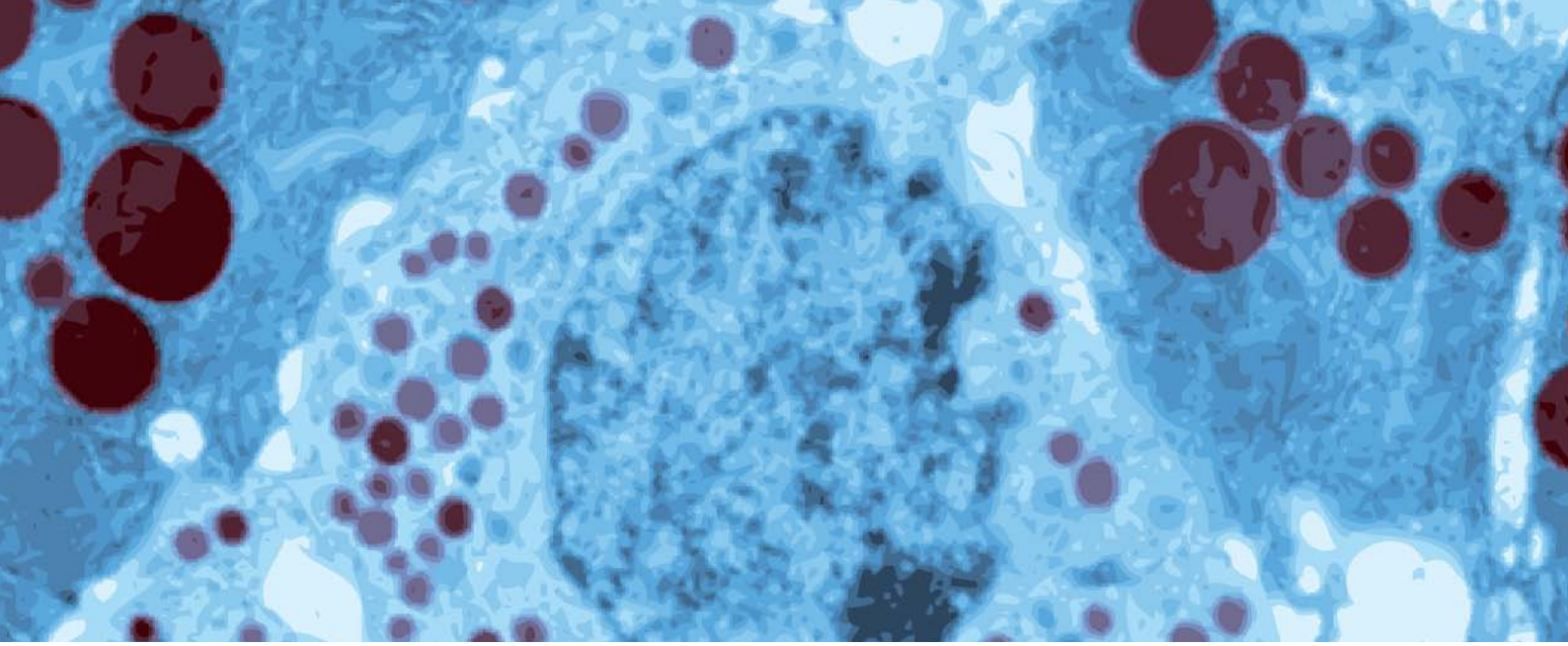


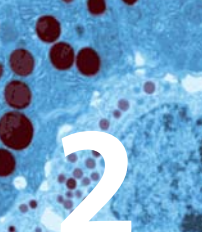
Annual Report 2009

CAST
CANCER • STEM CELL INNOVATION CENTER

Established by the Research Council of Norway
sfi Centre for Research-based Innovation

Oslo universitetssykehus

UNIVERSITY OF OSLO



Introduction

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

Using the stem cell tool kit to understand cancer - the concept behind SFI-CAST - 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 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 with high innovative potential and commercial value.

In the 3 years of its existence, SFI-CAST researchers have established a portfolio of tools that comprise a solid basis for innovative industry development. Moreover, a platform of validated cancer cell lines is emerging that will serve as a standard for industrial SFI-CAST projects. Our lead drug discovery projects have gained maturity and several chemotypes are currently evaluated by industry partners. One spin off company based on SFI-CAST technology is emerging, and a second spin off is on the drawing board. Finally, a pioneering clinical trial based on an in house developed immunotherapy protocol is in progress.

We have no illusions: very substantial scientific and commercial challenges lie ahead of the centre. We face these challenges with confidence that the chosen strategy is correct.

We would like to thank the Research Council of Norway for its support in the SFI-CAST innovation centre, and the academic researchers and industry partners for their dedication and commitment. We would also like to express our gratitude to Medinnova, the technology transfer office that has been enthusiastically committed 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

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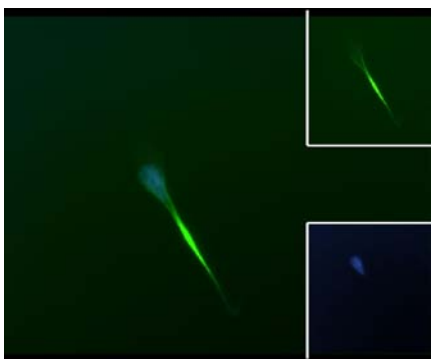
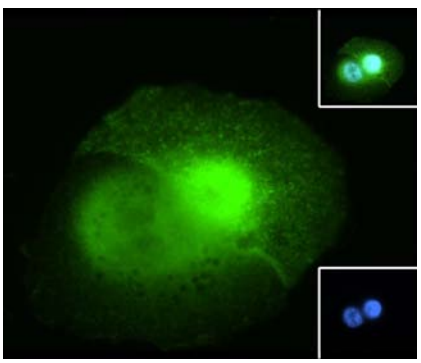
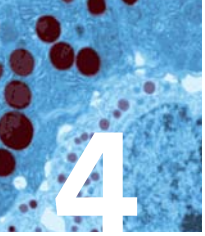


Vimentin-488 staining of a chemo resistant pancreatic adenocarcinoma cell (J.Dembinski)



Hif1a-staining of pancreatic adeno-carcinoma cells (one hypoxic, one normoxic) (J.Dembinski)



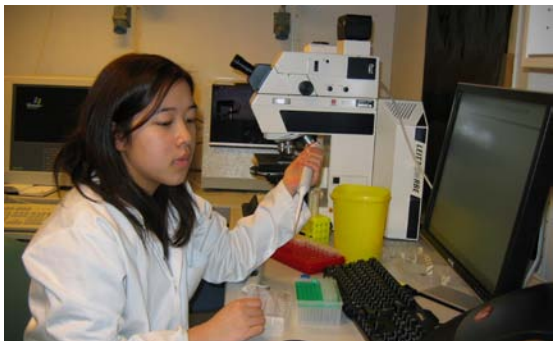
summary

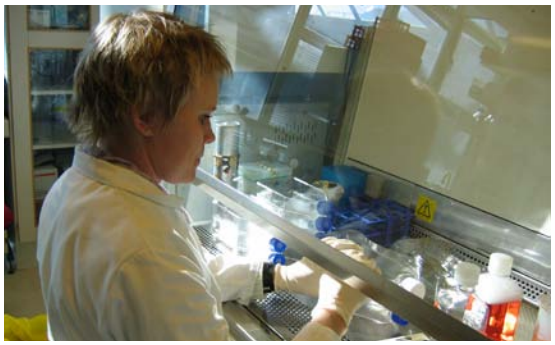
During the last decade, cancer research has gained substantial knowledge by applying a multidisciplinary developmental understanding of tumour formation and progression, as well as a precise analysis on individual differences in tumours with single cell resolution.

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 appear to be directed by autocrine and paracrine short- and long-range effects. Accordingly, evidence is now mounting that drug efficacy can be strongly attenuated by the heterogeneous nature of tumour sub-populations, by interactions between those populations itself and the local environment, the immune system and systematic variations in long-range signalling.

The emergence of developmental and stem cell tools, combined with advanced validated high throughput analytical tools providing single cell (or sub cellular) resolution and high sensitivity, has dramatically enhanced our ability for addressing fundamental questions in oncology. We are now finally able to generate the necessary understanding for addressing and possibly predicting tumour spread, relapse and therapeutic efficacy in *ex vivo* systems as basic tools for drug discovery.

SFI-CAST is an integrated biomedical innovation centre that works towards the identification and characterization of stem cell parameters in tumours. SFI-CAST develops innovative approaches for finding small drugs, cancer vaccines and antibodies that address specifically stem cell issues 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.





innovative highlights of the cast-sfi biomedical innovation centre

During the last decade, cancer researchers have gained substantial knowledge by applying a multidisciplinary developmental understanding of tumour formation and progression, as well as a precise analysis on individual differences in tumours with single cell and gene level resolution.

It is now becoming increasingly evident that cancer cells comprise heterogeneity 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 effects. Accordingly, evidence is now mounting that drug efficacy can be strongly attenuated by the heterogeneous nature of tumour sub-populations, by interactions between those populations themselves and between the local environment, by the immune system, and systematic variations in long-range signalling (e.g. hormones).

Determining parameters that influence heterogeneity in solid tumours is a core activity of the SFI-CAST consortium. Particular focus is on breast cancer, melanoma, lung cancer, colon cancer, oesophagus carcinoma, mesenchymal tumours and pancreas adenocarcinoma.

A broad range of early stage discovery programs are in progress at SFI-CAST. The Lothe laboratory has performed exon-resolution genome-wide expression analysis comparing embryonic stem cells with their malignant counterpart embryonal carcinomas, where both cell types are capable of self-renewal and differentiation. Careful consideration of cell growth conditions and sorting for pluripotent populations in both cell types allowed the identification of malignancy-specific gene expression and alternative splicing events.

In the breast cancer arena, the Sørlie laboratory has characterized different sub-populations of cells, based on two different linage markers, MUC1 and p75. Remarkably, the results indicated a patterned heterogeneity in tumour cells similar to that of normal breast tissue. Thus, basal-like tumour cells give rise to lineage restricted tumour cells with luminal-like properties and that the luminal-like tumour cells were most aggressive. The interferon response gene EPSTI1 seems to be highly expressed in high grade breast cancers and the expression of EPSTI1 in cell lines led to an increase in tumoursphere formation. EPSTI1 seems to be able to replace activated fibroblasts in tumour environment, indicating an important role for this gene as a regulator of tumour cell properties. Furthermore, *in vivo* experiments by the Mælandsmo laboratory showed that the luminal like EpCAM subpopulation had the highest tumour initiating potential. Further analysis of the luminal-like EpCAM population revealed population heterogeneity with respect to cell surface markers, and the laboratory is now exploring whether this heterogeneity reflect different tumour initiating potential.

Also, selected cell lines derived from various other solid tumours, including lung cancer, oesophagus cancer, mesenchymal tumours and pancreas adenocarcinoma depict various degrees of heterogeneity. In pancreas adenocarcinoma, the Krauss laboratory has identified a slower cycling sub-population of cells at the invasive edge that show differential drug response and migration as well as tumour initiation potential. The Myklebost laboratory has continued the search for CSC (Cancer Stem Cells) in mesenchymal, breast, and lung cancers, identifying various sub-populations, by metabolic labelling, surface staining, and label-retention (slow cycling), and investigating their stem cell properties, in particular colony-forming ability in vitro and tumour-initiating ability in mice. A particular focus has been on the HMGA2 protein, which together with its antagonist microRNA let-7 is an important regulator of stem cell phenotypes.

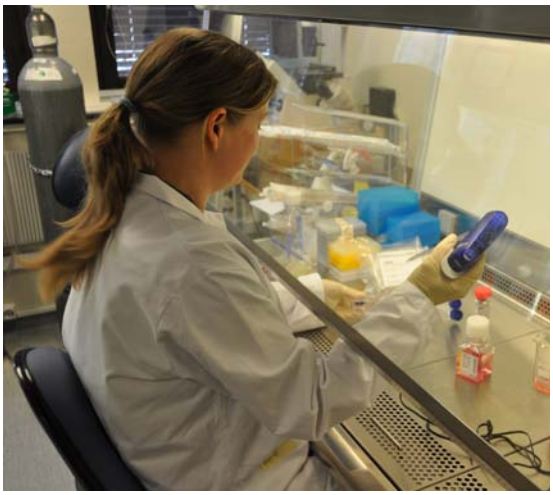
As part of the SFI-CAST core facility, a “Cancer Stem Cell Validation Platform” has been established. With the aim of creating a large panel of proprietary cancer cell lines for use within CAST, the Gaudernack group has established > 20 primary lung cancer cell lines and 10 primary prostate cancer cell lines, starting from fresh surgical specimens. In addition, 2 primary pancreas cancer cell lines have been established. These cell lines constitute a master cell bank. Several of these have now been transferred to the Cancer Stem Cell Validation Platform. The objective of this platform

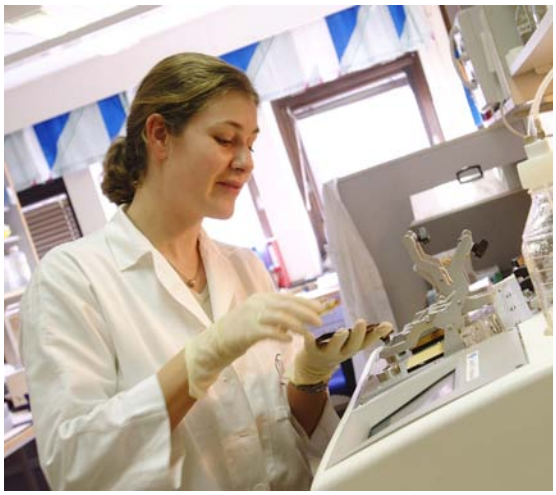
is to identify and validate a number of CSC (Cancer Stem Cells) model systems for the most important cancer types, and make these available for CAST partners. Cell types include breast cancer, lung cancer colon carcinoma, prostate cancer and pancreas adenocarcinoma. A further objective is to offer these models for validation of candidate treatments from the industry on a commercial or collaborative base. In collaboration with PCI Biotech, targeted therapy of CSC is currently evaluated.

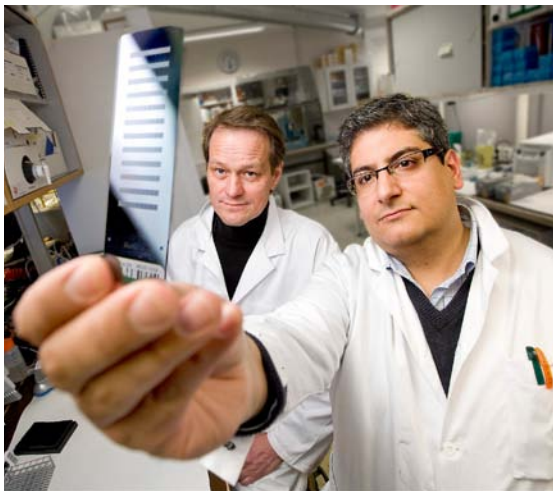
In the melanoma arena however, explored by the Mælandsmo laboratory, it was shown that a large fraction of melanoma cells, from multiple sub-populations and regardless of the expression of proposed CSC markers, are highly clonogenic and have the qualities needed for tumour initiation. These data propose that eradication of only rare cells hardly will lead to therapeutic benefit, since a majority of the cells from phenotypically different subpopulations must be eliminated to avoid recurrence of this disease.

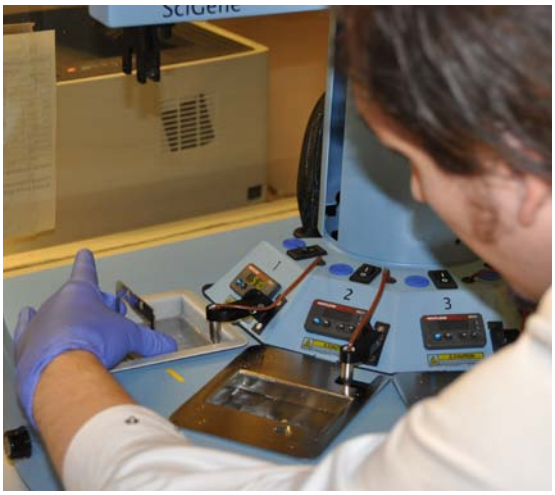
The SFI-CAST consortium has put a major focus on cellular signals that determine stemcellness. Based on this knowledge three drug discovery programs are now in place, two directed towards the stem cell pathways Wnt and Hh respectively, and a third program directed towards slower cycling sub-populations of cells in pancreas adenocarcinoma that show increased metastatic potential. For the Wnt drug discovery program, an explorative interaction has been initiated with a major pharmacological company. In addition, exploratory industry funding has been obtained by the Research Council of Norway to further develop the Wnt program.

A particular highlight in 2009 was the analysis of the endosomal sorting complex required for transport (ESCRT) machinery, a set of protein complexes that mediate lysosomal downregulation of signalling receptors. In collaboration with David Bilder´s group at the University of California, Berkeley, the Stenmark laboratory has identified subunits of the ESCRT-I, -II and -III complexes as tumour suppressors in fruit flies and shown that these complexes are crucial for attenuation of Notch and epidermal growth factor signalling, two pathways that are essential for stem cell maintenance and proliferation, respectively. The laboratory has also established that the ATPase Vps4, which disassembles ESCRT-III oligomers, is









a tumour suppressor in flies. Of note, all the ESCRT subunits are highly conserved from flies to humans, which make it likely that these proteins regulate human stem cells and behave as tumour suppressors in humans, although this remains to be investigated. Key results from the recent research on ESCRT proteins and their roles as tumour suppressors were discussed in a review article in *Nature* in 2009.

In the analytical field, the Lundanes laboratory has developed new nanoflow technology in proteomics of tumour stem cells. The pioneering technology will be tested in 2010.

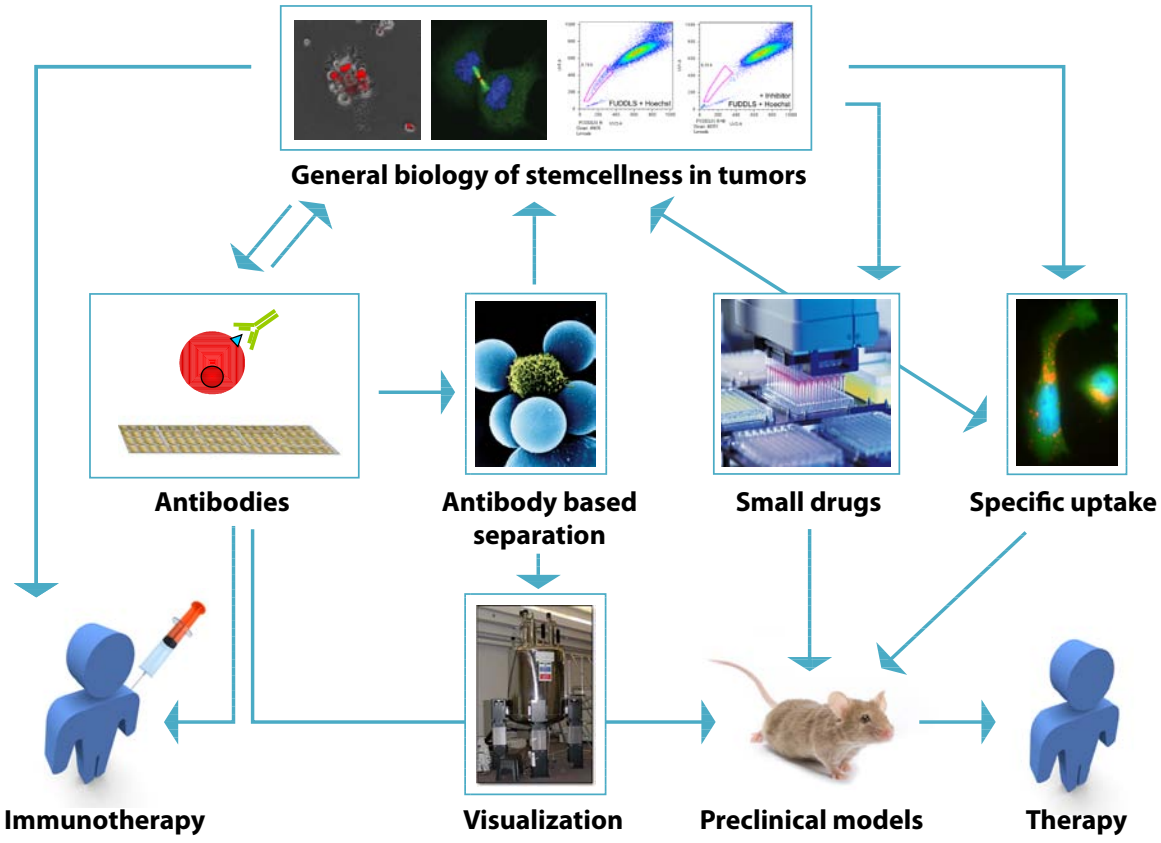
Working towards *in vivo* imaging of tumour stem cells, the Glover laboratory has established MRI (Magnetic Resonance Imaging) detection of magnetic bead-labelled tumour cells in living mice and used the technique for a comprehensive characterization of cell behaviour following labelling with magnetic beads.

Finally; in 2009 the first exploratory clinical trial has been initiated, human glioblastoma cells have been grown under stem cell conditions to yield neurospheres enriched in cancer stem cells. From these, mRNA is isolated and amplified under GMP conditions, and later electroporated into dendritic cells (DC). These are derived from monocytes isolated from the same patients, and the final product is used as a personalized vaccine. This clinical trial is a “first in man” trial testing this principle. To date, 12 patients have been included in the trial, and data from the first patients demonstrate that vaccination induces immune responses against the vaccine. Interestingly, this is associated with disease stabilization, but the results are preliminary and need to be confirmed by analysis of the other patients.

goals and research strategy

The SFI-CAST biomedical innovation centre has a work program aimed at advancing basic research on tumour stem cells to experimental clinical trials. Based on the outcome of this effort, several interactive biotechnology pipelines are fed. (i) Human therapeutic antibodies against drug resistant sub-populations of cells in a tumour are identified with industry partner Affitech AS. The antibodies will be used to identify novel epitopes and therapeutic targets. (ii) Tumour stem cell pathways are used for differential high throughput screens for drugs (a biotechnology start up company will be established for this goal in spring 2010). (iii) High resolution cell imaging of tumour stem cells *in vivo* using cutting edge magnetic resonance imaging (MRI) techniques is developed in animal models. (iv) Ways to find improved immunotherapy protocols and targets are being explored and tested. (vi) Specific receptors are tested for improved therapeutic photo-internalization (with industry partner PCI Biotech Holding ASA).

A major focus of the centre is translational research. Partners at the Norwegian Radium Hospital have been responsible for more than 25 phase I/II clinical trials of cancer vaccines and immune-gene therapy, and will cooperate with clinicians involved in the project to initial the first clinical trials targeting cancer cells with stem cell characteristics from the very beginning of the project. This ensures a swift start of the translational aspect as well as provides clinical material for the individual work programs.



During 2009 the host organisation of SFI-CAST went through a major merger. Rikshospitalet, Ullevål University Hospital and the Norwegian Radium Hospital are now part of the same organisation - The Oslo University Hospital. The organizational changes in the host organization have not affected the activity of SFI-CAST.

Management and members

SFI-CAST consists of 10 research groups; 8 groups at the Oslo University Hospital and 2 groups at the University of Oslo. There are four industry partners in the consortium. In 2009 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 Chemistry Department (University of Oslo) as well as in the different industries. During autumn 2009, a majority of the academic SFI-CAST partners co-localized in the novel research building at the Norwegian Radium Hospital. In total SFI-CAST employs 83 scientific staff.

SFI-CAST is headed by Stefan Krauss (Director) and Ola Myklebost (Assistant 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 the ten primary investigators (PI) and representatives of industry partners of the consortium.

Academic SFI-CAST members

Elsa Lundanes/Tyge Greibrokk, Department of Chemistry, University of Oslo

Gunhild Mælandsmo, Dept. of Tumour Biology, Oslo University Hospital, the Norwegian Radiumhospital

Gustav Gaudernack, Dept. of Immunology, Oslo University Hospital, the Norwegian Radiumhospital

Harald Stenmark, Dept. of Biochemistry, Institute of Cancer Research, Oslo University Hospital, the Norwegian Radium Hospital

Iver Langmoen, Dept. of Neurosurgery, Oslo University Hospital, Ullevål University Hospital/ Rikshospitalet

Joel Glover, Dept. of Physiology, Institute of Basic Medical Sciences, University of Oslo

Ragnhild A. Lothe, Dept. of Cancer Prevention, Oslo University Hospital, the Norwegian Radium Hospital

Ola Myklebost, Dept. of Tumour Biology, Oslo University Hospital, the Norwegian Radium Hospital

Stefan Krauss, Cell- and Genetic Therapy, Oslo University Hospital, Rikshospitalet

Therese Sørlie, Dept. of Genetics, Oslo University Hospital, the Norwegian Radium Hospital

Industry Partners

Affitech AS

Axellia Pharmaceuticals AS

Invitrogen-Dynal AS

PCI Biotech Holding ASA

The Board

The board is responsible for ensuring that SFI-CAST is developed in accordance with the current research plan. In 2009 the board members were:

Steinar Funderud, Oslo University Hospital, Rikshospitalet (Chairman)

Karen Marie Ulshagen, University of Oslo

Lars Engebretsen, Oslo University Hospital, Ullevål University Hospital

Martin Welschof, Affitech AS

Steinar Pedersen, Axellia Pharmaceuticals AS

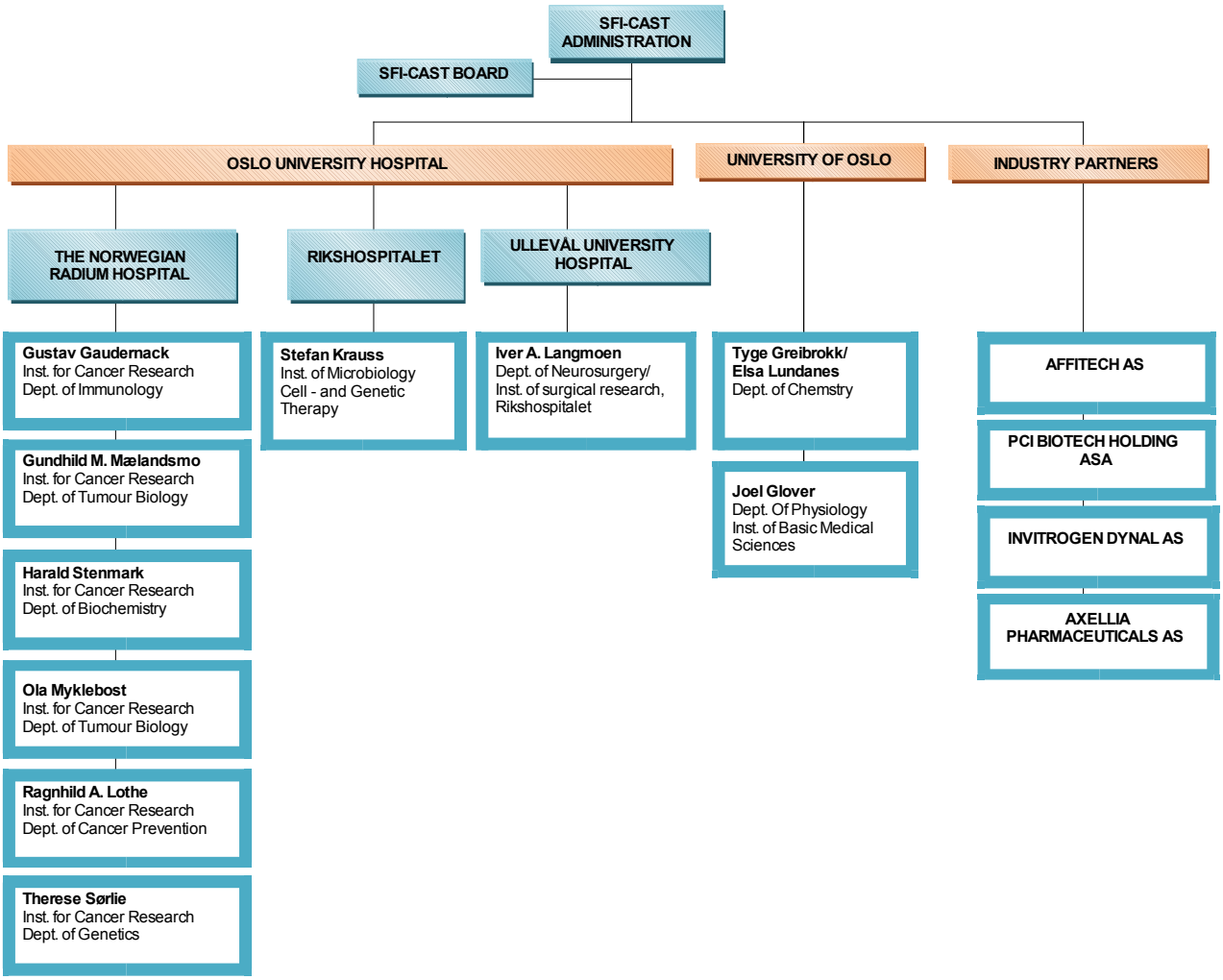
Erlend Ragnhildstveit, Invitrogen-Dynal AS

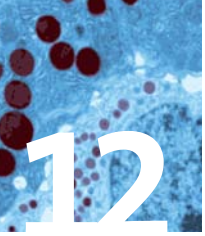
Anders Høgset, PCI Biotech Holding ASA

Øystein Rønning, Norwegian Research Council, Observer

Research Building at the Norwegian Radium Hospital (O. Myklebost)

Organisation structure

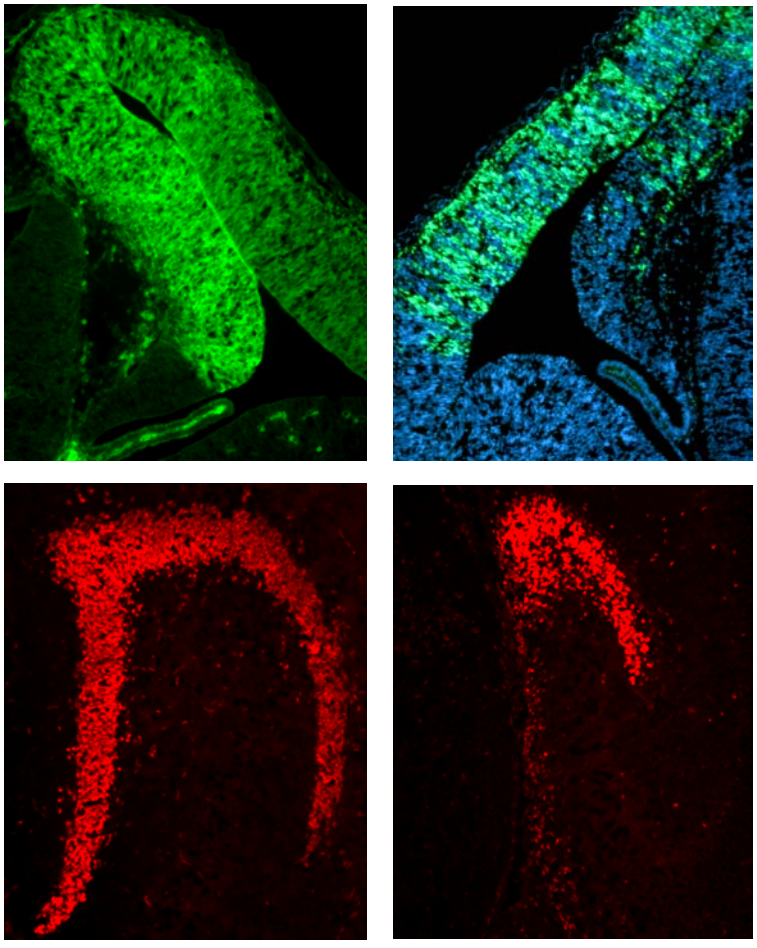




co-operation between partners in the center

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 SFI-CAST heterogeneity validated tumour cell bio bank, the antibody discovery platform, the immunotherapy platform, the emerging imaging platform and the photo internalization platform. Three retreats are annually organized to coordinate cooperation between the partners. In addition, project work groups are established.



Gustav Gaudernack-group
Immunology

Aim

The major aim of the immunotherapy group within the framework of CAST-SFI is to develop novel forms of immunotherapy for cancer targeting cancer stem cell, and to test these in early phase clinical trials.

Status

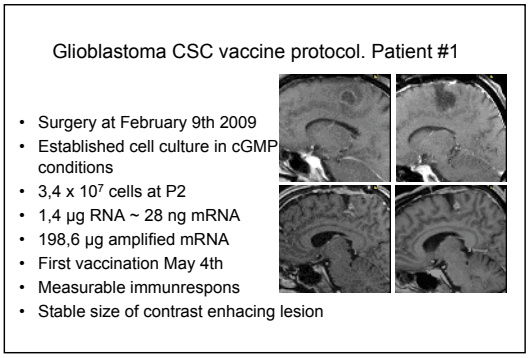
To this end we have focused on cooperation with clinicians at two levels. First to set up cooperative projects with surgical departments, in order to establish a set of primary cancer cell lines from common types of cancer, such as lung cancer and pancreatic cancer, in order to be able to establish a panel of proprietary primary cancer cell lines for use as sources of novel cancer vaccines and for cancer stem cell research. So far >20 lung cancer cell lines, 10 prostate cancer cell lines, 2 pancreas cancer cell lines and an ovarian cancer cell line have been established. These cell lines are now being extensively characterized by a broad array of methods to identify cell components with cancer stem cell characteristics. Two lung cancer cell lines have been stably transfected with reporter systems (luciferase and EGFP) that will allow *in vivo* tracking in animal models.

Secondly, we have in cooperation with the Langmoen group, initiated a Phase I/II clinical trial of immuno-gene therapy in patients with glioblastoma multiforme following standard chemo-radiation treatment. The clinical protocol has so far included 12/20 patients. Patients are treated weekly with injections of autologous dendritic cells transfected with mRNA amplified from glioblastoma neurosphere for 4 weeks, followed by monthly injections for up to one year. The clinical study is the first of its kind world wide. A similar clinical protocol, based on the ovarian cancer cell line established by us is now in the final stage of writing.

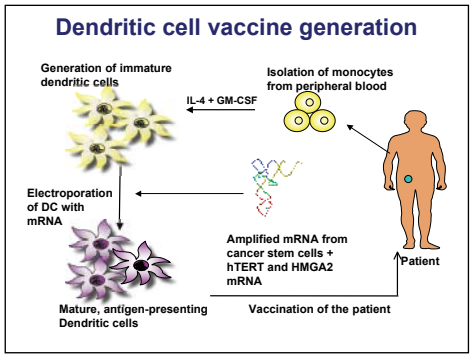
Further research plans

Several of the cell lines have been transferred to the Cancer Stem Cell Validation Platform for further characterization. These cell lines will be used for screening of small MW drugs, recombinant sc antibodies and for PCI experiments. The ovarian cancer stem cell vaccination study is expected to start in Q3-4 in 2010. Financing of the study is already in place.

Cooperation with other academic partners in the centre: We have ongoing and planned collaborations with the Langmoen, Myklebost, Krauss and PCI Biotech groups.



MRI image (top) of the brain of a vaccinated patient, indicating stable disease >12 months after surgery. In cooperation with I. Langmoens group. (I. Langmoen)



Overview of GMP production scheme for cancer stem cell mRNA transfected dendritic cells used as vaccines in glioblastoma and ovarian cancer.

Joel Glover-group
Imaging

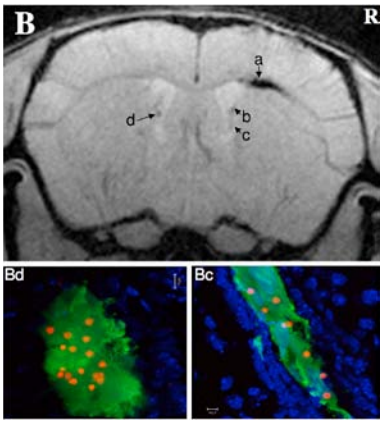
Aim
Establish methods for non-invasive dynamic tracking of tumour cells and tumour stem cells in animal models.

Status
The research interest of the group in the frame of CAST-SFI is to test and develop imaging systems that allow tracking of tumour stem cells *in vivo*. In the long term this will provide technologies for assessing treatment response and success. We have labelled human mesenchymal, adipose-derived, and fetal neural stem cells as well as human glioblastoma cells with MRI-detectable fluorescent magnetic beads, after having transfected these cells with GFP using lentivirus. We have assessed several cell biological parameters (proliferation rate, duration of cytokinesis, migration rate, differentiation of specific characters, electrophysiological properties) *in vitro* after labelling with beads and found that bead-labelled cells behave for all practical purposes normally. Efficiency of bead uptake varies among different cell types, both with respect to the proportion of cells that are labelled and the number of beads taken up per cell. Variation in the number of beads per cell appears to be dependent primarily on cell volume.
Injection of bead-labelled human fetal neural progenitors, mesenchymal stem cells and glioblastoma cells into NOD-SCID mice has shown that labelled cells can be detected *in vivo* by MRI over the course of several weeks and thereafter found post-mortem by virtue of their GFP expression.

Cell migration appears normal and can distinguish bead-labelled cells from free beads, which do not move from the injection site. FACS sorting can also be used to efficiently separate bead-labelled cells from unlabeled cells and from free beads prior to injection. MRI-detection of small groups of bead-labelled cells is possible *in vivo* – efforts are being made to push the detection limit to the single cell level.

We are also testing the behaviour of human glioblastoma cells *in vitro* and in animal models, including assessment of the role of intracellular signalling systems. Glioblastoma cells either alone or co-cultured with vertebrate embryonic neural cells are being assayed by phospho-flow techniques to map the activity of various second messenger cascades, and specific transduction with small inhibitory RNAs is being used to manipulate specific molecules in these cascades to test their roles in proliferation and tumorigenesis.

Further research plans
Ongoing experiments aim to establish routine procedures for effective bead-labelling and MRI detection of different types of tumour stem cells. In addition, beads will be conjugated with antibodies to specific tumour-related surface epitopes to test whether uptake can be directed to specific tumour cell sub-populations.



MRI image (top) of the brain of a living mouse 2 weeks after injection of magnetic bead-labelled glioblastoma cells near site "a", and post-mortem fluorescence images of the cells (bottom). Glioblastoma cells (green, GFP) containing beads (red) have migrated to sites "c" and "d" where they can be detected as darker grey areas in the MRI image.

Stefan Krauss-group
Stem cell signalling

Aim
The main goal of the groups within SFI-CAST is to develop antagonists to the stem cell pathways Wnt and Hh.

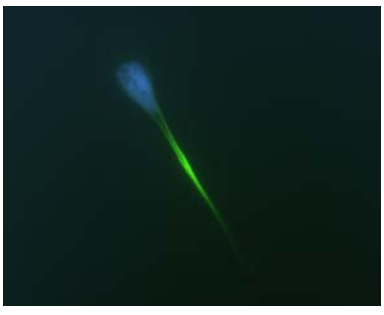
Status
During the last decade, cancer research has gained substantial knowledge by applying a multidisciplinary developmental understanding of tumour formation and progression, as well as a precise analysis on individual differences in tumours with single cell resolution.

Our laboratory has put a particular focus on identifying a sub-population of stem cell-like, slow cycling tumour cells in solid tumours. Using pancreas adenocarcinoma as a model, we recognized that such slowly cycling cells (SSCs) survive chemotherapeutic treatment, and are able to recreate the initial heterogeneous tumour cell population. SCCs exhibit an increased invasive and tumorigenic potential including morphological changes resembling cells that have undergone an epithelial to mesenchymal transition (EMT). Analysis of SCC cells by real time PCR revealed a selective up-regulation of tell tale components of the Hedgehog / Wnt pathways combined with a shift in crucial components implied in EMT.

Based on this knowledge, we identified two new small molecules that specifically inhibit canonical Wnt pathway at the level of the destruction complex (*Xenopus* double axis formation assay and in gene expression profile analysis). In the APC mutant colorectal cell lines the two compounds rapidly reduce the active form of β-catenin with a subsequent down-regulation of Wnt target genes. Long-term *in vivo* treatment with JW74 inhibits growth of grafted colorectal cells in immunodeficient mice and tumour formation in Apc^{Min} mice.

In the Hh signalling pathway, the Smoothened (Smo) receptor comprises a primary drug target with experimental small molecule Smo antagonists currently being evaluated in clinical trials. We identified a novel small molecule inhibitor of the Hh pathway with effective Hh signalling pathway inhibition at the level of Smo in the low nM range, and Hh pathway inhibition downstream of SuFu in the low µM range leading to reduction of growth in various pancreas adenocarcinoma tumour cell lines *in vitro* and *in vivo*.

The novel Hh and Wnt antagonists are currently being tested on sub-populations of cells in tumour models that show increased stemcell parameters.



Vimentin-488 staining of a chemo resistant pancreatic adenocarcinoma cell (J.Dembinski)

Further research plans
In the next period we will further validate the identified drugs, identify their molecular mode of action and attempt to develop the compounds to the clinical candidate stage. We will in parallel work towards an improved understanding how Hh and Wnt signalling are differentially regulated in sub-populations of cancer cells with stem cell characteristics.

Iver Arne Langmoen-group
Malignant brain tumours

Aim

The group has previously worked on neural cell physiology and neuronal differentiation of adult human neural stem cells. The main focus of the group in the frame of SFI-CAST is on cultivation, identification and characterization of brain tumour stem cells and identification of therapeutic targets through comparison of brain tumour stem cells vs neural stem cells and tumour stem cells from brain tumours.

Status

Glioblastoma is the most common tumour of the brain parenchymas. Despite the combined effort of surgery, chemo- and radiotherapy the median survival of patients is only ≈ one year (15 months in selected groups).

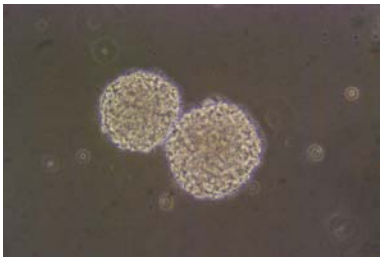
Previously, we have characterized similarities and differences in cells with stem like characteristics from the adult human subventricular zone and glioblastoma on a cell biology level. We have developed a technique for analysing the gene expression of single cells in a tumour-sphere. We have now carried out microarray studies in order to compare gene expression in these cells. To be able to study the function of possible target genes, we have established nucleofection as an efficient technique for over-expression and siRNA knockdown in our cells. Using bioinformatics approach we identified 20 genes that were up-regulated and 50 gene loci that were down-regulated in all the included GBM (Glioblastoma Mulitforme) tumour cultures. Our preliminary data indicate that the genes that are up-regulated in tumours are involved in cell-cycle/division, epigenetic regulation, signalling or have unknown functions. Few candidates seem to be down-regulating known tumour-suppressors. Among the genes that are down-regulated in tumours we found several growth inhibitors and loci on chromosome 10. Several of these candidates do not correspond to known genes.

In order to identify potential therapeutic targets we also assess differences between brain tumour stem cells, normal neural stem cells and normal brain tissue with proteomics approaches.

Based on the results we have so far we have designed a clinical phase I/II trial targeting brain tumour stem cells in patients with glioblastoma. The study has been fully certified by relevant authorities, and is the first of its kind worldwide. The trial has commenced and so far recruited eleven patients. The study is done in collaboration with the program on immunotherapy/vaccination at the Norwegian Radiumhospital.

Future research plans/in progress

1. Confirmation of differentially regulated genes at the protein level
2. Investigation of differentially regulated genes by knock-down and functional testing *in vitro*
3. Investigation of differentially regulated genes by knock-down and functional testing *in vivo*
4. Further clinical projects against selected targets



Tumoursphere derived from glioblastom.

Ragnhild A. Lothes-group
Stemcell biomarkers

Aim

We aim to identify and establish malignancy specific biomarkers in a stem cells context.

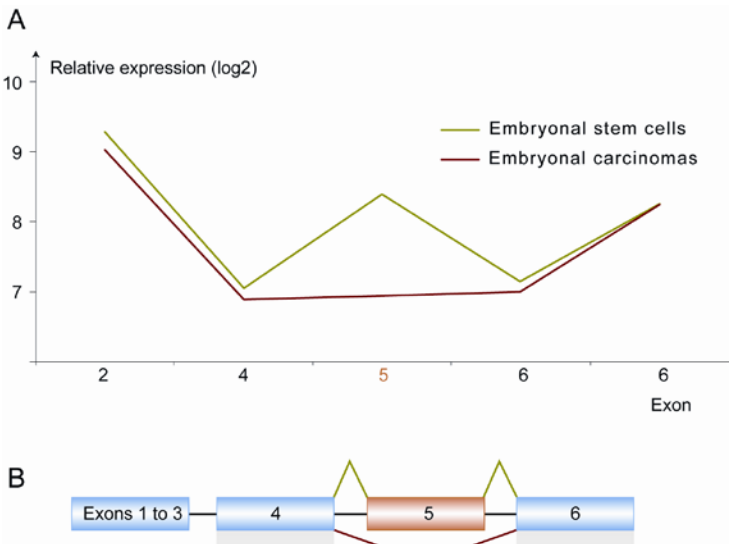
Status

Embryonal carcinoma cells found in testicular germ cell tumours can be considered the malignant counterpart of embryonic stem cells. Both cell types are pluripotent, share cell surface markers and overall gene expression programmes. In comparing the two, we access a non-malignant ('normal') counterpart of a cancer cell with stemness properties, and gain insight into the role of stem cells in the development and progression of stem cells related cancers. We have performed exon-resolution genome-wide expression analyses comparing RNA expression levels of a panel of embryonal carcinomas and embryonic stem cells. Careful consideration of cell growth conditions and sorting for pluripotent populations in both cell types allowed the identification of malignancy-specific gene expression and alternative splicing events between the two cell types. From the top-most differentially expressed genes and individual exons between embryonal carcinoma and embryonic stem cells, we have now validated the first few genes and transcripts.

Further research plans

We are in progress with a validation scheme for the most promising candidate malignancy specific genes and transcripts. This includes technical validation of the identified biomarkers, functional characterisation by knock-in and –out models, and use of bio bank material to evaluate their clinical utility by relating RNA and protein expression data of the novel biomarkers in conjunction with clinico-pathological data.

The project is carried out in collaboration with Professor Peter Andrews' lab at the University of Sheffield.



***A**, Candidate malignancy-specific splicing for a gene with differential exon-level expression pattern. The green and red lines represent the averages of four embryonic stem (ES) cell lines and three embryonal carcinoma (EC) cell lines, respectively. **B**, The anticipated splicing events assumed to be responsible for the interesting exon-wise plot are shown. The green and red lines represent the splicing events dominating in ES and EC cells, respectively.*

Elsa Lundanes and Tyge Greibrokk-group
Analytical chemistry

Aim
In the frame of the SFI-CAST, the analytical chemistry group is engaged in development of analytical methods for identifying proteome and metabolome markers for cancers stem cells and reagents that affect them.

Status
We have developed some highly sensitive and selective automatable capillary LC-MS quantification methods for potential novel drugs in different types of organs as liver, kidney, plasma etc, in cooperation with Stefan Krauss and his group.

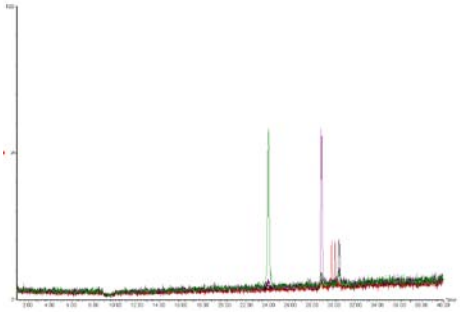
Miniaturized liquid chromatography mass spectrometric methods for identification of proteins have been explored; currently we are developing highly sensitive porous layer open tubular (PLOT) columns with 10 µm inner diameter suitable for separation of low abundance proteins/peptides (see Figure). This technology will be particularly suitable for analyzing heterogeneous sub-populations in cancer since protein markers for “cancer stem cells” are expected to be present at low concentrations.

Furthermore we develop analytical methodology for the drug discovery program at SFI-CAST, in particular for antagonists for the Wnt and Hh stem cell pathways. Emphasis is put on designing automatable and robust systems/methods, so e.g. pharmacokinetic information produced is reliable, quickly obtained, and little prone to contamination between sample and operator.

In a third program we elucidate the structure of unknown chemicals that are relevant regarding stem cell pathways. For instance, we identify degradation products of potential drugs, which gives important clues to e.g. why a drug works *in vitro* but not *in vivo*. Another example is determining the structure of unknown natural products that effect stem cell pathways. In this program we incorporate LC-MS, NMR and quantum chemistry calculations.

Future research plans
Development of methods for protein separation and identification methods based on miniaturized liquid chromatography and mass spectrometry. Trypsin PLOT columns will be explored in combination with PLOT protein separation column(s) in order to perform protein separation with subsequent on-line tryptic digestion and mass spectrometry (MS/MS) for protein identification. We will start working on methods for identification and determination of glycoproteins and oxysterols.

Overlay base peak intensity (BPI) chromatograms of protein standards (5 nL of 10 pg/nL solution injected) on a 10 µm ID x 3 m PLOT column at column temperature 40°C. The solvent gradient was 90 % A (0.1% FA, 0.05% TFA (v/v) in water) to 90 % B (0.1% FA, 0.05% TFA, 10% water (v/v) in acetonitrile) in 40 minutes. The retention order is cytochrome C, myoglobin, b-lactoglobulin B, b-lactoglobulin A and carbonic anhydrase.



Ola Myklebost-group
Cancer Stem Cell Programming

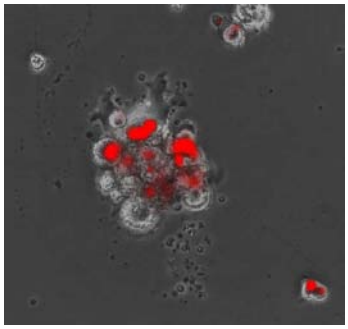
Aim
The Myklebost group has a focus on mesenchymal cancer, sarcoma, and investigates stem cell sub-populations in such tumours, but extends the studies of the mechanisms identified also to breast and lung cancer.

Status
Mesenchymal stem cell systems have been established to investigate the function of the candidate proteins. One such candidate protein is HMGA2, an architectural transcription factor that is amplified and rearranged in sarcomas. During the last couple of years a number of groups internationally showed that HMGA2 is central in the regulation of self-renewal and differentiation and also in the regulation of the stem cell phenotype especially in epithelial cancers. We have therefore intensified our research on HMGA2 and its microRNA counterpart Let-7, and have set up a number of assays to investigate its intracellular level in individual cells by flow cytometry, its subcellular localization by confocal microscopy, Let-7 reporter systems, and experimental systems to study its posttranslational modifications of HMGA2.

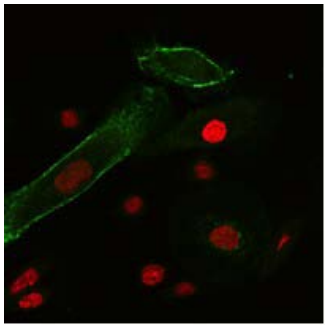
A number of stem cell phenotype assays have been established at the core facility, and small subpopulations have been identified in sarcoma cultures that are highly enriched for colony-forming ability. Phenotypes include Hoechst dye-exclusion, aldehyde dehydrogenase, slow cycling/label retaining cells, and a number of surface markers. Work is in progress with reporter assays for Let-7 microRNA activity (which regulates levels of HMGA2 and ras) in breast and lung cancer. A colony of NOD/SCID immunodeficient mice have been established for use by CAST at our animal facility. Assays of tumour-initiating potential of the various stem-like cell populations are on-going.

The investigations into HMGA2 are also being taken into other, more common cancer types, including lung, breast, pancreatic and ovarian cancer. Another project, headed by Dr. Meza-Zepeda, focuses on the epigenomics of stem cells.

Further research plans
The studies on HMGA2 are being expanded, and the involvement of this protein and two of its regulators, the Let-7 microRNA, and TGF-beta in the epithelial-mesenchymal transition (EMT) in breast, lung and ovarian cancer will be further investigated. Work is initiated to establish a number of cancer stem cell models from lung, prostate and pancreatic cancer, for use as drug validation systems. Dr. Munthe will in 2010 visit the MD Anderson Cancer Center to work on HMGA2 in breast cancer in collaboration with Dr. Sendurai Mani.



Slowly cycling, label-retaining osteosarcoma cancer stem-like cells (shown in red) (S. Lauvrak)



Breast cancer cells in the process of TGF-beta-induced epithelial-mesenchymal transition (EMT), stained for HMGA2 (red) and the epithelial marker e-cadherin (green). (E. Munthe).

Gunhild Mælandsmo-group
Tumour Heterogeneity group

Aim
In the frame of SFI-CAST, the group is studying the impact of stem or progenitor cells for initiation and progression of breast cancer and malignant melanoma.

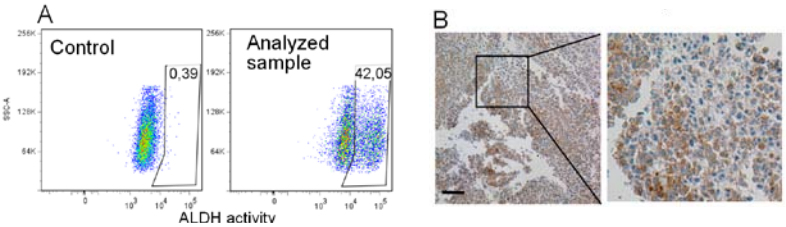
Status
A focus for the group has been to optimize methods for single cell preparation from tumour tissue, isolation and cultivation of various cell populations for maintenance and further evaluation of stemness characteristics and differentiation capability. In our studies we are utilizing clinical material obtained directly from the patients, or human tumours grown as xenografts in nude mice.

In the breast cancer project we utilize models representative for basal-like and luminal breast cancer grown orthotopically in nude mice. The primary purpose of the project is to investigate whether any of the two subtypes of breast cancer originate from cells with stem cell-like properties, and furthermore to study whether the ER negative basal-like subtype descend from a more primitive/less differentiated, potential pluripotent, stem cell compared to the ER positive luminal subtype.

In the melanoma project, we have shown that up to 60% of randomly chosen tumour cells have abilities for anchorage-independent growth in soft agar, spheroid formation and self-renewal i.e. properties often linked to the most aggressive tumour cells like CSCs. Comparison of the cell sub-populations differentially expressing various “CSC markers” revealed that these markers did not discriminate melanoma cells having the above-mentioned properties from cells lacking such properties. Altogether, this contradicts the traditional view of CSCs, which supposedly are rare and distinguishable from the rest of the cells, and raises doubt as to whether melanoma follows the CSC model.

In search for sub-populations demonstrating differential response to therapy, we have isolated melanoma cells differing in ALDH activity and compared tumourigenic properties as well as drug-response in ALDH+ versus ALDH- sub-populations. Both sub-populations demonstrated similarly high clone formation *in vitro* and tumour initiation *in vivo*. Interestingly, ALDH+ cells could recapitulate tumour heterogeneity *in vivo*, whereas ALDH- cells could not. These data suggests that the reestablishment of tumour heterogeneity is not a necessary characteristic of clone/tumour-initiating cells, which contradicts the earlier opinion about correlation between tumour-initiating abilities and reestablishment of heterogeneity.

Further research plans
We plan to investigate the tumorigenicity of sorted sub-populations of breast cancer cells isolated from the orthotopic models and organotypic implants form three-dimensional cultures in NOD-SCID mice. In addition we are searching for candidate molecules that may be examined for the possible use as novel markers for stemness in breast cancer. Such markers will be examined in the available assays for the possible enrichment of tumour cells with stem cell characteristics.



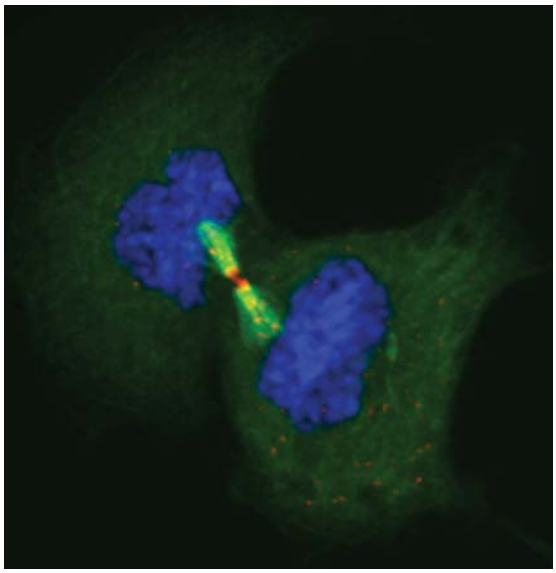
Expressing CSC-related molecule Aldehyde Dehydrogenase (ALDH) in xenografts (A) and in patient biopsies (B).

Harald Stenmark
Intracellular trafficking and signalling

Aim
In the frame of SFI-CAST the group focuses on intracellular trafficking and signalling of receptors that control the maintenance and proliferation of stem cells.

Status
We have recently identified several endosomal proteins that mediate degradation and thus attenuate signalling of Notch and EGF receptors, which are involved in stem cell maintenance and proliferation, respectively. In continuation of this, we are currently studying how these endosomal sorting proteins serve to modulate EGF and Notch signalling. In addition, we have performed a microarray analysis of EGF-stimulated fibroblasts and investigated how gene transcription is affected by EGF and how such signalling is modulated by regulators of membrane traffic. Increased cell migration is a hallmark of many invasive cancers, but the mechanisms are incompletely understood. We have recently obtained evidence that degradation of integrins plays a crucial role in cell migration, and we are currently pursuing these results in order to elucidate the precise mechanisms involved. This study involves a combination of siRNA knock-downs and live-cell microscopy. Finally, we study a class III PI-3-kinase that is a known tumour suppressor, but the molecular mechanisms are controversial. We have been investigating three cellular pathways controlled by this enzyme complex, namely endocytic membrane traffic, autophagy and receptor signalling. In addition, we have recently uncovered a function for class III PI 3-kinase in cytokinesis. We are currently continuing these studies in cell culture and Drosophila models to elucidate the tumour suppressor function of class III PI 3-kinase both *in vitro* and *in vivo*.

Further research plans
We plan to investigate the tumorigenicity of sorted sub-populations of breast cancer cells isolated from the orthotopic models and organotypic implants form three-dimensional cultures in NOD-SCID mice. In addition we are searching for candidate molecules that may be examined for the possible use as novel markers for stemness in breast cancer. Such markers will be examined in the available assays for the possible enrichment of tumour cells with stem cell characteristics. In the melanoma project we plan to investigate the importance of the tumour stroma and environmental factors for the aggressiveness and metastatic potential of the various sub-populations.



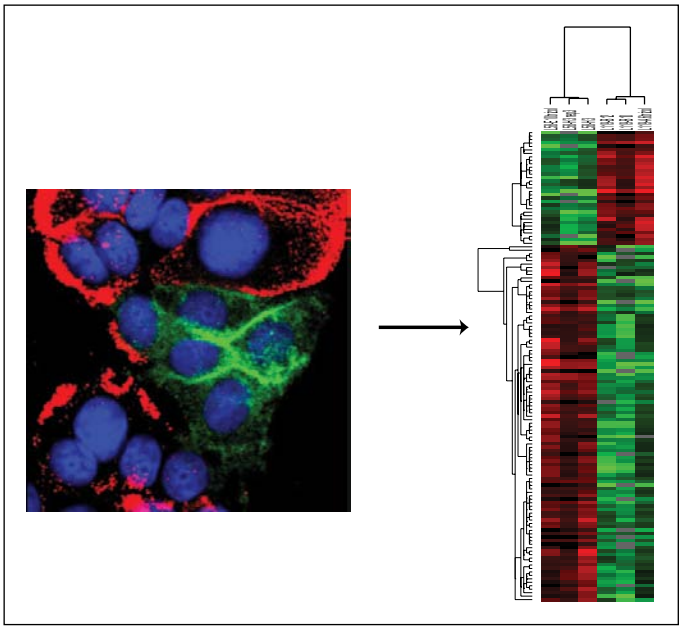
"Cells undergoing symmetric division. Microtubules are in green, nuclei in blue and class III PI 3-kinase in red. See Sagona et al, Nature Cell Biology, 2010. (C. Raiborg).

Therese Sørlie-group
Breast cancer heterogeneity

Aim
In the frame of SFI-CAST our group is focusing on stem cell biology related to breast cancer.

Status
We are interested in the origin of the cell subtypes in breast cancer and their possible ability to develop in a stem cell hierarchy. We have characterized several subpopulations from the breast cancer cell line MCF7 by using microarray technology. Copy number variations, expression of mRNA and miRNA were analyzed in these cells. More specifically, cells were sorted based on cell surface markers MUC1 and p75. Furthermore, based on the gene expression patterns, selected genes were further analyzed by RT-PCR. Different sub-populations from two xenograft models representative for the two main breast cancer subtypes are also being studied by genome-wide microarray technologies. These studies are being carried out in close collaboration with Gunhild Mælandsmo's group. We are focusing on identifying putative cell surface targets for further isolation of tumour initiating cells.

Further research plans
We are continuing to characterize by whole-genome microarray technologies, several different cell populations from the xenograft models. To start with, we are working with cells expressing EpCAM and/or CD49f. Expression patterns of these different populations will be compared to patterns from primary tumours. Identifying new surface markers for further purification will be an important part of the continued work. Furthermore, effort will be put into obtaining pure human cells through the sorting experiments. Cells will be subjected to various experiments to test for stem cell-like properties, including functional assays and mouse experiments.



Multicolour imaging of luminal-like cells (red = MUC1; green = NTR; blue = nuclei) and heat map showing gene expression differences of the representative FACS-sorted cells.

CAST core facilities

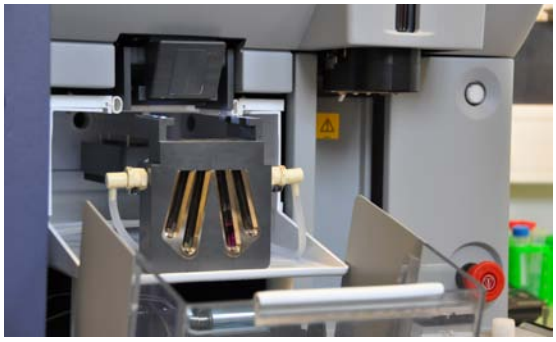
The SFI-CAST cell sorting core facility was established thanks to a grant from the Radium Hospital Legat. This facility provides advanced cell and animal technology, in particular high-speed cell sorting, but also cell isolation, propagation, and analysis, as well as immunodeficient mouse experiments. Three technical employees take care of these functions, and the facility, now in the new research building, also serves as a meeting place for CAST researchers. Thanks to the grant, funding has also been available to initiate a breeding colony for xenograft studies based on NOD/SCID mice. The level of activity is high, and more or less every day is now booked for sorting experiments, isolating small number of cells with stem cell properties from cancer cell cultures.

In 2009 core activity has been increased further, as SFI-CAST has started to establish a heterogeneity validated cell culture bio bank or cell culture platform. The main goal of the cell culture platform is to establish a collection of cancer stem cell (CSC) model systems for from several cancer types that are frequent and for which there is a lack of good therapies. The cell culture platform will be an important standard to internal CAST projects, but also for possible industry collaborations.

For the cell lines in the cell culture platform models we will validate the CSC phenotype assays already established within CAST, including label retention (slow proliferation), aldehyde dehydrogenase, and cell surface markers relevant for the tissue type, combined with ability to form colonies without attachment.

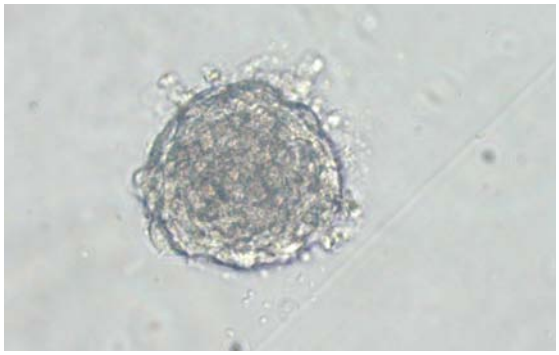
The objective is to establish at least 5 validated model systems for each selected cancer type. Initially we prioritise lung, pancreas and prostate cancer, followed by brain, breast- and colon cancer will follow. The selection is governed by clinical urgency, and thus reflects in commercialisation potential.

The efficacy of candidate therapies, from within CAST or from commercial collaborators, will be investigated on CSC sub-populations, with regard to specific toxicity, reduced colony formation, and ability to alter cellular phenotypes. Promising candidates can then be assayed further for tumour initiating ability in our NOD/SCID *in vivo* models.



Flow cytometry (O. Myklebost)

Flow sorting technician Nomdo Westerdaal (O. Myklebost)



Cancer cells grow as spheroids in 3D-assays (E. Munthe, A. Wennerström)

Personnel:

Anna Berit Wennerström, Cell technician, Petros Gebregziabher, Animal technician, Nomdo Westerdaal, Flow sorting technician, Else Munthe, Project leader, Post doc (50%). Menaka Sathermugathevan, Technician.

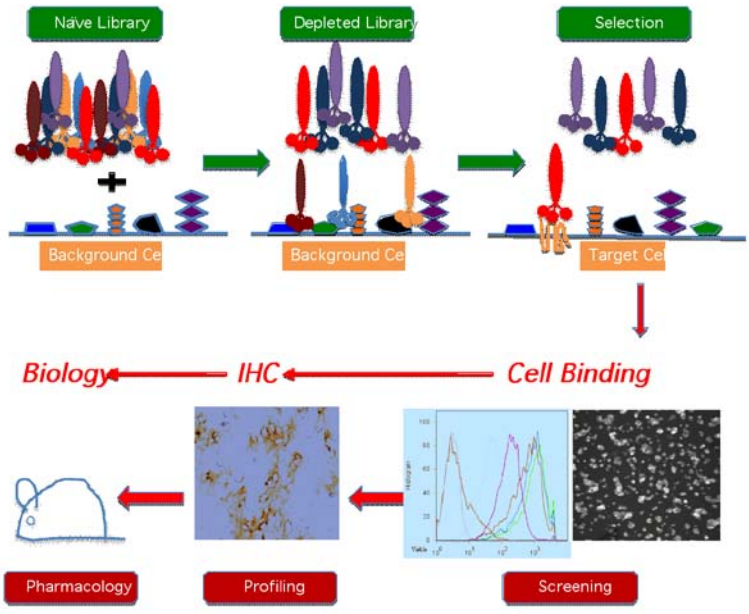
AFFITECH AS

About the company

Affitech AS, a biopharmaceutical company listed on the Nasdaq OMX Copenhagen stock exchange, 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 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. http://www.affitech.com/

SFI-CAST interaction

In the frame of SFI-CAST, Affitech together with its academic partners is working on an antibody discovery project to identify antibodies that preferentially bind to slow cycling (SSC) pancreatic cancer cells that show increased chemotherapy resistance and increased metastatic potential. Depending on future funding, Affitech is planning further strategies of targeting selected stem cell populations by using the existing techniques available at Affitech. Programs on lung cancer and glioblastoma are currently in discussion.



CBAS™ approach to isolate novel human antibodies against cell surface proteins.

Affitech's fully human naïve scFv antibody phagemid library, with diversity >10^{10} representing all VH families, is first subtracted on a relevant Background cell. The depleted library is exposed to Target cell for specific selection of antibodies. The candidates are screened for binding by in vitro assays and are furtherprofiled by immuno histochemistry (IHC) and tested in in vivo pharmacology.

AXELLIA PHARMACEUTICALS AS

About the company

Axellia Pharmaceuticals AS (Axellia, formerly known as Alpharma) is one of the leading Norwegian biotech companies, with more than 50 years of experience in the development and manufacture of antibiotics. Axellia is recognized for its expertise in fermentation and specialized recovery and purification technologies. During recent years, the company has established a platform in chemical synthesis and semi-synthesis. Over the last couple of years, Axellia has also built extensive capabilities in development and manufacturing of dosage form drugs, in particular injectables for use in hospitals.

SFI-CAST interaction

Axellia's interest in the frame of SFI-CAST has been to help develop small, organically synthesized molecules that can be demonstrated to have a potential for blocking pathways/preventing tumour cell proliferation/killing cancer cells.

INVITROGEN DYNAL AS

About the company

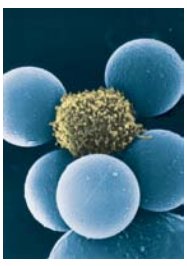
Invitrogen Dynal`s AS interest is to commercialise identified cancer stem cell markers to generate laboratory research reagents and diagnostic assays. Dynabeads® revolutionized separation methodologies in the 1980s. Today these magnetic beads are used in countless scientific applications and cited in thousands of published articles. Dynal® is committed to delivering absolute consistency and to reducing variability in your studies, diagnostic assays and therapeutic protocols.

SFI-CAST interaction

Invitrogen Dynal aims to develop cell isolation products based on antibodies specific for surface markers specifically expressed on cancer stem cell populations.

Invitrogen Dynal has a long term commitment to SFI-CAST and will provide competence and scientific personal in the context of surface antigen based cell separation. Invitrogen Dynal has many years of experience with immunomagnetic beads and cell isolation and will be responsible for implementation of cell isolation of cancer stem cells that SFI-CAST has identified and characterized.

IP image with Ab-dynal (Dynal)



Cell on beads (Dynal)

PCI BIOTECH HOLDING ASA

About the company

PCI Biotech® has developed a unique and patented photochemical drug delivery technology for use in cancer therapy and other diseases. The company's lead candidate drug is the proprietary photosensitiser Amphinex®. Our vision is to make cancer medicines better by improving drug delivery by photochemical internalization.

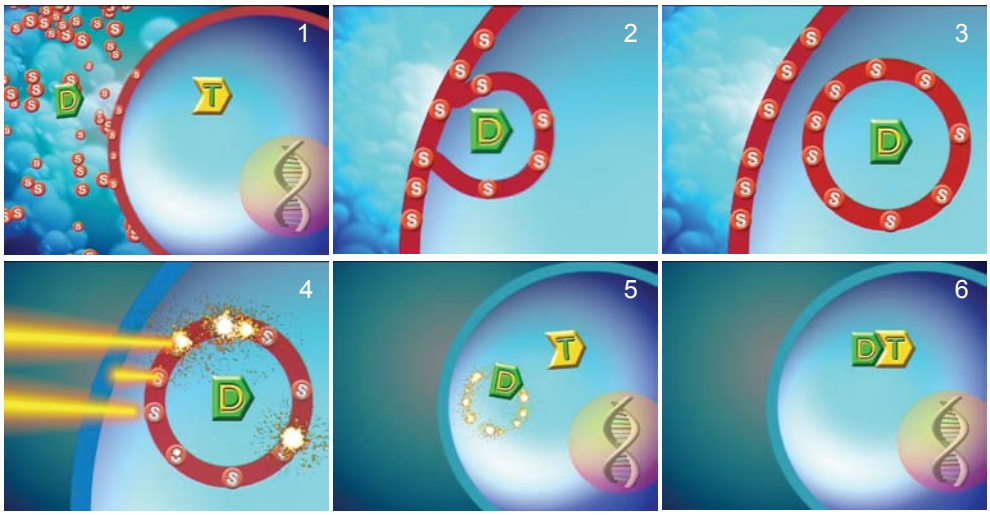
A breakthrough for PCI Biotech was the initiation of the first clinical study evaluating PCI: "Phase I, Dose-escalating Study to Evaluate Safety and Tolerance of Amphinex Based Photochemical Internalisation (PCI) of Bleomycin in Patients with Local Recurrence or Advanced/Metastatic, Cutaneous or Sub-cutaneous Malignancies". So far eleven patients with different kinds of cancer have been treated with PCI. The strong antitumor response seen in all patients treated with Amphinex® is far better than expected at the first dose levels and indicates that the positive pre-clinical results obtained with our PCI technology are transferrable to treatment in humans

SFI-CAST interaction

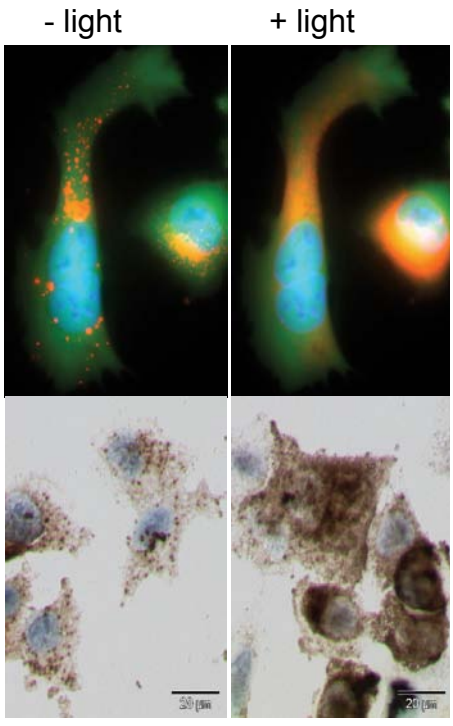
PCI biotech has together with several SFI-CAST partners initiated targeting of different cancer cells expressing relevant stem cell markers. Data obtained are very promising which warrant further preclinical evaluation of the technology.

Multi-Modality Therapeutics: Application of photochemical internalization to enhance efficacy of the antimelanoma fusion toxin scFvMEL/rGel. We have demonstrated enhanced tumour cell selectivity, cytosolic delivery and anti-tumour activity by applying PCI of the immunotoxin scFvMEL/rGel targeting the progenitor marker HMW-MAA/NG2/MGP/gp240. PCI of scFvMEL/rGel resulted in a synergistic effect ($p<0.05$) and complete regression (CR) in 33% of amelanotic melanoma tumour-bearing mice ($n = 12$). No apparent systemic adverse effects were detected. The work has been published in PLoS ONE.

Goals for 2010: We aim to further document the concept of combining PCI with cancer stem cell targeting toxins *in vivo*.



Principle of the PCI technology. 1, Administration of photosensitizer (S) and drug (D). 2, D an S is taken up by endocyosis and 3, sequester in endo-lysosomal vesicles. 4, Light activation of (S) leads to formation of reactive oxygen species, which burst the mebrane of the vesicles leading to 5, cytosolic release of the drug and 6, interaction with its biological target (T).



Light-triggered endo-lysosomal escape of photosensitizer and toxin-conjugate. Malignant melanoma cells before and after light exposure. PCI-photosensitizer (upper panel, red fluorescense) as well as toxin-conjugate (lower panels, drug stained brown) are entrapped in endocytic compartments (-light) and is released to the cytosol of the targeted cells after light exposure (+ light). Modified figure from Selbo PK et al. (2009) PLoS ONE 4(8): e6691. doi:10.1371/journal.pone.0006691

Oslo Cancer Cluster – From Cancer Research to Cure

Oslo Cancer Cluster, a non-profit member organization committed to improve the lives of cancer patients by accelerating the development of new cancer diagnostics and medicines. In June 2007 the cluster became a Norwegian Centre of Expertise (NCE).

Oslo Cancer Cluster is built on strong foundations dating from the early 1930s; Oslo's Radium Hospital is now Northern Europe's largest comprehensive cancer centre. Already, together with the Centre for Cancer Research and the Norwegian Cancer Registry, the Norwegian Radium Hospital has built a dynamic biomedical cluster for research into cancer and commercial spinout of cancer diagnostics and therapies.

Oslo Cancer Cluster already has nearly 60 members, including industrial companies, academic research institutions, health initiatives and support groups in the field of biotechnology with the main focus on cancer.

The cancer research and its application are in world-class in terms of innovation and quality. The region has also a unique infrastructure - from biobanks to extensive patient registries - that in Norway help accelerate the translational research crucial to converting ideas from the lab into diagnostics and treatment.

2009 has been a crucial year for the Oslo Cancer Cluster. 13 new and active members, promising clinical trials, important partnership deals and extensive media-exposure - our members continue their committed work to improve the lives of cancer patients by accelerating the development of new cancer diagnostics and treatments.

Algeta ASA showed that Norwegian biotech industry has great potential, when signing a deal that Norwegian analysts have named "the best deal in Norwegian biotech – ever". The deal with Bayer is estimated to be worth $800 million. The agreement secures Algetas further development of Alpharadin for treatment of bone metastases and disseminated tumour types.

Clavis Pharma ASA signed a partnership agreement with Clovis Oncology worth up to $380 million. This agreement secures the further development of a drug candidate against pancreatic cancer.

International partnerships are vital in order to support our members in commercialization and in the search for investors/partners. Along with Cancer-Bio-Santè in Toulouse, we organized the first European Cancer Cluster Partnering (ECCP) meeting in September 2009 in Toulouse in which the head of SFI-CAST gave a key note speech. ECCP will be repeated in Oslo from 15th-17th of September 2010. www.eccp2010.com. We hope that our members will actively support ECCP10 by participating at the conference, partnering meetings and investor streams.

Oslo Cancer Cluster supports its members with access to an international preclinical and clinical network in oncology, and we are broadening our network towards other cancer centres such as Heidelberg in Germany, Lund and Karolinska in Sweden and Copenhagen in Denmark. We are collaborating with The Hamner Institutes in Research Triangle Park in North Carolina. The Hamner Institutes will offer our member companies guidance and assistance in preclinical and clinical development in the USA. The Hamner is an independent non-profit institution. www.thehamner.org

The development of the Innovation Park next door to the Institute of Cancer Research where the majority of the SFI-CAST laboratories are located, will be voted upon in Oslo City Council in Sep/Oct 2010. The Innovation Park – if implemented - will physically integrate cancer research, clinical trials facility, biotech and biopharma companies with the purpose of accelerating innovation.

For updated information, see www.oslocancercluster.no

Bjarte Reve
CEO of Oslo Cancer Cluster

In 2009, SFI-CAST scientists were awarded a grant to arrange the "Norsk Hydro's Fund for Cancer Research" funded "Norwegian Cancer Symposium" with the title "Frontiers in Cancer Stem Cell Research: From basic science towards a cure". The highly successful symposium included 30 leading international speakers, and 263 participants, about half from foreign institutions.

A web site (cancersymposia.no) for the symposium series was made, where more information about the meeting is available, including the abstract book, and where information about the future meetings will be found.

Stem cell biology has a very substantial impact on cancer research, and opens for new therapeutic and diagnostic approaches. The societal importance was underscored as by the opening of the meeting by Anne-Grete Strøm-Erichsen, the Norwegian Minister of Health. The Ministry has been active in supporting stem cell research for several years, by allocating earmarked funding to stem cell research, and by successfully proposing the legislation that now allows research on embryonic stem cells. The topic also has the attention of local politicians, including the City Mayor of Oslo, Fabian Stang, who gave a reception for the conference in the City Hall.

We are grateful for the unanimous response from the European Association for Cancer Research (EACR), the Norwegian Cancer Society, and Oslo Cancer Cluster (OCC) to sponsor keynote lecturers. EACR Key Note speaker was Hans Clevers from University of Utrecht, The Netherlands, The Cancer Society Lecturer was William Matsui, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, USA, and the OCC Lecturer was Pier Giuseppe Pellicci, European Institute of Oncology, Milan, Italy.

The Norwegian Minister of Health, Anne-Grete Strøm-Erichsen (O. Myklebost)

Audience (O. Myklebost)

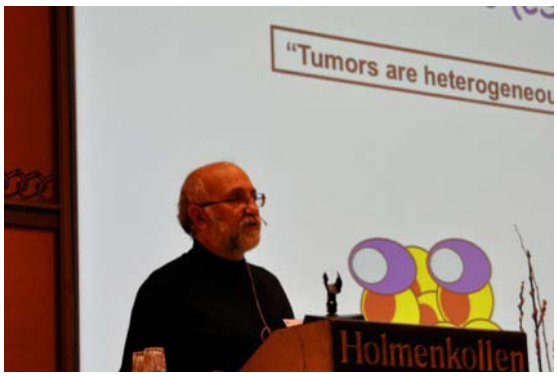
Speakers

- Pier Giuseppe Pelicci, *Milan, Italy;* Biological Properties of Cancer Stem Cells (Oslo Cancer Cluster Keynote speaker)
- Christopher Heeschen, *Madrid, Spain;* Pancreatic Cancer Stem Cells – Insights and Perspectives
- Christiane Bruns, *Munich, Germany;* Cancer stem cells - target for cancer therapy?
- Rolf Bjerkvig *Bergen, Norway*; Cancer Stem Cells - Can They be Defined?
- César Cobaleda, *Madrid, Spain;* The role of cellular plasticity in oncogenic reprogramming
- Ron McKay, *Bethesda, USA;* Cell interactions that control stem cells in mammals
- Hans Clevers, *Utrecht, The Netherlands;* Lgr5 Intestinal Stem Cells in self-renewal and cancer (EACR Keynote speaker)
- William Matsui, *Baltimore, USA;* The clinical translation of cancer stem cells in B cell malignancies (Cancer Society Keynote speaker)
- Hugues de Thé, *Paris, France;* LIC clearance by treatment-induced oncogene degradation
- Andreas Trumpp, *Heidelberg, Germany;* Dormancy in Stem Cells
- Eduard Batlle, *Barcelona, Spain;* Intestinal stem cell genes in colorectal cancer
- Mahendra Rao, *San Diego, USA;* Neural stem cells and cancer
- Eric Chi Wai So, *London, UK;* Dissecting the Molecular Pathways Mediating Self-Renewal of Leukemic Stem Cells
- Ariel Ruiz i Altaba, *Geneva, Switzerland;* Hedgehog-GLI1 signalling is essential in epithelial tumour cells and drives cancer stem cell expansion
- Rune Toftgard, *Stockholm, Sweden;* Hedgehog signalling in skin cancer and tissue stem cells
- Urban Lendahl, *Stockholm, Sweden;* Notch signalling in stem cells and cancer
- Marc LaBarge, *Berkeley, USA;* The role of the microenvironment in organizing and maintaining lineage specific domains in mammary gland
- John Stingl, *Cambridge, UK;* Mammary stem and progenitor cells: Understanding the cellular context of breast tumours
- Ole W. Petersen, *Copenhagen, Denmark;* Routes to breast cancer heterogeneity: Prospective cloning of functionally distinct subpopulations by use of markers from a normal human breast lineage hierarchy
- Amanda Fisher, *London, UK;* Stem Cells and Epigenetic Reprogramming
- Tracy-Ann Read, *Durham, USA;* Cancer Stem Cells Reflect the Origin of Pediatric Brain Tumours
- Maarten van Lohuizen, *Amsterdam, The Netherlands;* Role of Polycomb repressors in stem cells, cancer and development
- Peter Dirks, *Toronto, Canada;* Self renewal and lineage commitment in brain tumour stem cells

- Ralph A. Neumüller, *Vienna, Austria;* Controlling the balance between self-renewal and differentiation in Drosophila neural stem cells
- Monica Gotta, *Geneva, Switzerland;* Asymmetric division in C. elegans *(EMBO Young Investigator Lecture)*
- Peter Andrews, *Sheffield, UK;* Human Embryonic Stem Cells: Commitment, Adaptation and Cancer
- Thomas Brabletz, *Freiburg, Germany;* Tumour invasion and metastasis: EMT and cancer stem cells
- Sendurai Mani, *Houston, USA;* Generation of Stem-Like Cells via EMT: A New Twist in Tumour Initiation and Progression
- Christina Scheel, *Cambridge, USA;* Formation and Maintenance of Stem Cell Traits induced by EMT

Dr. Hans Clevers giving his EACR Keynote lecture (O. Myklebost)

Dr. William Matsui, giving his Cancer Society Keynote lecture (grant from Dentist Aas and Wife`s Donation) (O. Myklebost).



Dr. Pier Giuseppe Pelicci giving his OCC Keynote lecture (O. Myklebost)

Reception at the Oslo City hall; the welcome speech of Mayor Fabian Stang (O. Myklebost)

INTERNATIONAL CONFERENCES/ SYMPOSIA ORGANIZED BY SFI-CAST

- Course in mesenchymal cancer biology associated with the Annual meeting of the Scandinavian Sarcoma Group.

- International Cancer Symposium: "Frontiers in cancer stem cell biology; From basic science towards a cure". Holmenkollen 2-4/12-2009. Chief organiser Ola Myklebost, 270 participants (see detailed description earlier).

- Annual Retreat of the Norwegian Stem Cell Network, Losby, Norway October 7-8. Chief organizer Stefan Krauss, 87 participants.

DOCTORAL AND MASTER DEGREES

In 2009 SFI-CAST supervised 21 PhD-students and 9 master-students. 5 PhD-students and 5 master-students were examined.

Doctoral Degrees

Karolina Szokol
Functional organization of reticulospinal inputs to defined neuronal populations in the lumbar spinal cord.
6th of October 2009
Supervised by Joel Glover.

Ingrid Roxrud
Endocytic trafficking of membrane proteins. Mechanisms in human disease.
6th of November 2009
Supervised by Harald Stenmark.

Ravi Bains
Isoflurane and sevoflurane: Effects on mitochondrial function in the rat and human brain.
20th of November 2009
Supervised by Iver Langmoen.

Håvard Ølstørn
Neural Stem Cells form the Adult Human Central Nervous System and Brain Tumours. Properties in vivo following Xenotransplantation.
23rd of November 2009
Supervised by Iver Langmoen.

Aslaug Aamodt Muggerud
Genetic and epigenetic alterations in breast tumour progression: The transition from in situ to invasive cancer.
November 2009
Supervised by Therese Sørlie.

Master Degrees

Undis Ellevog
Development of a LC-MS/MS method for comparing brain tumour samples.
Supervised by Elsa Lundanes and Tyge Greibrokk.

Magnus Røgeberg
Porous layer open tubular columns for protein separations.
Supervised by Elsa Lundanes and Tyge Greibrokk.

Tina Hellenes
Mapping the expression of anti-apoptotic proteins and evaluation of the therapeutic potential of TRAIL receptor antibodies in "close-to-patient" melanoma models.
Supervised by Lina Prasmickaite and Birgit Engesæter.

Biruk Lueseged Abrha
The role of HMGA2 in adipogenic mesenchymal biology.
Supervised by Ola Myklebost

Anne Cathrine Bakken
Exon-specific biomarkers in cancer: Experimental validation of exon microarray data from colorectal and testicular cancers.
Supervised by Rolf Skotheim and Ragnhild A. Lothe.

SPECIAL AWARDS

An advanced Grant from the European Research Council was given to Harald Stenmark. 2.272 mill. Euro over 5 years starting 01.01.2010.

INTERNATIONAL AND NATIONAL COLLABORATIONS BETWEEN SFI-CAST MEMBERS AND OTHER ACADEMIC GROUPS OR RESEARCH INSTITUTIONS

The academic partners of SFI-CAST have established an extensive network of international and national collaborations.

International collaborations (academic partners)

Gaudernack-group
- The John van Geest Cancer Research Centre, Nottingham Trent University
- Danish Center for Cancer Immunotherapy (CCIT), Herlev Hospital, Copenhagen.

Glover-group
- Scott Fraser, California Institute of Technology

Krauss-group
- Bengt Norden, Chalmers University, Gothenburg, Sweden
- Toni Cathomen, University of Hannover, Germany
- Jens v Kries, Leibniz-Institut Für Molekulare Pharmakologie, Berlin, Germany
- Ernest Arenas, Karolinska institute, Stockholm, Sweden

Langmoen-group
- David Tirrell, California Institute of Technology, Los Angeles, USA
- Charles Liu, University of Southern California, Los Angeles, USA
- Monica Nistér, Karolinska Institute, Stockholm, Sweden
- Anders Björklund, Wallenberg Center/ University of Lund, Sweden
- Ernest Arenas, Karolinska Institute, Stockholm, Sweden
- Alan Mackay-Sim, Australian National Adult Stem Cell Centre, Brisbane, Australia
- Yasuhiro Watanabe, Tottori University, Japan

Lothe-group
- Peter Andrews, University of Sheffield, UK
- Katherine McGlynn/Stephen Chanock, National Cancer Institute, National Institutes of Health, Bethesda, Md, USA

Myklebost-group
- Sendurai Mani, MD Anderson Cancer Centre Houston Texas, USA
- William Matsui and Jin Eshleman, Johns Hopkins University Hospital, Baltimore, Maryland, USA
- Marcel Karperien, University of Twente / Faculty Science & Technology, Enschede, the Netherlands

Mælandsmo-group
- Lars Åhrlund-Richter, Department of Woman and Child Health, Karolinska Institute, Stockholm, Sweden
- Ole W. Pettersen, Department of Medical Anatomy, The Panum Institute, University of Copenhagen
- Mina Bissell, Lawrence Berkeley National Laboratory, Berkeley, CA, USA
- Mark LaBarge, Lawrence Berkeley National Laboratory, Berkeley, CA, USA
- Elisabetta Marangoni and Paul Cotton, Curie Institute, Paris, France

Stenmark-group
- David Bilder, University of California, Berkeley, USA

Sørlie-group
- Ole W. Petersen, Department of Cellular and Molecular Medicine, The Panum Building, University of Copenhagen, Denmark

International research networks

Gaudernack-group
- Nordic Center of Excellence for Immunotherapy (http://www.cck.ki.se/ncev/).
- ACT consortium (Danish Research Council Strategy Grant)
- EU projects EUCAPS, ENACT, CIMT, CHILDHOPE and NANOMEDPART (ERA-NET).

Krauss-group
- EU network “targeted sequence alteration” (coordinator)

Myklebost-group
- EU network of excellence on bone tumours, Eurobonet.EU
- Network of Excellence, the EurocanPlatform

Stenmark-group
- EU research training network ”ENDOCYTE”
- European Science Foundation network ”Tracking of phosphoinositide pools”

National collaborations

Gaudernack-group
- Member of CEVI (Center for Vaccinology and Immunotherapy), Medical Faculty, University of Oslo

Glover-group
- Norwegian Stem Cell Center (leader)
- FUGE MIC platform, St. Olavs Hospital, Trondheim (Olav Haraldseth, Marte Thuen)

Krauss-group
- Centre for Molecular Biology and Neuroscience (CMBN)
- Norwegian Stem Cell Center

Lothe-group
- Sophie D. Fosså/Gustav Lehne, Division for Surgery and Cancer Medicine, Oslo University Hospital

Lundanes/Greibrokk-group
- School of Pharmacy, within the Bioanalytics@UiO platform, Faculty of Mathematics and Natural Sciences, University of Oslo
- The Norwegian School of Veterinary Science

Myklebost-group
- Heidi K Blomhoff, IMBA, University of Oslo
- Anders Sundan, NTNU, Trondheim
- Ellen Tenstad, Institute for Micro System Technology, Faculty of Science and Engineering, Vestfold University College
- Fuge Consortium on Nuclear Programming
- Norwegian Microarray Consortium
- Norwegian Stem Cell Center

Mælandsmo-group
- Anne-Lise Børressen-Dale, Department of Genetics, Institute for Cancer Research, Oslo University Hospital.
- Ingrid Gribbestad, Department of Circulation and Medical Imaging Norwegian University of Science and Technology
- Lars Akslen, Department of Pathology, Gade Institute, University of Bergen
- Daniela-Elena Costea and Anne Chr Johannessen, Department of Pathology, Gade Institute, University of Bergen

Stenmark-group
- Terje Espevik, Institute for Cancer Research and Molecular Medicine, NTNU, Trondheim
- Oddmund Bakke, Institute for Molecular Bioscience, University of Oslo

RECRUITMENT

Visiting scientists in 2009 include Dr. Björn Stork (University Hospital Tübingen), Dr. Greger Abrahamsen (Eskitis Institute, Australia), Dr Nick de Penington (Oxford University, UK), Dr. Andrew Voronkov (Moscow State University), Dr. Naomi Dunning (John van Geest Cancer Research Center, Nottingham Trent University).

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Victoria Edwards

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Petros Gebregziabher, Animal technician
Nomdo Westerdaal, Flow sorting technician
Menaka Sathermugathevan, technician

FUNDING AND COST

Statement of Accounts

Funding

The Research Council	The Norwegian Research Council	11 640
The Host Institution	Oslo University Hospital (Rikshospitalet) HF	6 179
Research Partners	University of Oslo	1 298
Enterprise partners	PCI Biotech AS	1 228
	Axellia Pharmaceuticals AS	0
	Invitrogen Dynal AS, in kind (lab supplies)	100
	Affitech AS, in kind	963
Public partners	Ullevål University Hospital	1 399
	Total	22 807

All figures in 1000 NOK

Costs

The Host Institution	Oslo University Hospital (Rikshospitalet) HF	15 587
Research Partners	University of Oslo	2 668
Enterprise partners	PCI Biotech AS	1 530
	Affitech AS	963
Public partners	Ullevål University Hospital	2 059
Equipment		0
	Total	22 807

All figures in 1000 NOK

PUBLICATIONS (2008-2010)

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REPORTS

Oslo Cancer Clusters magazine, December 2008 featured SFI-CAST " From cancer research to cure, Norwegian cancer research and development".

PATENTS

Two patents from Oslo University Hospital HF have been filed during the period:

- "Screen using selected cancer cells", UK patent, Application No. 0907514.4
- "Compounds", European Patent, Application No. 09251497.5

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