Biomarkers of success

The Centre for Cancer Biomedicine has made great progress in analysing biomarkers for cancer in just a few years. Co-Directors, **Professors Harald Stenmark** and **Ragnhild A Lothe**, explain the Centre's achievements using state-of-the-art technology and hopes for expanding its work in the future






ADDITIONAL PRINCIPAL INVESTIGATORS: ERLEND B SMELAND, KIRSTEN SANDVIG, HÅVARD E DANIELSEN AND KNUT LIESTØL

Could you provide a brief overview of the history and remit of the Centre for Cancer Biomedicine (CCB)?

HS: CCB was established as a Norwegian Centre of Excellence four years ago. The background for establishing the Centre was that the research environment at the Norwegian Radium Hospital, a major cancer clinic, housed several strong research groups within patient-orientated and basic cancer research. We reasoned that if these research groups could be successful on their own, collaborations across the disciplines integrated with the clinic would stimulate further progress and be beneficial to future cancer diagnosis and therapy. It was also essential to team up with experts in advanced biostatistics and informatics. The joint efforts have already generated results that are very encouraging for further development of cancer diagnosis and therapy.

What progress have you made in your programme to investigate the functional analysis of potential biomarkers in cancer?

RL: During this first period of the Centre we have used the majority of our time to identify new and potentially useful biomarkers from integrative analyses of high resolution genome wide datasets. Just recently we have been able to start functional studies for the most promising biomarkers. One example of this is the SPG20 gene, which serves as a very good biomarker for early detection both of benign and malignant lesions in the large bowel. Harald's group showed a new function of the encoded Spartin protein relevant for the cytokinesis process of the cell cycle. This joint study was published in the Spring edition of *Oncogene*. It is also important to bear in mind that a useful diagnostic biomarker does not necessarily have important functions in the cell, but if this is the case, detailed knowledge is of particular importance to the development of new drugs and their use in cancer treatment.

Could you elaborate on your studies to produce advanced bioinformatics and develop novel imaging tools for cancer research?

HS: With state-of-the-art technology it is possible to determine the numbers and activities of thousands of genes in tumour biopsies, and we can even perform DNA sequencing at high throughput. Such analyses are extremely useful for identification of potential prognostic and diagnostic markers in cancer, but they create enormous amounts of biological information. In order to make sense of such data it is essential to team up with bioinformaticists and biostatisticians who can extract meaningful patterns and valid conclusions out of complex datasets.

On a similar note, our experiments also include microscopic analyses of cancer cells and tissues, and retrieving quantitative data from many images again requires the skills of informaticians and statisticians. We are fortunate enough to have extremely competent researchers of these categories within our Centre, and besides using existing tools for high-content analyses they are also developing novel tools ranging from automated analyses to web-based computer programmes.

What are the most common obstacles that you encounter in translating basic research

Strength in numbers

The **Centre for Cancer Biomedicine** in Oslo, Norway works alongside national and international collaborators, including young researchers, to foster understanding of the development of cancer diseases to improve diagnostics and treatments for the future benefit of patients

into advanced biomedicines for cancer patients? How do you overcome these difficulties?

RL: In R&D, the Development stage is a challenge. First, it is more difficult to obtain funding for the development of good research data or ideas than it is for the research projects themselves. Often the researcher has to contribute or even be responsible for the project development and raise funding for this, typically by grant applications. This is a challenge when time is a key issue in competitive fields.

How do you see the function and remit of the CCB evolving in the future? Are there any elements of your work or facilities that you are keen to develop?

HS: It is our ambition to develop CCB into a centre that makes major footprints in cancer biology and medicine. On the technological side, we are investing heavily in technologies for high-throughput genetic analyses, high-throughput analyses of cell signalling, and detailed microscopic analyses of cancer cells and tumours. Even though our research is hypothesis- and discovery-driven rather than technology-driven, it is clear that state-of-the-art infrastructure is going to be instrumental to our future success.

RL: We have a pool of very talented young scientists who will contribute with new ideas and to accomplish at least part of our initially set goals. We foresee national efforts to improve individual cancer diagnostics by extended use of new deep-sequencing technology similar to initiatives in other European countries, and researchers in CCB may contribute to such a project.

THE WELL-KNOWN PROVERB 'two minds are better than one' encapsulates how collaboration can enhance the problem-solving process. When it comes to treating complex diseases such as cancer, the research needs to be as diverse and multifaceted as the disease itself. At the Centre for Cancer Biomedicine (CCB) in Oslo, over 100 of the best minds are working together to generate a better understanding of cancer from beginning to end – from prevention and early detection to developing new tools for treatment.

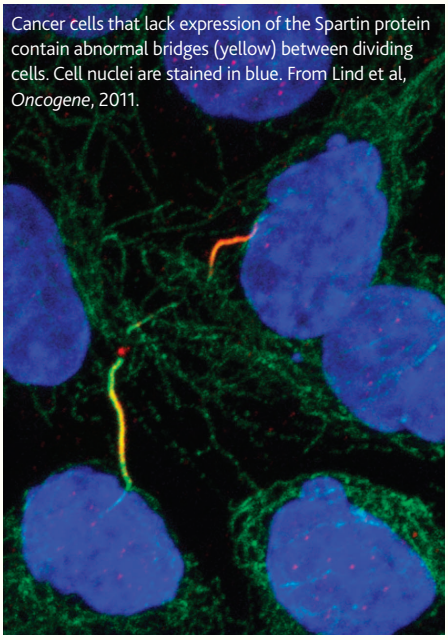
Founded in 2007, the CCB is an offshoot of the Norwegian Radium Hospital, the largest cancer centre in Northern Europe, also located in Oslo. The CCB functions as an academic centre under the University of Oslo, which means a combination of basic biological research and research of immediate clinical interest is being done, with some of its research teams leading international efforts to study cell signalling, cell division and intracellular trafficking.

Collaboration is taking place between cell biologists, geneticists, immunologists, informaticians and statisticians within the centre. The Centre's multidisciplinary work has already proven fruitful and is responsible for the identification and functional characterisation of a novel potential biomarker in colorectal cancer. Researchers have also located novel regulators of cell division and performed analyses of clonal evolution of follicular lymphoma – discoveries which could be applied to future cancer diagnostics and therapies. Professors Harald Stenmark and Ragnhild A Lothe, Co-Directors of the CCB agree that this multi-pronged approach is key to the Centre's progress: "Intersections between such basic biological research and patient-orientated research within CCB have already provided exciting results and one of the strengths of our Centre is that we are able to dissect cancer development at multiple levels, from molecules to cells to patients".

INNOVATION TARGETS

The Centre's work focuses on grasping the intricacies of the evolution of cancer and improving the ability to accurately predict the disease as well as a patient's response to treatment. To achieve this, research is divided into four programmes. The first of these covers genomic and epigenomics, meaning scientists working in this area seek to identify biomarkers with the potential of revealing cancer. By using relevant model systems and clinical samples to gain a better understanding of the dynamics of cancer progression, biomarkers have already been detected for different cancers. This work is taking place alongside the international NIH-directed Lymphoma/Leukemia Molecular Profiling Programme, in which Erlend Smeland at CCB is the site PI. Th CCB lymphoma group has recently published in the journal *Blood* a longitudinal study describing genetic changes in individual patients over time.

Furthermore, a group of scientists at the CCB are dedicated to unravelling the biological functions of potential cancer biomarkers and how they influence cell growth and migration. These investigations have the potential to lead to more accurate predictions of cancer prognosis and response to treatment. For example, DNA ploidy measurements by image cytometry are



Cancer cells that lack expression of the Spartin protein contain abnormal bridges (yellow) between dividing cells. Cell nuclei are stained in blue. From Lind et al, *Oncogene*, 2011.

CENTRE FOR CANCER BIOMEDICINE

OBJECTIVES

Centre for Cancer Biomedicine, a Norwegian Centre of Excellence with 120 members from 16 nationalities, unites basic and patient-orientated cancer research. The CENTRE'S vision is to develop novel tools and biomarkers for improved diagnostics and treatment of cancer, based on cutting-edge science and innovation approaches.

KEY COLLABORATORS

Division for Cancer, Surgery and Transplantations, Oslo University Hospital, headed by **Sigbjørn Smeland** • Lymphoma/Leukemia Molecular Profiling Project, coordinated by **Louis M Staudt**, NIH, Bethesda, USA • **Oslo Cancer Cluster – Norwegian Centre of Expertise** • **Professor Manuel R Teixeira**, Portuguese Oncology Institute, Porto, Portugal • **Professor Bo van Deurs**, Panum Institute, Copenhagen, Denmark

FUNDING

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Centre of Excellence Award 12.5 MNOK • The Research Council of Norway 7.9 MNOK • The Norwegian Cancer Society 17.4 MNOK • South-Eastern Norway Regional Health Authority 9.5 MNOK • International Sources 9.1 MNOK • University of Oslo 5.8 MNOK • Oslo University Hospital 24.5 MNOK • The Radium Hospital Foundation 0.6 MNOK

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CCB: CUTTING-EDGE SCIENCE FOR CRITICAL CANCER CARE

Director Harald Stenmark, cell biologist, and co-director Ragnhild A Lothe, geneticist, lead the Centre for Cancer Biomedicine, work with principal investigators Erlend Smeland, Immunologist, Håvard E Danielsen, informaticist, Kirsten Sandvig, cell biologist, and Knut Liestøl, statistician. They systematically build bridges between their fields of expertise to speed up novel scientific discoveries and transfer these into the cancer clinic.

Norwegian Centre of Excellence
Centre for Cancer Biomedicine

developed by the Håvard Danielsen group and are in use in the clinic to predict risk for relapse of ovarian cancer. These analyses have shown remarkably similar prognostic data for prostate and colorectal cancer, and the same group is in the process of launching 'Nucleotyping' as a prognostic tool, which is based on advanced computerised analyses of the tumour nuclei. According to Lothe, more accurate predictions for cancer prognosis and treatment responses are at the heart of the Centre's objectives. She explains this work in further detail: "We combine the use of well established methods in the clinic and apply them onto large and well-designed clinical studies to obtain conclusive results, with state-of-the-art technologies that allow new approaches towards the aim of improved personalised cancer care".

The Centre has pinpointed the development of affordable tools for advanced bioinformatics, imaging and early detection and tailored treatment as the focus of another research programme. From the start, the CCB has focused on early detection of colorectal cancer, for which they have developed a low-cost epi-marker panel based on hypermethylation (a type of chemical modification) at the regulatory regions of specific genes. "Obviously the high incidence and mortality of this disease implies that such findings have innovation potential and collaborative efforts with biotech companies are ongoing," Lothe points out. Another innovative piece of technology developed at the Centre is a proprietary microarray tool. The invention has dual applications: first as a research tool and secondly as a diagnostic tool for cancer diseases. However, further work still needs to be done to refine the tool before it can be used more widely.

Several patents have been issued to developments conducted by the Centre, covering a wide range of applications. "We hope that commercial tests beneficial for the cancer patient will eventually be developed based on our research data," Lothe adds.

MOMENTUM FOR THE FUTURE

The work at the CCB is done in collaboration with a number of international organisations and researchers, which has played a vital role in increasing access to advanced data and tools,

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for example through their involvement in the European Science Foundation Project entitled 'Tracking of Phosphoinositide Pools'. The Centre has established a longstanding partnership with the Portuguese Oncology Institute, whose Research Director, Manuel R Teixeira, currently serves as a guest professor in the Centre. "Such collaborations also have a financial upside, and they facilitate our training of young researchers through personnel exchanges," Stenmark adds.

Another way for the CCB to maximise the impact of its research is through dissemination of findings. Their work has been published in several international research journals and their study into prognostic classifiers for colorectal cancer is expected to be published shortly. As well as regularly updating their website, the Centre utilises other forms of mass media to spread word of their progress to the wider community. A recent partnership with the Oslo Cancer Cluster (a Norwegian Centre of Expertise) promises to offer another valuable showcase for their work and ideas through the Cluster's national and international meetings, where one of CCB's PIs, Professor Kirsten Sandvig, will travel to Toulouse, France to present a lecture on drug uptake.

The Centre also hosts its own annual seminars. This year's event will showcase the exemplary results of the Centre's mid-term evaluation conducted by the Research Council of Norway, who awarded the highest possible score to the CCB. This success will provide the CCB with Centre of Excellence support from the Research Council for the next six years. The seminar will also mark CCB's 4th anniversary, and will be an opportunity for reflection and assessment of future goals. Additionally, a special focus will be placed on the vital contributions garnered from collaboration across the disciplines and working with young scientists have played in the Centre's success.

The Norweigan Radium Hospital (left) and the Institute for Cancer Research (right) are joined by a bridge known as 'the translational bridge'. Image courtesy of Jarle Bruun.