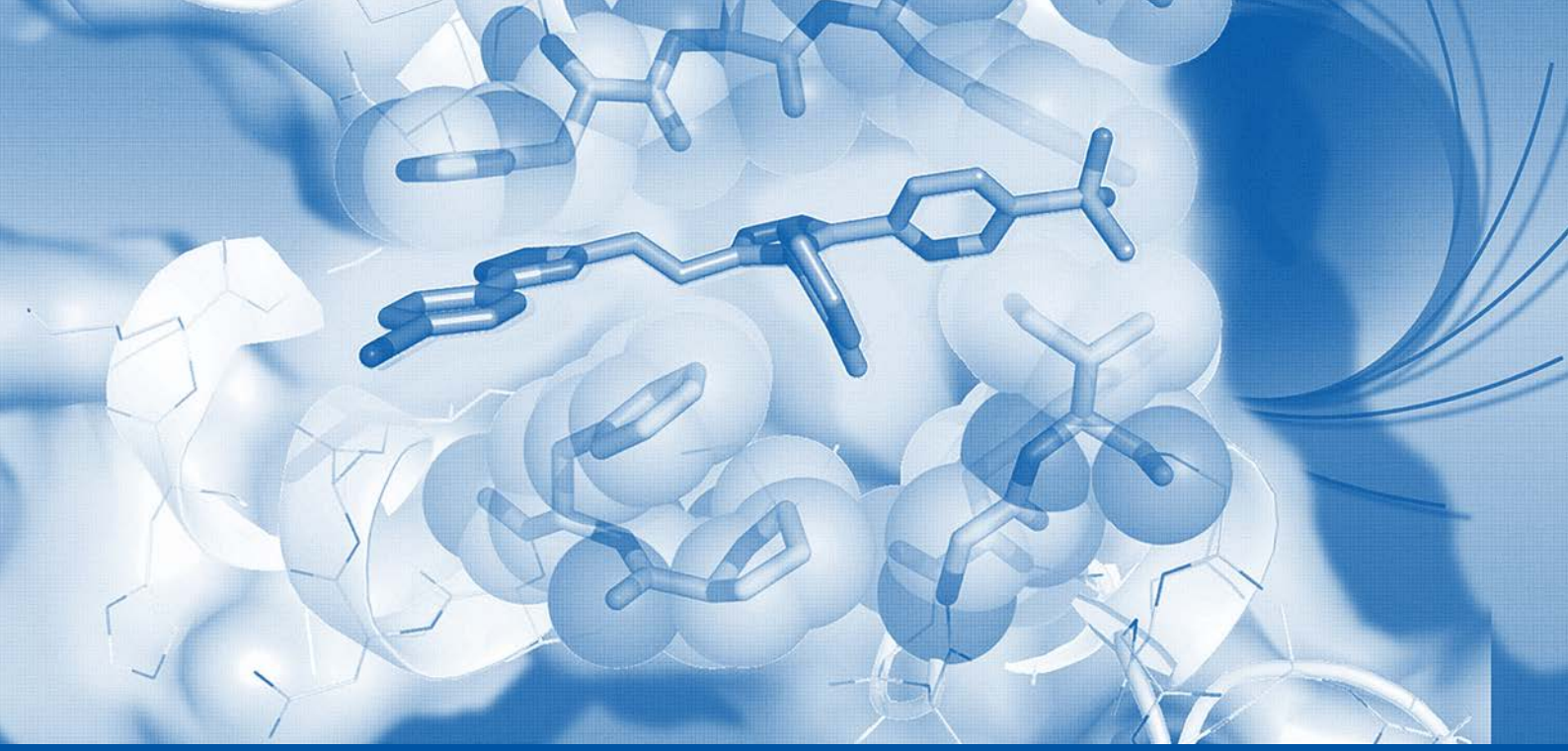


2012 Annual Report

CAST
CANCER • STEM CELL
INNOVATION CENTER

Established by the Research Council of Norway

sfi Centre for Research-based Innovation

Oslo University Hospital
Norwegian Radium Hospital

UiO : University of Oslo

Introduction

SFI-CAST has been established by the Research Council of Norway based on the strength of its concept and its strategic position at the crosslink between the internationally strong Norwegian cancer research and an emerging cluster of innovative biotechnology industries.

Using the stem cell tool kit to understand cancer comprises a major advance in cancer research. After years of gradual improvements in treating cancer, it is now apparent that the concept of stemcellness in cancer provides a solid basis for major leaps in both cancer diagnosis and treatment in the near future. It is fascinating to see how a novel scientific concept, as described in the initial centre application, turns into solid scientific evidence and subsequently forms the basis for product development.

In the 6 years of its existence, SFI-CAST researchers have established new analytical tools, identified novel therapeutic compounds that address the Wnt/β-catenin stemcell pathway, and advanced concepts for immunotherapy based on stemcellness in cancer. We are proud to be able to present a fully integrated research operation that covers all the way from basic research to experimental patient trials.

We would like to thank the Research Council of Norway, the Oslo University Hospital and the University of Oslo for its support. We want to thank the academic researchers and industry partners for their dedication and commitment. We would also like to express our gratitude to Inven2, the technology transfer office that has been supportive to the implementation of our commercialization strategy.

Finally, we would like to state that the ongoing research is not only about innovation and scientific or commercial progress; it is about saving lives. Cancer is a cruel, often un-curable disease that causes very severe suffering. In this context we feel privileged to be able to develop novel potential cures at the cutting edge of science and technology.

Stefan Krauss
Director

Ola Myklebost
Co-director

Table of contents

Summary

During the last decade, cancer research has gained substantial knowledge by applying a multidisciplinary understanding of tumor formation and progression, as well as a precise analysis on individual differences between and within tumors at single cell resolution.

It is now becoming increasingly evident that cancer cells comprise a heterogeneous cell population with dynamic sub-populations of cells showing different biological profiles including cell proliferation, invasiveness and metastatic potential. The temporal and spatial dynamics of heterogeneity appears to be directed by autocrine and paracrine short- and long-range signals.

The emergence of reagents that attenuate these signals, combined with personalized medicine has given new hope for addressing tumors more efficiently.

SFI-CAST is now a fully integrated biomedical innovation centre that works towards identifying new therapeutic interventions. SFI-CAST develops innovative approaches for developing small drugs and cancer vaccines that address specifically stem cell pathways in cancer. Furthermore, SFI-CAST works towards high resolution visualization of specific cell sub-populations in the body as a tool for tracking therapeutic success.

Photo: Affitech Research AS

PhD Viola Lobert

Anne Cathrine Bakken and Andreas Midbøe Hoff

Nadja Katheder, Fergal O´Farrell and Tor Erik Rusten

Vision/objectives

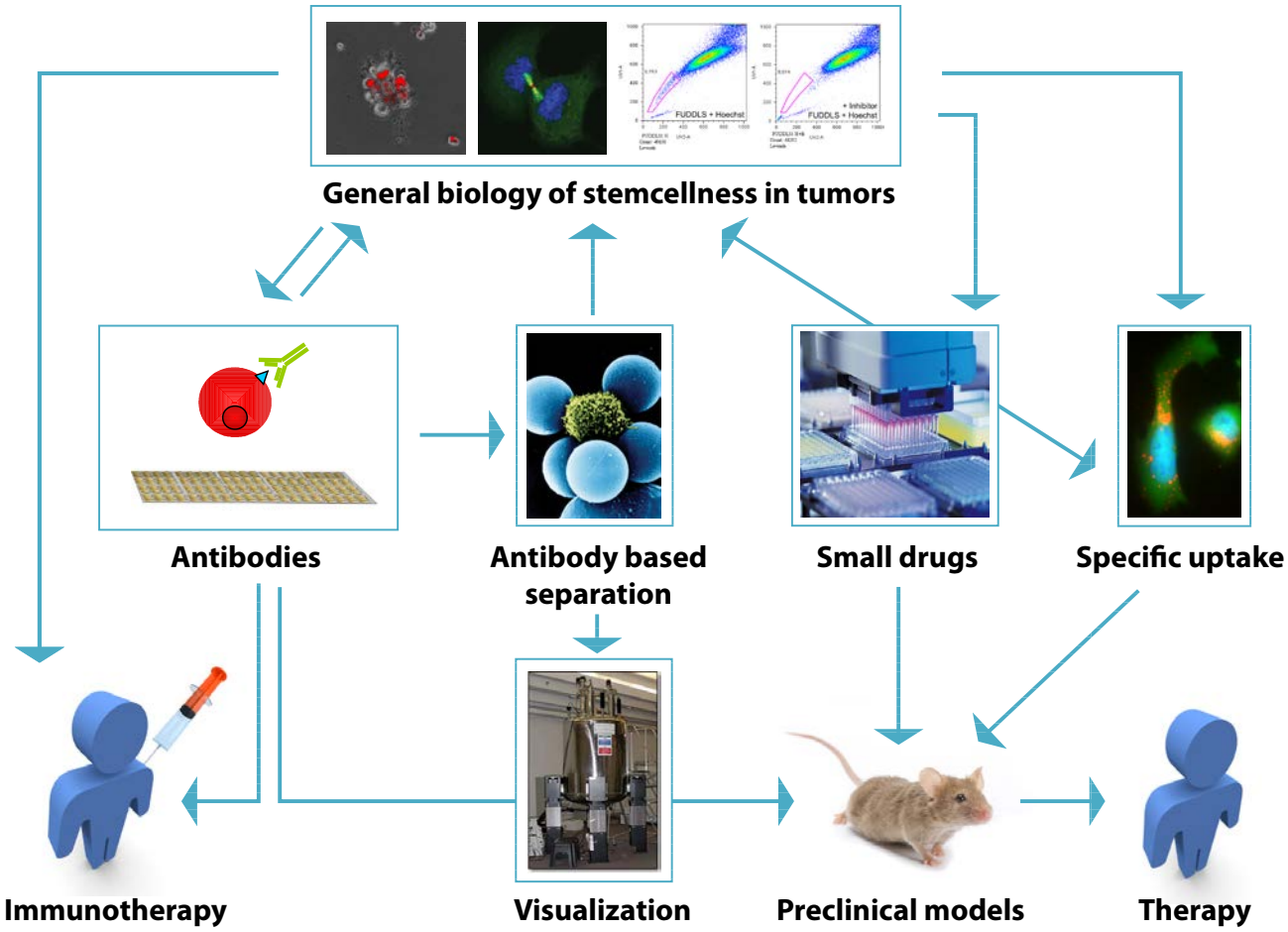
The SFI-CAST biomedical innovation center works towards identifying new therapeutic intervention points in stemcell pathways and to test these in cancer. Based on validated intervention points, novel therapeutic reagents are developed. A main research focus of the research center is on Wnt/β-catenin signaling.

Sharmini Alagaratnam

Working in the lab

Research plan/strategy

The SFI-CAST biomedical innovation centre has a work program that uses basic research on stemcelllness for developing new anti-cancer reagents, and for moving these reagents towards experimental clinical trials. For this aim, several interactive research programs are advanced. (i) Inhibitors of Wnt/β-catenin signaling are being developed and tested (with industry partner ODIN Therapeutics AS); (ii) Improved immunotherapy protocols based on growing tumor cells under stemcell conditions are being explored and tested; (iii) Specific receptors are tested for improved therapeutic photo-internalization (with industry partner PCI Biotech ASA and Affitech AS).



SCIENTIFIC HIGHLIGHTS

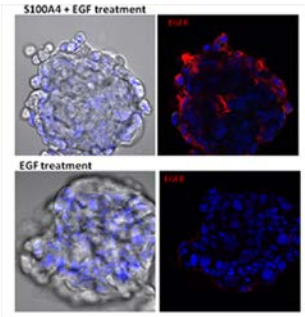
The **Krauss–group** has advanced a tankyrase specific inhibitor to lead stage and studied the impact of tankyrase inhibition on colon cancer and pancreas adenocarcinoma (Waaler et al., 2012; Voronkov et al., 2013; Lau et al., in press; Lehtio et al., in press). The lead compound G007-LK is currently used as an industry standard for selective tankyrase and Wnt/β-catenin inhibition. The group also carries out chemical and siRNA screens to identify enabling factors for tankyrase inhibition.

The **Langmoen-group** has finished work on optimizing culturing conditions for adult human brain derived neural progenitors and characterized differences between neurospheres and brain tumor derived stem cells. A glioblastoma immunotherapy study has completed recruitment, and final results are likely to be ready during 2014. Results are under preparation for publication.

The **Lundanes-group** has developed several tools for analyzing proteins and small molecules. Some highlights are the development of a highly sensitive analytical platform for studying oxysterols (Larsen et al., 2012), completion of an ultrasensitive/ultraresolving chromatography system for analyzing proteins/peptides (Wilson et al., manuscript in preparation), and the development of a fluorescence polarization platform for determining drug binding of 3DLC isolated proteins.

The **Myklebost-group** has characterized the of stemness-, differentiation- and tumorigenic potential in a panel of liposarcoma cell lines (Stratford et al. 2012), and tested the response of osteosarcoma cell lines to a selective tankyrase inhibitor (Stratford et al., manuscript in preparation).

The **Mælandsmo-group** is studying S100A4 in EMT and stemness. HMLE model systems with shRNA knockdown of endogenous S100A4 was established. S100A4-knock down cells did undergo TGF-β induced EMT. It is also well known that MMPs can induce EMT and an invasive phenotype in mammary epithelial cells. S100A4 mediated, MMP activating signaling programs were investigated. Three different model systems, was characterized on response to extracellular S100A4. MMP transcription was induced in all three cell



systems, and was in all cell systems dependent of EGFR phosphorylation and ERK activation. Our results propose a S100A4 dependent internalization and re-routing of the EGFR in response to extracellular S100A4.

The **Skotheim-group** has characterized novel genes with malignancy-specific expression from cancer cells with stemness properties. These potentially important cancer stem cell biomarkers were identified by comparing mRNA measurements from embryonal carcinoma cells with their phenotypically similar embryonic stem cells, and the results were published online in December 2012 (Alagaratnam et al., Stem Cells and Development).

The **Stenmark-group** has identified a novel regulator of protein trafficking through multivesicular endosomes (Pedersen et al., 2012) and has advanced characterizing sub-cellular responses within the Wnt/β-catenin signaling pathway upon selective tankyrase inhibition (unpublished).

The **Sørlie-group** is studying intra-tumor heterogeneity in breast cancer using various cell surface markers and has identified multiple cell populations with "stem-like" traits within cancer cell lines and tumors that exhibit tumorigenicity (Kim et al. PNAS 109, 6124-9, 2012). Furthermore, using a luminal breast cancer xenograft model we have identified and isolated four different cell sub-populations with different capacity of initiating tumors in NOD/SCID mice, and with different responses to anti-estrogen treatment. The group has shown a differential response to evacizumab in different types of breast cancer xenograft models and proposed glycerophosphocholine (GPC) as a potential response marker for bevacizumab (Borgan et al. Mol Oncology 7, 130-42, 2013).

Organization

MANAGEMENT AND MEMBERS

SFI-CAST consists of 8 research groups; 7 groups at the Oslo University Hospital and one group at the University of Oslo. There are three industry partners in the consortium. In 2012 the Centre's activities were located at the Norwegian Radium Hospital, Oslo Research Park, Rikshospitalet, Ullevål Oslo University Hospital, and at Domus Medica and the Department of Chemistry (University of Oslo) as well as in the different industries. In total SFI-CAST employs 80 scientific staff.

SFI-CAST is headed by Dr. Stefan Krauss (Director) and Dr. Ola Myklebost (Co-director). The administrative manager of SFI-CAST is Line Mygland.

The Centre has a project leadership group who meets on a regular basis. This group consists of ten primary investigators (PI) and representatives of industry partners of the consortium.

ACADEMIC SFI-CAST MEMBERS

Dr. Stefan Krauss, Unit for Cell Signaling, Dept. of Microbiology, Oslo University Hospital, Rikshospitalet

Dr. Iver Langmoen, Department of Neurosurgery, Oslo University Hospital, Ullevål University Hospital, Rikshospitalet

Dr. Elsa Lundanes/ Dr. Tyge Greibrokk/ Dr. Steven Wilson, Department of Chemistry, University of Oslo

Dr. Ola Myklebost, Department of Tumor Biology, Insitute for Cancer Research, Oslo University Hospital, the Norwegian Radium Hospital

Dr. Gunhild Mælandsmo, Department of Tumor Biology, Oslo University Hospital, the Norwegian Radium Hospital

Dr. Rolf I. Skotheim, Department of Cancer Prevention, Oslo University Hospital, the Norwegian Radium Hospital

Dr. Harald Stenmark, Department of Biochemistry, Institute for Cancer Research, Oslo University Hospital, the Norwegian Radium Hospital

Dr. Therese Sørlie, Department of Genetics, , Insitute for Cancer Research, Oslo University Hospital, the Norwegian Radium Hospital

INDUSTRY PARTNERS

Affitech Research AS
Gaustadalléen 21
N-0349 Oslo
Norway

ODIN Therapeutics AS
Gaustadalleén 21
N-0349 Oslo
Norway

PCI Biotech AS
Strandveien 55
N-1366 Lysaker
Norway

SCIENTIFIC ADVISORY BOARD

Dr. Thorarinn Gudjonsson
Biomedical Center
University of Iceland

Dr. Jens Peter von Kries
Institut für Molekulare Pharmakologie
Germany

Dr. Henrik Semb
Copenhagen University
Danish Stem Cell Center

THE BOARD

The board is responsible for ensuring that SFI-CAST is developed in accordance with the current research plan. In 2012 the board members were:

Dr. Jonny Østensen, Vice President Technology, Inven2 AS (Chairman)

Dr. Stein Kvaløy, Oslo University Hospital

Dr. Kari Kværner, Oslo University Hospital

Dr. Henrik Schultz, University of Oslo

Dr. Michael Braunagel, Affitech Research AS

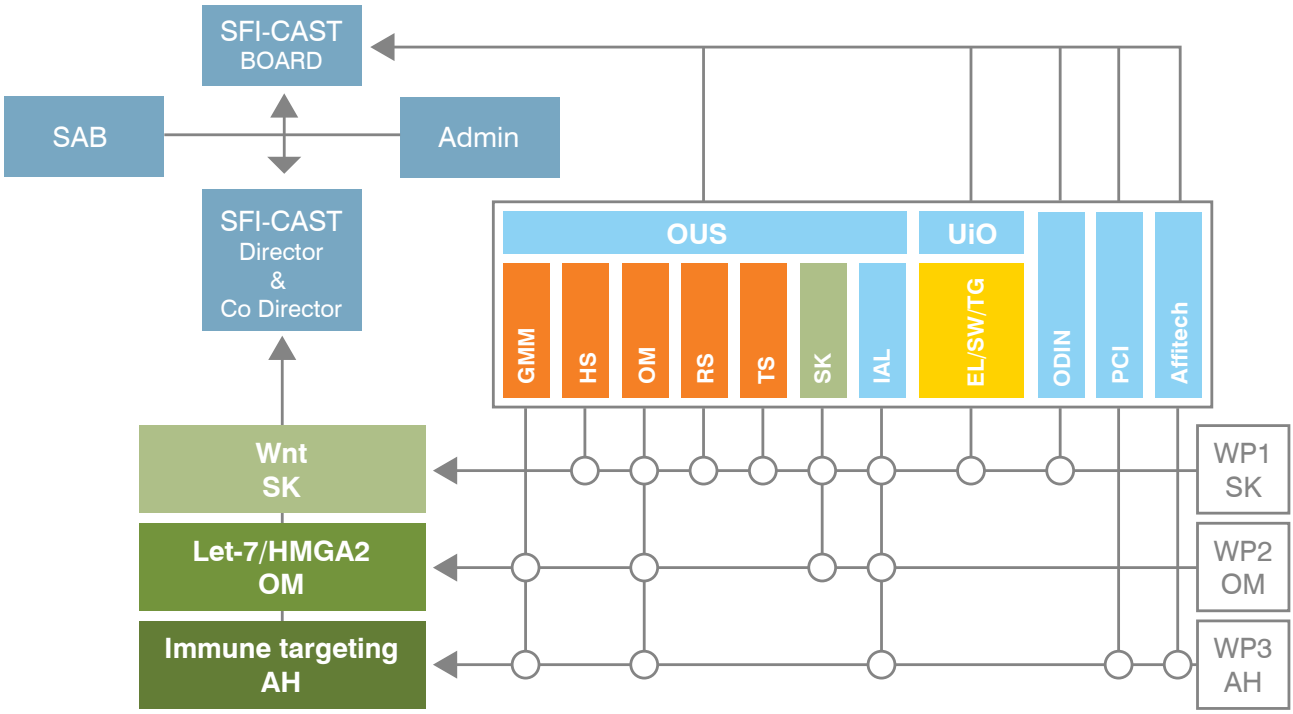
Olav Steinnes, ODIN Therapeutics AS

Dr. Anders Høgset, PCI Biotech AS

Dr. Øystein Rønning, Norwegian Research Council (Observer)

ORGANIZATION STRUCTURE

All partners (OUS, UiO and each industry partner) have a representative in the board. The project leadership group is responsible for the scientific progress and the CAST director reports to the board. All work packages have work package leaders.



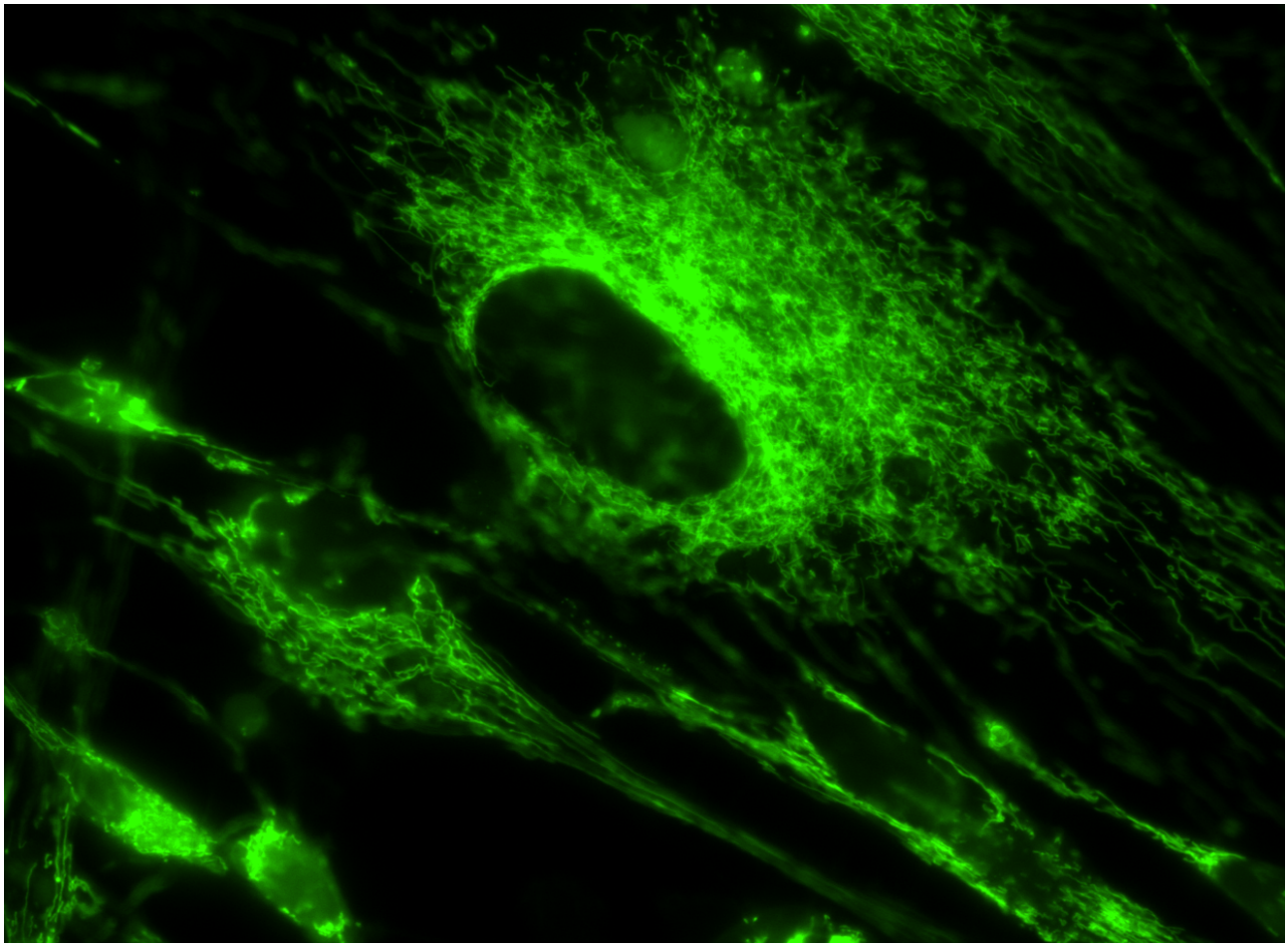
Abbreviations
OUS – Oslo Universitetssykehus (Oslo University Hospital)
UiO – Universitetet i Oslo (University of Oslo)
GMM - Gunhild Mari Mælandsmo -group
HS - Harald Stenmark -group
OM - Ola Myklebost -group
RS - Rolf Skotheim -group
TS - Therese Sørlie -group
SK - Stefan Krauss -group
IAL - Iver Arne Langmoen -group
EL/TG/SW - Elsa Lundanes/Tyge Greibrokk/Steven Wilson -group
PCI - PCI Biotech AS
Affitech - Affitech Research AS
ODIN - ODIN Therapeutics AS
WP - Work Program

Partners

COOPERATION BETWEEN PARTNERS IN THE CENTRE

The SFI-CAST innovation centre is designed as an integrated structure where the academic partners are exchanging technology, materials and know-how, while the industry partners can connect at any point they see potential for innovation.

The collaborations between the academic partners, and in selected areas with the industry include the SFI-CAST drug discovery platform, the immunotherapy platform and the photo internalization platform. Two annual retreats are held to track the progress of the partners. In addition, project work groups have been established that communicate on a daily/weekly basis.



Cytoskeleton imaging in glioblastoma cells

STEFAN KRAUSS-GROUP
STEM CELL SIGNALING

AIM

The main goal of the group within SFI-CAST is to gain understanding on stemcellness in cancer, and to use this knowledge for developing antagonists to the stem cell pathway

STATUS

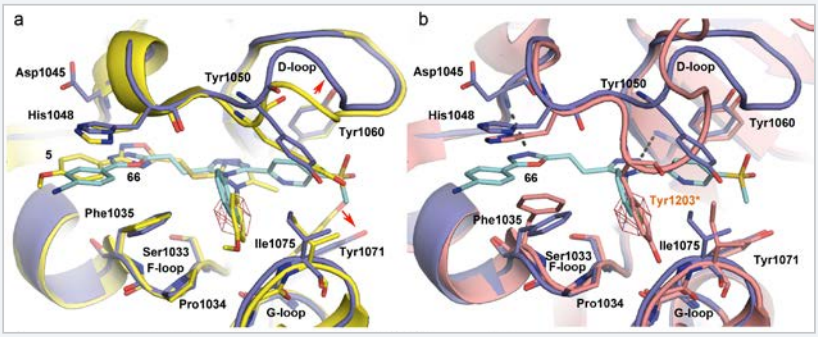
Wnt/β-catenin signaling is a functional network that regulates central stem cell properties in a cell and broad range of biological systems, including organ development and control of intracellular metabolism. Deregulated canonical Wnt signaling is a common denominator in a variety of tumors. We have identified the adenosine binding pocket of tankyrase as an attractive biotarget to inhibit Wnt/β-catenin signaling. We have developed a series of highly specific tankyrase inhibitors that show efficacy in vitro in various tumor cell lines, and in vivo in mousexenografts. The inhibitors are now tested with the aim of using the inhibitors as potential human therapeutics (Waaler et al., 2011; Waaler et al., 2012; Voronkov et al., 2013; Lau et al., 2013).

INNOVATIVE POTENTIAL

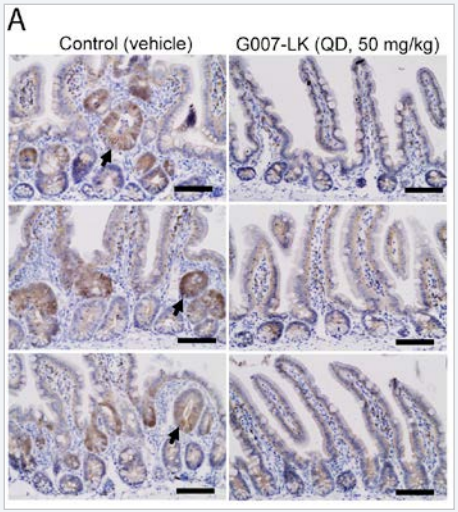
The tankyrase inhibitors have been patented and negotiations for external funding are ongoing.

COLLABORATIONS WITHIN THE CENTER

We actively collaborate with Lundanes/Greibrokk/Wilson-group on analytical tools, with O. Myklebost and I. Langmoen, G. Mælandsmo and T. Sørlie on tankyrase inhibitors in various tumor models and with H. Stenmark on subcellular alterations upon tankyrase inhibition. We work with CAST associated member J.P. Morth on crystallography.



Drug binding pocket of G007-LK in the PARP domain of tankyrase 2. A, Top view of G007-LK represented as sticks and colored cyan in the binding pocket of TNKS2 (pale blue). Superimposed with TNKS1 (yellow) bound with c24 (yellow). B, TNKS1 in the apo-form (pink) is superimposed with TNKS2 and G007-LK (crytallography in collaboration with J.P. Morth).

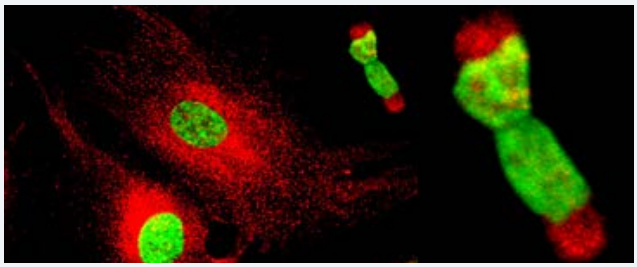


G007-LK treatment decreases development of adenomas in conditional Apc knockout mice, $Apc^{CKO/CKO}Lgr5$-$CreERT2^{+}$. A, representative microscopy images showing b-catenin-stained intestinal (ileum) sections that demonstrates a substantial decrease in adenoma development in the small intestine of G007-LK-treated (left panels, 50 mg/kg)(n=5) mice when compared to untreated control mice (right panels, vehicle) (n=5). The epithelial lesions are indicated by black arrows.

IVER LANGMOENS-GROUP
MALIGNANT BRAIN TUMORS

AIM

The main focus of the group in the frame of SFI-CAST is on cultivation and characterization of cancer stem cells in primary cultures from brain tumors and identification of new therapeutic targets in glioblastoma.



Expression of NAA30 in GMB-T0595 and normal cells

STATUS

Both normal and tumor stem cells show a high proliferation rate when cultured. Interestingly, the proliferation rate falls dramatically also in tumor stem cells when they are induced to differentiate. Normal and tumor stem cells show a similar pattern of differentiation, i.e. in neuronal and glial directions, although differentiated cells from the tumor were clearly abnormal morphologically and differentiation in itself progressed much faster. We performed a number of experiments studying the effect that *in vitro* culture of tumor stem cells has on the cells' ability to form tumors, to differentiate and to undergo genotypic and expressional changes. We have also explored the cellular organization of neuro- and tumor spheres, looking at the cellular heterogeneity of such spheres. By sorting tumor cells based on surface antigens, we hope to establish methods for better identification of the progenitor population.

We used microarray technology to compare the global gene expression in normal stem cells and tumor stem cells, in order to identify possible targets for treatment and to better understand the biology of the cell population that escapes current treatment and causes recurrences. The results of this comparison study show a significant up-regulation in tumor stem cells of genes connected to regulation of focal adhesion, actin cytoskeleton, axon guidance as well as the Wnt signaling pathway. Putative target genes have been confirmed at the protein level using immunohistochemistry and Western blot. This work is currently submitted for publication. The roles of the possible targets in the Wnt pathway are investigated using Wnt inhibitors. In particular, we investigated a set of 20 genes that were highly up-regulated in GBM tumor cultures using micro-array data. Currently, the genes' roles in glioma are investigated using shRNA-knockdown based technology and its effect on proliferation, apoptosis and sphere-forming capacity. Preliminary results look very promising with publications in preparation. Based on the pre-clinical data we have established a clinical protocol. This protocol is designed to harness the patients' own immunity. The inclusion of patients into the "Phase I/II trial of vaccine therapy with hTERT, surviving and tumor stem cell derived mRNA transfected dendritic cells in patients receiving standard therapy for glioblastoma" started in February 2009. This clinical trial is backed up from the collaboration through the Cancer Stem Cell Innovation Centre (SFI CAST) and its collaboration with the Neurosurgical department, Section for Clinical Cancer Research and Resource Development, Dept. for Microbiology, and Dept. for Immunology, Inst. for Cancer Research, the Norwegian Radium Hospital and the Oncological Dept. at Oslo University Hospital.

INNOVATIVE POTENTIAL

We advance FACS (facilitated cell sorting and cytometry) to carry out specific measurements of cell sub-group behaviour within cell populations and allow for elaborate assessment of experimental parameters. The ability for distinction of many wavelengths of fluorophore as well as the development of sophisticated antibody-fluorophore conjugates means that data relating to cell cycle, division rate, phenotype and even transitory signaling pathway activation can be assessed within control and experimental cell populations.

COLLABORATIONS WITHIN THE CENTRE

We actively collaborate with S. Krauss.



ELSA LUNDANES, TYGE GREIBROKK AND STEVEN WILSON -GROUP ANALYTICAL CHEMISTRY

AIM

We develop analytical tools for analysis of proteins and small molecules, mostly based on liquid chromatography and mass spectrometry, with emphasis on sensitivity, resolution and automation.

STATUS

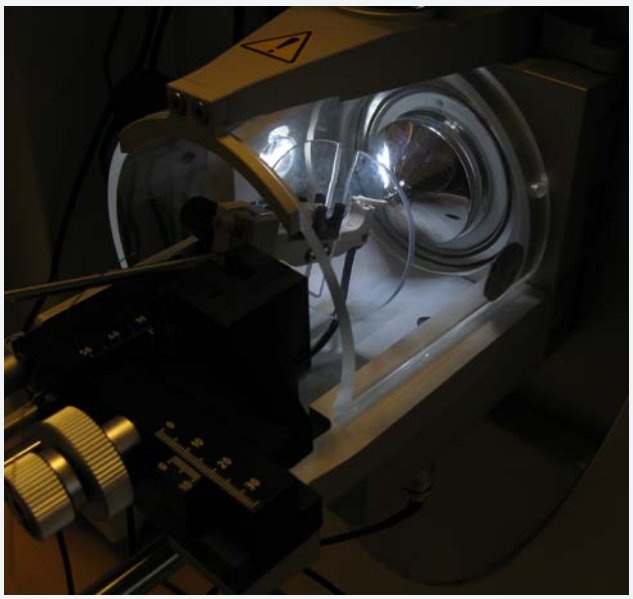
The Lundanes-group has developed analytical tools and methodology for sensitive determination of metabolites which may be potential cancer biomarkers, such as oxysterols. The methodology is currently being used to study interplay between central signal pathways such as Wnt and Hh. The Lundanes-group is currently also focusing on mass spectrometric methodology combined with in-house synthesized chromatography columns. Application areas are development of targeted proteomics for accurate and precise determination of central proteins in Wnt and Hh, as well as post translational modification analysis.

INNOVATIVE POTENTIAL

The Lundanes-group is developing materials, methodology and instrumentation with focus on targeted compounds. Such efforts, which are typically more sensitive and selective alternatives to common approaches, may be of interest from a commercial perspective.

COLLABORATIONS WITHIN THE CENTRE

The Lundanes-group is pro-active in cooperation with other CAST members, especially the Krauss-group, and co-publish regularly.




The Lundanes group develops novel technology able to study complex cellular processes with minimal amounts of sample.

OLA MYKLEBOST-GROUP
MESENCHYMAL PROGRAMMING

AIM

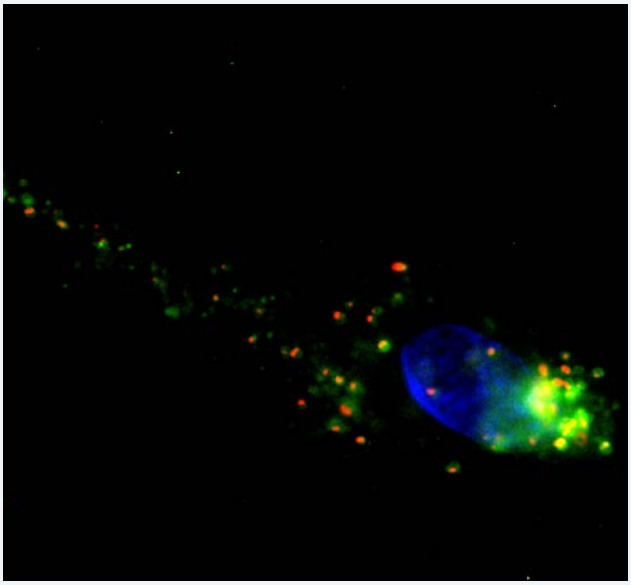
The Myklebost-group is focused on the biology of mesenchymal cancers, also known as sarcomas, and is investigating the regulation and properties of stemness and differentiation in these tumors. The studies are extended to mesenchymal, i.e. stem-like, programming of breast cancers.

STATUS

The microRNA let-7 is considered a tumor suppressor and a regulator of stemness and differentiation, and is normally highly expressed in well differentiated tissues. The expression of let-7 is frequently lost in cancer, which has prognostic value in a wide range of cancers, and let-7 replacement therapy shows great potential as a cancer therapeutic. To date let-7 isoforms have not been fully characterized in sarcoma, so we are focused on determining expression level in a panel of liposarcoma cell lines. We are also investigating the effect of introducing let-7 mimics in chosen LPS cell line models to study the effects on growth rate, cell stemness and differentiation, in order to evaluate whether let-7 replacement therapy is also beneficial as therapy for sarcoma.

We also examine the role of let-7 miRNAs in aggressive breast cancer cells, and found that they reduce cell growth as well as the cells capacity to generate spheroids *in vitro*. Furthermore, we have performed global analyses of the transcriptome and the proteome to identify changes that may explain these functional effects. In parallel, we have also analyzed the global effects of reducing the let-7 target gene HMGA2, which is an embryonic gene encoding an architectural transcription factor that is associated with the stemness program. The comparisons identified some interesting differences that may enlighten processes involved in the balances between cell stemness and differentiation.

Wnt/β-catenin signaling is frequently up-regulated in osteosarcoma and is thought to contribute to the disease. We have evaluated the effect of tankyrase inhibitors JW74 and JW55 on osteosarcoma cell lines, both at the molecular level and at the functional level. Interestingly, we have shown that the drug has the ability to induce differentiation in cell lines which have a block towards differentiation, thus enabling poorly differentiated cancer cells to overcome their resistance to differentiation, which may render the cells more susceptible for standard therapies.



Mitochondria in MDAMB231 cells

INNOVATIVE POTENTIAL

Therapeutic strategies based on Let-7 and miR34 will be evaluated in collaboration with Mirna Therapeutics (Austin, Texas).

COLLABORATIONS WITHIN THE CENTRE

We actively collaborate with S. Krauss and PCI Biotech.

GUNHILD MÆLANDSMO-GROUP TUMOR HETEROGENEITY

AIM

The aim of the group has been to optimize methods for isolation of various cell populations from the heterogeneous tumor mass for subsequent evaluation of stemness characteristics, differentiation capability and drug sensitivity.

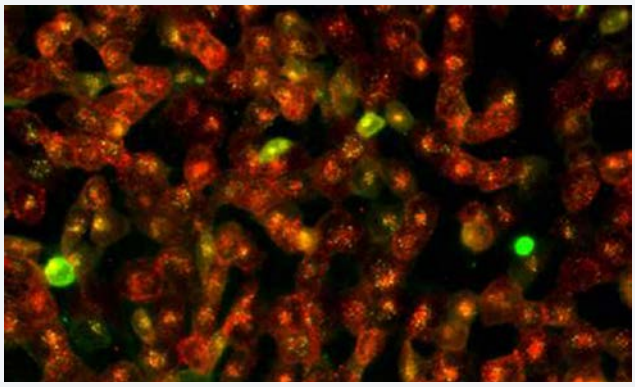
BREAST CANCER PROJECT

Intratumoral heterogeneity: We have isolated tumor cell populations from two orthotopically growing patient-derived breast cancer xenograft models (PDBCX) and characterized their intracellular heterogeneity. In both cancer subtypes (luminal and basal-like) all tumor cells expressed EpCAM, and in vivo experiments showed that the luminal like EpCAM subpopulation had the highest tumor initiating potential. Further analysis of this population revealed intracellular heterogeneity with respect to in vivo tumorigenicity. In collaboration with T. Sørlie, whole genome expression analysis and mass spectrometry based proteome analysis were performed. Studies of the differences in miRNA and epigenetic patterns between the populations have also been initiated. To unravel the general value in the identified molecular patterns five new ortothopically growing PDBCX models from Curie Institute, Paris, has been established, and included in the studies. The PDBCX has been used for testing subpopulation specific effects of estrogen withdrawel. In addition will Wnt inhibitors and CSGP4-targeted PCI therapy be tested.

S100A4 in EMT and stemness: To study the importance of the mesenchymal marker S100A4 during EMT, HMLE cells with shRNA knockdown of endogenous expression has been established. Epithelial HMLE-S100A4-knock down cells has the ability to undergo TGF-β induced EMT. We are currently investigating whether S100A4 acts as a stabilizer of the mesenchymal phenotype, thereby contributing to both EMT and MET. It is well known that MMPs can induce EMT and an invasive phenotype in mammary epithelial cells and furthermore that S100A4 induce expression of MMPs in various cell systems. We are currently characterizing extracellular S100A4 mediated signaling programs responsible for inducing MMP expression. Three different model systems, have been characterized and S100A4-mediated MMP transcription was induced in all cell systems. Preliminary data suggest that S100A4 mediated MMP induction involve activation and internalization of EGFR and activation of ERK.

MELANOMA PROJECT

Melanoma seems not to follow the "classical" CSC model, which suggests the presence of an exclusive



HMLE cells, red stain is EGFR, green is S100A4

"stable" small cell subpopulation distinguishable by specific markers. Rather, our data suggests that most of melanoma cells have the potential to exhibit "stemcellness". This is in agreement with the new theory, which proposes that acquisition of CSC characteristics in melanoma might be a dynamic process and most of melanoma cells can switch into transient CSC-like phenotype given appropriate signals from the microenvironment. This signifies the importance of better understanding the microenvironment-driven signals that might regulate phenotype-switching i.e. generation of invasive/metastatic, therapy-resistant, stem-like subpopulations. We have developed in vitro and in vivo melanoma models allowing investigation of tumor-microenvironment interaction and its role on the phenotype and functional properties of melanoma cells.

INNOVATIVE POTENTIAL

By better understanding intratumoral heterogeneity and how the subpopulations respond to treatment, more optimized combinations of targeted therapy may be revealed. S100A4 is a marker for mesenchymal cells but the functional importance is still elusive. The involvement in MMP regulation and EGFR-mediated responses may have therapeutic impact and is further explored.

COLLABORATIONS WITHIN THE CENTRE

We actively collaborate with T. Sørlie, S. Krauss and PCI Biotech.

ROLF SKOTHEIM -GROUP
STEM CELL BIOMARKERS

STEM CELL BIOMARKERS AND MUTATIONS IN COMPONENTS OF THE WNT SIGNALING PATHWAY

AIM

We study the role of stem cells in the development and progression of cancer, and we have throughout the CAST project particularly focused on the pluripotent cancer cells developing from testicular germ cells. Specifically, we compare mRNA profiles of embryonal carcinomas and embryonic stem cells to identify genes with malignancy specific expression, genes which are relevant for development into cancer stem cell biomarkers and drug targets. We are also interested to identify mutations of the Wnt proteome in colorectal cancer, and characterize their implications on tumor stem cells.

STATUS

We have carried out detailed transcriptome studies of panels of both embryonal carcinoma (EC) and phenotypically similar, but non-malignant, embryonic stem (ES) cell lines. Genome technologies such as exon microarrays and whole-transcriptome RNA-sequencing have been used to identify genes with malignancy specific expression or transcript structures. From the top-most differentially expressed genes and individual exons between EC and ES cells, we have now validated several genes and transcripts that we are in progress of defining their role in cancer. We recently published parts of this work in Stem Cells and Development (Alagaratnam *et al.*, 2013).

We have as well ongoing work on a particular gene fusion in colorectal cancer, where the gene encoding the Wnt effector TCF4 (alias *TCF7L2*) is one of the partner genes. We have characterized a clinical colorectal cancer biobank, and found that chimeric RNA molecules involving both *VTI1A* and *TCF7L2* sequences are frequent among cancers, although at low levels. The relevance for the tumourigenesis of this fusion transcript is yet to be determined.

INNOVATIVE POTENTIAL

Molecules which are specific to cancer cells with stemness properties can be used both as cancer biomarkers and as targets for therapy. Relevant patent applications are filed, and we work with the hospital's TTO, Inven2, for collaborations with aim of commercialization.

Involved in the CAST-project from the Skotheim -group are, from left, Sigrid Marie Kraggerud, Anne Cathrine Bakken, Ragnhild A. Lothe, Rolf I. Skotheim, Andreas Hoff, and Sharmini Alagaratnam

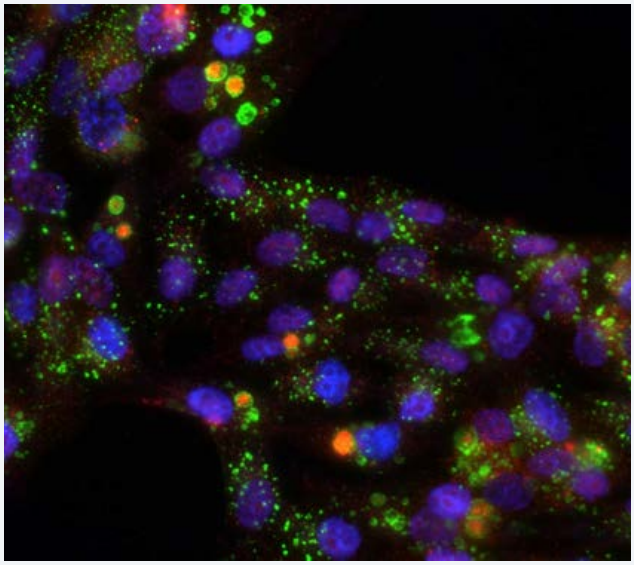
HARALD STENMARK-GROUP
INTRACELLULAR TRAFFICKING AND SIGNALING

AIM

The aim of this group's research is to understand how intracellular membrane trafficking serves to regulate stem cell signaling, in particular signaling in the Wnt pathway.

STATUS

The group works on a molecular dissection of the Wnt signaling pathway, with focus on components of the endocytic pathway. Recent evidence suggests that endosomal sequestration of inhibitory factors is a key event in Wnt signaling, and the group is exploring this further as a possible target for therapy. The group is also collaborating with the Krauss -group on understanding the dynamics of "destruction complexes" involved in negative regulation of Wnt signaling, and how these respond to inhibitors of the Wnt pathway.



The picture shows cancer cells with nuclei stained blue, early endosomes stained green and multivesicular endosomes stained red (Picture curtesy of Nina Marie Pedersen).

INNOVATIVE POTENTIAL

This research has innovative potential to point out new avenues for therapeutic targeting of Wnt signaling – one of the key signaling pathways in cancer stem cells.

COLLABORATIONS WITHIN THE CENTRE

Within CAST, the group collaborates closely with the group of S. Krauss in pharmacological targeting of the Wnt pathway, and with the group of R. Skotheim in identification of tumorigenic hits on the Wnt pathway.

THERESE SØRLIE-GROUP
WNT AND HH SIGNALING IN BREAST CANCER DEVELOPMENT

AIM

In this second phase of CAST our group focuses on the interplay between Hedgehog and Wnt signaling pathway and LGR5-dependent signaling on mammary cancer stem cells and tumor development.

STATUS

Wnt signaling is important for mammary gland development and is implicated in mammary oncogenesis. LGR5 is a downstream target of Wnt, it marks stem cells with an active Hh pathway in the intestine and skin and Lgr5+ cells were recently found to be sufficient and essential for mammary gland organogenesis. In many cell types the Hh and Wnt pathways are counter regulated. Understanding the interplay between these pathways and their regulation in stem cells can help identify novel diagnostic and therapeutic targets. To address the role of the Hh and Wnt pathways in mammary tumor development, we have established chemically and genetically inducible mouse mammary gland tumor models. In particular, we breed transgenic mice expressing the Hh pathway effector GLI1 or the stem cell marker LGR5 in the mammary epithelium. In addition, we breed transgenic mice for analyses of Lgr5 expression pattern in normal and tumor tissue as well as lineage tracing from Lgr5+ cells.

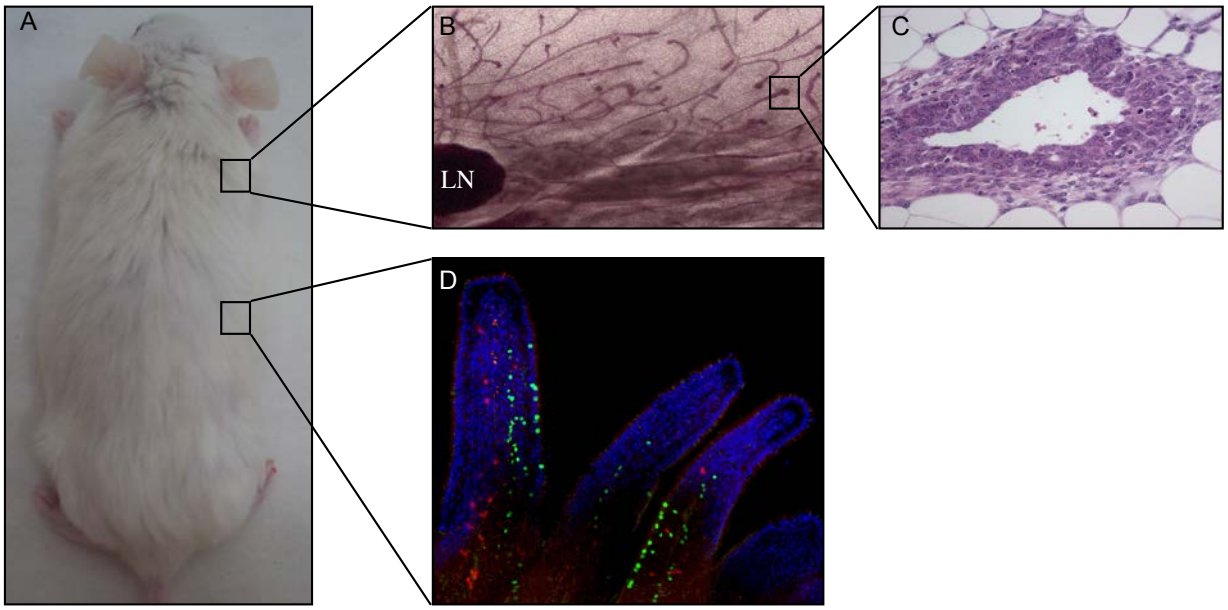
INNOVATIVE POTENTIAL

Pre-clinical studies are essential for testing of the efficacy and safety of drugs. The models we have established provide useful tools for such testing of existing drugs and novel small molecule compounds identified in the cancer biomarker projects.

COLLABORATIONS WITHIN THE CENTRE

We collaborate with G. Mælandsmo, S. Krauss, H. Stenmark and PCI Biotech.

Figure 1. We use transgenic mouse models to address the roles of Wnt and Hh signaling in formation of the mammary gland and tumors. A, the transgenic laboratory mice are followed closely to detect any phenotypically changes. B, Carmine stained whole-mounted mouse mammary gland from 9 weeks old mice with a boxed terminal end bud (TEB) ("LN" stands for lymph node). C, Hematoxylin and eosin staining of mouse mammary gland TEB (40x). D, Seven days lineage tracing from intestinal Lgr5 positive cells with the R26R-Confetti mouse. The traced cells are labeled with green (nuclear) or red (cytoplasmic). The cell nuclei are stained with Hoechst dye (blue).



Industry Partners

www.affitech.com

AFFITECH RESEARCH AS

ABOUT THE COMPANY

Affitech Research AS, a privately owned biopharmaceutical company, is dedicated to the discovery and development of human antibody therapeutics in cancer and other diseases with unmet medical needs. The repeated use of antibodies as therapeutic agents to fight cancer, autoimmune or infectious diseases, requires antibodies that are non-immunogenic in humans. Affitech has therefore been focusing on the discovery and development of fully human antibodies, which we believe have the maximum potential for becoming ideal therapeutics for a variety of diseases combined with a lowered risk of immunogenicity.

SFI-CAST INTERACTION

In the frame of SFI-CAST, Affitech together with its academic partners is working towards the discovery of antibodies targeting possible stem cell subpopulations of pancreatic cancer cells that show increased chemotherapy resistance and increased metastatic potential. The project is funded by the Research Council of Norway through the Industrial PhD scheme.

STATUS 2012

Affitech's Russian partner IBC Generium is currently conducting phase I clinical trials for testing r84, an antibody developed by Affitech in collaboration with Peregrine Inc. The proprietary compound is a human monoclonal antibody specifically recognizing human vascular endothelial growth factor (VEGF), and is being developed as a potential treatment of cancer. The anti-VEGF antibody will be evaluated in patients with various cancers and is a potential competitor to bevacizumab (Avastin® –Roche).

Also in 2012, Affitech's first anti-GPCR antibody program AT008, designed to block the binding of chemokine ligands to its cell surface receptor CCR4, resulted in a potential product candidate which is currently in pre-clinical testing. The antibody was licensed to IBC Generium for further development and use in Russia and the CIS states and might potentially be used in a variety of cancers and immunological diseases.

Photo: Affitech Research AS

www.odintherapeutics.no

ODIN THERAPEUTICS AS

ABOUT THE COMPANY

ODIN Therapeutics AS is a spinoff company of the research in the S. Krauss laboratory. ODIN Therapeutics AS is owned by Dr. Dan Holsworth and Inven2, the TTO of the Oslo University Hospital and the University of Oslo

SFI-CAST INTERACTION

ODIN Therapeutics AS collaborates with SFI-CAST on chemical analoguing with the aim of advancing the specific lead tankyrase inhibitor series to achieve good PK/PD in humans. Furthermore, it is collaborating on identifying parameters for patient inclusion/exclusion, initially in the colon cancer arena.

Working in the laboratory.

www.pcibiotech.no

PCI BIOTECH AS

ABOUT THE COMPANY

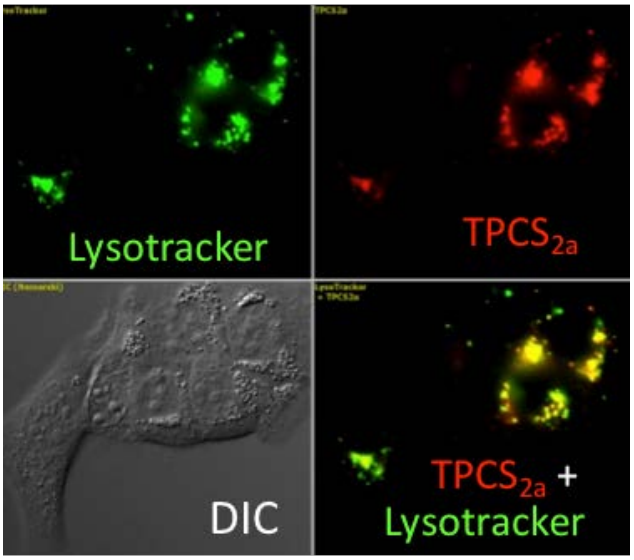
PCI Biotech AS is an oncology-focused company developing products for localised cancer treatment. The products are based on PCI Biotech's patented drug-delivery technology, photochemical internalization (PCI), which can enhance the effect of anticancer drugs by targeted, light-directed drug delivery into cancer cells. PCI Biotech's lead candidate is the photosensitizer Amphinex® developed for treatment of head & neck cancer and bile duct cancer. A second priority is to develop PCI for vaccination.

A single arm, multi-centre Phase II study was initiated in 2012. Conducted at 5 leading cancer centers in Europe, this study will evaluate the safety and efficacy of Amphinex in combination with the generic cytotoxic agent bleomycin with superficial and interstitial laser light application in patients with recurrent head and neck squamous cell carcinoma unsuitable for surgery and radiotherapy and without distant metastases. The study will include approximately 80 patients, and patient inclusion will be in 2012 and 2013. Progression free survival at 6 months is the primary endpoint.

SFI-CAST INTERACTION

PCI Biotech has ongoing projects together with several SFI-CAST partners (Myklebost, Mælandsmo, Sørlie, Stenmark and Krauss) on the targeting of stem cell markers in different cancers including sarcoma, carcinoma of breast, colon and pancreas.

Principle of the PCI technology. PCI photosensitizer (S) and drug (D) is taken up by endocytosis and accumulate in endolysosomal vesicles (left panel). Light activation of PCI photosensitizer leads to formation of reactive oxygen species, which burst the membrane of the vesicles leading to cytosolic release (mid panel) of the drug and interaction with its biological target (T).



Co-localization of PCI photosensitizer TPCS2a (Amphinex®) and lysotracker green in breast cancer cells (Photo: Pål K. Selbo).

Recruitment

DOCTORAL DEGREES

Eldrid Borgan, PhD, *Transcriptomics and metabolomics of breast cancer to improve the understanding of disease mechanisms and treatment response,* supervised by Therese Sørlie

Viola Helene Lobert
Ph.D. 19.10.2012 at the Faculty of Medicine, NTNU,with the thesis
"*Identification of novel regulators of epithelial polarity and cell migration*".
ISBN 978-82-471-3875-5 (printed version). ISBN 978-82-471-3877-9 (electronic version).
Supervised by: Harald Stenmark.

PhD Viola Lobert

MASTER DEGREES

Dorna Misaghian. *Porous layer open tubular (PLOT) protein separation and trypsin open tubular (TOT) columns.* Supervised by: Elsa Lundanes

Anders Grimsmo. *Bestemmelse av oksysteroler i Hedgehogsignalveien i kreftstamceller med kapillær væskekromatografi – massespektrometri.* Supervised by: Elsa Lundanes

Khanh Quang Huynh. *Karakterisering og metabolomanalyse av tarmkreftceller behandlet med en Wnt/tankyrase-hemmer.* Supervised by: Elsa Lundanes

Tore Vehus. *Drug target deconvolution in cancer cells using liquid chromatography, fluorescence polarization and mass spectrometry.* Supervised by: Elsa Lundanes

Anastassia Serguienko, *"Targeting of cancer stem cells by Let-7 miRNA",* Supervised by: Ola Myklebost

MSc. Khanh Quang Huynh, MSc. Tore Vehus og MSc. Anders Grimsmo

International Cooperation

INTERNATIONAL NETWORKS

European Network for Oxysterol Research (ENOR).

The Liddy Shriver Sarcoma Initiative

EuroBoNet (www.eurobonet.eu)

NordForsk network on Cilia and Centrosomes.

NordForsk network on Autophagy

European Science Foundation network on "Tracking of Phosphoinositide Pools"

Patient Derived Xenografts European Consortium, headed by Sergio Roman-Roman, Institutt Curie, Paris, France

INTERNATIONAL COLLABORATIONS

Dr. Mani Sendurai, MD Anderson Cancer center, USA
The role of HMGA2 and Let-7 miRNA in EMT and cancer

Dr. Andy Bader, MiRNA Terapeutic, USA
The role of Let-7 miRNAs and mir-34 in sarcoma and breast cancer

Dr. David Thomas, PeterMacCallum Cancer center, Australia
Function of liposarcoma stem cells

Dr. Winston Hide, Harvard School of Public Health, Boston, USA

Dr. Wiaam Badn, Glioma immunotherapy group, Lund University, Sweden

Dr. Nobuo Tanaka, Kyoto Institute of Technology, Japan
Collaboration in development of high resolution, high speed chromatography for proteomics applications

Dr. Lars Âhrlund-Richter, Department of Woman and Child Health, Karolinska Institutet, Stockholm, Sweden
Collaboration on stem cells and invasive properties of melanoma cells

Dr. Meenhard Herlyn, Wistar Inst., Philadelphia, USA
Cooperation on studies of melanoma heterogeneity and the role of tumor microenvironment on melanoma properties by using 3D in vitro systems

Dr. Ole W. Pettersen, Department of Medical Anatomy, The Panum Institute, University of Copenhagen

Dr. Peter W. Andrews, University of Sheffield, South Yorkshire, England

Dr. Mina Bissell and Mark LaBarge, Lawrence Berkeley National Laboratory, Berkeley, CA, USA
Collaboration on stem cells and tumor-microenvironment interactions in breast cancer

Dr. Elisabetta Marangoni and Paul Cotton, Curie Institute, Paris, France
Exchange of orthotopic breast cancer models of luminal and basal-like breast cancer

Dr. Thorarinn Gudjonsson, Department of Pathology, Landspitali University Hospital and School of Health Sciences, University of Iceland, Reykjavik, Iceland
Role of S100A4 in the EMT process and stemness of a mammary gland progenitor cell line

Dr. Rune Toftgård, Karolinska Instiutet, Stockholm, Sweden
Development of breast cancer using transgenic mouse models

Dr. Mina Bissell, Lawrence Berkeley National Laboratory
Intra-tumor heterogeneity and the impact on tumorigenicity

Dr. Peter James, Lund University, Sweden
Proteomic characterization of cells from xenograft tumor models representing different tumor subtypes

Dr. Elisabetta Marangoni, Curie Institute, Paris, France
Establishment and studies of orthotopic breast cancer xenografts

Dr. Jens v Kries, Leibniz-Institut Für Molekulare Pharmakologie, FMP, Berlin, Germany
Chemical screens

Dr. Ondrej Machon, Institute of Molecular Genetics, Czech Academy of Sciences, Prague, Czech Republic
Animal models

Dr. Dietmar Gradl, Karlsruhe Institute of Technology Zoological Institute, Cell and Developmental Biology, Karlsruhe, Germany
Xenopus embryology

Dr. G Drewes, Cellzome AG, Heidelberg, Germany
Deconvolution

Dr. Lari Lehtiö, Biocenter Oulu and Department of Biochemistry, University of Oulu, Finland
Crystallography

Dr. Mike Costa, Genentech Inc., South San Francisco, California, USA
Target validation

National Cooperation

NATIONAL COOPERATION

Dr. Jens Preben Morth (NCMM): Collaboration for expressing proteins for studies with chromatography, mass spectrometry and binding studies with fluorescence polarization
Crystallography

Dr. Gareth Sullivan, Norwegian Stem Cell Center, University of Oslo and Oslo University Hospital
Collaborator on iPS reprogramming in cancer, academic

Lytix Biopharma – Industry

Analytical chemistry at School of Pharmacy, University of Oslo within the platform Bioanalytics@UiO: Collaboration in development of analytical chemistry technology

Dr. Terje Espevik, Institute for Cancer Research and Molecular Medicine, NTNU, Trondheim
Intracellular trafficking and signaling of Toll-like receptors in innate immunity

Dr. Terje Johansen, Institute of Medical Biology, University of Tromsø
Cellular function of autophagic adaptor proteins

Partner in OSBREAC and K.G.Jebsen Center for Breast Cancer Research:

Dr. Rolf Kåresen, OSBREAC – Oslo Breast Cancer Research Consortium,
OUS Ullevål.
The groups participating in OSBREAC perform molecular and functional characterization of breast cancer patients/cells at different steps during cancer development with the aim of identifying biomarkers to be utilized for stratification into more personalized treatment regimes for the patient

Dr. Anne-Lise Børresen-Dale, The K.G. Jebsen Center for Breast Cancer Research,
The KGJ-Center is based on the OSBREAC initiative

Anne-Lise Børressen-Dale, Department of Genetics, Institute for Cancer Research, Oslo University Hospital
Partner in OSBREAC and Head, KGJ-Center
Collaborator on molecular characterization

Ingrid Gribbestad/Tone Frost Bathen, Department of Circulation and Medical Imaging Norwegian University of Science and Technology.
Partner in OSBREAC and the KGJ-Center
Collaborator on function and molecular MR spectroscopy

Collaboration with NCM:

Dr. Toni Hurtado will be collaborating with OSBREAC on molecular characterization of breast cancer and the involvement of stem cell subpopulations

Dr. Lars Akslen, Department of Pathology, Gade Institute, University of Bergen
Collaborator on tumor-stroma interactions in breast cancer and melanomas with special focus on vascularization and endothelial markers

Dr. Olav Engebråten, Dep. of Tumor Biology and Oncology, Oslo University Hospital
Tumor heterogeneity and the use of transgenic mouse models for studying breast cancer development and response to treatment

Dr. Ingrid Gribbestad, Dep.of Circulation and Medical Imaging, NTNU
MR spectroscopy of breast tumors

Communication and dissemination activities

MEDIA COVERAGE

TV

"Forscher på vaksine mot hjernekreft", NRK TV, Lørdagsrevyen, 25. August 2012, http://tv.nrk.no/serie/dagsrevyen/nnfa02082512/25-08-2012#t=14m25s (I. Langmoen)

NEWSPAPERS

VG, "Flere vil bli kurert", 28th Apr 2012 (O. Myklebost, T. Sørlie)
http://csc.rr-research.no/?aid=12469&k=cast%2Fmedia


FREMTIDENS KREFTHÅP

FLERE VIL BLI KURERT

VG, "Nytt håp for kreftpasienter", 13th Apr 2012 (O. Myklebost)
http://csc.rr-research.no/?aid=12457&k=cast%2Fmedia


NYTT HÅP FO

Samme mutasjon kan gi kreft flere steder i k

Kreft på helt ulike steder i kroppen kan ha samme årsak, viser ny forskning. Det åpner for nye muligheter for behandling.

– Samfunnsøkonomisk gunstig

Får 35 millioner i støtte

KROMOSOMET:

Kreftforeningen, **Sammen mot kreft** Nr 4 (2012) s18-19 "På vei mot persontilpasset kreftmedisin" (O. Myklebost)

Kreftforeningen benyttet professor Myklebost som frontfigur til **juleinnsamlingen** 2012

Biotech Scandinavia Dec 12, - Intervju "Norway invests in personalized cancer care" (O. Myklebost)

"Kreftbekjemperen" Aftenposten 10. March 2012 (I. Langmoen)

"På sporet av en kreftvaksine," Aftenposten, 1. September 2012 (I. Langmoen)

"Vaksinerer mot tilbakefall av kreft," Annonsebilag fra Oslo Cancer Cluster, i Dagens Næringsliv, November 2012. (I. Langmoen)

INTERNET

Nrk.no, "Skal kartleggje kreftgenar hos 4000 nordmenn", 6th Feb 2012 (O. Myklebost) http://www.nrk.no/vitenskap-og-teknologi/1.7984911

Nature.com, "Norway to bring cancer-gene tests to the clinic", 2nd Feb 2012, (O. Myklebost) http://www.nature.com/news/norway-to-bring-cancer-gene-tests-to-the-clinic-1.9949

Dagensmedisin.no, "Vil ha nasjonal kreftsatsning", 13th Jan 2012 (O. Myklebost) http://www.dagensmedisin.no/nyheter/vil-ha-nasjonal-kreftsatsing/

Oppdatert 13.01.12 Nyheter

Vil ha nasjonal kreftsatsing

Et norsk forskningsprosjekt kan bli starten på et norsk program for målrettet kreftbehandling. Oslo Cancer Cluster vil ha nasjonal satsing.

Kommentarer » Skriv ut » Send »

Tagger: Kreft

Den nasjonale forskningsgruppen Norwegian Cancer Genomics Consortium (NCGC) har nå søkt midler til et treårig forskningsprosjekt for å studere genetiske forandringer i kreftsvulster.

I går, 12. januar, arrangerte Oslo Cancer Cluster sitt fjerde Cancer Crosslink, og temaet for dagskonferansen var målrettet kreftbehandling.

– Studien kan være en første start på et nasjonalt program for målrettet kreftbehandling, sier styreleder Jónas Einarsson i Oslo Cancer Cluster.

Lærer av britene

Storbritannia har kommet langt i arbeidet med genanalyser og målrettet kreftbehandling. Det nasjonale Cancer Research har et eget prosjekt, i samarbeid med blant andre legemiddel-industrien.

– Dette handler ikke bare om behandling med legemidler, men også om å identifisere høyrisikopasienter og bidra til at de følges opp for å forebygge sykdom, sa britiske James Peach (bildet), som innledet konferansen.

Han leder Storbritannias program for målrettet kreftbehandling.

Relaterte artikler

13.01.12 Advarer mot helsegarantier

12.01.12 To sykehus vil bytte HPV-test

21.12.11 Vil gjøre det lettere å screene for kreft

08.11.10 Vil vite om arvelig risiko

14.10.10 Høy prostatakreft-risiko ved genfeil

24.02.10 Mutasjonstesting på vei inn ved ikke-småcellet lungekreft

Forskning.no Intervju om NFR-prosjektene om Persontilpasset kreftmedisin http://www.oslocancercluster.no/News/tabid/69/articleType/ArticleView/articleId/165/NCGC-granted-millions-for-personalized-cancer-medicine.aspx

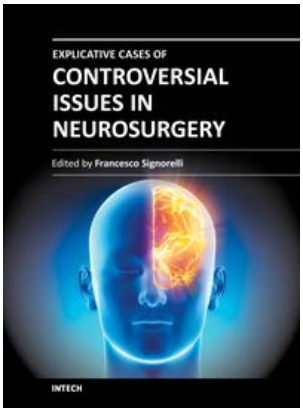
Aftenposten.no: "Fra science fiction til nobelpris", 17th Oct. 2012, (S. Krauss) **http://www.aftenposten.no/meninger/kronikker/Fra-science-fiction-til-nobelpris-7019596.html**

RADIO

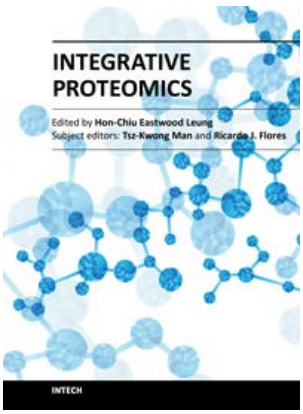
Professor Myklebost has been interviewed for NRK Ekko, Morgennytt and Forskningswed during 2012.

BOOKS

Vik-Mo EO, Fayzullin A, Moe MC, Olstorn H and **Langmoen IA**. The Role of Neural Stem Cells in Neurorestoration doi: 10.5772/29754 in "Explicative Cases of Controversial Issues in Neurosurgery", book edited by Francesco Signorelli, ISBN 978-953-51-0623-4, 2012 May 23



Hanne Kolsrud Hustoft*, Helle Malerod, **Steven Ray Wilson**, Leon Reubsaet, **Elsa Lundanes** and **Tyge Greibrokk**. A critical review of sample preparation for LC-MS based proteomics Intech 2012 "Proteomics / Book 2", ISBN 979-953-307-693-4



Appendix

PERSONNEL

PRINCIPAL INVESTIGATORS

Tyge Greibrokk
Anders Høgset
Stefan Krauss
Iver Langmoen
Else Lundanes
Ola Myklebost
Gunhild Mælandsmo
Rolf Skotheim
Harald Stenmark
Therese Sørlie

ASSOCIATED PRINCIPAL INVESTIGATORS

Gunnar Kvalheim
Jens Preben Morth
Ranghild A. Lothe

ADMINISTRATIVE MANAGER

Line Mygland

SENIOR SCIENTISTS

Anita Langerød
Leonardo Meza-Zepeda
Petter Angell Olsen
Lina Prasmickaite
Tor Erik Rusten
Pål Selbo
Steven Ray Wilson

POSTDOCTORAL RESEARCHERS

Sharmini Alagaratnam
Kristin Andersen
Chandu Chilamakuri
Paolo Conrotto
Jennifer Dembinski
Iwona Grad
Hege Karine Jacobsen
Stine Kresse
Silje Lauvrak
Viola Lobert
Helle Malerød
Elsa Munthe
Jens Henrik Norum
Linda Paulson
Nina Marie Pedersen
Biljana Stangeland
Eva Wessel Stratford
Einar O. Vik-Mo
Andrey Voronkov

PHD STUDENTS

Awais Mughal Ahmad
Ingrid Johanne Bettum
Hanne K. Hustoft
Andreas M. Hoff
Elin Johnsen
Kaja Lund
Lene Malerød
Sandrine Pacchini
Magnus Røgeberg
Hanne Røberg-Larsen
Martin F. Strand
Nirma Skrbo
Jo Waaler

MASTER STUDENTS

Svein R. Angel
Marius Strømbo Eng
Hong Diem Nguyen
Siri Olsen
Anastassia Serguienko
Guro Tveit
Tore Vehus

TECHNICAL PERSONNEL

Anne Cathrine Bakken
Monica Bostad
Russel Castro
Jeanette Daffinrud
Victoria Edwards
Bie Ekblad
Petros Gebregziabher
Monika Gelazauskaite
Birthe Mikkelsen
Dorna Mishagian
Menaka Sathermugathevan
Anastassia Serguienko
Kobra Sultani
Huyen Mong Thi Dinh
Anna-Berit Wennerström
Nomdo A.C. Westerdaal

FUNDING AND COST

Funding

		Amount
The Research Council	The Norwegian Research Council	10 895
The Host Institution	Oslo University Hospital (Rikshospitalet) HF	10 323
Research Partners	University of Oslo	2 639
Enterprise partners	PCI Biotech AS	2 280
	Affitech Research AS, in kind	850
	Total	26 917

All figures in 1000 NOK

Costs

		Amount
The Host Institution	Oslo University Hospital (Rikshospitalet) HF	21 148
Research Partners	University of Oslo	2 639
Enterprise partners	PCI Biotech AS	1 880
	Affitech Research AS	750
	Odin Therapeutics AS	500
Total		26 917

All figures in 1000 NOK

PUBLICATIONS

JOURNAL PAPERS 2012

Waaler J, Machon O, Tumova L, Dinh H, Korinek V, **Wilson SR**, Paulsen JE, Pedersen NM, Machonova O, Gradl D, von Kries JP, **Krauss S**,
The novel tankyrase ½ inhibitor JW55 interferes with canonical Wnt signaling in colon carcinoma cell lines in vitro and reduces tumor growth in conditional APC mutant mice in vivo.
Cancer Res. 2012 Jun 1, 72(11):2822-32.

Roberg-Larsen H, Strand MF, Grimsmo A, Olsen PA, Dembinski JL, Rise F, **Lundanes E, Greibrokk T**, **Krauss S**, **Wilson SR**,
High sensitivity measurements of active oxysterols with automated filtration/filter backflush-solid phase extraction-liquid chromatography-mass spectrometry.
J. Chromatogr A. 2012 Sep 14, 1255, 291-7,
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Waaler J, Machon O, Tumova L, Dinh H, Korinek V, **Wilson SR**, Paulsen JE, Pedersen NM, Eide TJ, Machonova O, Gradl D, Voronkov A, von Kries JP, **Krauss S,**
A novel tankyrase inhibitor decreases canonical Wnt signaling in colon carcinoma cells and reduces tumor growth in conditional APC mutant mice.
Cancer Res. 2012 June 1, 72 (11), 2822-32
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Solberg N, Machon O, Machonova O, **Krauss S**,
Mouse Tcf3 represses canonical Wnt signaling by either competing for β-catenin binding or through occupation of DNA-binding sites.
Mol Cell Biochem, 2012 June, 365 (1-2), 53-63
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Solberg N, Machon O, **Krauss S**, Characterization and functional analysis of the 5'-flanking promoter region of the mouse Tcf3 gene. **Mol Cell Biochem** 2012 Jan, 360 (1-2), 289-99
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Skårn M, Namløs HM, Noordhuis P, Wang MY, Meza-Zepeda LA, **Myklebost O**,
Adipocyte differentiation of human bone marrow-derived stromal cells is modulated by microRNA-155, microRNA-221, and microRNA-222. **Stem Cells Dev**. 2012 Apr 10, 21(6):873-83

Namløs HM, Kresse SH, Müller CR, Henriksen J, Holdhus R, Sæter G, Bruland OS, Bjerkehagen B, Steen VM, **Myklebost O**,
Global gene expression profiling of human osteosarcomas reveals metastasis-associated chemokine pattern.
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Identification of osteosarcoma driver genes by integrative analysis of copy number and gene expression data.
Genes Chromosomes Cancer 2012 March 27, 51(7):696-706. doi: 10.1002/gcc.21956.

Kresse SH, Meza-Zepeda LA, Machado I, Llombart-Bosch A, **Myklebost O**,
Preclinical xenograft models of human sarcoma show nonrandom loss of aberrations.
Cancer 2012 Jan 15, 118(2):558-70. doi: 10.1002/cncr.26276

Stratford EW, Castro R, Daffinrud J, Skårn M, Lauvrak S, Munthe E, **Myklebost O**,
Characterization of liposarcoma cell lines for preclinical and biological studies.
Sarcoma 2012; 2012:148614
Epub 2012 Jul 14

Namløs HM, Meza-Zepeda LA, Barøy T, Ostensen IH, Kresse SH, Kuijjer ML, Serra M, Bürger H, Cleton-Jansen AM, **Myklebost O**,
Modulation of the Osteosarcoma Expression Phenotype by MicroRNAs.
PLoS One 2012; 7(10):e48086. doi: 10.1371/journal.pone.0048086
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Kresse SH, Rydbeck H, Skårn M, Namløs HM, Barragan-Polania AH, Cleton-Jansen AM, Serra M, Liestøl K, Hogendoorn PC, Hovig E, **Myklebost O**, Meza-Zepeda LA,
Integrative analysis reveals relationships of genetic and epigenetic alterations in osteosarcoma.
Plos One 7(11):e48262. doi: 10.1371/journal.pone.0048262
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Ohnstad HO, Castro R, Sun J, Heintz KM, Vassilev LT, Bjerkehagen B, Kresse SH, Meza-Zepeda LA, **Myklebost O**,
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Fossdal G, Vik-Mo EO, Sandberg C, Varghese M, Kaarbø M, Telmo E, **Langmoen IA**, Murrell W,
Aqp 9 and brain tumour stem cells.
ScientificWorldJournal 2012;2012:915176. doi: 10.1100/2012/915176. 2012 Jan 4

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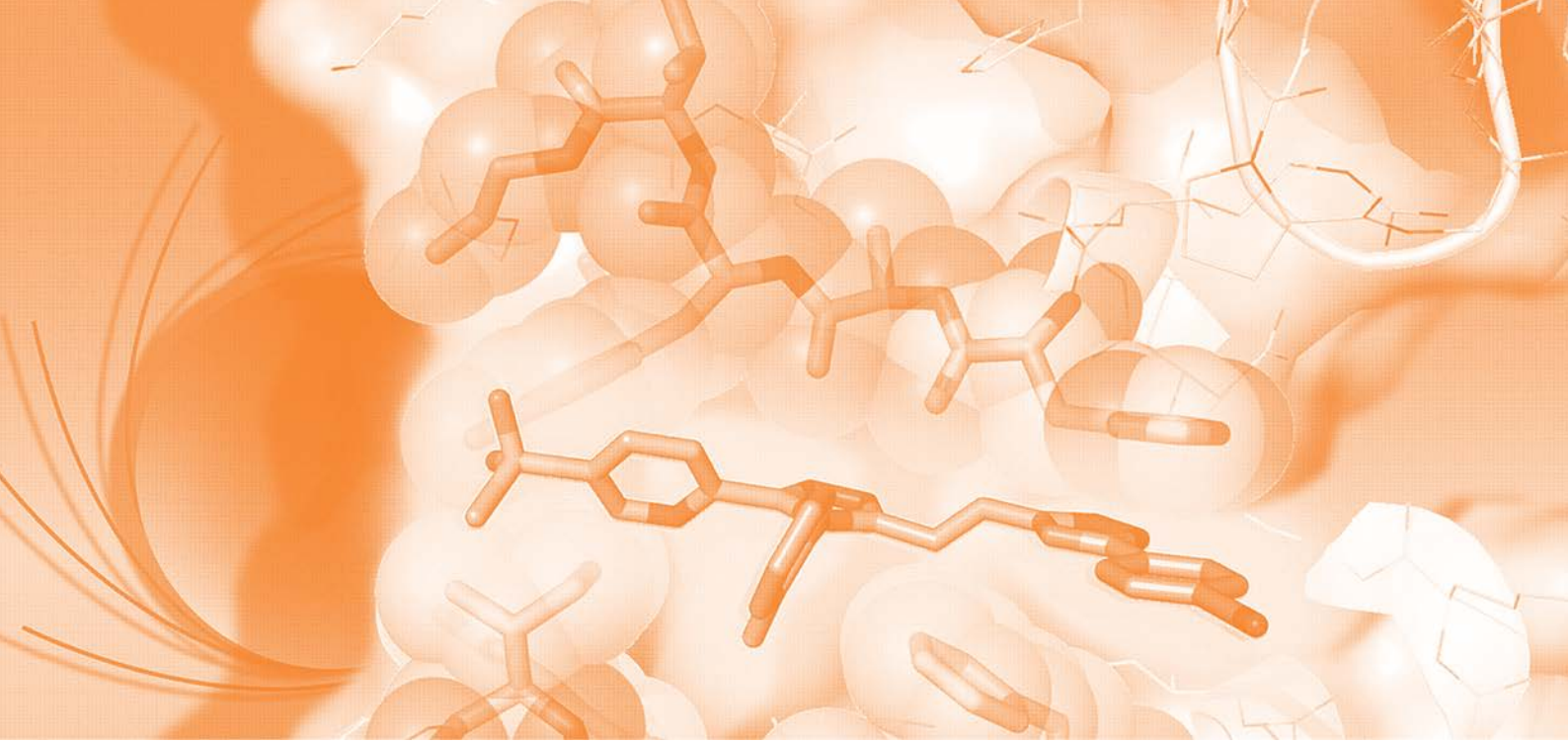

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