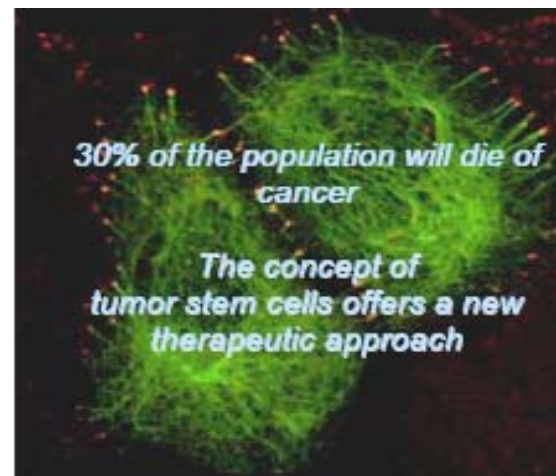


Annual report 2007

SFI - CAST

Cancer Stem Cell Innovation Center



Effective therapies for cancer patients require a thorough understanding of mechanisms leading to tumour development and drug resistance.



Summary

It has long been known that tumours contain heterogeneous cell populations with respect to growth kinetics, drug resistance, and metastatic potential. Advances in understanding pathways and mechanisms that determine stem cell ness open new possibilities for improved strategies within detection and treatment of cancer.

The CAST centre for innovation based research works towards:

- (i) The identification and characterization of cell populations (side-populations) enriched for cells with high tumorigenic potential.
- (ii) The development of innovative approaches for finding small drugs, cancer vaccines and antibodies that destroy specifically stem-like cancer cells.
- (iii) High resolution visualization of specific cell sub-populations in the body as a tool for tracking therapeutic success, and possible future diagnosis.

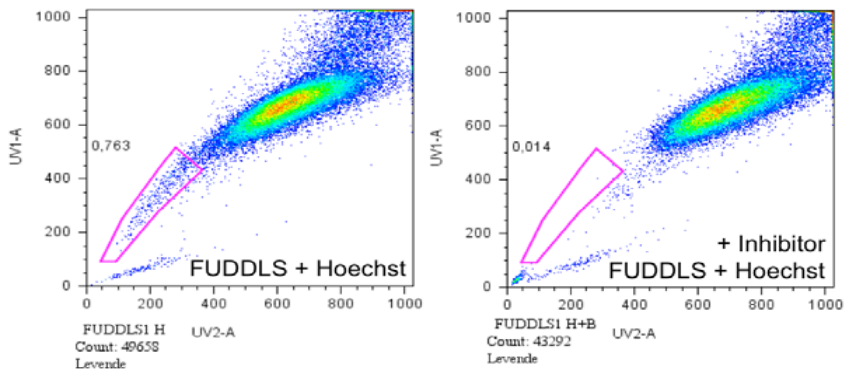


CAST – Vision and background

Effective therapies for cancer patients require a thorough understanding of mechanisms leading to tumour development and drug resistance. For many severe cancer types, including melanoma, glioblastoma, pancreas carcinoma and breast tumour, patients are given very aggressive treatments to improve their chances of survival. Unfortunately, these treatments often have serious side effects. Moreover, conventional treatments are often not even effective in fighting the most serious forms of these cancers.

Evidence suggests that at many tumours derived from cells with stem cell like character that function as the "root" of the tumour (TSC's). Therefore, substantial effort is done to understand stem cells, and to identify cells with TSC properties in cancer. By defining the biological properties of TSC's, highly targeted approaches to treating the roots of these cancers can be developed. There is now accumulating substantial evidence that this new approach could improve cancer therapy and reduce harmful side effects.

If parallels are drawn with normal stem cells one would expect that cancer cells in many tumours still follow hierarchical structures and thus develop heterogeneous population of cancer cells.



Side population in a mesenchymal tumour as determined by classical Hoechst stain exclusion (Myklebost laboratory).

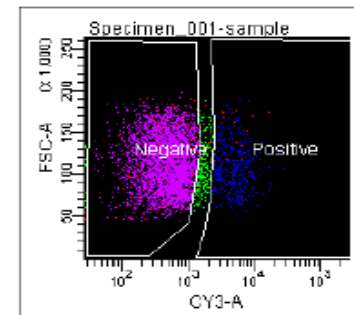


In particular, tumours, whether they are solid tumours (e.g., breast and lung) or hematological (e.g., leukemia), are predicted to be heterogeneous with respect to their cycling states. Cells that contain high proliferate potential but are in a reversible state of slow cycling – as frequently observed in stem cells – would easily escape traditional treatment.

Furthermore, depending on the status of various stem cell pathways that may be active in the tumour cells, tumour cells may be heterogeneous in the potential to metastasize. Thus, the molecular machinery used by normal stem cells for homing to or mobilizing from the niche may be "hijacked" by cancer stem cells for invasion and metastasis.

Recently it also got evident that the micro-environment of stem cells and cancer cells is important in understanding cancer and developing treatment. The stem cell niche in adult somatic tissues plays an essential role in maintaining stem cells or preventing tumour genesis by providing primarily inhibitory signals for both proliferation and differentiation. However, the niche also provides transient signals for stem cell division to support ongoing tissue regeneration. The balance between proliferation-inhibiting and proliferation-promoting signals is the key to homeostatic regulation of stem cell maintenance versus tissue regeneration.

CAST uses advanced stem cell understanding to develop new experimental therapeutic schemes for advanced cancer therapy.



Identification of cell cycle heterogeneity within a pancreas adenocarcinoma cell line creates a basis for advanced antibody and drug screens (Krauss laboratory).



CAST - strategy

The CAST innovation centre has a work program aimed at advancing from 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 tumour stem cells are identified (Affitech). The antibodies will be used to identify novel epitomes and therapeutic targets (Invitrogen).
- (i) Novel whole cell reporters that are capable of distinguishing molecular signalling in stem cells and tumour stem cells are developed.
- (i) Tumour stem cell pathways are used for differential high throughput screens that are coupled to combinatorial genetic platforms.
- (i) High cell resolution imaging of tumour stem cells *in vivo* using cutting edge magnetic resonance imaging (MRI) techniques is developed in animal models.
- (i) Ways to find improved immunotherapy protocols and targets are being explored and tested.
- (i) Antibodies are tested for improved therapeutic photo-internalization (Photo cure).

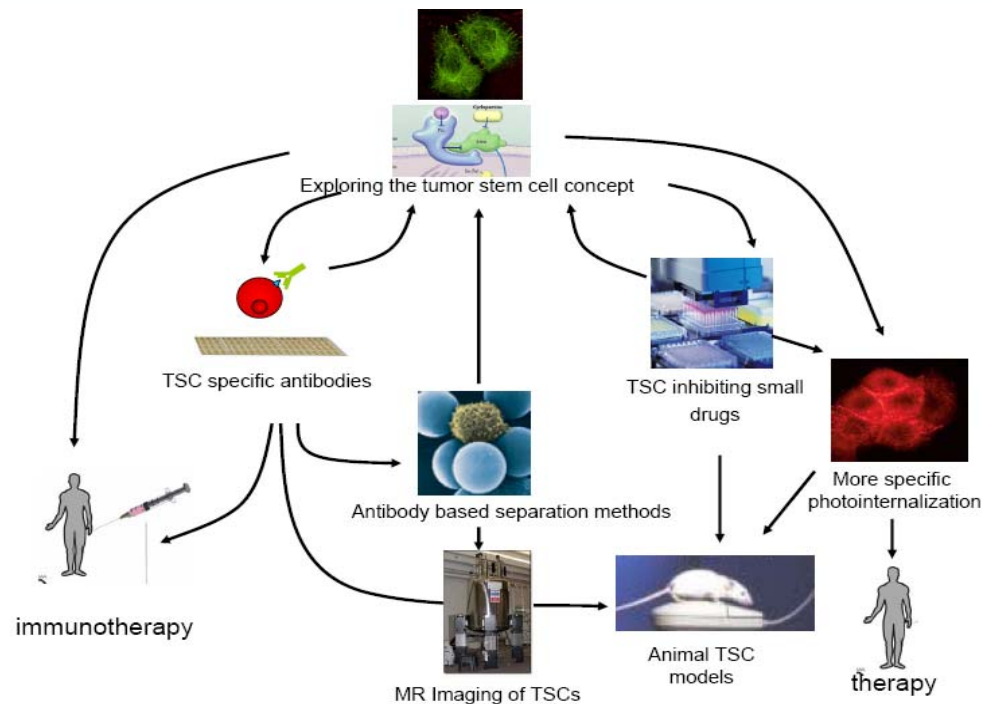


SFI-CAST hosted by Rikshospitalet-Radiumhospitalet (RH HF)



A major focus of the centre is translational research. Partners at the Radium hospital have been responsible for more than 20 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 TSC from the very beginning of the project.

This ensures a swift start of the translational aspect as well as provide clinical material for the below work programs. For all central tasks the consortium has substantial international networks, including EU framework networks and European Science foundation networks.



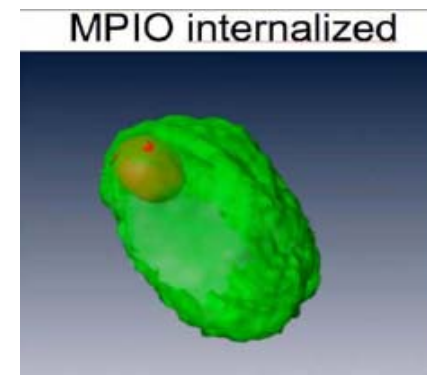
CAST- scientific activity2007

In 2007 CAST scientists have published 68 articles in international peer reviewed journals. A substantial number of these articles are in high impact journals.

CAST was established as a biomedical innovation center in June 2007. In the first project phase the main focus was in establishing the scientific and administrative infrastructure for the center.

Selected scientific milestones that were reached in 2007 are:

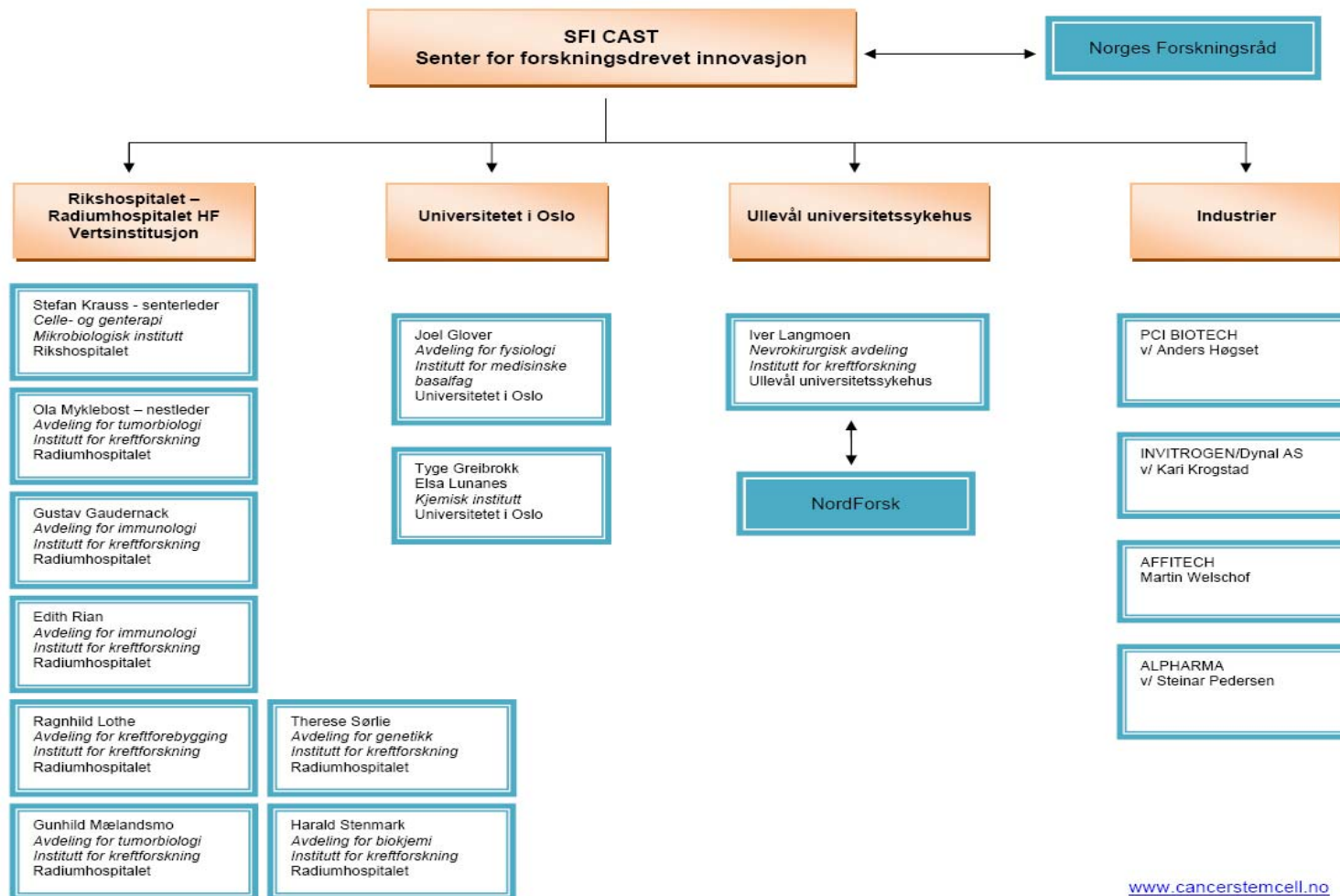
- Isolation and molecular characterization of various tumour stem cell populations
- Assay development for drug screening
- MPIO marking of tumour stem cell
- Stem cell/tumour stem cell pathway characterization
- Development of analytical tools



Glioblastoma cell marked with magnetic fluorescent beads (MPIO) (Joel Glover laboratory)



CAST- organization



www.cancerstemcell.no



CAST- academic and administrative staff

Administration

Karina Saksberg

Line Mygland

Peder H. Utne

Kassahun Zelleke

Pi Edith Rian

Else Munthe – postdoctoral

Nomdo Westerdal - cell sorter

Heidi Stubberud - cell sorter

Oleg Tsinkalovsky - cell sorter

Pi Stefan Krauss (centre chair)

Nina Solberg - PhD - student

Martin Strand – PhD - student

Ondrej Machon - postdoctoral

Olga Machonova – technician

Jennifer Dembinski – postdoctoral

Jo Waale – PhD - student

Pi Gustav Gaudernack

Ping Wang – PhD - student

Quanli Gao – postdoctoral

Pi Harald Stenmark

Pi Ola Myklebost (centre co-chair)

Hege Oma Ohnstad – PhD - student

Thea Sogn Smedsrud – engineer (over-)

Unn-Hilde Grasmø - postdoctoral

Russell Castro - engineer

Ingrid Østensen – engineer (over-)

Stine Kresse - postdoctoral

Eva Wessel Pedersen - postdoctoral

Leonardo Meza-Zepeda - postdoctoral

Pi Ragnhild Lothe

Rolf Skotheim - postdoctoral

Sharmini Alagaratnam - postdoctoral

Pi Iver Langmoen

Einar Vik-Mo - PhD - student

Cecilie Sandberg - PhD - student

Birthe Mikkelsen - engineer

Linda Paulsson – PhD - student

John Bianco – postdoctoral

Sandrine Pacchini – PhD - student

Pi Joel Glover

Doreen Leung - postdoctoral

Nedim Kasumacic - postdoctoral

Pi Gunhild Mælandsmo

Olav Engebråten - postdoctoral

Geir Olav Hjortland - postdoctoral

Lina Prasmickaite - postdoctoral

Evy Storeng - engineer

Trine Lillehammer – PhD - student

Hanne K. Høifødt - engineer

Kari A. Aaslund - engineer

Alexander Kristian - engineer

Thomas Halvorsen – engineer

Pi Tyge Greibrokk

Elsa Lundanes - postdoctoral

Sandra Rinne Dahl – PhD - student

Steven Wilson - postdoctoral

Helle Malerød – PhD - student

Pi Anders Høgseth

Pål Kristian Selbo - postdoctoral

Victoria Tudor Edwards - engineer

Kristian Berg – postdoctoral

Pi Therese Sørli

Anna Bergamaschi - postdoctoral

Anne-Lise B-Dahle - professor

Anita Langerød - postdoctoral



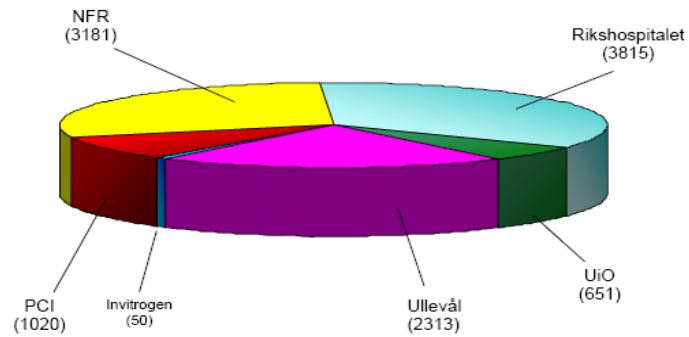
CAST- international cooperation and networks (excerpts)

- **Prof. Peter W. Andrews, Department of Biomedical Science, University of Sheffield, UK**
 - ✓ Comparison Embryonic Stem Cells and Testicular Cancer
- **Prof. Scott Fraser, California Institute of Technology, USA**
 - ✓ Small animal imaging (MRI)
- **Prof. William Matsui, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA**
- **Dr. Christiane Bruns, Klinikum Grosshadern, University of Munich, Germany**
- **Prof. Bengt Norden, Chalmers, Sweden (former chairman of Nobel commission chemistry)**
 - ✓ Sterols in changing membrane embedding of signal receptors
- **Prof. Ahmen El Zewail, California Institute of Technology, Pasadena, USA (Nobel price chemistry 1998)**
- **European Network of Excellence on Bone Tumours**
 - ✓ Bone Tumour biology, incl. Cancer stem cells
- **European Science Foundation EUROSTELLS program (coordination)**
- **Several Cancer/Stem Cell groups**
 - ✓ D Prof Horst Bürger - University of Münster, NL Drs AM Cleton-Janssen - University of Leiden, S Prof F Mertens - University of Lund
- **Meenhard Herlyn, Program of Molecular and Cellular Oncogenesis, The Wistar Institute, Philadelphia, USA**
- **Prof. Lars Åhrlund-Richter, Karolinska Institutet, Stockholm, Sverige**
 - ✓ Studies of embryonal imprinting of melanoma
- **Prof. Ole W. Petersen, Panum Institute, Denmark**
 - ✓ Stem cell hierarchy in breast, cell sorting
- **Prof. Mina J. Bissell, Lawrence Berkeley Laboratory, California, USA**
 - ✓ Microenvironment in normal and malignant breast development
- **Several medical chemistry groups in Berlin, Germany (Jörg Rademann, Jens Von Kries)**
 - ✓ Designing drug screens

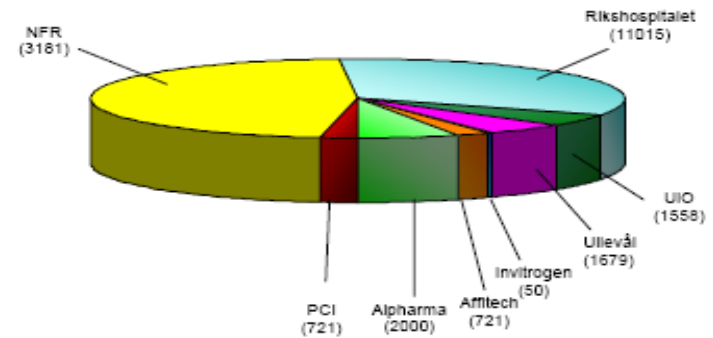


CAST-budget

Total budget 2007



Total budget 2008



CRI Annual Work Plan 2007 - FUNDING

Type of Partner	Item	Type of research	Revenue project	Revenue category	PCI	Acad	Other public	Other private	Multi-fund	University of Oslo	Ullevål hospital	Amtech	Alharma	Invitrogen	PCI	Total state aid	Total funding	State aid	Total funding
Project WP 1a	F	1111	1	2279	3 507					476	1877					2749	8136	0	8136
Project WP 1b	F	1111	0	0	0					0	0					0	0	0	0
Project WP 2a	F	1111	0	0	0					0	0					0	0	0	0
Project WP 2b	F	1111	0	0	0					0	0					0	0	0	0
Project WP 2c	F	1111	0	0	0					0	0					0	0	0	0
Project WP 3a	F	1111	0	0	0					175	430					587	1271	0	1858
Project WP 3b	F	1111	0	0	0					0	0					0	0	0	0
Project WP 3c	F	1111	0	0	0					0	0					0	0	0	0
Project WP 4a	F	1111	0	0	0					0	0					0	0	0	0
Project WP 4b	F	1111	0	0	0					0	0					0	0	0	0
Project WP 4c	F	1111	0	0	0					0	0					0	0	0	0
Project WP 5a	F	1111	0	0	0					0	0					0	0	0	0
Project WP 5b	F	1111	0	0	0					0	0					0	0	0	0
Project WP 5c	F	1111	0	0	0					0	0					0	0	0	0
Equipment																1000	367	1267	6000
Admin																312	312	0	624
Total budget										651	2313	0	0	0	1020	3422	10943	0	14365

CRI Annual Work Plan 2007 - Cost

Item	Cost	University of Oslo	Ullevål hospital	Amtech	Alharma	Invitrogen	PCI	Total
Project WP 1a	5123	540	2165					7828
Project WP 1b								0
Project WP 2a								0
Project WP 2b								0
Project WP 2c	626	360	576					1562
Project WP 3a								0
Project WP 3b								0
Project WP 3c								0
Project WP 4a								0
Project WP 4b								0
Project WP 4c							1267	1267
Project WP 5a								0
Project WP 5b								0
Project WP 5c								0
Equipment	312							312
Admin								312
Total budget	6076	900	2741	0	0	0	1267	10984



Presentation of the partners

Stefan Krauss

The laboratory for cell signalling focuses on Shh and canonical Wnt signalling in development, stem cells, and tumors. Since its discovery in 1993 (Krauss et al., Cell 75, 1431-1444) Shh has shown to be a central signal in numerous developmental systems. Hh and Wnt signalling play important roles in various tumours and in stem cells. The laboratory currently works on pathways that feed into Hh and Wnt signalling, and on ways of influencing pharmaceutically Hh and Wnt signalling.

Mælandsmo

The group is studying the impact of stem or progenitor cells for initiation and progression of breast cancer and malignant melanoma. In our studies we are utilizing either clinical material obtained directly from the patients, or human tumors grown as xenografts in nude mice. We are in the process of establishing optimized methods for preparing the tissue, isolating the tumor-initiating cell populations and cultivating the cells for maintenance of stemness characteristics and differentiation capability.

Tyge Greibrokk / Elsa Lundanes

We are developing highly sensitive and selective capillary LC-MS methods for potential novel drugs in different types of organs as liver, kidney, plasma etc, in cooperation with Stefan Krauss and his group, in order to determine if the drugs reach the target organs and for pharmacokinetic studies.

We are also developing miniaturized liquid chromatography methods for identification of proteins, especially membrane proteins, in cooperation with Iver Langmoen and his group. Novel separation technology in the nano-flow region will be explored for the ability to separate the hydrophobic membrane proteins.

On-line multidimensional capillary liquid chromatographic methods with mass spectrometric detection of peptides have already been developed for identification of the proteins.



Therese Sørli

Our research interests are in functional genomics and breast cancer. We are using DNA microarrays to study patterns of gene expression in clinical breast cancer samples. By using this technology in combination with statistical and bioinformatical tools, we have been able to identify specific patterns of gene expression that provided distinctive molecular portraits of breast tumors.

Ola Myklebost

The Mesenchymal Cancer Biology Group are studying sarcomas, malignant tumours with mesenchymal characteristics, and focus on osteo- and liposarcomas, as well as normal mesenchymal stem cells as model systems. Our CAST projects involve identification and characterization of stem-like cells in sarcomas, and the involvement of stem cell pathways in sarcoma development.

Harald Stenmark

Receptor signalling guides the maintenance and fate of stem cells and their progenitors, including renewal, proliferation and choice of differentiation pathways. Dysregulated receptor signalling is associated with oncogenesis and is probably a central cue in the development of cancer stem cells. Our group studies receptor signalling and how it is attenuated by endocytosis. In particular, we have been studying epidermal growth factor (EGF), a strong proliferative signal, and how EGF receptors become endocytosed and degraded after EGF binding. Ligand binding causes ubiquitination of EGF receptors, and we have identified and characterized a ubiquitin-binding endosomal machinery that recognizes ubiquitinated receptors in endosomes and mediates their sorting to lysosomes. Preliminary studies suggest that components of this machinery serve as tumour suppressors, and we are now performing further studies to characterize the functional mechanisms of endosomal sorting complexes in receptor downregulation and tumour suppression. As model systems we use cultured human cell lines as well as *Drosophila* models for cell signalling and oncogenesis. Confocal microscopy is central in our work, and in addition to characterizing stem cell relevant signalling pathways we will also contribute to the SFI project by characterizing the intracellular localization and trafficking of relevant cancer stem cell markers.



Edith Rian

We recently got a new laboratory in Radiumhospitalet. Anna Wennerstrøm has been employed as an engineer. We have bought a Flow cytometer (special made FACSria with 4 lasers) and this is now now running.

Our group has been identifying the factor of the transcription TIEG1, which is a possible mediator for TGFb/BMP6 and stroma mediated inhibitor of leukaemia cell dividing. This inhibitor is the reason why a larger part of leukaemia cells survive with cytostatika treatment. This task submits within June 1st, and will be presented (orally) at the European Hematology Association meeting in Copenhagen in June.

Furthermore we have showed that b-catenin is not passing on signals from Wnt16 in leukaemia cells with the translocation of E2A-PBX1. Instead, the b-catenin is connected to the N-cadherin mediated cell-cell adhesion. Until now this is the first time this type of interaction is shown for leukaemia cells. The connection between N-cadherin/b-catenin in adhesion of hematopoietic stem cells in the micro environment has been reported. This task is being submitted within June 15th.

Ragnhild Lothe

Germ cell tumors can develop in both males and females but are far more common among males. In fact, testicular cancer (usually of germ cell origin; TGCT) is the most common cancer type among young and adolescent males, and the incidence has almost quadrupled during the past 50 years. Pluripotent cells in TGCTs may differentiate along embryonic or extraembryonic lineages into various histological subtypes, and as such, the development of this cancer type is a caricature of the early embryogenesis. We and others have collected strong evidences for this also being the case for the transcriptional and epigenetic programs of these tumours. Genetic studies of embryonal stem cells and their adaptation to culturing have revealed striking similarities to genomic changes in the germ cell tumour genome, in particular embryonal carcinomas. By comparative studies of embryonic stem cells and *in vitro* cultures of their malignant counterparts, we aim to identify genes with malignancy-specific expression patterns in a stem cell context. The resulting markers will be functionally as well as clinically validated, the latter through the use of large patient series available in our department. Furthermore, the genes with malignancy-specific expression will be interrogated from profiles of isolated side populations from other tumour types, as obtained by the other consortium members.



Invitrogen Dynal

Dynabeads® which are magnetic polystyrene beads have revolutionized separation technology ever since their inception and can be used to separate both biomolecules and cells in countless scientific applications. They are especially known for their consistency based on their narrow size distribution.

As an industrial partner of the SFI consortium, Invitrogen Dynal is committed to provide its cell-isolation and analysis tools and know-how for all applicable needs of the other partners of the consortium. This includes generation of specific cell-isolation beads for cancer stem cells of different cancer origin by targeting unique markers that are being discovered within the consortium. We will also contribute to the *in vitro* culture of these cells with our custom-made cell-culture media, provide specific labeling tools for cancer stem cells based on our FACS dies just to name a few of our input.

Alpharma

Alpharma AS is one of the leading Norwegian biotech companies, with more than 50 years of experience in development and manufacturing of antibiotics. Alpharma is recognized for its expertise in fermentation and specialized recovery and purification technologies. During the later years, Alpharma has also established a solid platform in chemical synthesis and semi-synthesis. Alpharma's predominant role within CAST is to assist in industrializing new products developed by the SFI-members, both biologicals/fermentation based in addition to synthetic and semi-synthetic products. Furthermore, Alpharma will have particular focus on small, chemically synthesized molecules with a potential of interfering with signal pathways of cancer stem cells and will attempt to increase input of candidate molecules through collaboration with other companies.

Affitech

Affitech is still waiting for a suitable target cell population before we can start the work for the SFI CAST project. Once the work is started one whole project will take 2-3 full-time scientists (depending on the complexity of the target population) and 1 full-time senior scientist (Ph.D.) for 1 year and 4 months (timeline also depending on complexity of the project).



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