting point to implement ICR knowledge, research and competencies into OUH practise*.

3. **Build further excellence in research.** Hereunder:
a) Develop and document more projects, focus on originality, depth, quality and international value;
b) Find collaborators and partners internally and externally that enables a);
c) Increase number of applications, specifically targeting unexplored grant opportunities.

4. **Establish a new SAB for ICR**, recruit members, and organise a SAB-visit and evaluation in 2020, to follow up on the SAB visit in 2018 (to CCC).

5. **Increase internationalisation and technology development**: Increase mobility (particularly outgoing shorter research stays) to develop new networks, new competencies and find new project ideas.

WHAT VALUES AND WHICH CULTURE DO WE NEED AT THE ICR IN ORDER TO REACH OUR GOALS? (see figure, right)

- **INTEGRITY** for us means: We all take **responsibility**. We have high **ethical standards** in all our research. We show **integrity** in what we do and how we act, we stand for what we report in our research. Our **demands are high** and we show **loyalty** to objectives and team.
- **QUALITY** for us means: We have **high standards** scientifically in everything that we do and all that we produce and deliver, this is the basis of our **excellence**. All categories of staff with different backgrounds and training are equally important and form the basis for an overall quality that goes through the entire project portfolio. We set **demands** to our collaborators, and in return we offer and expect **trust** in the scientific quality of the data we produce jointly.
- **TEAMWORK** for us means: We accomplish more if we **work together as a team**, we work to elicit **synergy** in our research and between our projects. We need different competencies to achieve our goals and we appreciate **diversity** and differences in scientific and cultural background. We show **respect** for all categories of staff. We exercise **generosity** in collaboration, education and development. We work as teams at the level of projects, in research groups, at the level of the departments and at the ICR as a whole. We aim for synergy in the whole organisation to reach our most ambitious goals. We cheer each other along and celebrate our successes jointly.
- **VISION** for us means: We draw on our integrity and quality and our abilities for teamwork to raise our expectation of what we can accomplish and fulfill our vision. We exercise **courage**, dare to think big and set our **ambitions** high. We go for **passion**, support **visionary thinking** and work for **international visibility** and **global influence** in cancer research.

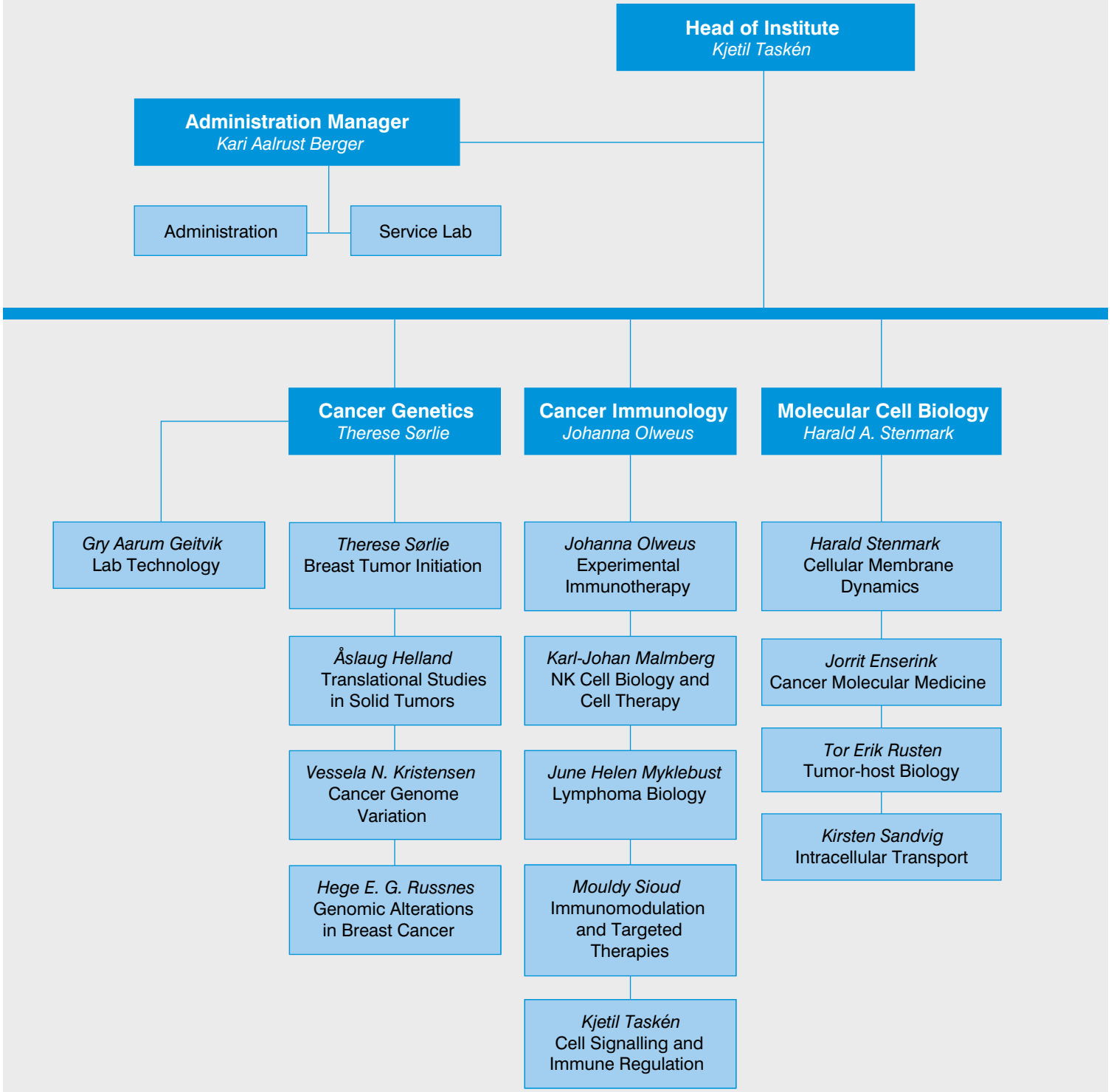
With basis in these values and culture, our vision is:
«Excellence in Fighting Cancer»

ICR Leadership, March 2019

*Start with use of the DCM research administrative system being developed.

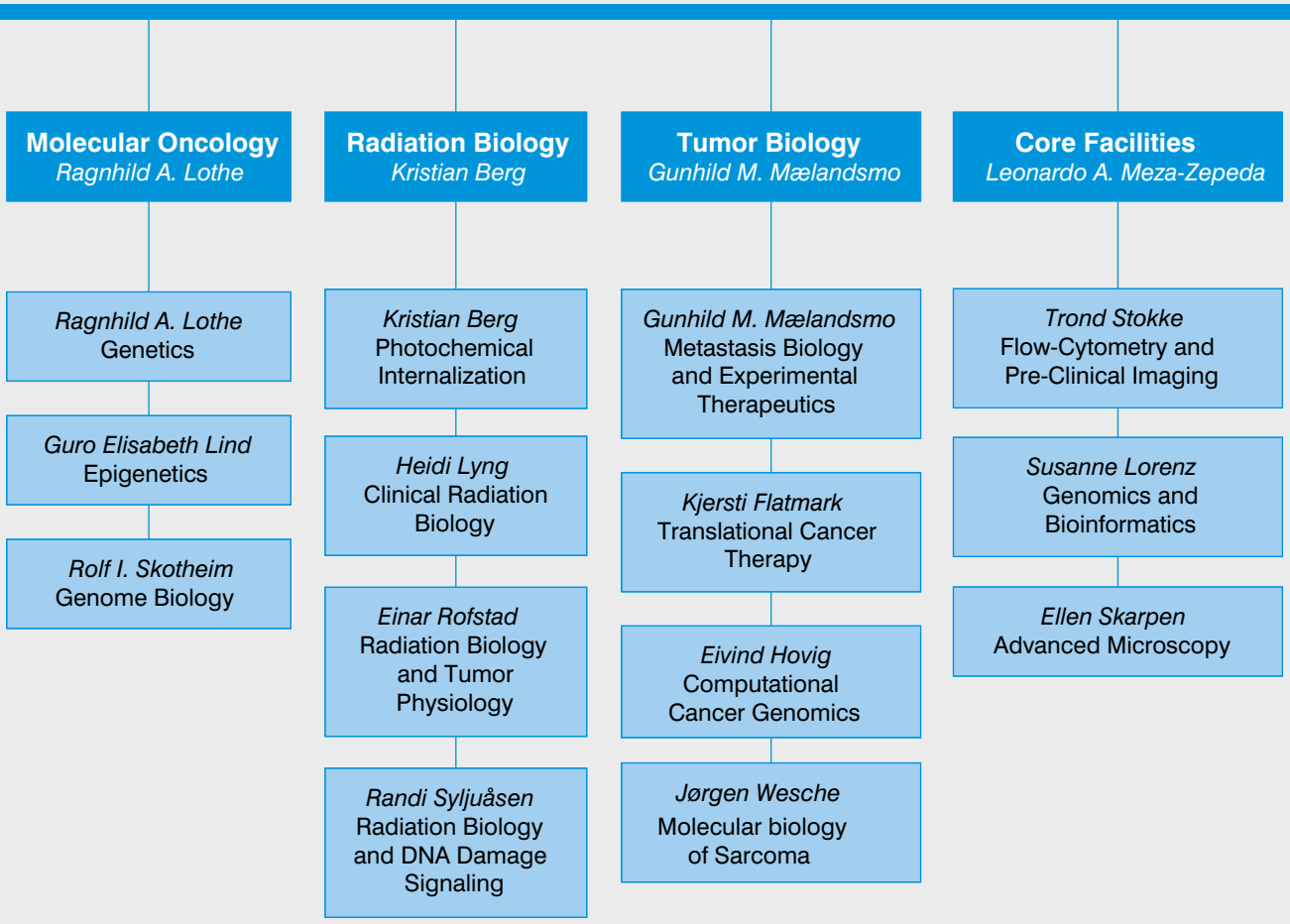
ICR leadership: Harald A. Stenmark, Therese Sørlie. Kristian Berg, Gunhild M. Mælandsmo, Leonardo A. Meza-Zepeda, Kjetil Taskén, Johanna Olweus, Ragnhild A. Lothe, Kari Aalrust Berger.

Organisation

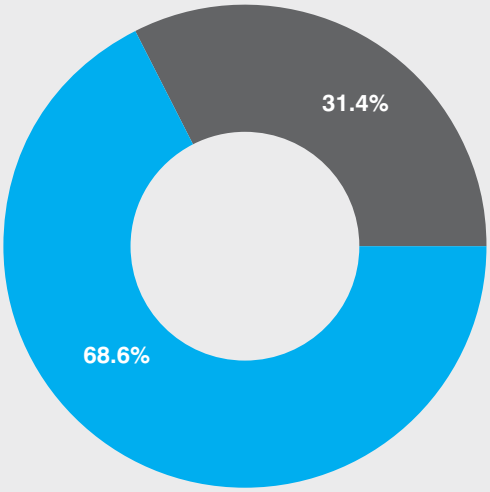


The Institute for Cancer Research

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



Key figures 2018



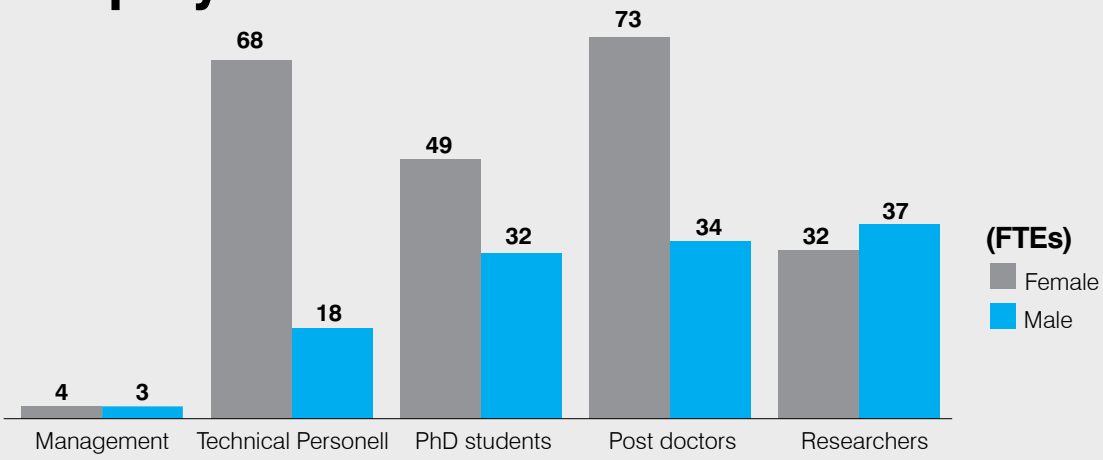
Funding

Percent

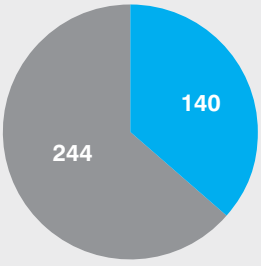
Actual Institute expenditure for 2018 by internal and external funding sources (total 310,1 MNOK = approx. 31,8 M€)

Internal funding
External funding

Employees

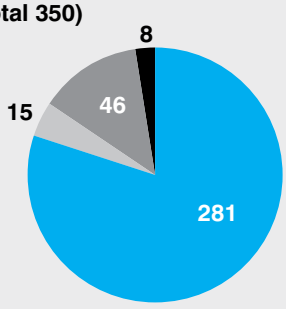


Employees by Gender
(total 384)



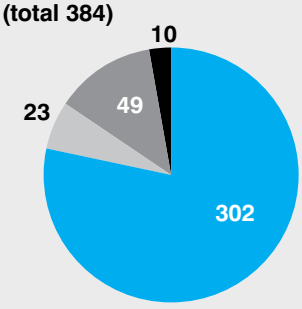
Female Male

FTEs by Employer
(total 350)

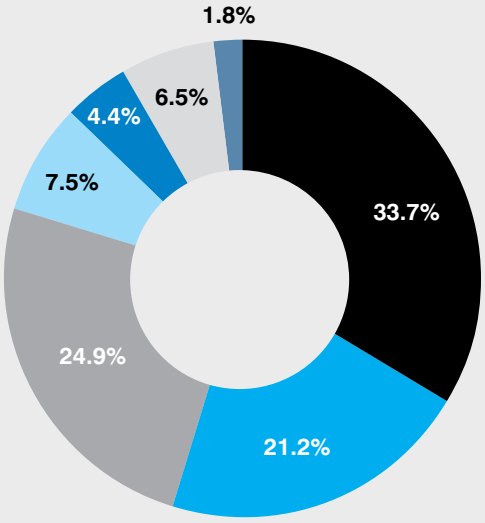


ICR OUS UiO Other

Employed by
(total 384)



ICR OUS UiO Other



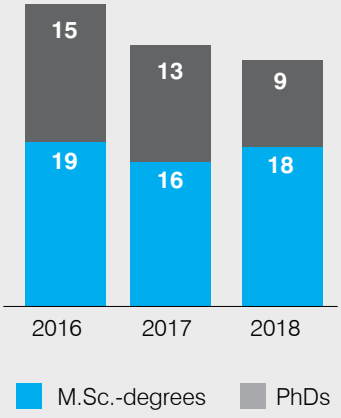
External funding by source

Percent

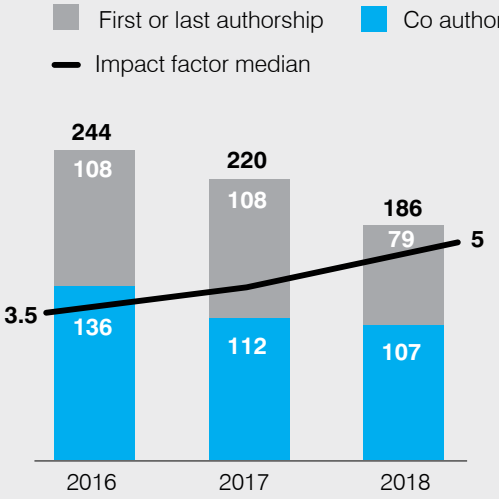
Sources of external competitive funding for 2018, based on actual expenditure (total 212,7 MNOK= approx. 21,4 M€)

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

Completed PhDs and M.Sc.-degrees



Articles published



IMPACT FACTOR			
Mean	5.8	5.8	6.5
Median	3.5	4.1	5

Oslo University Hospital Comprehensive Cancer Centre

The Institute for Cancer Research (ICR) has through its 65 years of history built research activity at a high international level within basic and translational cancer research. Furthermore, the collaborations between ICR and clinicians within the next door Radium Hospital (now part of Oslo University Hospital) has led to a large number of clinical trials and multiple innovations for the benefit of patients. This interaction has since been extended to the entire Comprehensive Cancer Centre within Oslo University Hospital (OUH CCC, accredited by OECI in 2017). ICR is closely associated with The University of Oslo, but is organized within the Division of Cancer Medicine in OUH, which is internationally quite unique for a research institute, further securing close interaction between basic/translational and clinical research. For the last ten years ICR has been located in a modern research building and today next door to the Oslo Cancer Cluster Innovation Park with Ullern high school and the Cancer Registry of Norway, giving unique infrastructure for innovation, education and population-based research. Several Centers of Excellence, up to date- core facilities, strong international and national collaboration, and not at least the highly qualified, enthusiastic and dedicated staff are all essential elements. Most are full time scientists and technicians, in addition to clinicians in combined research positions, and researchers in combined positions as university professors. In order to fully exploit its potential, the Institute is strongly dependent on even further interaction with the clinical environment and the Cancer Registry. Being the core engine within research in OUH CCC, the Institute will benefit from the integrated organization of all cancer related activities, and will play a key role in further promoting OUH CCC as a leading cancer centre in Europe.

Sigbjørn Smeland
Head of Division of Cancer Medicine,
Chair, OUH CCC Board

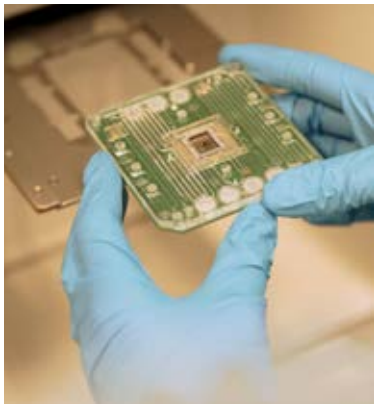
Gunnar Sæter
Research Director, Division of Cancer Medicine
Head, OUH CCC Research Committee

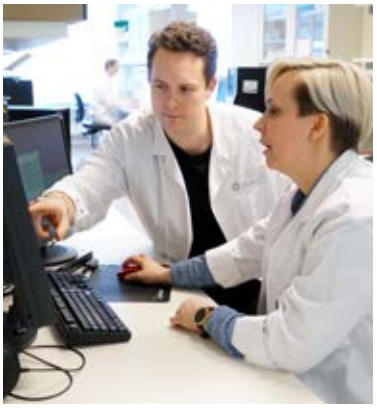
Oslo University Hospital
Comprehensive Cancer Centre

OECI COMPREHENSIVE Cancer Centre

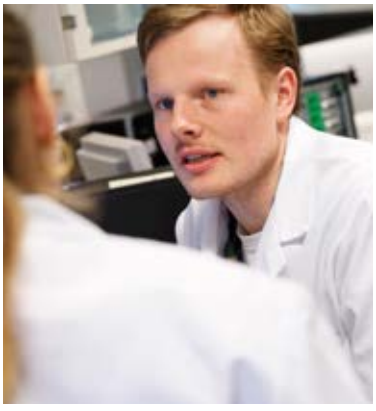
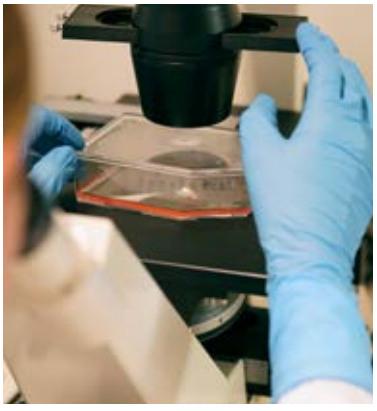
Departments

16 Department of Cancer Genetics
22 Department of Cancer Immunology
30 Department of Molecular Cell Biology
36 Department of Molecular Oncology
42 Department of Radiation Biology
48 Department of Tumor Biology
54 Department of Core Facilities





"Our mission is to improve the lives of cancer patients with solid tumors by performing translational research"

Department of

Cancer Genetics

Headed by Therese Sørlie

Our aim is to improve risk estimation, achieve earlier diagnosis and improve prediction of treatment response and outcomes for patients with early and advanced stages of breast, lung, pancreatic and ovarian cancer. Our research is translational in nature and through molecular classification, data integration, pan-cancer analyses and functional studies; we work towards facilitating the implementation of discoveries to clinical use. A common theme across groups is to achieve deeper molecular understanding of inter- and intra-tumor heterogeneity and tumor evolution using human tumor cohorts and mouse models. We are an interdisciplinary team of 50 members with medical doctors, molecular biologists, bioinformaticians and highly specialized engineers organized in 4 research groups and one lab-technology unit. Two of the group leaders hold part-time clinical positions. The lab technology unit reinforces the department's skills of "state of the art" technology and improves exchange of knowledge across research groups and cancer types.

We have a pipeline for high-quality biobanking (>200 000 vials, > 3000 patients) and data handling of patient cohorts with long-term follow-up and perform multilevel molecular characterization of tumors down to single cell levels. We are involved in the following clinical studies:

- NeoAva - Neoadjuvant chemotherapy in breast cancer with/without bevacizumab.
- IBCT - Improved breast cancer therapy in the neoadjuvant and metastatic setting
- EMIT -Establishment of molecular profiling for individual treatment decisions in early breast cancer
- OPTIMA-Optimal personalized treatment of early breast cancer using multi-parameter analysis
- ComIT - Evaluation of the benefit of radiation in combination with immune therapy for lung cancer
- TREM – Lung cancer patients with EGFR mutations and primary TKI-resistance
- ThoRaT - Lung cancer patients receiving radiotherapy
- NorPACT-1 and 2 - Neo-adjuvant chemotherapy for pancreatic cancer
- ICON - Randomized phase IIb study evaluating immunogenic chemotherapy combined with ipilimumab and nivolumab in patients with luminal B breast cancer
- ALICE – Atezolizumab combined with immunogenic chemotherapy in patients with metastatic triple-negative breast cancer
- Oslo2 - Observation trial including comprehensive biobanking

We have extensive institutional, national and international collaborations and are partners in several networks and consortia; the National Breast Cancer Research Network, the Regional Research Network on Extracellular Vesicles, Personalized Cancer Treatment and Metaflammation, International Cancer Genome Consortium, EuroPDX, the Breast Cancer Association Consortium; and EU funded projects (EpiMark, Cancer-ID, Gender-Net Plus). We host The National Competence Center for Lung Cancer. The total number of peer reviewed publications in 2018 was 76.

Breast Tumor Initiation

"Understanding cell fate decisions in tumor progression"

Group leader: Therese Sørlie

ABOUT

The group counts 11 members, including one professor (TS), one senior researcher and project leader (SN until March 2018), one scientist, three postdocs, three PhD students, one master student and two engineers. We hosted en ERASMUS student for 2 months. Two members are MD and one is DVM. Our group studies molecular aspects of breast tumor initiation and progression including functional effects of known risk variants, identifying cell(s) of origin of molecular subtypes and the transition from in situ to invasive breast cancer. We have a broad expertise in laboratory technologies which includes high-throughput genomic technologies, in vivo lineage-tracing, 2D and 3D in vitro culture techniques, 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 bioinformatics and statistical modeling.

AIMS

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

PROJECTS

- Characterize the functional effect of breast cancer risk variants
- Characterize subtype-specific progression pathways of pre-invasive lesions in the breast
- Investigate the role of Hedgehog/GLI1 signaling in breast cancer progression
- Explore the role of LGR5-expressing cells in mammary tumorigenesis
- Investigate the role of FOXA1 in endocrine resistant breast cancer

RECENT ACHIEVEMENTS

6 publications by group members in 2018. One student completed the Medical Student Research Programme and one master thesis completed.

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.

We are organized into three project groups, headed by Elin H. Kure (Professor USN), Odd Terje Brustugun and Åslaug Helland (Professor UIO) , with a total of 17 members. Six of these are MDs. We are three researchers, three postdocs, six PhD-students, one study nurse and four engineers.

AIMS

The ultimate goal is to personalise cancer treatment, and improve prognosis. We aim for:

- 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 characterization (*-omics*) of pancreatic- and lung cancers
- Proteogenomic analysis of pancreatic tumors and characterization of circulating biomarkers in free plasma and exosomes
- Identification of circulating plasma biomarkers in colorectal cancers (the Nordic VII clinical trial)
- Protein (TMA) analyses in lung cancers
- Serum predictive markers for therapy response
- Elucidate mechanisms for therapy resistance
- Expand biomarker identification material to stool (microbiome) and urine
- Investigate combination of radiotherapy and immunotherapy
- Gender differences in side effects on immunotherapy

RECENT ACHIEVEMENTS

In 2018, the group published 21 papers in peer-review journals. We have had several talks at national and international meetings, and are PIs on >20 translational and clinical studies. An ERA-network we are part of received funding (Gender-net). We are partners in several HSØ networks (NORSMAN, ReMics, NIRO), and received approximately 13 mill NOK in research funding (Elin Kure 1.2 mill, Odd Terje Brustugun 2 mill, Åslaug Helland 10 mill).

Cancer Genome Variation

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

Group leader: Vessela Kristensen

ABOUT

The group at ICR hosts two project groups, lead by two senior scientists, and consists of 4 postdocs, 2 PhD students, 2 MSc students, 2 research technologists and 1 ERASMUS student in 2018. Two other postdocs are shared with other groups at the Department and Institute. Vessela Kristensen is a professor I at the Faculty of Medicine, UiO, and works towards intensive and fruitful collaboration between ICR and University of Oslo, where she also leads a group of 3 postdocs, 2 PhD students, 1 MSc and 1 research technologist. Group members work closely together and in collaboration with breast clinicians, pathologists and oncologists.

AIMS

The Cancer Genome Variation group is working to understand how genetic variation affects occurrence of somatic alterations, gene expression patterns and genome wide copy number alterations in human tumours http://ous-research.no/kristensen/

PROJECTS

Together with our collaborative network we are part of Convergence grant from UiO-Life Science (Personalised Patient Care, PerCaThe) and we are member of the TRANSCAN EpiMark EU network. Projects:

- **Genome variation:** In the breast cancer association consortium we identified 65 new breast cancer risk loci (published in *Nature*) and ten variants - with risk of ER-negative breast cancer (*Nature Genetics*) as highlighted in CNN and other media world-wide.
- **Genomic instability.** We observed a systemic shift in genomic aberrations in a time series analysis of neoadjuvant chemotherapy and bevacizumab-treated breast carcinomas (published in *Genome Medicine*)
- **DNA methylation** at enhancers was identified in distinct breast cancer lineages (Published in *Nature communications*)
- **Data integration:** Integrative Genome-wide characterization of the human disease landscape (published in *Cell Systems*)
- **Non-canonical transcriptomes**: Wide-spread alternative exon usage was identified in clinically distinct subtypes of BC (published in *Scientific Reports*)
- **Immune signaling:** Bioinformatic approaches to profile the tumor microenvironment in association with disease progression, ER activity, genomic complexity and age (Publications *in OncoImmunology, highlight in New England J Medicine* and others).

RECENT ACHIEVEMENTS

Publication activity. 20 publications in 2018, 1 book chapter.

Genomic Alterations in Breast Cancer

"Exploring inter- and intra-tumor heterogeneity to improve molecular classification of breast cancer"

Group leader: Hege G. Russnes

ABOUT

The group was founded January 2018 and have a total of 2 scientists, 1 postdoc, 3 research engineers, one MD-PhD student and one MSc student. In addition, 1 prof. emerita (A-L Børresen-Dale, UiO), 1 researcher (group leader A. Matheliér, NCMM), 1 oncologist (L. Ottestad) and 1 professor in bioinformatics (O. C. Lingjærde, UiO) are associated with the group (part-time).

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, both at diagnosis and during disease progression.

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. The group is active in the IMI/EU funded project CancerID aiming at standardizing liquid biopsies for cancer diagnostics. Hege G. Russnes is also senior consultant at Dept. of Pathology, OUS where she is scientific head of "Unit for translational Oncopathology", a lab performing molecular diagnostics for clinical trials. She is also appointed "Young Associated Investigator" at NCMM (Centre for Molecular Medicine Norway).

AIMS

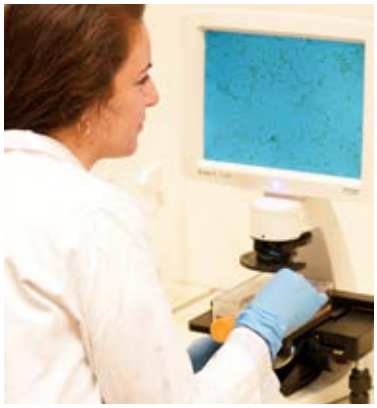
Our group aims at defining, refining and implementing molecular classification and biomarker analyses to improve stratification of breast cancer patients into treatment relevant groups. We are addressing the impact of inter- and intra-tumor heterogeneity as well as host response on disease progression,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

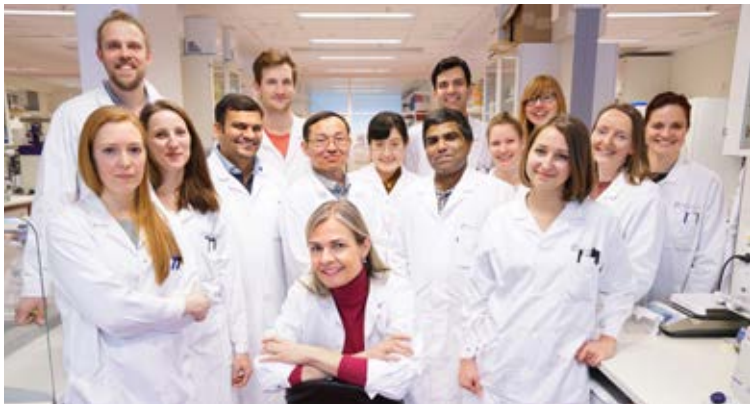
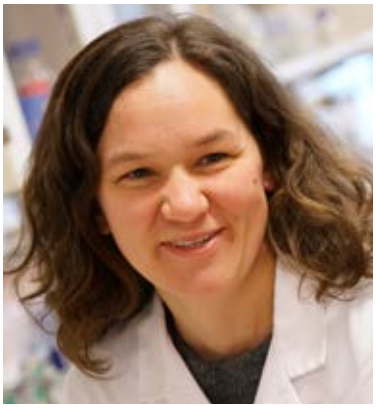
PROJECTS

- 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
- Liquid biopsies; cell-free tumor DNA in blood, circulating tumor cells (CTCs) and disseminated tumor cells (DTCs)
- Prediction of early vs. late relapse of breast cancer

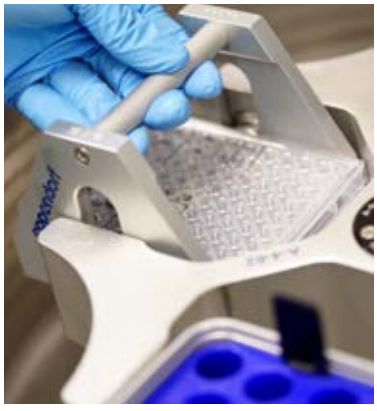
RECENT ACHIEVEMENTS

- 5 original publications in 2018 (affiliated members had 24 publications in addition)
- One master thesis completed and defended



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



Department of

Cancer Immunology

Headed by Johanna Olweus

ABOUT

The Department of Cancer Immunology (DCI) consists of five research groups (Olweus, Taskén, Sioud, Myklebust, Malmberg) and one project group (Kyte). Four DCI members are full professors at the University of Oslo. Groups at the DCI are partners of two K.G. Jebsen Centers (Cancer Immunotherapy and B-cell malignancies) and several EU-funded research programs in cancer immunotherapy. The groups provide complementary expertise in molecular and cellular immunology, including a broad experimental tool-box for antigen discovery and studies of immune cells at the single cell level. The aim is to decipher the molecular regulation of key cellular components of the innate and adaptive immune system, including dendritic cells (DC), B cells, T cells, regulatory T cells (Treg) and NK cells. The key driving force is to develop better tools for cancer diagnostics and new therapeutic strategies. The latter include investigator-initiated clinical trials to alleviate immune suppression and improve the use of checkpoint inhibition, and the design of gene-edited T- and NK cells for adoptive cell therapy.

PROJECTS:

- Lymphocyte biology, by deciphering
  - ontogeny and function 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 human antibodies and lytic peptides
  - cell therapy across HLA barriers to overcome immune tolerance
  - clinical trials using experimental immunotherapy
  - small molecules

RECENT ACHIEVEMENTS (2018)

- 20 publications; 11 with first/last authors from DCI (mean IF 7,8)
- 5 filed DOFIs and one granted patent on technology to identify T cell receptors
- 5 PhD degrees
- Renewed 2-year collaborative agreement with Fate Therapeutics to develop off-the-shelf NK cell therapy. Licensed pending patent concerning a method for selective expansion of educated NK cells.

Clinical trials:

- Reported the first Phase I/II clinical trial based on transfer of allogeneic NK cells to patients with high-risk AML and MDS (*Björklund et al., Clinical Cancer Research 2018*)
- Recruited first 100 patients to the ASAC trial that examines the effect of reversing prostaglandin E2-mediated inhibition of tumor immunity in patients with metastatic colorectal cancer by the end of 2018 (www.asac.no)

Experimental Immunotherapy

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

Group leader: Johanna Olweus

ABOUT

The group counts 16 members (F/M 60/40); 1 full professor (JO), 6 postdocs, 6 PhD students and 2.5 engineers, and two associated clinicians. Three members have MD background. Twelve members are recruited from abroad. The group is partner of a K.G. Jebsen Centers (2013-); "Cancer Immunotherapy (JCIT)". 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

- Several novel TCRs targeting self-antigens were discovered and characterized, and two DOFIs were accepted by Inven2

Strategy 2

- A novel TCR reactive to a recurrent mutation occurring in 7% of patients with Acute Myeloid Leukemia was discovered and characterized
- Tumor-reactive T cells in biobanked material from patients responding to immunotherapy were sorted for single cell T-cell receptor sequencing using our recently established platform *(Lymvac II trial)*
- A patient-derived xenograft model for Acute Myeloid Leukemia was established in collaboration with Karolinska Institute

Recent achievements (2018-): Described a technology for identification of neoantigen specific T cells from healthy donors (Ali/Foldvari/Giannakopoulou et al, *Nature Protocols in press, 2019*). Patent granted on technology for identification of specific T-cell receptors (WO 2015/071763A2). The research group continued their research collaboration with biotech company Kite Pharma (acquired by Gilead) on development of T-cell receptors to target cancer. One PhD student graduated and two DOFIs were accepted by Inven2. Olweus was invited speaker at a large number of international conferences in 2018, including the Nobel Forum, European Congress in Immunology, Keystone Symposium (Colorado) and 2nd International NTNU Symposium on biomarkers in cancer.

NK Cell Biology and Cell Therapy

"Towards the next generation NK cell therapy"

Group leader: Karl-Johan Malmberg

ABOUT

The Malmberg Lab in Oslo counts 12 members (F/M: 7/5); 1 full professor (KJM), 1 scientist, 1 project manager, 2 postdocs, 6 PhD students, 2 engineers. Malmberg is a visiting Professor at the Karolinska Institute (KI) and a partner in the K.G. Jebsen Center for Cancer Immunotherapy. Affiliated to the group is a Project group in Translational Cancer Immunotherapy led by Jon-Amund Kyte.

AIMS

The group seeks to develop new strategies for cell-based immunotherapy based on insights into the functional regulation of natural killer (NK) cells. We use a combination of single-cell assays, including live cell imaging, high-dimensional immune profiling by mass cytometry, flow cytometry and RNA-seq to decipher the cellular and molecular mechanisms involved in calibration of effector function in human NK cells. The Kyte group aims to develop new combinations of check point inhibition and CAR-engineering.

PROJECTS

1) Diversification of human NK cell repertoires in health and disease
2) Cell therapy with iPSC-derived NK cells

RECENT ACHIEVEMENTS

- Reported the first Phase I/II clinical trial based on transfer of allogeneic NK cells to patients with high-risk AML and MDS. (Björklund et al., Clinical Cancer Research 2018).
- Defined a method for selective expansion of adaptive NK cells and showed their efficacy against acute leukemia and as a platform for CAR engineering. (Cancer Immunology Research 2018).
- Identified Bim splicing as an important regulator or IL-15 addiction in NK cells, with implications for cell therapy (Journal of Immunology 2019).
- Described a role for lysosomal remodeling in tuning NK cell function (Nature Communications, 2019).
- Innovation: Main inventor of a pending patent concerning a method for selective expansion of educated NK cells. Licensed to Fate Therapeutics Inc. January 2018. A clinical trial exploring this concept will be launched during 2019. "Modulation of function of immune effector cells". A PCT application describing the use of agents to altered signalling from secretory granules was filed 25 September 2017.
- Renewed a 2-year collaborative agreement with Fate Therapeutics to develop off-the-shelf NK cell therapy.

Lymphoma Biology

"Understanding B-cell lymphoma biology to identify new therapeutic targets and treatment strategies"

Group leader: June Helen Myklebust

ABOUT

The group counts 13 members with research background in medicine, biology and biotechnology, and includes one professor/assistant group leader (Erlend B. Smeland), 1 associate professor (JHM), 1 scientist (Kanutte Huse, 50% research and 50% at Flow Cytometry core facility), 5.5 postdocs, 1 postdoc located at MGH/Broad Institute, Boston (Jillian Wise), 2 PhD students and 1 technician. Five members have MD background and four members are recruited from abroad (USA, China, Macedonia, Sweden). The group is part of KG Jebsen Centre for B-cell malignancies (JHM is co-director).

AIMS

The group performs translational studies in B-cell lymphoma to define clonal evolution patterns, cancer driver genes, actionable targets and new targets for immunotherapy.

PROJECTS

We apply whole exome and RNA sequencing, high-dimensional flow cytometry/mass cytometry and mass cytometry imaging to characterize tumor cells and intratumor immune cells from patient biopsies. We also use CRISPR/Cas9 genomic editing and have established patient-derived xenograft (PDX) mouse models for pre-clinical drug testing. Ongoing projects are:

- Clonal evolution and recurrent mutations associated with therapy relapse
- Functional characterization of recurrent driver mutations
- Novel targets for immune checkpoint blockade
- Cancer sensitivity drug screen and preclinical testing
- Clinical register studies

RECENT ACHIEVEMENTS

We identified the co-inhibitory receptor TIGIT as a potential new target for immune checkpoint blockade in B-cell lymphoma (Josefsson, Clin Cancer Res 2018 and Cancer Immunol Res 2019), and that the malaria drug Artesunate had potent anti-lymphoma activity (Våtsveen, J Hematol Oncol 2018). The group collaborated with OUS clinicians to validate a prognostic assay for identification of high risk mantle cell lymphoma patients (Holte, Br J Haematol 2018), and demonstrated that chemotherapy-free initial treatment of advanced indolent lymphoma had durable effect with low toxicity (Lockmer, J Clin Oncol 2018). Three PhD students graduated in 2018: Chloé B. Steen, Lise K. Bollum and Sarah E. Josefsson.

Immunomodulation and Targeted Therapies

"Our goal is to develop novel biological therapies and biomarkers to improve cancer treatment"

Group leader: Mouldy Sioud

ABOUT

The group consists of 6.5 members, including 1.5 postdocs, 1 research assistant, 1 PhD student, 2 master students and the group leader (DEA Pharm, PhD) with formal research experience in immunology, molecular/cell biology, microbiology, and medicine. Sioud is a visiting professor at University of Tunis. The group is a part of the OUS-focus area cancer immunotherapy and H2020 NANO-D-SIRE consortium. Research in the group is focused on (i) fingerprinting the changes in cancer cell surface and patient sera using high-throughput display technologies, and (ii) the development of targeted immunotherapies.

In addition to several breakthrough findings (e.g., Sioud & Sørensen 1998, *Nature Biotech*), our previous studies uncovered the mechanisms responsible of RNA sensing by immune cells and gene regulation by endogenous antisense transcripts (Røsok & Sioud *2004, Nature Biotech;* Sioud 2006, *Nature Biotech*; Sioud 2006, *Trends Mol Med).* With respect to clinical translation, we engineered the first siRNA-modified dendritic cell cancer vaccine that is available to patients under compassionate use. This immunogenic vaccine demonstrated promising responses in cancer patients (Sioud 2019, *Cancers*).

AIMS

Our aim is to develop antibodies and peptides for use in cancer therapy, and to fingerprint immune responses in patients with the aim to uncover new serological markers associated with disease activity.

PROJECTS

- Analysis of cancer cell surface proteome changes using high-throughput display technologies
- Development of antibodies and peptides for cancer immunotherapy
- Fingerprinting immune responses
- RNAi and CRISPR as immune modulators

RECENT ACHIEVEMENTS

- 5 publications, including a 15 pages long paper published in the well-known *FASEB J*. It describes the development of a new human monoclonal antibody for universal use in cancer immunotherapy.
- New targeted lytic peptides against macrophages and malignant cells (manuscript submitted).
- A book on RNAi and CRISPR technologies to be published by Springer Nature.

To date, the group has published **188** peer-reviewed original articles (mean IF = **5.865**) and reviews, with 1st and/or last authorship on 85% of the papers.

Cell Signalling and Immune Regulation

"We want to perturb tumor immune evasion mechanisms to boost anti-tumor immunity"

Group leader: Kjetil Taskén

ABOUT

The group relocated from NCMM and joined the Department of Cancer Immunology in 2018. In 2018 the group counted 17 members (F/M: 9/8), 1 senior consultant, 2 researchers, 9 postdocs, 1 PhD student, 2 technicians and 1 M.Sc. student in addition to the PI. The group is part of K.G. Jebsen Center for Cancer Immunotherapy and K.G. Jebsen Centre for B Cell Malignancies.

AIMS

The Taskén group aims to understand intracellular signalling networks, their anchoring and localization through scaffold proteins, how these signalling networks mediate physiological and pathophysiological processes and can be perturbed using drug-like small molecules. We aim to understand tumor immune evasion strategies, and how we can perturb such strategies to boost anti-tumor immunity. We proceed with cancer drug sensitivity screening (CDSS) to explore individual drug responsiveness and resistance patterns in patient cancer cells and aiming to develop models to assist individualised clinical decisions in precision medicine in oncology and haematology.

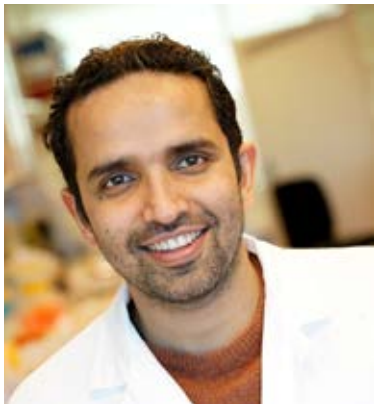
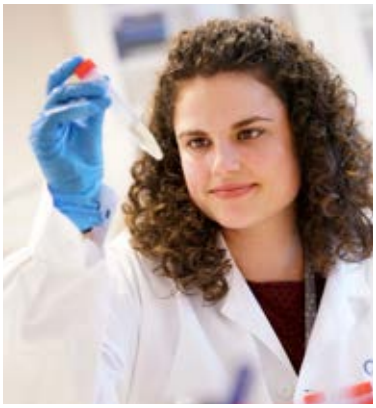
PROJECTS

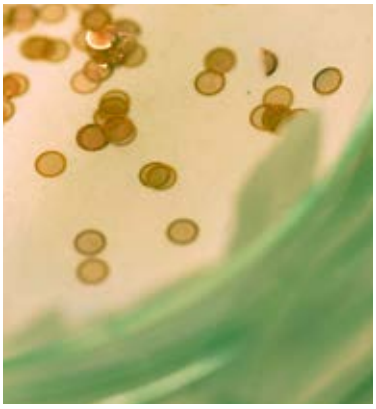
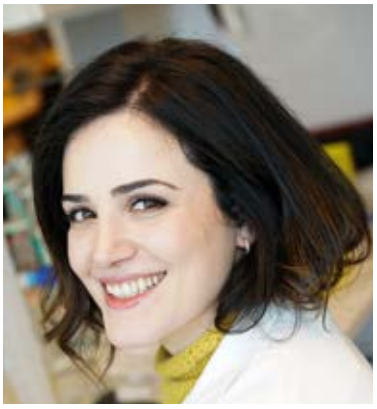
- T cell function in cancer and immune-related diseases
- Identification of regulatory T cell targets that can be perturbed to reverse tumor immune suppression
- Role of Prostaglandin E2, cAMP and AKAPs in signaling and regulation of T cell function
- Targeting the cAMP signalling pathway for cancer immunotherapy
- Cancer drug sensitivity screening in Chronic Lymphocytic Leukemia and Multiple Myeloma
- Acetyl Salicylic Acid Intervention study in metastatic colorectal cancer (ASAC)

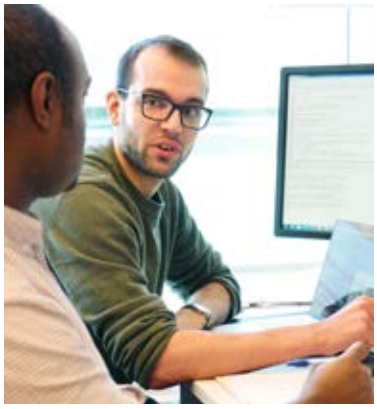
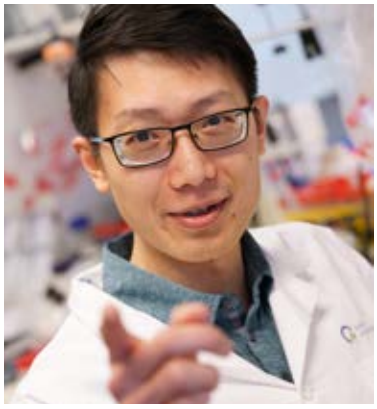
RECENT ACHIEVEMENTS

Highlights include winning a major grant from the RCN Biotek2021 Digital Life Norway programme for a new systems pharmacology project to model on our data from CDSS to see if we can predict drug combinations that will synergize in a precision medicine approach (PIs Taskén, Enserink, Frigessi, OUH/UiO). This is a pending research question and important to make the best use of the patient sample for patient benefit as we cannot test all combinations.

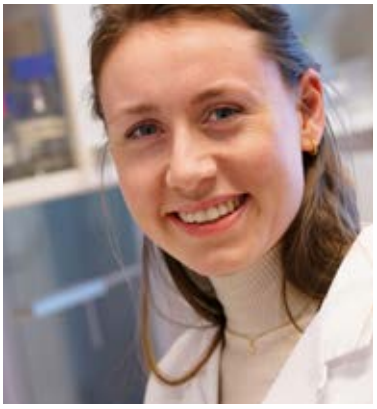
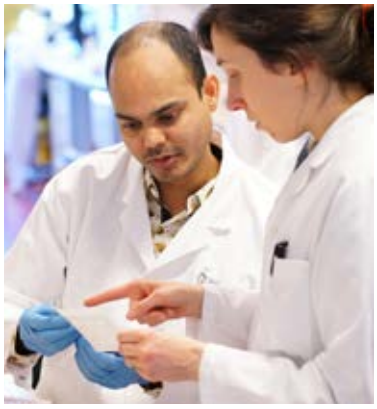
Another highlight and milestone included the establishment of a new company SERCA Pharmaceuticals by Inven2 based on an innovation project in my lab that has been running for 10 years where we have developed small molecule PPI disruptors with application in ischemia reperfusion injury. Publication highlights include papers in Oncotarget and Sci. Rep. on CLL patients from our precision medicine programme, in J. Immunol. (Jan. 2019) on regulatory T cells and tumor immune suppression in CLL by idelalisib and on signalling complexes in Mol. Biol. Cell. Furthermore, in co-authored papers we have contributed to understanding the autoimmune phenotype of patients with CTLA4 deficiency (JACI 2018) and metabolic regulatory programmes for aerobic glycolysis (Nature, Jan 2019).

“Uncovering the cellular basis of cancer development”

Department of

Molecular Cell Biology

Headed by Harald Stenmark

The department has a staff of 78 and hosts 4 research groups (Enserink, Rusten, Sandvig and Stenmark), 10 project groups, and a departmental service unit. Research in the department comprises various aspects of cancer relevant cell biology, including membrane traffic, cell signaling, cell metabolism and cell division. In addition, the department carries out biotechnological research on nanoparticles and translational research on leukemia drug sensitivity and cancer derived exosome biomarkers.

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, genetics, drug screening 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, molecular mechanisms of cell division, exosome secretion and biomarkers for prostate cancer. In general, the department's groups have been successful in obtaining national and international external funding.

Three of the groups of the department (Stenmark, Rusten and Enserink) are members of a Norwegian Centre of Excellence, Centre for Cancer Cell Reprogramming (CanCell), which is led by Harald Stenmark. Kirsten Sandvig has been heading a national project on Biodegradable Nanoparticles in Cancer Diagnosis and Therapy, which ends in April 2019. Harald Stenmark heads the Norwegian Advanced Light Microscopy Infrastructure Network, NALMIN. Stenmark is also member of a Convergence Environment under UiO Life Science, called "Programmable cell-like compartments". Jorrit Enserink participates in a new project under the Norwegian Centre for Digital Life, called "Pipeline for individually tailoring new treatmets in hematological cancers".

Cellular Membrane Dynamics

"Understanding how remodelling of cellular membranes contributes to cancer"

Group leader: Harald Stenmark

ABOUT

The group studies the dynamics of cellular membranes with the aim of understanding their relevance to cancer. Cellular membrane dynamics 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, cell invasion models, organoid models, and fruit flies.

The group has 34 members from 12 nations and is headed by Harald Stenmark (group leader) and Camilla Raiborg (assistant group leader). Its 6 project groups are led by Andreas Brech, Kaisa Haglund, Camilla Raiborg, Kay O. Schink, Eva Wenzel, and Antoni Wiedlocha.

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

- Phosphoinositides in regulation of membrane dynamics
- Mechanisms of autophagy and lipid droplet biogenesis, and their role in cell metabolism
- Membrane dynamics in cell invasion and metastasis
- Centrosome dynamics in cancer
- Cytokinesis in development and carcinogenesis
- The b-catenin destruction complex in physiology and cancer
- Membrane dynamics in promotion of genome integrity

RECENT ACHIEVEMENTS

- Establishment of protein dynamics during endosomal downregulation of growth factor receptors (Wenzel et al., *Nature Communications* 2018).
- Identification of a novel molecular mechanism for controlling positioning of the mitotic spindle (Malerød et al., *EMBO Journal* 2018)
- Identification of a novel molecular mechanism for repair of damaged lysosomes (Radulovic et al., *EMBO Journal* 2018)
- An Advanced Grant from the European Research Council (2.5 MEUR) was awarded on the project "Co-incidence detection of proteins and lipids in regulation of cellular membrane dynamics", led by Harald Stenmark.
- Project leader Kaisa Haglund obtained research grants from both the Norwegian Cancer Society and the Research Council of Norway in 2018. She was also awarded Ragnar Mørk's Prize 2018 for excellent cancer research.
- Assistant group leader Camilla Raiborg obtained a research grant from the Norwegian Cancer Society in 2018.
- PhD student Anette Lie Jensen was awarded the "best short talk" award at the Biochemical Society conference "New horizons in ESCRT biology" in London 17-20 April 2018.
- Members of the group published 12 original papers and 2 reviews in 2018.

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 group leader (with 20% professorship at Department of Molecular Biosciences), two externally funded senior scientists, seven post-docs, one clinician in a 20% post-doc position, two PhD students, five MSc students and one Erasmus student. A large fraction of the group consists of scientists from abroad , including the Netherlands, Austria, Spain, Colombia and the UK. The group 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. A major focus is on hematopoietic cancers, including –but not limited to– Acute Myeloid Leukemia (AML). A second research theme is to better understand cellular responses to sudden environmental changes.

PROJECTS

- High-throughput drug combination screens to identify drug synergies and to reveal correlations between driver mutations and drug sensitivity profiles
- Development of novel immune therapy for AML
- Modeling of leukemia in fruit flies to better understand the genetic networks that drive AML
- Genome-wide CRISPR-Cas9 screens in leukemic cells to identify novel mechanisms of resistance to tyrosine kinase inhibitors
- Cellular responses to nutrient stress; particularly the identification of the upstream pathways that control the dynamics of autophagy

RECENT ACHIEVEMENTS

- Dr. Helene Knævelsrud, a senior researcher in the group, was elected to the Young Academy of Sciences.
- The group is a founding member of the Norwegian Center of Excellence "CanCell", which was awarded in 2017.
- Funding obtained: Two research grants (one of which awarded to Ignacio Garcia, a senior researcher in the group) and one innovation grant from The South-Eastern Health Authorities, as well as funding within the Center for Digital Life funded by the Norwegian Research Council (together with Prof K. Tasken and Prof A Frigessi).
- The group published three articles, including one in the journal *Cell*. Two MSc degrees were completed.

Tumor-host Biology

"Tumor-host interactions during cancer progression"

Group leader: Tor Erik Rusten

ABOUT

The research group counts 12 members representing 8 nationalities in 2019 (Finland, India, Ireland, Iran, Germany, Hungary, France, and Norway): 1 group leader, 2 scientists, 4 postdocs and 1 PhD student, 1 technician and 3 master 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 studying these processes can uncover new ways to intercept carcinogenesis.

To mechanistically probe how tumor cells and non-tumor cells and organs communicate to foster tumor growth and cause cancer cachexia we develop *novel* genetic tools in Drosophila. These tools will allow us to selectively and independently manipulate tumor and either tumor microenvironment or somatic organs in vivo.

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 fruit fly *Drosophila melanogaster*, as an animal model system. In this work we employ a wide array of techniques and collaborate with experts in cell biology, genetics, imaging, electron microscopy, tumor biology, metabolism, bioinformatics and clinical cancer cachexia in order to survey, measure and mechanistically understand these complex aspects of cancer biology.

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.
- Tumor-microenvironment interactions and growth support.
- Mechanisms of cancer cachexia.
- Roles of autophagy in metabolic reprogramming, nutrient mobilization and breakdown of muscle and adipose tissue during 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).
- The tumor suppressor LKB1,responsible for the Peutz-Jegher cancer syndrome, is controlled by endocytic vesicle trafficking and its derailment contributes to tumor growth (O´Farrell, F. et al, *Nature Cell Biology*, 2017).
- Former PhD student Nadja Katheder was awarded H.M. the King's gold medal for best PhD thesis in 2018.
- Tor Erik Rusten obtained a "Toppforsk" grant from the Research Council in 2018.

Intracellular Transport

"All the way from basic research to translation"

Group leader: Kirsten Sandvig

ABOUT

Sandvig's group, counting 16 members, 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 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, and runs until March 2019. 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, RNA 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 72 (~330 publications). The group has extensive national and international collaboration.

AIMS

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

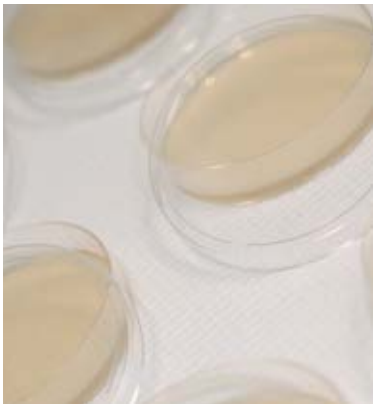
PROJECTS

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

RECENT ACHIEVEMENTS:

- Mechanistic studies of different types of endocytosis and intracellular transport.
- Further studies of exosome biogenesis and release, as well as biomarkers for prostate cancer.
- Investigations of cytotoxic effects of different types of nanoparticles with and without drugs *in vitro* and *in vivo*.
- In 2018 the group published on all these topics; 6 articles in different journals and 2 articles in the biology preprint server bioRxiv. Concerning innovations, see separate paragraph.

”Biological discoveries for precision cancer medicine”



Department of Molecular Oncology

Headed by Ragnhild A. Lothe

As a research department within the Oslo University Hospital (OUH) Comprehensive Cancer Centre, it is our responsibility and goal to accomplish high quality and interdisciplinary biomedical research for improved precision medicine and management of cancer patients. Our main research programs are devoted to colorectal cancer and prostate cancer, and we have a longstanding project portfolio also on other solid tumor types. Our expertise in biomedical research spans several disciplines from cell biology to translational research, including also active partnerships in clinical studies, and we have a broad range of advanced technologies and analytical tools established in-lab. The department scientists are inventors of several biomedical patents and active innovation projects.

The department host three research groups (38 employees in total) and the group leaders are adjunct professors at the University of Oslo. The scientists in the department are devoted to teaching and supervision, and 58 MSc/PhD degrees with supervisors from our department have successfully been completed since the inauguration of the department in 2006.

Members in the research groups are partners of the K. G. Jebsen Colorectal Cancer Research Centre, the OUH priority area for colorectal cancer, the Norwegian Cancer Genomics Consortium, and several international networks including a European multicenter study on MPNST, the European network for study on Cholangiocarcinoma, the Global Testicular Cancer Consortium, and Cooperation Studies on Colorectal Cancer (COST action).

In 2018, we published 19 papers including the following prime journals: Ann Intern Med, Ann Oncol (2), Cell, Clin Cancer Res, Eur Urol (2), Sem Cancer Biol.
During the past 3-years, scientists affiliated with our department have published 69 scientific papers, with 1st and/or last authorships on 54% and with a mean IF of 7.1. Five PhD and 9 MSc students with main supervisors from the department received their academic degrees during 2016-2018. The innovation projects have been granted funding from U of Oslo, the Health Region and Research Council, and we were granted 4 patents, 2 PCT applications and 2 priority applications in the period.

Our main research goals for the next three to five years are three-fold, (i) to decipher spatio-temporal tumor heterogeneity in colorectal cancer and prostate cancer, (ii) to monitor minimal residual disease, early recurrence and clonal evolution by analyses of repeated liquid biopsies and tumor samples, and (iii) to predict treatment response in translational studies and within clinical trials by a combination of genomics and *ex vivo* drug screening of tumor cell-derived organoid cultures.

Genetics

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

Group leader: Ragnhild A. Lothe

ABOUT

Our main research program involves translational studies of primary and metastatic colorectal cancers (CRC), using genomics, drug screening, digital pathology and functional analyses. The group has 22 employees (group leader, 7 scientists/ postdocs, 9 PhD students, 5 research assistants/engineers) and 2 current MSc students, and includes two project groups in Cell signaling and Computational oncology.

AIM

Our overarching goal is to translate novel biomedical knowledge into 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 CRC
- Pharmacogenomics of metastatic CRCs using patient-derived organoid models
- E3 ubiquitin ligases in intercellular communication and CRC pathogenesis

RECENT ACHIEVEMENTS

We have identified new biomarkers and new clinical associations of well-known biomarkers in CRC. Addressing the gene expression-based consensus molecular subtypes (CMSs) as a framework, we demonstrated that the poor prognostic value of *KRAS* and *BRAF* mutations is specific to individual subtypes (Smeby et al., Ann Oncol 2018). Furthermore, aberrant splicing expands the prognostic value of *KRAS* beyond mutation status in early stage CRC, highlighting molecular heterogeneity in the clinically relevant *KRAS* wild-type subgroup (Eilertsen et al., Int J Ca 2019). From analyses of ~2000 CRC samples and preclinical models we identified the long non-coding RNA *MIR31HG* as a bona fide prognostic marker in CRC, providing clinical stratification beyond the major gene expression phenotypes, and with prognostic value independent of tumor immune and stromal cell infiltration (Eide et al., Int J Ca 2018). CDX2 is an emerging prognostic biomarker with implications also for the decision to treat early-stage CRCs with adjuvant chemotherapy. Our analyses indicate that its prognostic impact is greatest in late stage disease, and drug screen data of 69 chemotherapeutics in preclinical models support also a predictive potential for response to such standard therapies (Bruun et al., Mol Oncol 2018). Finally, pharmacogenomic analyses of cell lines and patient-derived xenografts identified HSP90 inhibitors as potent drugs to overcome chemoresistance in patients with an aggressive subtype of CRC (Sveen et al., Clin Cancer Res 2018). We have also written a review of the clinical potential of various combination therapies with HSP90i against CRC (Kryeziu et al., BBA-Reviews on Cancer, 2019).

In a European multicentre study of MPNST, we identified a subgroup of patients with poor prognosis defined by an aberrant TP53 network (Høland M et al., Modern Pathol, 2018).

Peter Andreas Wold Eide defended his PhD "Colorectal cancer subtypes and pharmacological sensitivities", Faculty of Medicine, and May-Britt Five and Sebastian Basing completed their MSc degrees, U of Oslo, in 2018.

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 genome-wide methylome data with detailed candidate gene characterization. The research is performed across cancer types, with a main focus on colorectal and urological cancer. In 2018 the group counted ten members, including three postdocs, two PhD student, two engineers, two MSc students and the group leader.

AIMS

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

PROJECTS

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

RECENT ACHIEVEMENTS

Using methylome sequencing in combination with standardized digital PCR technology, we have identified novel DNA methylation biomarkers for non-invasive monitoring of bladder cancer. The biomarker panel achieves an outstanding accuracy in urine from bladder cancer patients and healthy controls. Blinded validation has been initiated in an international prospective urine-series. The pilot reveals a perfect classification of cancers and controls. Both the biomarkers and the optimized technology have been protected by patent applications. The PhD of Pharo, covering parts of this work, is awaiting defense.

To evaluate the biomarker accuracy for detecting recurrence of bladder cancer, we are, in collaboration with the Wahlqvist team at Aker, following 50 post-surgery individuals for two years. Recruitment has been completed and >half the patients have been followed >1 year. Preliminary data indicate that the urine test is more accurate than the routinely used cystoscopy. Presenting the project at the clinical autumn meeting, Lind received the NUF* price. The preliminary results have released "Klinbeforsk" funding to initiate a prospective national multi-center study evaluating the clinical utility of the test. The group also received funding from the Cancer Society and HSØ including a career grant to Jeanmougin.

*Norsk Urologisk Forening

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. Through 2018, the group consisted of eleven members, including one researcher, two postdocs, one engineer, two PhD students, three MSc students, a study nurse and the group leader.

AIMS

The research group aims to improve the diagnosis and management of cancer by utilizing genome technologies. This includes identification and characterization of genes that are critical for development of cancer.

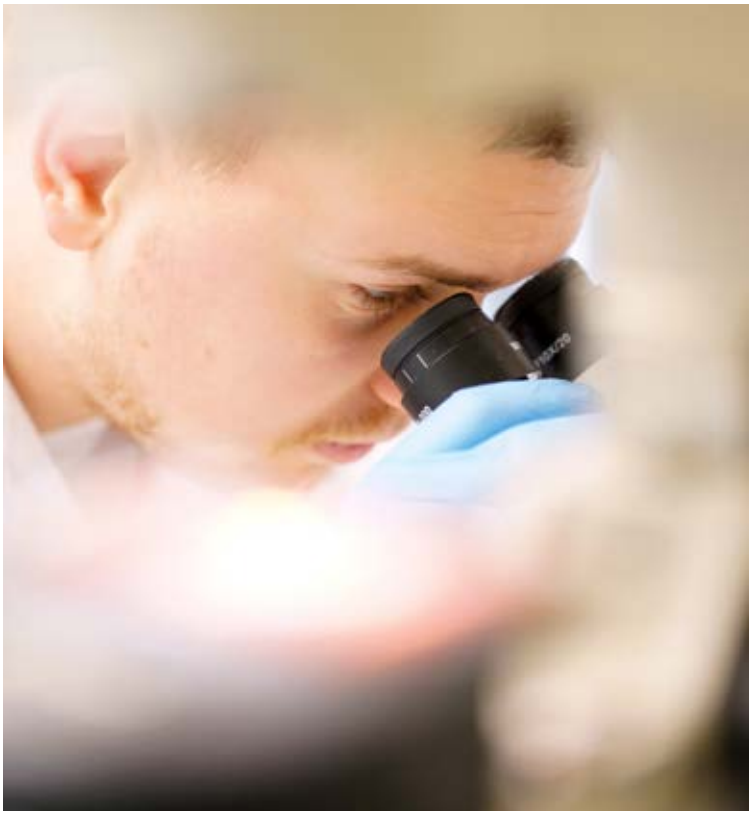
PROJECTS

- Interfocal heterogeneity of prostate cancer
- RNA variation caused by aberrant splicing and as a source of cancer biomarkers
- Fusion gene identification and characterisation

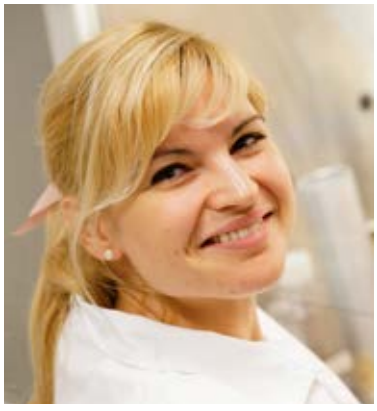
RECENT ACHIEVEMENTS

During 2018, the group continued the development of a large prostate cancer research program, primarily utilising a biobank resource with multiple frozen tissue cores from multifocal primary prostate cancer. The first major research paper from this effort was published in the prestigious journal European Urology with Marthe Løvf as a first author. Here, we performed the first large in-depth genomic heterogeneity study of primary prostate cancer. High-coverage exome sequencing of 89 tumor foci from 41 patients and demonstrated convincingly that different tumour foci within the same patient only exceptionally have any somatic gene mutations in common. These results have major implications for any implementation of gene-based testing in future treatment of prostate cancer patients as information from all tumor foci is necessary to draw valid conclusions about the cancer. The group was also involved in one other important study on prostate cancer, where Andreas M. Hoff published as shared first author on a study of metastatic castration-resistant prostate cancer in the journal Cell. This study, originating from the Meyerson lab at the Broad Institute, where Hoff recently spent 12 months as a postdoc, investigated the genomic aberrations of the androgen receptor locus and identified a novel tandem duplication phenotype. The group continued to develop bioinformatics pipelines for high-throughput sequencing of DNA and RNA and utilized these in analyses of data from several cancer cohorts. In 2018, Eirik Berg Nordheim completed his MSc degree.

DNA
S96_T1
p4532



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



Department of

Radiation Biology

Headed by Kristian Berg

The Department has more than 60 employees organized in 4 research groups and 6 project groups. The research at the department is focused on the biological responses to ionizing and non-ionizing radiation, including γ-radiation, radiation from radionuclides, ultraviolet radiation, visible light as well as proton therapy. 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. The department is also involved in delivering radionuclides to cancer tissue. Another research area is the use of visible light to activate photosensitive compounds that are used for cancer detection and therapy. In that respect a technology has been developed, photochemical internalization (PCI), which enables site-directed intracellular delivery of anticancer therapeutics. Both PCI and ionizing radiation induce reactive oxygen species as a part of their mechanism of action. 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

- Pancreatic carcinoma xenografts treated with sunitinib show less abnormal microvessels but larger hypoxic regions after treatment than before treatment.
- Cervical cancer patients with tumors showing high hypoxic fraction in combination with high interstitial fluid pressure have particularly poor prognosis with a 5-year survival rate of only 13 %.
- A novel mechanism of activation of the DNA damage kinase ATR (Ataxia Telangiectasia and Rad3-related) was identified
- 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 production unit for biomolecular therapeutics has been established
- A new method to image hypoxia in prostate cancer based on integration of images reflecting oxygen consumption and supply has been developed
- We gained important new knowledge about the regulation of translation in response to cellular stress as well as about the function of the stress-response kinase GCN2 in human cells

Photochemical Internalization

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

Group leader: Kristian Berg

ABOUT

Group members: 22, including 5 researchers, 3 postdocs, 4 PhD students, 7 technical positions and 3 MSc students, including the project groups of Asta Juzeniene, Pål Kristian Selbo, Anette Weyergang and Theodossis Theodossiou.

Project *Photochemical Internalization (group leader Berg, project leaders Selbo, Weyergang and Theodossiou)*: Endocytic entrapment is a hurdle for therapeutic utilization of macromolecular therapeutics with intracellular targets. Photochemical internalisation (PCI) is a technology for cytosolic release of therapeutic macromolecules subjected to endocytosis. PCI is invented and developed in our research group and is currently evaluated in clinical trials.

Project *Targeted alpha therapy (project leader Juzeniene)*: Metastases are the primary cause of death in cancer patients. Targeted alpha-particle therapy *is* a promising treatment for eradicating *micrometastases.*

AIMS

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

Project *Radionuclide therapy*:
The main goal is to develop a novel technology with potentially broad therapeutic applications for cancer micrometastases by means of dual targeted alpha particle radiation.

PROJECTS

- Design and development of recombinant immunotoxins for activation by PCI
- Light-controlled delivery of cancer immunotherapeutics including PCI of 1) immunotoxins targeting cancer stem cells (CSCs) and 2) CSC-derived vaccines.
- 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
- Using mitochondria-powered chemiluminescence to non-invasively treat inaccessible tumours
- Utilizing other radiation sources to induce PCI effects
- Targeted alpha radionuclide therapy for bone and visceral metastases of osteosarcoma, prostate and breast cancer

RECENT ACHIEVEMENTS

- Documented the potential of PCI of bleomycin to induce anti-tumor immunity.
- Established a biomolecule production unit based on recombinant technology.
- New grants in 2018: FET-OPEN project (Theodossiou), the 2nd FET-OPEN of the group; PhD stipend from HSE (Selbo); Project support from Radforsk (Weyergang)
- The following project groups were established in 2018:
  - Anette Weyergang (project leader): Recombinant Light Activated Therapeutics
  - Pål Kristian Selbo (project leader): Light-controlled delivery of cancer immunotherapeutics;
  - Theodossis Theodossiou (project leader): Protonics
- No. of papers in 2018: 11 (1 non peer reviewed)
- PhD thesis: 1
- MSc thesis: 1

Clinical Radiation Biology

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

Group leader: Heidi Lyng

ABOUT

Group members: 10, including one researcher, four postdocs, three PhD students, 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 at the hospital. 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. 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 cancer
- 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

In 2018, the group published 3 articles and contributed to a review article with collaborators in Germany. For the paper Hompland T et al *Combined MR imaging of oxygen consumption and supply reveals tumor hypoxia and aggressiveness in prostate cancer patients,* which was published in Cancer Research, we received the OUS article prize for first half year of 2018. In this paper, we report a novel method to visualize hypoxia based on diagnostic, multiparametric diffusion weighted MR images that potentially can be translated into clinical practice using the hospital's current state-of-the-art infrastructure and diagnostic procedures without additional increase in treatment cost.

Radiation Biology and Tumor Physiology

"Our goal is to identify strategies for personalized radiation therapy of cancer"

Group leader: Einar K. Rofstad

ABOUT

Group members: 9, including 2 researchers, 4 postdocs, 2 PhD students, and 1 technician.

The focus of the group is to improve the outcome of radiation therapy of cancer. Poor outcome is a consequence of radiation resistance and elevated metastatic propensity of the primary tumor, and our research is based on the hypothesis that poor outcome is caused primarily by an abnormal physicochemical tumor microenvironment. 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 physicochemical parameters.

AIMS

To reach the primary goal, our research is divided into two arms with the following aims:

- To develop MRI-based methods that can provide information on the physicochemical microenvironment, metastatic propensity, and radiocurability of tumors
- To develop treatment strategies for normalizing the physicochemical microenvironment, decreasing the metastatic propensity, and enhancing the radiocurability of tumors

PROJECTS

- Clinical MRI of locally-advanced cervical carcinoma
- Preclinical MRI of cervical carcinoma, pancreatic carcinoma, and malignant melanoma
- Antiangiogenic and antifibrotic treatment of tumors
- Mechanisms governing the physicochemical microenvironment of tumors

RECENT ACHIEVEMENTS

The group published 5 papers in 2018. Important findings include:

- Pancreatic ductal adenocarcinoma xenografts treated with sunitinib (antiangiogenic agent) show less abnormal microvessels after treatment than before treatment, but due to treatment-induced vessel pruning, the overall function of the microvasculature is impaired after treatment, resulting in increased tumor hypoxia.
- Patients with locally advanced cervical cancer with tumors showing low hypoxic fraction in combination with low interstitial fluid pressure have particularly good prognosis (5-year survival rate of 100 %) whereas those with tumors showing high hypoxic fraction in combination with high interstitial fluid pressure have particularly poor prognosis (5-year survival rate of 13 %).

Radiation Biology and DNA Damage Signaling

"Our goal is to obtain new knowledge about cellular responses to radiation and utilize it to improve cancer therapy"

Group leader: Randi Syljuåsen

ABOUT

Group members:
13.4 including 4.1 researchers, 2 postdocs ,4 PhD students and 3.3 technicians.

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 signaling, in addition to more applied projects to understand how inhibitors of DNA repair and checkpoints can be used in an optimized manner for cancer treatment. Three project groups, headed by Beata Grallert, Trond Stokke and Sebastian Patzke, are members of our group.

AIMS

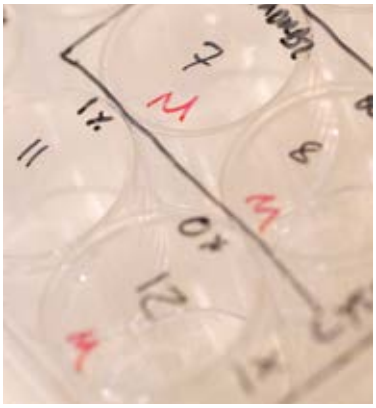
- Obtain new knowledge about cellular responses to radiation, with focus on cell cycle checkpoints, DNA damage signaling and repair, and explore how such knowledge can be used to improve radiotherapy.

PROJECTS

- Pre-clinical exploration of the effects of checkpoint kinase (CHK1, WEE1, ATR) and PARP inhibitors
- Functional roles of Protein phosphatase 1 (PP1) targeting subunits in DNA damage signaling
- Identification of drugs that inhibit DNA repair after radiation, through flow cytometry-based 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 and translational regulation in the cell cycle and cellular stress

RECENT ACHIEVEMENTS:

In 2018 totally 8 articles were published (including articles in press). Members of the group were senior/first authors on 3 of these, published in Nucleic Acids Research, Journal of Cell Science and Scientific Reports. 4 M.Sc degrees were completed. One new grant was obtained from the Norwegian Cancer Society.



“Preclinical and clinical efforts towards precision oncology”

Department of Tumor Biology

Headed by Gunhild M. Mælandsmo

The department has four research groups and 56 employees with a common vision to better understand the biological mechanisms involved in cancer progression and metastasis. Our strategy is, through basic and translational research in the areas of cancer biology and computational science, to enhance systems understanding and thereby identify novel intervention strategies. We emphasize multidisciplinary competence and collaboration between researchers, clinicians and patients to stimulate the necessary synergy for improved cancer care.

We are performing basic, translational and clinical research, and our scientific goal is to provide knowledge for clinical translation of precision cancer medicine. We will do so by contributing with expertise in genomics and bioinformatics and by utilizing patient samples as model systems for investigation of therapeutic efficacy. We have a large collection of patient-derived xenograft models 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.

To foster a strong link between translational and clinical research we have several researchers holding part-time clinical positions. An ambition for the department is to participate in design and conduct of clinical trials, and to provide molecular and bioinformatics competences in multidisciplinary tumor boards in the area of precision cancer medicine.

Key achievements over the last 3-4 years include project leader responsibilities in large collaborative projects in the area of precision cancer medicine:
NCGC - The Norwegian Cancer Genomics Consortium, a national project aiming to sequence tumors across nine tumor types. All exomes have been sequenced and are currently being analyzed. Several papers are now under publication.

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. Collection of samples was successfully completed in 2018.
MetAction - Actionable targets in cancer metastasis. A diagnostic pipeline was established which allowed the first clinical trial in Norway where treatment decision is based on targeted NGS data. 50 patients were enrolled, actionable targets detected in 13 and long-term clinical effects where observed in two patients.
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.
The EuroPMP Cost Action – European research network in rare cancer pseudomyxoma peritonei was initiated in September 2018.

Other clinical studies with substantial collaborative 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)

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 20 members with multidisciplinary background and expertise (cell- and molecular biologists, medical doctors, physicists, laboratory- and animal technicians), including two MDs in shared clinical positions. Several of the technicians are trained in specialized technologies and compose resources for all groups in the department.
Research focus: Investigations on mechanisms of resistance and metastasis for improved treatment of cancer.
Methodology: Molecular and functional analyses utilizing clinical samples, human cell cultures and patient-derived models (*ex vivo*, *in vitro* and *in vivo*).

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 working with malignant melanoma, breast cancer and prostate cancer.

PROJECTS

1. Basic research revealing mechanisms causing treatment resistance and metastasis
   - Molecular and cellular determinants regulating cancer cells plasticity, with special emphasis on the role of tumor-stroma interactions
2. Preclinical research investigating novel drugs and drug combinations
   - Mechanistic studies and assessment of treatment efficacy in patient-derived models in vivo and ex vivo
   - Biomarker detection by molecular and functional techniques
   - Response evaluation of experimental drugs (often in collaboration with commercial partners, *eg.*: Lytix Biopharma)
3. Clinical trials in precision medicine – clinical and translational efforts
   - NeoAva: bevacizumab in combination with neoadjuvant chemotherapy for patients with locally advanced breast cancer (patient inclusion closed)
   - 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 (patient inclusion closed)

RECENT ACHIEVEMENTS

- The group was credited with 8 publications in 2018, of which two with group members as first and/or last author; two Master degrees completed
- One clinical intervention trial in breast cancer open for inclusion (I-BCT)
- Successful establishment of a user board for breast cancer research
- One major grant approved for further studies on stratification biomarkers in breast cancer
- Two DOFIs filed

Translational Cancer Therapy

"New treatment for metastatic colorectal cancer"

Group leader: leader Kjersti Flatmark

ABOUT

In 2018, the Translational Cancer Therapy group comprised 16 members (including part-time employees and students) with a broad variety of expertise, including basic biologists, translational scientists, and clinician-scientists. Our 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 make new, efficacious treatment(s) available to patients with colorectal cancer (CRC). This will be accomplished by bringing the clinic and lab together in translational research projects utilizing 1) preclinical models for efficacy and mechanistic studies 2) clinical cohort studies to understand CRC biology and identify biomarkers and therapeutic targets 3) clinical intervention trials to test new drugs and therapeutic concepts in patients

PROJECTS

- Peritoneal metastasis – molecular targets and new therapies
  - Personalizing CRC therapy – identification of biomarkers and therapeutic targets in locally advanced and metastatic CRC, involving generation and use of our extensive biobanks, molecular and bioinformatics analyses (subprojects include: genomics, microRNA, mRNA, and immune cell analysis, participation in the BigMed project)
  - Novel drugs and therapeutic concepts in models of peritoneal and liver metastases
- Translational studies within the METIMMOX multicentre trial (Colorectal Cancer Metastasis – Shaping Anti-Tumor Immunity by Oxaliplatin), which will investigate the combination of oxaliplatin and checkpoint inhibition (nivolumab) in microsatellite stable CRC
- Commercial development of MOC31PE and BM7PE immunotoxins for cancer therapy

RECENT ACHIEVEMENTS

- Group members were credited with 14 publications in 2018
- The multicenter METIMMOX trial started accrual in March 2018, and all study centers have now opened for accrual.
- Grant support was obtained from the Norwegian Cancer Society (project support) and from the South-East Norway Regional Health Authority (PhD project).
- Our COST Action, EuroPMP, European Research Network on rare cancer pseudomyxoma peritonei, was initiated with official kick-off in September. EuroPMP currently comprises >50 members from 16 European countries.
- Two DOFIs filed

Computational Cancer Genomics

Group leader: Eivind Hovig

"Enabling the transition to clinical utility"

ABOUT

The 10-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 centered on computational aspects of deep sequencing for cancer, with downstream analysis. The group facilitates 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, 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 signaling 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

- Group members were credited with 14 publications in 2018, of which 7 with group members as first and/or last author.
- 1 Master degree was completed

Molecular Biology of Sarcoma

"Towards precision medicine to improve treatment of sarcomas"

Group leader: Jørgen Wesche

ABOUT

The 15-member group has a long-standing interest in the biology of mesenchymal tumors (sarcomas). The current focus is on precision medicine for sarcomas. To achieve this, the group has broad expertise in basic cell biology, genomics and translational research and, in addition, one MD in a shared clinical position. The group is part of a Centre of Excellence (CanCell).

AIMS

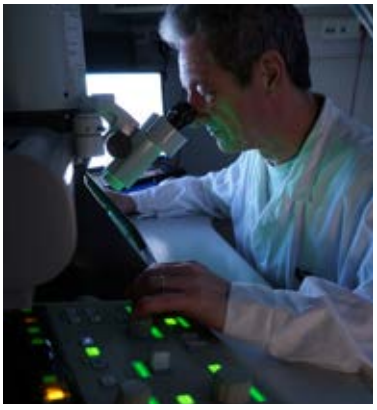
The group aims to improve the treatment of sarcoma patients by combining extensive genomic characterization of clinical cohorts with preclinical investigation in cell lines and xenografts to better understand the biology of sarcomas. The generation and characterization of in vitro and in vivo sarcoma models make the framework for pre-clinical studies.
Sarcomas are rare cancers with poor treatment options, and we aim to use our biological knowledge to identify new treatments opportunities by repurposing approved drugs for other cancers types.

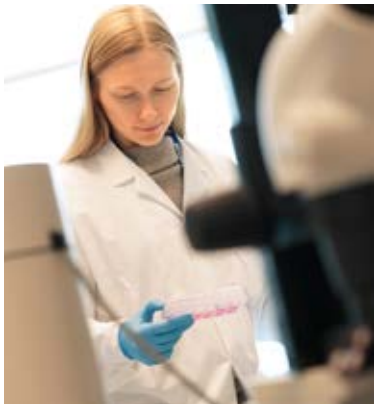
PROJECTS

- Sarcoma cell biology – Gaining understanding of the development and progression of rhabdomyosarcoma, liposarcoma and osteosarcoma, and potentially identify biomarkers and novel drug targets. A main focus is the study of the role of fibroblast growth factor receptors (FGFRs).
- Norwegian Sarcoma Consortium (NoSarC) – Biobanking and genomic characterization of patient material of 3-4 national cohorts of sarcomas (~500 samples). The project will provide unique, population based datasets including the many rare subtypes of sarcomas.
- Establishment of ex vivo drug sensitivity/resistance screen for sarcoma primary tumors, and search for novel anti-sarcoma drugs using drug screens on panels of liposarcoma and osteosarcoma cell lines.
- Exploration of "liquid biopsies", as a non-invasive methods for detection of tumor-derived DNA in blood, to monitor disease progression, treatment response and tumour evolution.

RECENT ACHIEVEMENTS

- 15 publications in 2018
- 1 PhD degree was completed.
- The group obtained 4 major grants.
- 1 DOFI was filed.
- A sarcoma user board was successfully established.





“Providing cutting-edge technology and competence to excel research”

Department of Core Facilities

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 competence, infrastructure and services to regional, national and international users. The Department aims to deliver easy access to cutting-edge advanced technologies and competence, and to improve research quality through optimal choice of technology, ultimately increasing the scientific competitiveness of our users. The Department of Core Facilities is organized in three units; Flow Cytometry and Pre-Clinical Imaging, Advanced Microscopy and Genomics and Bioinformatics, with a total of 19 employees. More information at: www.ous-research.no/corefacilities.

ADVANCED LIGHT MICROSCOPY
Unit Leader: Ellen Skarpen
Scientifically responsible: Harald Stenmark
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 super-resolution microscopy. Current instruments include a Zeiss LSM 880 FAST airyscan microscope, a Zeiss LSM 710 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 competent core facility personnel.

ADVANCED ELECTRON MICROSCOPY
Unit Leader: Ellen Skarpen
Scientifically responsible: Andreas Brech
Facility staff: 1

The Core Facility for Advanced Electron Microscopy (AEM) includes nodes at the Radium Hospital and Rikshospitalet, and provides service, training and access to microscopes for ultrastructural studies. Available techniques at the facility include conventional plastic embedding, immune EM, correlative light/electron microscopy (CLEM), high pressure freezing, electron tomography, cryo-EM and STEM. The facility staff is actively developing new methods in order to offer state-of-the-art microscopy solutions for researchers. We cooperate with the imaging platform at the Institute for Biosciences, University of Oslo and are part of the Norwegian Advanced Light Microscopy node within EuroBioImaging.

Department of Core Facilities

Bioinformatics

Unit Leader: Susanne Lorenz
Scientifically responsible: Eivind Hovig
Facility staff: 6

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

Unit Leader: Trond Stokke
Scientifically responsible: Trond Stokke
Facility staff: 3

The Flow Cytometry Core Facility (FCCF) provides analysis and sorting services for users within the South-Eastern Health Region of Norway. We have received grants for a new state-of-the-art analyzer (BD Symphony) with 5 lasers that may measure up to 28 fluorescence parameters simultaneously. In total, the core facility provides services using 3 analyzers and two sorting instruments. Flow cytometry analysis is performed by the users themselves. Sorting experiments are either performed by experienced core facility personnel (in the BD Aria), or by the users in the 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 also have a "mass-spec flow cytometer" (CyTOF 2, which will be upgraded to Helios). This instrument can measure up to 60 parameters simultaneously at single cell resolution. We have recently obtained grants for an add-on to the Helios, Hyperion, which allows for imaging of sections labeled with up to 60 heavy metal-tagged antibodies. The FCCF collaborates with facility nodes at the Rikshospitalet and Ullevål campuses of OUH.

High-throughput Sequencing and Microarrays (Genomics)

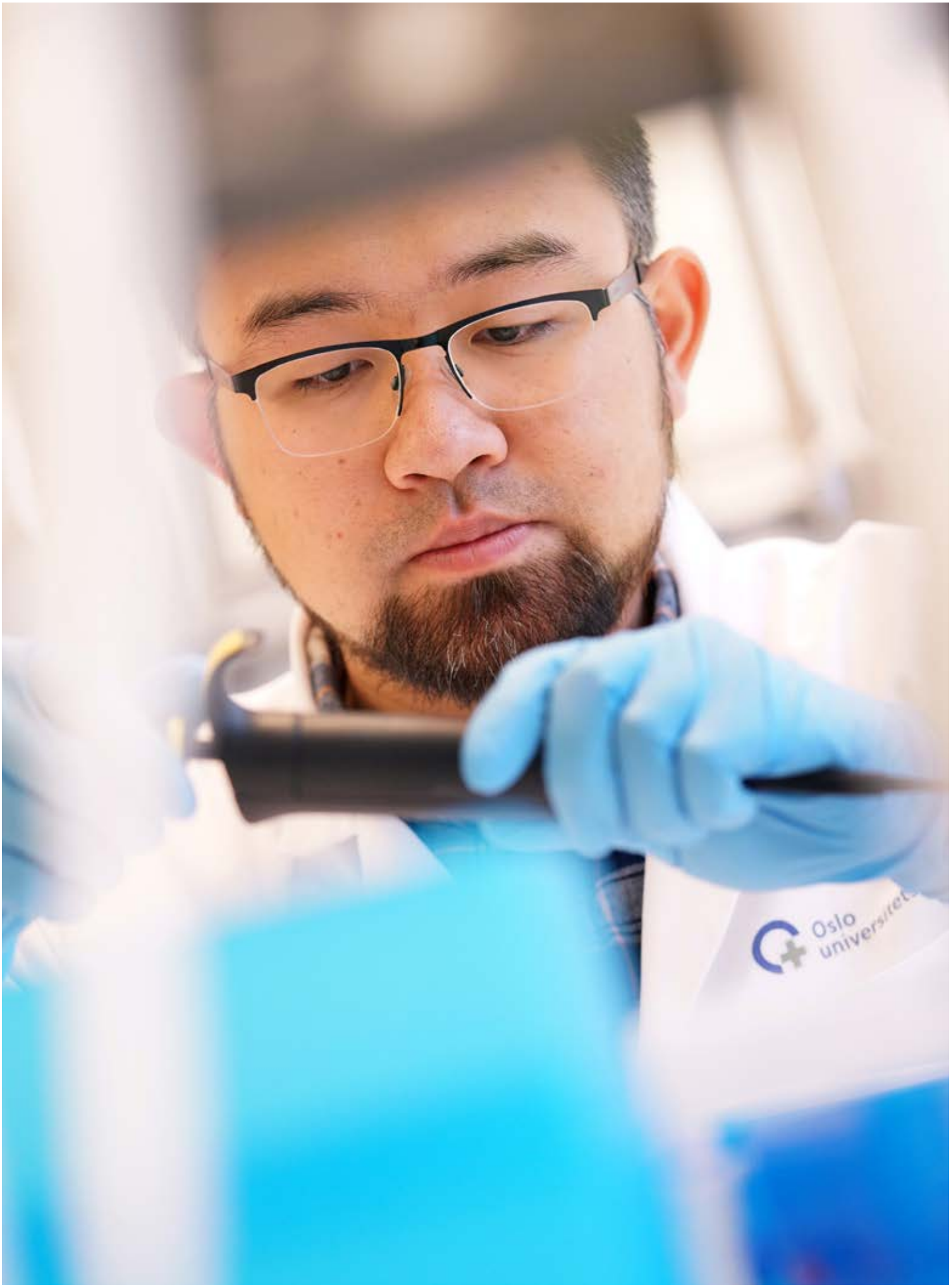
Unit Leader: Susanne Lorenz
Scientifically responsible: Leonardo A. Meza-Zepeda
Facility staff: 5

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 and competence to study genome structure, dynamics and function using high-throughput sequencing, NanoString and microarray technologies. Our highly experienced service personnel provide advanced support to clinical, translational and basic research projects. Our services include standard and custom solutions to study the transcriptome, genome and epigenome from multi-genes analysis to genome-wide level. The core facility collaborates with similar nodes at the Ullevål campus for sequencing and microarray services. The GCF is a founding member of the Norwegian Consortium for Sequencing and Personalised Medicine (NorSeq) running the National platform for sequencing technology, and provides the sequencing infrastructure and competence for the National Personalised Medicine initiative (NCGC). In 2018 we have established the first single-cell sequencing service in Norway, providing expertise and instrumentation for single cell analysis using 10x Genomics and BD Rhapsody platforms. In addition, we have implemented the NanoString nCounter technology to provide targeted genomic, transcriptomic and proteomic services.

Preclinical Imaging Facility

Unit Leader: Trond Stokke
Scientifically responsible: Tord Hompland
Facility staff: 2

The Preclinical Imaging Facility provides access to a state-of-the-art non-invasive imaging equipment for mice and rats. The equipment is situated within the animal facility and consist of a 7T Bruker MRI, IVIS spectrum and Zeiss Stereo Macroscope for optical imaging, and a Multirad 225 small animal irradiator capable of doing x-ray imaging. The facility also provides 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 imaging protocols are available, and custom-protocols can be developed upon user request. We are at present developing a protocol for synchronization of images obtained by MRI, IVIS and X-ray imaging. The service offered by the core facility includes design, development and running of the imaging 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.


Oslo
universitet

Research centres

60

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 (CanCell) is funded for 5 + 5 years (if recommended for extension following a mid-term evaluation). The total basic funding is ~167 million NOK.

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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 with the possibility of a 2-year extension. The selected Centres receive 16-18 million NOK in basic funding over the first four years from the Foundation and support from the host institutions, University of Oslo (KG Jebsen Centre for Cancer Immunotherapy, KG Jebsen Centre for B Cell Malignancies) or Oslo University Hospital (KG Jebsen Colorectal Cancer Research Centre).

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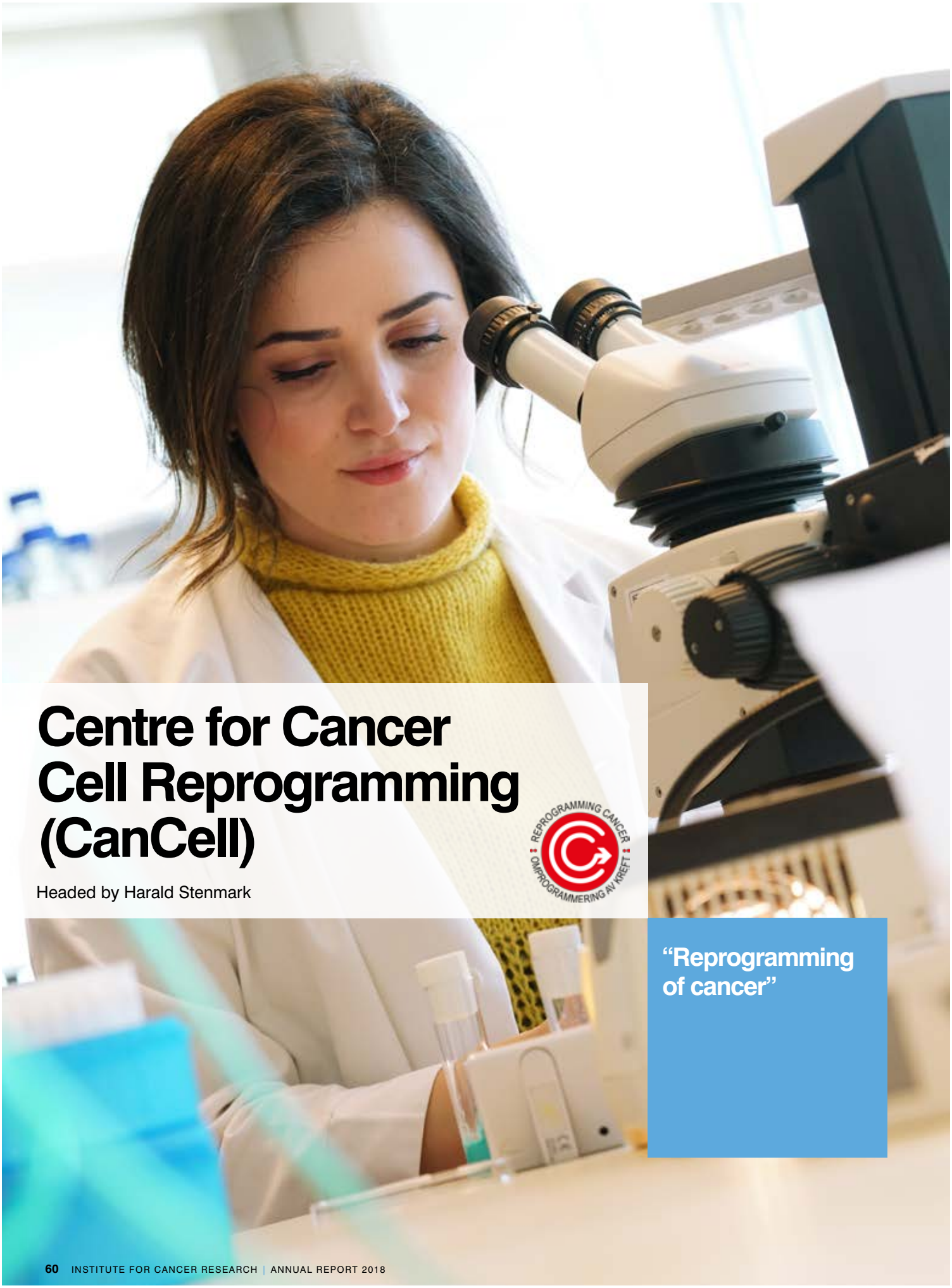
Norwegian Cancer Genomics Consortium

The establishment of Norwegian Cancer Genomics Consortium (NCGC) 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 was 75 million NOK received from the Norwegian Research Council. The final report from NCGC was delivered to the Minister for Health in March 2019.

Centre for Cancer Cell Reprogramming (CanCell)

Headed by Harald Stenmark



"Reprogramming of cancer"

ABOUT

Centre for Cancer Cell Reprogramming (CanCell) is a Norwegian Centre of Excellence (CoE) which opened 01.01.2018 and has a planned CoE funding period of 10 years. CanCell is led by Harald Stenmark at Institute for Cancer Research, whereas Anne Simonsen at Institute of Basic Medical Sciences is co-director. The centre consists of 6 research groups and has 7 associate members (Eivind Hovig, Åslaug Helland, Yngvar Fløisand, Philippe Collas, Arnoldo Frigessi, Emmet McCormack, and Terje Johansen) and 4 international visiting professors (Kristian Helin, Ivan Dikic, Eileen White, and Eyal Gottlieb). By the end of 2018, CanCell had 98 members.

AIMS

CanCell's vision is to identify novel vulnerabilities of cancer cells that can be targeted for cancer cell reprogramming. The centre's founding hypothesis is that pathway intersections between chromatin regulation, membrane dynamics, cell signaling and metabolism during cancer progression represent potential "Achilles' heels" of cancer cells. These will be identified through close cooperations between specialists within these four cellular processes, and will be targeted by genetic and pharmacological regimens to achieve reprogramming of cancer cells into harmless (or dying) cells.

PROJECTS

- Membrane dynamics in cancer
- Autophagy in immunity and cancer
- Molecular medicine of leukemia
- Tumour-host interactions
- Molecular biology of sarcomas
- Mechanisms of epigenetic regulation in cancer

RECENT ACHIEVEMENTS

- Demonstration that the centromere directs mitotic chromosome condensation, a collaboration between Enserink's group and Yves Barral's group at ETH Zürich (Kruitwagen et al., *Cell* 2018).

- Identification of a novel mechanism for controlling positioning of the mitotic spindle (Malerød et al., *EMBO Journal* 2018).

- Establishment of timing and mechanisms of protein recruitment during receptor sorting into multivesicular endosomes (Wenzel et al., *Nature Communications* 2018).

- Identification of a protein tyrosine phosphatase that controls fibroblast growth factor receptor activity and drug sensitivity (Kostas et al., *Molecular & Cellular Proteomics* 2018).

- Demonstration that control of tRNA synthesis occurs via regulation of RNA polymerase III activity (Herrera et al., *Nucleic Acids Research* 2018).

- Identification of a mechanism which mediates lysosome repair, and demonstration that this mechanism promotes cell viability (Radulovic et al., *EMBO Journal* 2018).

- Demonstration that SNX18 regulates ATG9A trafficking from recycling endosomes during autophagy by recruiting the GTPase Dynamin-2 (Søreng et al., *EMBO Reports* 2018).

- CanCell published 20 papers in 2018 in journals of good international reputation. CanCell scientists were first or corresponding authors of 11 of these papers. One PhD student was graduated in 2018.

- CanCell members have been successful in obtaining major external grants in 2018, including grants from the European Research Council, the Norwegian Cancer Society, the Research Council of Norway, and the South-Eastern Norway Regional Health Authority.

GROUP LEADERS/STEERING COMMITTEE

CanCell was established by the following 6 group leaders, who also serve as CanCell´s steering committee:

Harald Stenmark, Institute for Cancer Research, OUS, and Institute of Clinical Medicine, UiO

Anne Simonsen, Institute of Basic Medical Sciences, UiO, and Institute for Cancer Research, OUS

Jorrit Enserink, Institute for Cancer Research, OUS, and Department of Biosciences, UiO

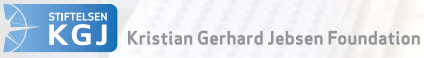
Ragnhild Eskeland, Institute of Basic Medical Sciences, UiO

Tor Erik Rusten, Institute of Clinical Medicine, UiO, and Institute for Cancer Research, OUS

Jørgen Wesche, Institute for Cancer Research, OUS, and Institute of Clinical Medicine, UiO

K.G. Jebsen Center for Cancer Immunotherapy

Headed by Johanna Olweus



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 granted maximal prolongation following the first 4-year period, throughout 2019. The partnering groups of JCIT span complementary competencies ranging from basic proteomics, cell signaling and T-cell receptor engineering to expertise in experimental clinical immunotherapy trials. This places the center in a unique position to pursue novel therapeutic opportunities, and the strong focus on translating therapeutic opportunities is a fundamental characteristic of JCIT. Results from basic research are pursued through the necessary translational steps to testing in patients, and in-depth mechanistic studies of patient material obtained in experimental clinical trials are performed with the aim of improved designs of immunotherapeutic strategies.

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

- Reported a new method to validate thousands of antibodies in parallel using mass spectrometry data as reference. (*Sikorski et al, Nat Methods 2018*)
- Reported the first Phase I/II clinical trial based on transfer of allogeneic NK cells to patients with high-risk AML and MDS (*Björklund et al., Clinical Cancer Research 2018*).
- Reported low and variable tumor reactivity of the intratumoral TCR repertoire in human cancers (*Scheper et al, Nat. Med. 2018*)
- Described a role for lysosomal remodeling in tuning NK cell function (*Goodridge et al, Nature Communications, 2019*).
- Patent granted on technology for identification of specific T-cell receptors (WO 2015/071763A2)
- Described a technology for identification of neoantigen specific T cells from healthy donors (Ali et al, *Nature Protocols in press, 2019)*
- Renewed a 2-year collaborative agreement with Fate Therapeutics to develop off-the-shelf NK cell therapy.
- Licensed pending patent concerning a method for selective expansion of educated NK cells to Fate Therapeutics Inc. January 2018. A clinical trial exploring this concept will be launched during 2019. "Modulation of function of immune effector cells".
- Included 9 patients in Lymvac-2, an experimental immunotherapy trial combining intratumoral immunotherapy with anti-PD1 for treatment of patients with follicular lymphoma, in collaboration with Merck.
- Recruited first 100 patients to the ASAC trial that examines the effect of reversing prostaglandin E2-mediated inhibition of tumor immunity in patients with metastatic colorectal cancer by the end of 2018 (www.asac.no).
- Demonstrated that idelalisib preferentially inhibits human regulatory T cells, which enhances anti-tumor immunity but also contributes to adverse effects in patients with chronic lymphocytic leukemia (*Chellappa et al, J Immunol., in press des 2018*).

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 Taskén (MD, PhD), Dept of Cancer Immunology, Institute for Cancer Research, OUH-Radiumhospitalet and Inst. of Clinical Medicine, UiO

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

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

K.G. Jebsen Centre for B-cell malignancies

Headed by Ludvig A. Munthe and June H. Myklebust

Kristian Gerhard Jebsen Foundation

"From basic research and preclinical studies to precision medicine for B-cell malignancies"

ABOUT

The **K.G. Jebsen Centre for B-cell malignancies** was established in June 2018 and is hosted by the University of Oslo. B-cell malignancies include lymphomas (Non-Hodgkin and Hodgkin lymphomas), B-cell leukemias (ALL, CLL) and multiple myeloma. The centre bridges 4 basic/translational research groups with 3 clinical groups; placing us in a unique position to translate pre-clinical results into clinical trials. The centre utilizes "cutting edge" technologies for deep profiling of tumor biopsies, including whole exome DNA sequencing, bulk and single cell RNA sequencing, single cell proteomics by mass cytometry and mass cytometry imaging, cancer sensitivity drug screens, and development of integrative bioinformatics' pipelines for precision medicine. Patient-derived xenograft (PDX) models and syngeneic tumor mouse models are used for pre-clinical testing of new treatments. Collectively, the Centre represents a multidisciplinary integration of life science research with preclinical development of personalized medicine, drug discovery and cell-based immunotherapy, as well as clinical trials and establishment of best practice on how to treat B-cell malignancies.

AIMS

The centre aims to identify, develop and test new therapeutic options for patients with B-cell malignancies and to initiate new therapeutic trials in both industry- and investigator driven initiatives.

PROJECTS

- Identify molecular biomarkers to guide precision medicine and to identify high risk patients
- Deciphering signal integration and interactions with the tumor microenvironment to reveal actionable targets and targets for immunotherapy
- Develop novel therapeutics: identify antigens for vaccination, T cell epitope discovery, and CAR T cell design
- Preclinical testing: immunotherapy and personalized medicine
- Translating results into clinical initiatives – from bench to bedside and back

RECENT ACHIEVEMENTS/CLINICAL TRANSLATION

- The centre currently encompasses 67 clinical trials of which 13 are in startup, 28 are actively recruiting and 24 are in follow up; 21 of these are phase II studies and 28 are phase III studies
- Participated in the multicenter double-blind, randomized, placebo-controlled phase 3 trial for testing the efficacy of the proteasome inhibitor ixazomib given orally as maintenance therapy following autologous stem cell transplantation (TOURMALINE-MM3) in multiple myeloma (*Dimopoulos et al, Lancet in press 2018*)
- Participated in the international clinical phase II trial for testing of CD19 CAR T cell therapy in adult relapsed or refractory Diffuse Large B-Cell Lymphoma, and reported a 52% overall response rate *(Schuster SJ et al, N Engl J Med. in press 2018*).
- Demonstrated that the PI3Kδ inhibitor idelalisib enhances anti-tumor immunity preferentially through inhibition of human regulatory T cells in patients with CLL (*Chellappa et al, J Immunol. in press 2018*).
- Identified the co-inhibitory receptor TIGIT as a potential new target for immune checkpoint blockade in B-cell lymphoma (*Josefsson et al, Cancer Immunol. Res. in press 2018*)
- Identified that bone marrow T helper cells with a Th1 phenotype can induce activation and proliferation of leukemic cells in precursor B-ALL patients (*Traxel et al, Oncogene 2018*)
- Identified and characterized a novel mechanism of action of CD4+ T cell-mediated immunotherapy (*Fauskanger et al, Front Immunol. 2018; Haabeth et al. Cancer Res. 2018*)

Home page
https://www.med.uio.no/klinmed/english/research/centres/kgj-b-cell-malignancies/

GROUP LEADERS/STEERING COMMITTEE

Ludvig A. Munthe (MD, PhD, Centre Director), Div. for Laboratory Medicine, Dept. of Immunology, OUH-Rikshospitalet and Institute for Clinical Medicine, University of Oslo (UiO)

June H. Myklebust (PhD, Assistant Director), Institute for Cancer Research, Dept of Cancer Immunology, OUH-Radiumhospitalet and UiO

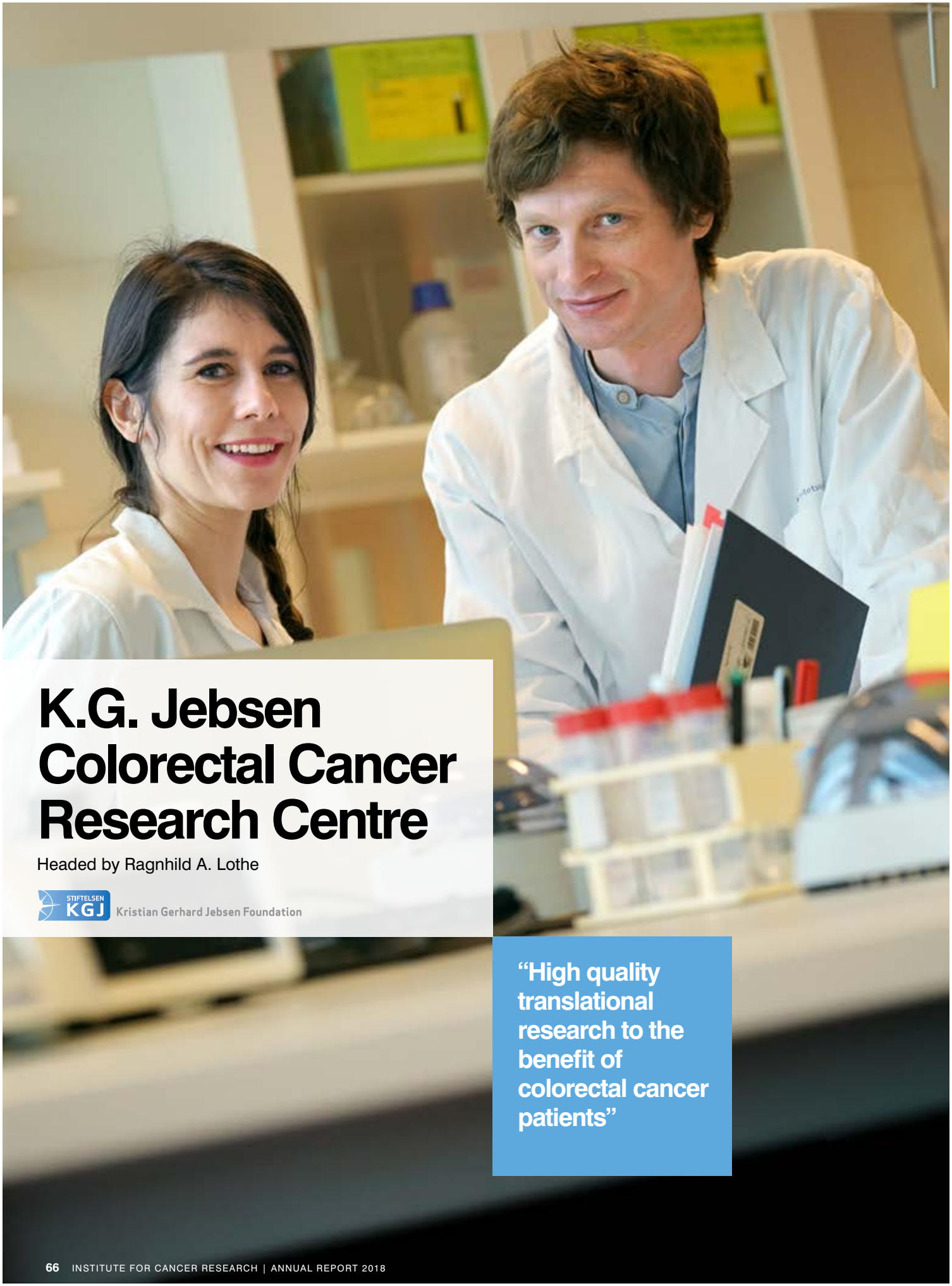
Geir E. Tjønnfjord (MD, PhD), Div. for Cancer Medicine, Dept. of Haematology, OUH-Rikshospitalet and UiO

Hilde Schjerven (PhD), Dept. of Immunology, OUH-Rikshospitalet and Dept. of Laboratory Medicine, University of California, San Francisco.

Harald Holte (MD, PhD), Div. for Cancer Medicine, Dept. of Oncology, OUH-Radiumhospitalet

Erlend B. Smeland (MD, PhD), Institute for Cancer Research, Dept. of Cancer Immunology, OUH-Radiumhospitalet and UiO

Kjetil Taskén (MD, PhD), Institute for Cancer Research, Dept. of Cancer Immunology, OUH-Radiumhospitalet and UiO



K.G. Jebsen Colorectal Cancer Research Centre

Headed by Ragnhild A. Lothe

STIFTELSEN KGJ Kristian Gerhard Jebsen Foundation

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

ABOUT

Colorectal cancer (CRC) is a major health burden, and the focus of our Centre is to meet the challenges in the management of the disease, by improved patient monitoring and stratified 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-CRC priority area (2014-18). Home page: www.colorectalcancer.no

GROUP LEADERS/STEERING COMMITTEE

- **Professor Ragnhild A. Lothe** (MSc, PhD, Centre leader), Dept. of Molecular Oncology, Institute for Cancer Research, OUH and Institute for Clinical Medicine, University of Oslo (UiO)
- **Professor Arild Nesbakken** (MD, PhD, deputy Centre leader), Dept. of Gastrointestinal Surgery, OUH and Institute for Clinical Medicine, UiO
- Until 2018/06: **Associate Professor Mette Kalager** (MD, PhD), Institute of Health and Society, UiO, and Dept. Epidemiology, Harvard T.H.Chan School of Public Health, USA
- **Professor Rolf I. Skotheim** (MSc, PhD), Dept. of Molecular Oncology, Institute for Cancer Research, OUH, and Dept. of Informatics, UiO.
- **Senior Consultant Marianne G. Guren** (MD, PhD), Dept. of Oncology, OUH
- From 2018/06: **Professor Guro E. Lind** (MSc, PhD), Dept. Molecular Oncology, Institute for Cancer Research, OUH and Dept. of BioSciences, UiO

Our Centre has an active Patient advisory board established in 2016.

AIM

Translate biomedical knowledge of CRC in the context of tumor heterogeneity into improved stratified medicine.

PROJECTS

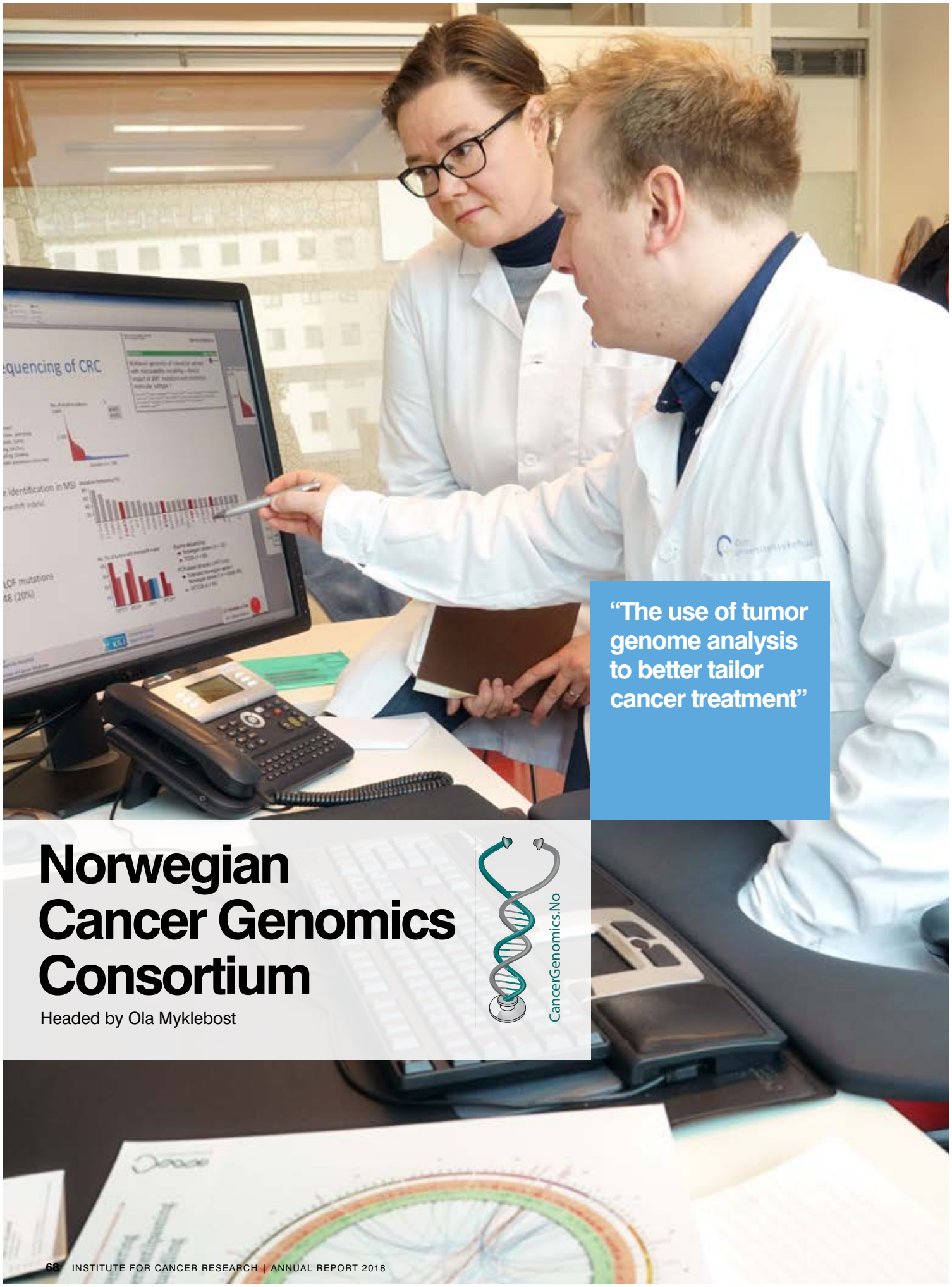
- Clinical and molecular biomarkers for improved risk stratification of patients
- Model tumor heterogeneity and clonal evolution to monitor early relapse and treatment failure
- Pharmacogenomic profiling of organoid models derived from the patients' own tumor cells for therapy guidance, identification of biomarkers for response prediction, and development of synergistic drug combinations

RECENT ACHIEVEMENTS

In 2018, we were granted a 2-year prolongation period of the Centre, to continue the translational and clinical research program on primary and metastatic CRC.
The PI groups published 33 peer-reviewed papers related to CRC in 2018 (incl ahead of print), including Ann Oncol (2), BBA Reviews on Cancer, Clin Cancer Res, Lancet Oncol (2), Sem Cancer Biol. Peter Andreas W. Eide defended his PhD at the Institute for Clinical Medicine, UiO. Anita Sveen was appointed assoc. professor at the Institute for Clinical Medicine, UiO, and received a young researcher talent grant from the Research Council of Norway. The first 15 patients were successfully included in our newly established *ex vivo* pharmacogenomics pipeline, involving drug screening and molecular profiling of patient-derived organoids from multiple CRC liver metastases of each patient. The initial results were presented in an invited talk at the AACR-meeting "Intestinal Stem Cells and Colon Cancer: Biology to Therapy" in Washington D.C. in Sept 2018. The annual meeting of the Centre was held in November at the Norwegian Academy for Science and Letters, Oslo. Key invited speakers were international and national oncologists Rodrigo Dienstmann – VHIO-Barcelona, David Church-University of Oxford, Anne Hansen Ree - Ahus, Bjørn Erikstein – OUS (Director).

Clinical research
Centre surgeons participated in an international multicentre study showing that differences among European countries in survival from CRC was best explained by patient selection for surgery (Benitez et al., Lancet Oncol 2019). For elderly rectal cancer patients specifically (>80 years), variation in 5-year relative survival depended on variation in the use of preopereative radiotherapy, and on the resection rate in stage IV (Claassen et al., Brit J Ca 2018). Furthermore, complications following CRC surgery have been evaluated in frail older Norwegian patients (Ommundsen et al., Eur J Surg Oncol 2018), and by the European Society of Coloproctology collaborating group, in which professor Nesbakken has participated with data from patients enrolled in our Centre project (Colorectal Dis. 2018 20: 1028-1040; plus 5 additional publications in Suppl 6: 15-32, 33-46, 47-57, 58-68, 69-89).

Translational research
Benefiting from the national public health system and our collaboration with the Cancer Registry of Norway, we are assembling a national population-representative patient series. Diagnostic tumor material from 5,000 patients from all health regions will be collected and used for development of prediction models for patient outcome based on clinical and molecular biomarkers.
We completed several biomarker studies in 2018. KRAS mutation is a clinically relevant biomarker and a negative predictive factor for anti-EGFR treatment in metastatic CRC. We found that its prognostic value is dependent on the tumor's gene expression subtype (Smeby et al., Ann Oncol 2018). Furthermore, among KRAS wild-type cancers, aberrant splicing by low relative expression of KRAS-4A vs KRAS-4B transcript variants identify patients with inferior survival (Eilertsen et al., Int J Ca 2018). From analyses of more than 2000 tumor samples and pre-clinical models, we identified a microRNA as a novel bona fide prognostic marker in CRC, independent of cytotoxic lymphocyte and fibroblast infiltration (Eide et al., Int J Ca 2018). We also refined the prognostic and predictive value of CDX2 in CRC (Bruun et al., Mol Oncol 2018). Non-invasive analyses of the clinical biomarkers CEA and CA19-9 in liquid biopsies (serum) was found to provide independent poor prognostic information in metastatic CRC, and elevated CA19-9 was associated with BRAF mutations (Thomsen et al., Brit J Ca 2018).
In a recent study of pre-clinical models, we demonstrated that HSP90 inhibitors have the potential to overcome chemoresistance in an agressive subtype of CRC (Sveen*, Bruun* et al. Clin Cancer Res 2018), and we have written a review on the clinical and preclinical evidence for combination treatments with HSP90i in CRC (Kryeziu et al, BBA-Reviews on Cancer, 2019).



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

Norwegian Cancer Genomics Consortium

Headed by Ola Myklebost

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, is expected to provide huge benefits to the patients by better adapting the treatment, especially by targeted drugs, to the specific properties of the disease of the individual. The hope is that this will at least give prolonged survival and better quality of life, 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 DNA sequence, the detailed structure, 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 sarcomas, colon, prostate, myeloma, and lymphoma samples from standard-of-care 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 200 sample pairs exome sequenced by NCGC, about 150 additional pairs are being sequenced with additional funding from the Radium Hospital Legacy. Up to now approximately 1800 samples from 630 patients have been sequenced. Promising targets for which drugs are available, but without documentation of clinical effect in the cancers investigated, are tested pre-clinically in relevant cell culture and xenograft models. The intention is to propose small, exploratory clinical trials to indicate activity in selected patients, and that promising results could lead to extension to 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 genetic variants (SNPs) detected in the germ lines (blood samples), and the frequencies in the cohort. Other environments are preparing to add Norwegian SNP data, which will be a valuable resource for many types of genetic research and diagnosis.

Upon completion of the two first large projects funded by the Norwegian Research Council, a printed report has been made which provides an introduction to the field, recommendations to the Health Service, evaluation by the institutional board members, and overview of the projects and results so far. A pdf version can be downloaded from rapport.kreftgenomikk.no (Norwegian only). The report was presented to the Minister of Health, Bent Høie, in a meeting in March 2019.

CLINICAL TRANSLATION

The project is investigating patient samples either prospectively 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 outreach and dialogue, with continuous discussions on the strategies and how they may be implemented in the clinics 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/OCC), Hilde I. Nebb (UiO), Knut Martin Torgersen (Pfizer), Bjørn Gustafsson (StOlav/NTNU), Tove Flem Jacobsen (Link Medical), Olav Mella (HUS/UiB), Anne Sameline Grimsgaard (UNN/UiT).

see CancerGenomics.No

International Collaboration

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- CANADA
- PORTUGAL
- SPAIN
- FRANCE
- UNITED KINGDOM
- GERMANY
- ITALY
- DENMARK
- NORWAY
- SWEDEN
- FINLAND
- POLAND
- AUSTRIA
- GREECE
- AUSTRALIA
- ICELAND
- IRELAND
- THE NETHERLANDS
- BELGIUM
- SWITZERLAND
- CZECH REPUBLIC
- HUNGARY
- CROATIA
- INDIA
- SINGAPORE
- ISRAEL
- RUSSIA
- TUNISIA

AUSTRALIA
- Garvan Institute, Sydney
- 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
- McGill University, Montreal
- Princess Margaret Hospital, Toronto
- University of Ottawa, Ottawa

CROATIA
- University of Zagreb, Zagreb

CZECH REPUBLIC
- Charles University, Prague
- Institute of Experimental Biology, Masaryk University, Brno
- Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague
- National Institute of Public Health, Prague

DENMARK
- Aalborg University Hospital, Aalborg
- Aarhus University Hospital, Aarhus
- Copenhagen University Hospital, Copenhagen
- University of Copenhagen, Copenhagen
- University of Southern Denmark, Odense

FINLAND
- Biomedicum Helsinki, University of Helsinki, Helsinki
- Finnish Institute of Molecular Medicine, Nordic EMBL partner, Helsinki
- Tampere University of Technology, Tampere
- Zora Oy, Espoo

FRANCE
- Centre National de Génotypage, Paris
- EurOPDX - European Consortium on Patient-derived Xenografts, Paris
- Institut Gustave Roussy, Paris
- Institut National de la Sante et de la Recherche Medicale, Paris
- Institute Cürie, Paris
- Institute of Systems and Synthetic Biology Genopole, UEVE, CNRS, Évry
- International Agency for Research on Cancer (IARC), Lyon
- Université Lyon, Villeurbanne
- Université Paris-Sud, Orsay

GERMANY
- EMBL, Heidelberg
- Institut für Biochemie, University of Stuttgart, Stuttgart
- Jacobs University, Bremen
- University of Bayreuth, Bayreuth
- University of Bochum, Bochum
- University of Cologne, Cologne
- University of Freiburg, Freiburg
- University of Heidelberg, Heidelberg
- University of Mainz, Mainz
- University of Marburg, Marburg

GREECE
- National and Kapodistrian University of Athens, Athens
- National Centre for Scientific Research “Demokritos”, Athens
- University of Ioannina, Ioannina

HUNGARY
- University of Szeged, Szeged

ICELAND
- University of Iceland, Biomedical Center, Reykjavik

INDIA
- Indian institute of Technology, Hyderabad
- Savitribai Phule Pune University, Pune

IRELAND
- National Institute for Bioprocessing Research and Training (NIBRT), Dublin

ISRAEL
- Technion - Israel Institute of Technology, Haifa
- Weizmann Institute, Rehovot

ITALY
- IFOM, Milan
- International School for Advanced Studies, Trieste
- Istituto Nationale di Tumori, Milano
- The Rizzoli Institute, Bologna
- University of Bologna, Bologna
- University of Padova, Padova
- University of Salento, Lecce

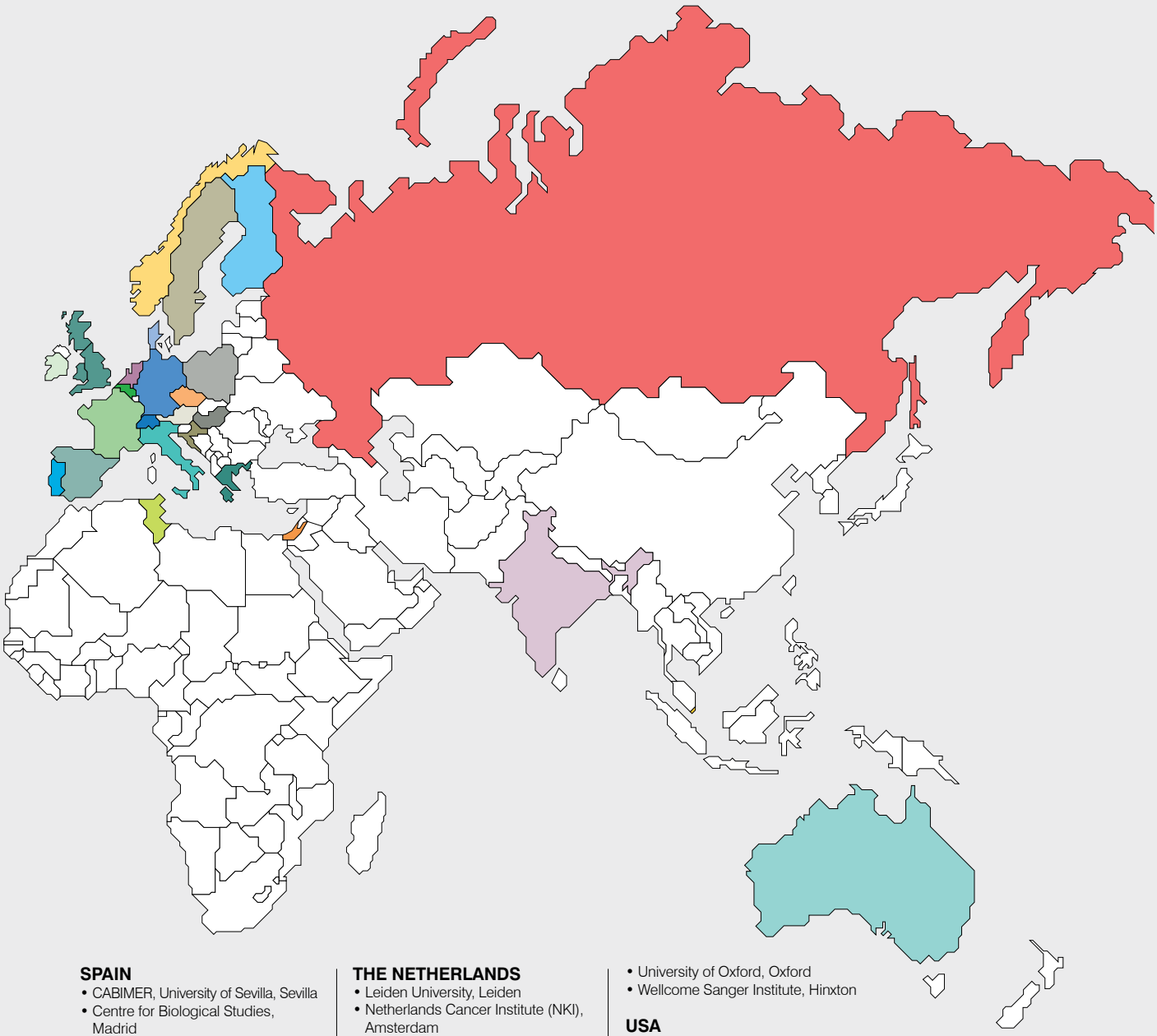
NORWAY
- Cancer Registry of Norway, Oslo
- Haukeland University Hospital, Bergen
- Norwegian University of Life Sciences, Ås.
- Norwegian University of Science and Technology, Trondheim
- Stavanger University Hospital, Stavanger
- Trondheim University Hospital-St. Olavs Hospital, Trondheim
- University hospital of North Norway, Tromsø
- University of Bergen, Bergen
- University of Oslo, Oslo

POLAND
- Faculty of Biotechnology, University of Wroclaw, Wroclaw
- Jagiellonian University, Kraków
- University of Gdansk, Gdansk

PORTUGAL
- Institute of Molecular Pathology and Immunology, University of Porto
- Portuguese Oncology Institute, Porto

RUSSIA
- Institute of Cytology and Genetics, Novosibirsk

SINGAPORE
- Cancer Science Institute of Singapore, Singapore



SPAIN
- CABIMER, University of Sevilla, Sevilla
- Centre for Biological Studies, Madrid
- Fundacion Instituto Valenciano de Oncologica (FIVO), Valencia
- ICGC, Technical validation group and Ivo Gut, Barcelona
- University of Lleida, Lleida
- University of Valencia, Valencia
- Universitat Politècnica de València, Valencia
- Vall d'Hebron Institute of Oncology, Barcelona

SWEDEN
- Karolinska Institutet and University of Stockholm, Stockholm
- Lund University, Lund
- The Sahlgrenska Academy at the University of Gothenburg, Gothenburg
- Uppsala University Hospital, Uppsala

SWITZERLAND
- University Hospital Zurich, Zurich

THE NETHERLANDS
- Leiden University, Leiden
- Netherlands Cancer Institute (NKI), Amsterdam
- Radboud University Nijmegen, Nijmegen
- The Netherlands Proteomics Centre, Utrecht
- University Medical Center, Groningen
- VU Medical Center, Amsterdam

TUNISIA
- University of Tunis, Tunis

UNITED KINGDOM
- Cambridge Cancer Institute, Cambridge
- Hampshire Hospitals/Southampton University, Southampton
- London Research Institute,The Francis Crick Institute, London
- Royal National Orthopaedic Hospital, Stanmore, Middlesex
- The Beatson Institute for Cancer Research, Glasgow
- The European Bioinformatics Institute (EMBL-EBI), Hinxton
- University College London Medical School, UCL, London
- University of Cambridge, Cambridge
- University of Liverpool, Liverpool
- University of Oxford, Oxford
- Wellcome Sanger Institute, Hinxton

USA
- Buck Institute for Research on Aging, Novato, California
- Dana Farber Cancer Institute, Boston, Massachusetts
- Dartmouth College, Hanover, New Hampshire
- Duke University Medical Center, Durham, North Carolina
- Fred Hutchinson Cancer Research Center, Seattle, Washington
- Georgetown University, Washington DC
- Harvard University, Boston, Massachusetts
- Johns Hopkins Medicine, Baltimore, Maryland
- Lawrence Berkeley National Laboratory, Berkeley, California
- Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina
- Masonic Cancer Center and University of Minnesota, Minneapolis
- Massachusetts General Hospital, Boston, Massachusetts
- MD Anderson Comprehensive Cancer Center, Houston, Texas
- National Institutes of Health (NIH), Bethesda, Maryland
- Oregon State University, Corvallis, Oregon
- 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
- University of Washington, Seattle, Washington
- Washington University, St Louis, Missouri
- Weill Medical College of Cornell University, New York

Recent Innovations

Registered Declaration of Inventions (DOFIs) and Patent Applications

Research group	Department	DOFI #
Bioinformatics Core Facility	Core Facilities	18155
J. Wesche group	Tumour Biology	18154
K. Flatmark group	Tumour Biology	18153
G. Lind group	Molecular Oncology	18146
J. Olweus group	Cancer Immunology	18140
K. Tasken group	Cancer Immunology	18130
J. Myklebust group	Cancer Immunology	18118
J. Enserink group	Molecular Cell Biology	18104
J. Enserink group	Molecular Cell Biology	18098
G. Mælandsmo group	Tumour Biology	18053
K. Sandvig group/G. Mælandsmo group/K. Flatmark group	Molecular Cell Biology/Tumour Biology	18030
J. Olweus group	Cancer Immunology	18003
J. A. Kyte group	Cancer Immunology	18126

Application type	Research group	Department	DOFI #
Priority Application	J. Enserink group	Molecular Cell Biology	16126
Priority Application	J. Myklebust group	Cancer Immunology	16123
Priority Application	G. Lind group	Molecular Oncology	18146
Priority Application	G. Lind group	Molecular Oncology	17135
PCT Application	G. Lind group	Molecular Oncology	17135
PCT Application	K. Flatmark group	Tumour Biology	15189
PCT Application	A. Weyergang group	Radiation Biology	16153
PCT Application	T. Theodossiou group	Radiation Biology	17061
PCT Application	R. Lothe group	Molecular Oncology	16092

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