Midterm Evaluation

A - The Centre Self-evaluation

K.G. Jebsen Center for Breast Cancer Research

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- <Name of the host department: Institute for Cancer Research, Department of Genetics
- <Project period: 01.10.2011 – 31.12.2015

The Report is prepared by the director and co-director in close collaboration with the members of the management team and all group leaders.

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1. Objectives

The overall aim of the research Center as stated in the contract/project-description is to open up for stronger collaboration between its clinical and basic scientists, and to motivate exchange of ideas on how to best utilize the huge collection of patient materials and data generated for the benefit of the patients. By such synergism we will be able to explore genes/pathways/networks involved in basic processes like cell cycle, DNA repair, apoptosis, and immune response and their impact on breast cancer (BC) development, progression and response to therapy. By performing longitudinal studies of samples at different stages of the disease and characterize such patient materials in full molecular details, we aim to develop more individual treatment protocols.

The specific aims of the Center are to:

- Develop validated stratification criteria based on phenotypic/genotypic profiling of breast tumors.
- Use validated phenotypic and genotypic stratification criteria for assessing individual response and prognosis in patients with breast cancer
- Identify molecular pathways and biomarkers predicting treatment response and/or resistance using cell lines and orthotopic xenograft models representing the various subgroups of breast cancer
- Translate and validate molecular and imaging biomarkers from preclinical models into clinical trials

2. Brief summary

The project utilizes a number of previously and newly collected clinical cohorts (outlined in Figure 1) and consists of several well integrated activities: 1) High throughput molecular characterisation of primary tumors; 2) Detection and characterization of occult tumor cells in bone marrow (BM) (DTC), blood (CTC) and sentinel lymph nodes (SLN) as well as detection of cell free tumor DNA (ctDNA) in blood as a new development; 3) Functional studies in experimental model systems; 4) Metabolic and physiological characterization and 5) Data integration.

The following results are highlighted:

- In primary tumors data of miRNA, mRNA and copy number variation (CNV) were generated and are in the process of being integrated with the clinical data for the first set of 450 cases of Oslo2 and all included patients in the Oslo3 (NeoAva) study. Deep sequencing of selected samples have identified newgenes involved in breast cancer, and novel mutational processes that evolve across the lifespan of a tumor, with cancer-specific signatures of point mutations and chromosomal instability often emerging late but contributing extensive genetic variation. A new cohort (OsloVal) with long term follow up was analysed and the data used as the main validation cohort in a worldwide computational competition to predict outcome.
- Single DTCs from two breast cancer patients were analysed by single-cell array comparative genomic hybridization (SCaCGH) and next-generation sequencing following whole-genome amplification based on methods developed in this project. Comparing copy-number profiles of the DTCs and the corresponding primary tumor generated from sequencing and SNP-comparative genomic hybridization (CGH) data revealed tumor clonality and DTC cell diversity, respectively.
- Our current results support the potential use of DTC analysis for monitoring purposes during follow up for selection of patients to secondary treatment intervention within clinical trials.
- A method for *in-situ* RNA expression in DTCs (by Quantigene ViewRNA) is established.
- Within the Oslo2 early breast cancer observational study, approximately 1000 patients have been analysed for DTCs/CTCs. The results of these analyses compared to primary tumor characteristics and outcome are pending.
- Heterogeneity in primary tumors is studied by an advanced *in-situ* technique for detection of molecular alterations down to the single cell levels using specific probes for tumor specific DNA rearrangements, transcripts (RNA) and proteins, making it possible to visualize molecular abnormalities with regard to tissue architecture. Novel software was developed and applied to a series of HER2 positive tumors neoadjuvantly treated with HER2 targeted therapy.

- A proof of principle detection of cell-free tumor DNA (ctDNA) in blood has been performed using several sensitive methods including targeted massive parallel sequencing and digital PCR.
- Orthotopic xenograft models have been established and tumor physiology, molecular and metabolic parameters have been characterized. The xenografts have been utilized for assessment of therapeutic effects and for identification of biomarkers predicting response to anti-angiogenic treatment in combination with cytotoxic therapy.
- Drug screens have been performed in order to study whether identified miRNAs modulate the response to HER2-targeted therapy and to identify drugs that can sensitize resistant cells to HER2-targeted therapy, - and miRNAs targeting HER2, B7-H3 and S100A4 have been identified
- More than 300 tumor tissue samples from the Oslo 2 study have been subjected to HR MAS MRS and four distinct metabolic subgroups were identified. The data have been combined with transcriptomic and proteomic data from the same patients to statistically evaluate relationships between metabolic profiles and molecular subtypes of BC.
- Combined analyses of the molecular data generated in Activity 1 (CNV, mRNA and protein expression), and Activity 4 (metabolic profiles and imaging) point to biological functions and molecular pathways being deregulated in multiple cancers, and will be used to identify novel patient subgroups for tailored therapy and monitoring.

Series	No	Mouse models	Healthy breast	Benign	DCIS	Small invasive	Invasive	Adv. stage	Blood	Tissue	Other
MDG-N	120								X, G, S	E	C
MDG-T	66								X, G, S	E	C
MicMa[1]	123								X, G, S	E	C, CTC, DTC
Oslo2	1500								X, G	X, E	C, CTC, DTC
AHUS	131								X, G	X, E	C
MAM04	450								X		RT
NeoAva	144								X,G,S		C, T, CTC, DTC
OsloVal	184								X	X, E	C
Oslo1[1]	903[2]									FFPE	C, CTC, DTC
NeoTax	236								X	X, T	C, CTC, DTC
HER2	40									FFPE	C, T
SATT	1121									FFPE	T, C, DTC
I-BCT[3]	160[3]								X[4]	X, T[4]	C[4]
MetAction	11[5]									X	C
Xenografts	7									FFPE	C

Figure 1: Clinical cohort related to stage of breast cancer development and tissue/information available. X: Blood/ fresh frozen tissue available. G: Genotyping, S: Glycan profiling, E: Gene expression profiling, C: Clinical information, T: Treatment (chemo), RT: Radiotherapy, CTC: Circulating tumor cells, DTC: disseminated tumor cells, FFPE: formaling fixed paraffin embedded. [1]MicMa is part of the 865 patients with localised breast cancer included in Oslo1. [2]Localised breast cancer (n=865) and DCIS (n=38).[3] The I-BCT study will start Q2/3 2014. Planned number to be included.[4]To be collected. [5]Brain metastases – inclusion ongoing (the "N-of-1" trial (starting Q2 2014) will include an uncertain number of breast cancer patients)

3. Research

Activity 1. High throughput molecular characterisation of primary tumors.

The first half of the project period was used for accumulation of patient material, isolation of DNA, RNA and protein, and the laboratory work on high throughput molecular analysis at all levels: somatic DNA copy number alterations (CNA), DNA methylation, mRNA expression, miRNA expression and protein levels by RPPA (reverse phase protein analysis). Data analyses integrating miRNA, mRNA and CNA

using various statistical methods are ongoing for the first set of 450 cases (see activity 5). These analyses include integrative clustering, functional characterisation of abrogated pathways (PARADIGM) and PAM50 classification. Following the discovered cytokine signalling by PARADIGM, we used another bioinformatic tool, Nanodissect, to *in silico* identify signatures of specific immune cells: B cells, Th1 cells, Th2 cells, T17 and CTLs (Dannenfelser et al, manuscript). We used this technique to also identify differential enrichment for these cells in tumors with TP53 mutation (Quigley et al, manuscript). The effect on miRNA on the translation from mRNA to protein has been explored and manuscript is duly submitted (Aure et al. manuscript). DNA from blood leukocytes has been isolated and genotyped for the SNPs in the International Breast Cancer Association Consortium http://ccge.medschl.cam.ac.uk/research/consortia/icogs.

Samples from several cohorts have been analyzed at noumerous molecular levels, including deep sequencing, both in our own lab and in collaboration with international partners. These studies have identified new genes involved in BC, and we could show that novel mutational processes evolve across the lifespan of a tumor, with cancer-specific signatures of point mutations and chromosomal instability often emerging late but contributing extensive genetic variation. Subclonal diversification was prominent, and every tumor studied had a dominant subclonal lineage, representing more than 50% of tumor cells. These studies have resulted in several publications (Stephens et al, Nature 2012, Nik-Zainal S. et al, Cell 2012, Nik-Zainal S, van Loo P et al, Cell 2012) and data integration is on the agenda.

In the Oslo3 study of neoadjuvant effects of the antiangiogenic drug bevacizumab (NeoAva), DNA and RNA have been isolated from the primary tumors and we have finalised the lab work for 3 molecular levels from the entire patient set (n=150) (miRNA, mRNA and CGH). DNA methylation analysis is ongoing in the lab. The clinical data has been collected and the BC patients evaluated for response or resistance to bevacizumab. An advanced SNP-CGH analysis is applied to identify the subclones and their dynamics in the course of the treatment. These results were presented at the San Antonio meeting in 2013. Data analysis and extraction of endpoints with clinical significance will be the main priority in the upcoming 2014.

Cell-to-cell variation within the primary tumor is acknowledged to be substantial for some patients. Estimation of intratumor heterogeneity by ImmunoFISH has been performed on 40 patients with HER2-positive tumors. The method was established in collaboration with K. Polyak, Boston USA and is published this year (Almendro et al. Cell Reports 2014). As anti-HER2 treatment was given in a neoadjuvant setting, tissue biopsies taken before and after the treatment have been analysed. The preliminary results show that patients that did not respond to therapy had an increased diversity prior to treatment, and for several cases a clonal selection occurred during therapy. In a collaboration with F. Markowitz, Cambridge UK, we have developed a software program for analyses of such complex three-dimensional images. The software will be published this spring, as will the result from studies of the HER2 cohort.

Activity 2: Detection and characterization of occult tumor cells in bone marrow (BM) (DTC), blood (CTC), cell-free tumor DNA (ctDNA) and sentinel lymph node (SLN).

A single-cell array high-resolution comparative genomic hybridization (SCaCGH) method providing molecular aberration profiles of immunomorphologically detected circulating tumor cells (CTCs) or disseminated tumor cells (DTCs), has been developed (Mathiesen et al. IJC 2012). Furthermore, we have now performed whole-genome amplification and subsequently next-generation sequencing of single DTCs from the first two breast cancer patients, and compared copy-number profiles of the DTCs and the corresponding primary tumor generated from sequencing and SNP-comparative genomic hybridization (CGH) data, respectively. This study provides a proof-of-principle for sequencing of DTCs and allows insight into tumor cell dissemination and copy-number evolution in DTCs compared to the primary tumors (Møller et al., Frontiers in Oncology 2014). Currently, 30 additional single DTCs from 6 patients are analyzed with the same technique. As a complementary approach to measure presence of tumor at a sub-clinical level we have established sensitive and robust methods for detection of cell-free tumor DNA in peripheral blood and bone marrow plasma. We have performed digital PCR analysis for 10 Oslo2 patients and estimated ctDNA. We have also established targeted massive parallel sequencing for detection of DNA copy number alterations, and are now testing multiple different

targeted approaches aiming at a novel method that has a high sensitivity for detection of both point mutations, copy number alterations and structural DNA changes.

In the NeoTax study, CTCs and DTCs were analyzed prior to, at the completion of, and 1 year after neoadjuvant chemotherapy (NACT) for locally advanced breast cancer. The results showed that especially presence of DTCs after NACT indicated high risk for relapse and death (Mathiesen et al. BCR 2012). These results will now be followed by analysis of ctDNA at all three time points. The primary tumors are now characterized by genome wide massive parallel sequencing by our collaborators P.E Lønning, Bergen and M. Stratton, Cambridge UK. Knowing the mutation specter of every patient will enable us to tailor the search for ctDNA in a patient specific matter. Analysis of the first 90 patients in the Oslo3/NeoAva study for presence of DTCs (by immunocytochemistry), CTCs (with the CellSearch System) and circulating endothelial cells (CECs) before, during and after neoadjuvant treatment +/- bevacizumab has been performed. The results are currently being up-dated before final analyses of the CTC/DTC/CEC-status and -change as a marker of treatment response. As tumor biology may affect the morphology of tumor cells, a morphological analysis of immunostained DTCs was performed in the Oslo1 study. The results showed that clinically significant DTCs have different morphological appearance according to breast cancer subtypes (Synnestvedt et al., BREA 2013). An intervention study (SATT) based on use of docetaxel secondary adjuvant treatment of patients with presence of DTCs after completion of adjuvant FEC chemotherapy, show that about 75% of the DTC positive patients experience DTC disappearance after docetaxel (Synnestvedt et al., BMC Cancer 2012), and preliminary results indicate a markedly improved outcome for these patients. Further characterization of the DTCs (expression of M30 and Ki67) is planned in this study. The method has been established in model system. A method for *in-situ* RNA expression in DTCs (Quantigene ViewRNA) has also been established. Within the Oslo2 study, so far approximately 1000 patients have been analysed for DTCs/CTCs. The results of these analyses compared to primary tumor characteristics and outcome are pending. A gene expression primary tumor signature predictive of the presence of CTCs, has also been detected (Molloy et al PLoS One, 2012).

Activity 3: Model systems and functional studies

Model systems: Access to preclinical model systems representing the different subclasses of BC is of crucial importance to study molecular and physiological features involved in cancer development and progression, and to evaluate new treatment modalities. We are now equipped with orthotopic xenograft models representing the main subclasses of the disease (basal-like, luminal-like and HER2-amplified). The models have been characterized by histological and physiological parameters utilizing magnetic resonance imaging (MRI) and positron emission tomography (PET) (Huuse et al, 2012; Kristian et al, 2013), and also by metabolic profiling using high-resolution magic angle spinning MR spectroscopy (HR-MAS MRS) (Moestue et al, 2010; Grinde et al, 2014). The models resemble the clinical situation and constitute an extremely valuable resource for preclinical evaluation of classical and novel drug/drug combinations.

In an experimental set-up resembling the Oslo3 / NeoAva clinical protocol, the effect of doxorubicin in combination with bevacizumab was investigated and we demonstrated that MR-imaging could be used for early assessment of response (Lindholm et al, 2012, Moestue et al, 2013). The benefit of anti-angiogenic therapy in BC is debated, and in attempts to identify predictive biomarkers tissue from the xenografts has been subjected to multilevel molecular characterization (Borgan et al, 2012). Inhibition of the PI3K/AKT/mTOR pathway was suggested to sustain the anti-angiogenic effect in the basal-like model - a combination that was found promising when tested in vivo (Moestue et al, 2013; Lindholm et al, 2013).

Response monitoring allowing optimal scheduling of anti-angiogenic treatment when given in combination with cytotoxic therapy may have great clinical impact. Dynamic PET depicts the distribution of labelled glucose and may reflect treatment-induced responses on tumor vasculature and metabolism. We have demonstrated that anti-angiogenic treatment result in reduced perfusion and metabolism, and enhanced growth retardation was obtained when the drugs were given simultaneously compared to delayed administration of the cytotoxic drug (Kristian et al, 2013). Thus, dynamic PET is a non-invasive method useful for assessment of vasculature and physiology during cancer therapy, and may add valuable information for optimization of person-adapted treatment protocols.

Functional studies: miRNA screens were used to identify HER2 targeting miRNAs, and by gene expression profiling we identified which genes and pathways these miRNAs target. miRNAs negatively regulating the HER2 pathway may open new strategies for therapeutic inhibition of HER2-positive BC (Leivonen et al, Molecular Oncology 2013) and sensitization screens with lapatinib and trastuzumab were therefore performed (Leivonen et al, in preparation). Furthermore, drug screens with a library containing FDA approved drugs were utilized to identify drugs able to sensitize resistant cell lines to trastuzumab and lapatinib. Dasatinib was identified as the most promising candidate, and *in vivo* experiments evaluating the combination have been initiated (Sahlberg et al, in prep). Promising effects have also been observed by the use of an Akt inhibitor in cells that do not respond to HER2 targeted treatment (Jernstrøm et al, submitted). miRNAs screen to identify regulators of the metastasis-promoting proteins B7-H3 (Tekle and Kveine et al, British Journal of Cancer, in press) and S100A4 has also been performed with the aim of unravelling novel targets for anti-metastatic therapy. We have demonstrated that multiple inflammatory cytokines are induced in cancer cells subjected to S100A4 (Bettum et al, 2013) and S100A4-stimulated BC cells promote differentiation of tumor supportive M2 macrophages (Tenstad et al, in prep). Our hypothesis is that S100A4 is involved in forming a growth-permissive environment allowing growth at the metastatic site.

Activity 4: Metabolic and tumor physiological characterization by MR

Tumor tissue samples from 300 patients the Oslo 2 study have been analyzed by HR MAS MRS, and the resulting metabolic data have been statistically combined with gene expression data and reverse phased protein array (RPPA) results from the same patients to determine the relationship between metabolic profiles and molecular subtypes of BC. Four distinct metabolic subgroups of breast carcinomas were identified. The results have been submitted as an abstract to the ISMRM 2014 conference in Milan. Further work will now focus on defining metabolic subgroups within the genetic subtypes, and further identify how the genes are differentially expressed in these subgroups. Furthermore, the results will be combined with clinical data in order to detect frequencies of traditional prognostic and predictive factors within the clusters. Serum samples from the NeoAva/Oslo3 study were analysed and the metabolic profile of >400 samples has been characterized by high resolution MRS. Data analysis of the resulting metabolic profiles is ongoing. HR MAS analyses of the corresponding tumor tissue samples from the same NeoAva/Oslo3 patient cohort are in process, and so far 196 tumor tissue samples have been analyzed. Approximately 175 remaining samples will be analyzed by February 2014, and will be included in the multilevel data analysis in collaboration with the Chemometrics group at Radboud University Nijmegen, the Netherland.

Activity 5: Data integration.

Cancer involves dysregulation of key biological processes and pathways in the cells, and the aim of Activity 5 is to reveal the mechanisms of this dysregulation. This may then be used to identify potential molecular prognostic and predictive markers, as well as therapeutic targets applicable to selected patient subgroups. Statistical and computational analysis of the data generated in Activity 1 play a major role in this enterprise, and the fact that these span multiple molecular levels (including e.g. sequence alterations, DNA copy number, DNA methylation, miRNA expression, mRNA expression and protein expression) substantially increases our power to detect relevant deviations. For example, in a recent study (Aure et al, 2013, Genome Biology) we demonstrated that several miRNAs - molecules known to be involved in pathway dysregulation in cancer - can be affected by both DNA methylation and DNA copy number alterations. In other recent studies (Enerly et al, 2011 and Tahiri et al 2013), we showed that key genes are likely to be dysregulated by several miRNAs (either alone or in concert) in both invasive but also benign tumors. This suggests that joint and possibly coordinated effect by several miRNAs may play a larger role in gene regulation than can be observed on the individual miRNA level. In an ongoing study (Aure et al manuscript) on Oslo2, the aim is to catalogue such coordinate behaviour of multiple miRNAs on cancer genes, by estimating the effect of each individual miRNA in the genome on the translation of mRNA to protein. The resulting miRNA-protein 'interactome map' may guide future studies in narrowing down on the most relevant miRNA-protein interactions.

Alterations in DNA methylation patterns have been shown to be of biological and clinical importance, and we recently reported on the integrated analysis of molecular alterations including the methylation status of 27 gene promoters analyzed by highly quantitative pyrosequencing, and the association to gene expression, germline genotype and clinical parameters including survival (Fleischer et al 2013).

Common to all the above mentioned approaches is that we demonstrate or map the diversity of molecular mechanisms that may lead to altered expression of a miRNA, an mRNA, or a protein. A natural extension of this was to identify and catalogue the multitude of molecular events that may lead to aberrant behaviour of a biological process or pathway (Kristensen et al PNAS, 2012). Further, we designed an algorithm to search for genomic alterations that lead to observable transcriptional perturbations both in-cis and in-trans and through these perturbations affect some process or pathway. This was applied to data from Oslo1 (MicMa) to derive a list of 56 candidate breast cancer driver genes (Aure et al, PLoS One 2013), many of which were already known to play a role in breast cancer as well as other promising candidates that will be subject to further study within the Jebsen Centre. Finally, our previously published method of allele specific analysis of copy number variation (ASCAT) (van Loo et al 2010, 2012) is now being extended to detect subclonality. In combination with mRNA expression data and novel characterizations of genomic architecture (including our previously published CAAI and WAAI and the ongoing CARMA project) this will be particularly valuable for treatment course studies, such as the Neoadjuvant Avastin (NeoAva) treatment study (Oslo3).

4. Approach to translation and innovation

To stimulate translation of research data into clinical studies, we have established a close collaboration and integration with the Breast Cancer Clinical Research Group (headed by Bjørn Naume and Erik Wist). Also other key clinical researchers and pathologists (Olav Engebråten, Hege Russnes, Torill Sauer, Elin Borgen, Ellen Schlichting) are partners in K.G. Jebsen Center. Subprojects such as the studies of DTCs, the immunological profiles, the methylation profiles, and response to radiation and chemotherapy, have immediate translational potential. After discovering that we can recognise distinct immune signalling in primary tumors by complex integrated molecular profiling, we set up studies to see whether these profiles are reflected in plasma and can be monitored non-invasively (results under analysis). Our molecular and metabolic classification will be coupled to imaging techniques to hopefully refine diagnostics and improve treatment strategies. Assessment of tumor vasculature by longitudinal dynamic PET or MR have confirmed the optimal timing of anti-angiogenic treatment in combination with chemotherapy, and have relevance both for the performed clinical neoadjuvant anti-angiogenic therapy study (NeoAva) and may also have impact in person-adapted treatment protocols.

One of the most profound effects of molecular classification on clinical studies is that it leads inevitably to a paradigm shift from large randomized clinical trials tailored for stratified patient groups, down to N-of-1 trials, where a single patient is the entire trial. This will fundamentally alter the way we statistically model and evaluate treatment strategies, from identifying patient groups that respond to treatment, to identifying altered pathways and biological entities that are druggable. Thus, we will expand our approach from evaluating the response in randomized arms, using the other arm as a control, to also include evaluation of response to experimental and control interventions in each individual using the same individual as a control. Two spin-off projects from the Center address new translational developments, 1) the N-of-1 concept: the MetAction project (PIs: GMM and ALBD); and 2) identification of DNA targeting treatment sensitivity by in-depth genomic aberration pattern analyses: the I-BCT-1 randomized study (PIs: OE, HKV, OCL), funded by NFR and Helse SørØst, respectively.

In the clinical N-of-1 trial in the **MetAction** project we aim to offer approved targeted therapy to patients with metastases from solid tumors, including BC, where biopsies from the metastatic lesion has confirmed presence of the corresponding actionable target. This is the first clinical trial of this kind in Norway and the protocol was recently approved by the Medical Agency and the Regional Ethical Committee (Eudract No 2013-001363-23; National coordinator: Kjersti Flatmark, MD, PhD). The first patient is planned enrolled before summer 2014 and the goal is to enroll 50 patients on intention-to-treat basis. The study centers are Oslo University Hospital and Akershus University Hospital. The effect of the targeted therapy will be evaluated by radiology (RECIST criteria) and also by examination of molecular effect in the targeted pathway in the metastatic lesion. Planning the first N-of-1 clinical trial has given the involved institutions important experience regarding design of person-adapted treatment

protocols, necessary infrastructure and logistics, and composition of the multidisciplinary teams in charge of data interpretation and treatment decisions. The work has been followed closely by the National Cancer Genome Consortium (http://kreftsatsing.no/persontilpasset-behandling/) and has received considerable interest from the public (eg. VG, April 5th 2013). The MetAction study also includes an explorative part where we by multilevel molecular characterization of prospectively collected metastatic biopsies aim to identify novel actionable targets and to study the molecular basis for treatment failure in metastatic BC.

The I-BCT-1 (Improved Breast Cancer Therapy) trial. Our work on allele specific analysis of CNA has resulted in a promising prognostic tool, and together with our previous work on total copy number architecture (CAAI and WAAI, Russnes, Vollan et al. 2010, Vollan et al., manuscript) form the basis for a new neoadjuvant treatment trial in breast cancer: I-BCT-1. The purpose of this trial is to determine whether these parameters can be used for the selection of additional therapeutic measures targeting the DNA instability found in BC. Applications for such a study have been submitted to the Regional Ethics Committee and to the Norwegian Medicines Agency, with a planned treatment start in summer 2014. Two cohorts are included in the trial: The neoadjuvant cohort will constitute the largest part of the study, with patients randomized to standard therapy alone or the addition of carboplatin to standard therapy. In the metastatic cohort, randomization will be performed between taxane therapy given alone, or taxane in combination with carboplatin. An extensive program for obtaining tissue samples and analysis of these are planned in both cohorts, similar to the logistics recently used in the NeoAva study. The NeoAva study has given us an extensive expertise in how to perform such studies.

Our participation in international collaborative projects culminated last year with organising and coordinating the **DREAM Competition** project, an important step in the translational direction. Participants from various laboratories worldwide competed to create an algorithm that could predict, more accurately than current benchmarks, the prognosis of breast cancer patients from clinical information (age, tumor size, histological grade), genome-scale tumor mRNA expression data, and DNA copy number data. The winners used a mathematical approach to identify biological modules that might, with continued investigation, teach us something about cancer biology. These examples support the notion that utilizing the expertise of participants outside of traditional biological disciplines may be a powerful way to accelerate the translation of biomedical science to the clinic. The results were published in the prestigious journals Science Translational Medicine and PLOS Computational Biology (Margolin et al, 2013, Bilal et al. 2013).

5. Internationalisation

The participation of the Center in several EU projects has opened the doors to a diversity of large networks in Europe and worldwide, such as Eurocan, http://eurocanplatform.eu/ comprising of 28 European cancer Institutions, Glycohit, http://www.glycohit.eu/ including also scientist from China and Japan in addition to leading European groups, and The Breast Cancer Somatic Genetics study, BASIS, http://www.sanger.ac.uk/research/areas/humangenetics/basis.html, a leading next generation sequencing project financed by the Welcome Trust. A new EU project EpiMark ("An integrated approach for epigenetic risk assessment and biomarker development for breast cancer in prospective cohorts / Identifying early epigenetic predictors of breast cancer risk and their etiology determinants") within the ERA-Net TRANSCAN, with the participation of our Center, will start this year under the leadership of IARC, Lyon, France. Further, we are engaged in a European Consortium on patient-derived xenograft models (EurOPDX) (headed by Dr. Sergio Roman-Roman, Institute Curie) aiming to conduct multi-Center preclinical drug testing to unravel predictive biomarkers and optimal drug combinations for person-adapted treatment.

The Center has close collaboration with exchange of personnel with the following Cancer Centers/ Universities:
MD Anderson Cancer Center (Gordon Mills),
UCSF, Helen Diller, Family Cancer Centre (Allan Balmain),
Sanger Center UK (Michael Stratton),
Cambridge Cancer Institute (Carlos Caldas, Florian Markowitz),
Chicago University (Kevin White),

Centre National de Génotypage, Paris (Jorg Tost)
Princeton University (Olga Troyanskaya)
Karolinska Institutet (Knut Steffensen and Janne Lehtiö),
Lawrence Berkley (Mina Bissell),
Finsen Laboratory (Ole W Pettersen),
University of Iceland (T Gudjunson),
Harvard Medical School/Dana-Farber Cancer Institute, US (Kornelia Polyak).
Radboud University Nijmegen, the Netherland (Lutgarde Buydens and Arend Heerschap)
Johns Hopkins Medicine, Radiology, Baltimore, USA (Kristine Glunde)

The Centre has facilitated the initiation and continuation of the following DTC/CTC-based collaborations:
MD Anderson Cancer Centre, TX, USA (Ricardo Alvares and James Reuben, planned CTC study); Department of Human Genetics, Leuven, Belgium and Wellcome Trust Sanger Institute, Hinxton, UK (Thierry Voet, Peter Van Loo, Kevin P. White, NGS of CTCs/DTCS), and The Cancer Institute in New Jersey (amplicon analyses; RAST study).

Scientists in the Centre are involved in several International sequencing consortia:

- Using RNA seq to identify markers of diagnostic as well as therapeutic value, in collaboration with Ravi Shachaninandam Mt Sinai, NY.
- Using RNA seq to identify splice variants and alternative usage of promotors in a subtype specific manner, collaboration G. Bhanot, IAS, Princeton and S. Ganesan, Cancer Inst. of NJ. A PhD student from the Centre performs the RNA seq analyses in US.
- Using exome sequencing to detect copy number variations (CNVs), rare single nucleotide variants (SNVs) and single nucleotide polymorphisms (SNPs) in relation to occurrence of disseminated tumor cells, KP White, Institute for Genomics and Systems Biology, University of Chicago. A visiting PhD student from the Centre performs many of the analyses.
- Single cell sequencing of disseminated tumor cells, KP White, Institute for Genomics and Systems Biology, University of Chicago.

6. Cooperation within Norway

The Center has an important role in the breast cancer research collaboration between institutions in Norway. The main national collaborator is NTNU Trondheim, where the group of Tone Bathen is an integral part and a founding member of the Center, with joint seminars being held every autumn at Kongsvoll Fjellstue, Dovre. Further, a joint seminar was held with the Stavanger breast cancer research group (led by Emiel Janssen, and Håvard Søiland) last fall, and many common activities were planned and have already been initiated (integrated analysis of miRNA/mRNA, mutual validation in the respective datasets).

Another axis of expansion nationally is the collaboration with Østfold Hospital (Fredrikstad) and Vestre Viken (Drammen), who have become invaluable partners in sample collection and willing recipients of scientific projects streaming from the University hospitals. Also, our analytic approaches have been disseminated to similar studies of other cancer forms (lung, pancreas melanomas, and colorectal) through the close collaboration with other groups of the Department of Genetics, and within the MetAction project, not members of the K.G.Jebsen Center, studying these respective cancer forms.

Further, our progress led us to revitalize an old collaboration with Haukeland Hospital, Bergen, which has been based on discovery of predictive markers for chemotherapy and targeted therapies (FUMI, doxorubicin, taxanes, b-raf inhibitors). Our recent studies on mRNA, miRNA and DNA methylation levels bring novel insights and will lead to a new and exciting phase of this collaboration.

Another long lasting collaboration that will be intensified in the coming period is with University of Tromsø and the NOWAC project, a prospective study of 150 000 Norwegian women, with the prospective collection of tumor tissue from breast cancer cases originating in the postgenome cohort in collaboration with all major Norwegian hospitals and the Norwegian Breast Cancer Group. The analysis of the micro-array was performed at the FUGE platform in Trondheim and at the Department of Genetics, Radiumhospitalet in collaboration with the FUGE platform of bioinformatics in Bergen. All

biomarkers will be measured at leading Norwegian laboratories. The project will be the start of a systematic work to create a library of exposure patterns necessary for the interpretation of the forthcoming nested case-control studies. On a clinical and translational basis the collaborative members are Oslo University Hospital, Akershus University Hospital, in collaboration with Sykehuset Innlandet, Sykehuset Østfold, Sørlandet Sykehus, Stavanger University Hospial, Ålesund Sykehus, University Hospital North Norway in the SATT study.

7. Recruitment of early stage researchers

In the period 2011-2013 there have been 9 PhD students who have defended or delivered their thesis, and 14 PhD student projects are ongoing, 4 of which are directly funded by the Center. All projects use the datasets collected by the Center. At present there are 5 research associates and 14 postdocs associated to the Center. All PhD students are supervised by the core people in the Center, either as main supervisors or as co-supervisors. They are all organized in the PhD program at the Faculty of Medicine, UiO, and have a PhD forum organized by the Institute and rigorous internal journal club initiated on their own. In addition the Center has supervised 7 MSc from NTNU, Trondheim, UMBV, Ås and Høyskolen i Oslo, 4 of whom have been recruited as PhD students or technical research associates in the project. Internationally we have hosted a MSc on the Erasmus program from Germany (2012) and from the NKI, Amsterdam (2013) and we supervise presently two PhD students with affiliations abroad: one from the USCF, California and one from Rutgers University and Mt Sinai, USA. There are three MD students, two "forskerlinje" students and one working on her science project in the 5th semester. The director and the deputy director of the Center are actively teaching at the Faculty of Medicine, both at the graduate level in PhD courses and at undergraduate level (medical students) in the 2. and 3. semester in cell biology and immunology. Another member is actively involved in teaching bioinformatics at Institute of Informatics, UiO where his main affiliation is. Other members of the group teach through their external professorships at University of Oslo, Tromsø and Trondheim. Scientists in the Center are also collaborating with Oslo Cancer Cluster and Ullern Videregående skole and are supervising 6-8 third year students in practical laboratory projects one week every year.

<u>PhD students directly funded by The K.G. Jebsen Center</u>

Ongoing:

PhD student Alexandr Kristian, 1/1-2012-31/12-2014, main supervisor E. Malinen
PhD student Tonje Haukaas, 1/1-2012-31/12-2015, on maternity leave from June 2013- April 2014.
main supervisor T. Bathen
PhD student Elen K Møller, 1/1-2014-31.12-2014 (co-funded KF),
main supervisor V.N. Kristensen
PhD student Hans Kristian Moen Vollan, MD, 1/12-2013 - 31/12-2014 (co funded OUS),
Main supervisor A.L. Børresen-Dale

<u>PhDs funded by other sources, operating costs for experiments and sample collection supported by K.G. Jebsen Foundation</u>

Defended PhD:

PhD: Randi Ruud-Mathiesen. NFR. Analyses and clinical relevance of tumor-related single cells in blood and bone marrow in breast cancer. Defended 23.05.13, main supervisor B. Naume
PhD: Margit Hesla Riis, UiO, Molecular Analysis of Pre- and Postoperative Biopsies in Breast Carcinomas, defended 25.05.13, main supervisor V.N. Kristensen
PhD: Evita Maria Lindholm, NFR/KF. Antiangiogenic treatment in breast cancer – identifying responders and mechanisms driving resistance. Defended 07.06.13,
main supervisor O. Engebråten
PhD: Fatemeh Kaveh, NFR, Genomic signatures in progression of breast cancer with reference to gynecological carcinomas, Defended 10.10.13 , main supervisor V.N. Kristensen

PhD: Miriam R Aure, NFR, From DNA to RNA to protein: Integrated analyses of high-throughput molecular data from primary breast carcinomas, Defended 27.11.13, main supervisor V.N. Kristensen

Delivered:

PhD: Jovana Klajic, UiO, From normal breast to invasive carcinoma: DNA methylation profiling of stage and response to chemotherapy, delivered November 2013, Dissertation planned May 2014, main supervisor V.N. Kristensen

PhD Himanshu Joshi, Helse SørØst, Towards pathway and network- based medicine in breast cancer, delivered November 2013, Dissertation planned April 2014, main supervisor V.N. Kristensen

PhD: Thomas Fleischer, UiO, Epigenetic alterations in breast cancer: implications on classification and prognosis, delivered December 2013, Dissertation planned June 2014, main supervisor V.N. Kristensen

PhD: Marit Synnestvedt. NFR. Targeting occult tumor cells in breast cancer. UiO. Dissertation planned June 2014. main supervisor B. Naume

Ongoing:

PhD: student Inga Hansine Rye, Helse SørØst. startet 2012, main supervisor H. G. Russnes

PhD: student Gro Nilsen, UiO, started 2012, main supervisor O.C. Lindgjærde

PhD student Shakila Jabeen, Helse SørØst, started 2013, main supervisor V.N. Kristensen

PhD student Andliena Tahiri, Helse Sør Øst, started 2012, main supervisor V.N. Kristensen

PhD student Leslie Euceda Wood, NFR, started in May 2013 main supervisor T. Bathen

PhD student Sunniva Bjørklund, Helse SørØst, started 2012, main supervisor A.L. Børresen-Dale

PhD student David Quigley, UCSF/UiO, started 2011, main supervisor A.. Børresen-Dale

PhD student Sandra Järnstrøm, Helse SørØst, 2011, main supervisor K. Kleivi

PhD student Laxmi Silwal-Pandit, KF, 2011, main supervisor A.L. Børresen-Dale

PhD student Helga Bergholtz, Helse Sør-Øst, 2013, main supervisor T. Sørlie

Postdocs and Research associates directly funded by the K.G. Jebsen Foundation

postdoc Suvi-Katri Leivonen, 1/1 -2012-31/12-2013.

postdoc Ellen Margrethe Tenstad, 1/12-2011-31/11-2014.

Xi, Zhao , Research associate,15/9-2011- 15/12-2011

Inger Riise Bergheim, Research associate , 1/11-2011- 31/10 2015.

Daniel Nebdal, Research associate, 1/01-2012- 31/10 2015.

Postdocs recruited in the project, financed by other sources

postdoc Riyas Vettukattil, Funded by the Mid-Norway health authorities, started in September 2013

postdoc Hege G. Russnes, KF, Helse SørØst

postdoc Surendra Kumar, Helse SørØst

postdoc Miriam R Aure, HelseSørØst

postdoc Jovana Klajic, Helse SørØst

postdoc Thomas Fleischer, KF

postdoc Vilde D. Haakensen, KF

postdoc Jiqiu Cheng, Helse SørØst

postdoc Marit Krohn, KF

postdoc Olga Østerud, NFR

postdoc Einar Rødland NFR

postdoc NN, KF (will start in the fall 2014)

Master students

Completed:

Veronica Skarpeteig: Significance of WRAP53 in Breast Cancer: Mutation Analyses and Gene Expression Studies, 2012

Tone Olsen: Differentially Regulated pathways of Potential Importance for Treatment Response and Cardiac Toxicity after Administration of Doxorubicin to BC Patients.2012

Catrine Pedersen: The B7-H3 protein and its role in breast cancer treatment Response, 2012
Idunn Landa: Expression and function of microRNAs in HER2+ breast cancer, 2012
Eldrid U. Due: Establishment of the Ba/F3 method to test the oncogenic potential of cancer gene mutations.2013
Bente Risberg, Establishment of PCR based methods for detection of ctDNA in blood, 2013
Vibekke Rognlien: The role of the metastasis-promoting protein S100A4 during EMT in mammary gland epithelial cells.2013
Ongoing:
Ingunn Sivertsen, 2014

Forskerlinje students, Medical Faculty UiO
Christian Fougner
Arne Pladsen
Ivan Potapentko (former forskerlinje student, PhD recruit after completed internship)

The recruitment and "brewing" of young scientists in the Center has culminated with new project groups established with funding from Helse SørØst to postdoc/scientist Hege G. Russnes last year and with a career stipend from Helse SørØst (4 years x 2mil/year) this year for one of the senior postdocs, Silje Nord.

8. Funding

Since its establishment the Center has been able to obtain funding through all national funding bodies (NFR, KF, Helse SørØst, HelseMidt), local hospital grants (Kreftklinikken strategic funds, Ahus strategic funds, Radiumhospitalet legater) and has been also additionally supported by several large international projects through EU: BASIS, GlycoHit, Eurocan, EpiMark.

The major funding from external sources (2011-2013) :

Helse SørØst (~Total 15 mill)
2011-2013- Towards personalised therapy for breast cancer through forming the Oslo Breast Cancer Research Center: OSBREAC
2012-2014 - The participation Ahus in the K.G.Jebsen Center
2013-2015 - Regional Networks. Exosomes and extracellular vesicles
2013-2015 - Targeting occult tumor cells in breast cancer
2013-2015 - Reduced Adjuvant Systemic Treatment in node negative breast cancer (RAST)
2013-2016 - Cell-free tumor DNA in blood; non-invasive monitoring of therapy response and disease progression in breast cancer patients.
2014-2017 - Career stipend, Making sense of GWAS
2014-2017 – Intensifying breast cancer therapy (I-BCT) in the neoadjuvant and metastatic setting: A translational clinical study for selecting tumor therapy."

Helse Midt (~Total 2.8 mill)
2014-2016 -Molecular effects of exercise and chemotherapy on breast cancer

Norwegian Research Council (~Total 10 mill)
2012-2014: Neoadjuvant Avastin in Breast Cancer (NeoAva)
2013 – 2016 (FRIPRO): "Met-NESTING; Metastatic Niche Establishment by Stromal-Tumor cell INteractions; Going towards novel therapies"
2013 – 2016 (FRIPRO): Imaging the Breast Cancer Metabolome
2012-2016 (The publicly-initiated clinical cancer studies program 2012-2016): "MetAction: Actionable targets in cancer metastasis – from bed to bench to byte to bedside

Kreftforeningen/Rosa Sløyfe (~Total 8 mill)
2011-2014: General Funding to the PIs in the center
2012-2014: Neoadjuvant Avastin in Breast Cancer (NeoAva)

EU (~Total 286 000 EUR)
BASIS :Breast Cancer Somatic Genetics Study (2010-2014)
GlycoHIT: Glycomics by High-throughput Integrated Technologies (2011-2014)
EurocanPlatform: A European Platform for Translational Cancer Research(2011-2015)
TRANSCAN: An integrated approach for epigenetic risk assessment and biomarker development for breast cancer in prospective cohorts / Identifying early epigenetic predictors of breast cancer risk and their etiology determinants(2014-2017)

9. Research leadership

The Center is headed by Anne-Lise Børresen-Dale, and the Host institutions are Institute for Cancer Research (ICR), Oslo University Hospital, Radiumhospitalet (OUHR), and the Institute for Clinical Medicine, University of Oslo. The management team, headed by research coordinator Gry Geitvik, consist of the director and co-director and all group-leaders in the Center (see below). The role and the activities of the Principle Investigator and the management team, have been well defined and these have functioned in good coordination. The PI of the Center has together with the leader of OSBREAC, Rolf Kåresen, ensured a smooth process of sample collection and collaboration between the different hospitals (see also National collaboration). The PI of the Center, has also actively profiled the Center internationally and set the road to multiple EU networks (see International collaboration).

The Center consist of six research groups:

- Clinical groups: Ellen Schlichting, Rolf Kåresen (surgery), Torill Sauer, Elin Borgen, Hege G. Russnes (pathology), Erik Wist, Olav Engebråten og Bjørn Naume (oncology)
- Molecular groups : Anne-Lise Børresen-Dale (director) and Vessela N. Kristensen (deputy director)
- Micro-metastases groups: Bjørn Naume and Øystein Fodstad
- Model-systems and functional groups: Gunhild M. Mælandsmo og Øystein Fodstad Metabolic profiling and imaging group: Ingrid S. Gribbestad (deceased April 2013) and Tone F Bathen NTNU
- Bioinformatics/biostatistics group: Ole Christian Lingjærde

The molecular groups (ALBD and VNK) have successfully performed the molecular profiling at all levels and in close collaboration with the bioinformatics/biostatistic group (OCL) developed novel tools for integrated analysis. The molecular profiling from this stage is integrated with the metabolic profiling and imaging (TFB, NTNU) and candidate markers from these studies are investigated by functional studies in model systems (GMM and ØF). The DTC and CTC research team has high competence in processing large number of samples for analysis, suitable for both large clinical studies and for future routine-based analyses. Furthermore, the team has established method for isolation of single tumor cells for high resolution molecular analyses, as well as oligo-marker analyses. Also, the team has succeeded in initiating multi-centre intervention-based study based on DTC analysis, and have been able to integrate these analyses in other studies, as exploratory objectives. Most importantly and with increasing intensity during the second part of the project term, the activity of the clinical groups (BN, OE, and HGR) will define the profile of the Center with clinical trials as NeoAva, MetAction and the I-BCT in the focus. The Center is well integrated at the host institution (IKF and MedFak, UiO) and seeks the interaction of other K.G. Jebsen Centers at the Institute as that of immunology (Prof Olweus) and colorectal (Prof Lothe).

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The Center has an external Scientific Advisory Board (SAB) consisting of:

- Professor Gordon Mills, Chair, Department of Systems Biology, MD Anderson Cancer Center, Houston, TX, US
- Professor Carlos Caldas, Group Leader, Cancer Research UK Cambridge Institute, University of Cambridge, UK
- Professor Joaquin Arribas, Director of Preclinical Research, Vall D'Hebron Institute of Oncology, University Hospital Barcelona, Spain

They have seen the report form 2012 and this Midterm report, and will give the Foundation their feedback.

10. Dissemination and public outreach

Knowledge management, evaluation and dissemination of scientific results are important aspect of the work of a multidisciplinary Center like ours. Reshaping scientific knowledge dissemination and evaluation in the age of the internet and web-based communication has been a major goal of our participation in the DREAM Competition project (seep point 4, Translation and innovation) supporting the idea of free publication and interactive review of scientific data online. Communication of knowledge through the dissemination of research findings is a key element of the work of the Centre. Ensuring that research findings, best and promising practices, and other innovations reach, strengthen and support the field—and that the feedback loop remains unbroken—requires comprehensive, active dissemination planning, and a multi-faceted, strategic approach to carrying out dissemination activities.

In addition to the over 70 Scientific publications from the Center, listed in the attached publication list, several of them in high profiled/ indexed journals such as Nature, Cell, Science TM, PNAS, the researchers in the centre have been involved in writing book chapters and web tutorials for the developed methods. An active dissemination of results through scientific meetings and meeting research communities as well as public web sites and newspapers is in focus. The Center has been profiled in two additions of the Public Service Review: European Union 23 in March 2012, and June 2013. We also highlight our activities through our own web page http://ous-research.no/kgjebsen/ in addition to the Foundations own Web page. In 2012 the Center was co-organizer of the 7. International Symposium on Personalized Cancer Care, taking place in Oslo, 7-9 September, with >200 participants from all over the world and with speakers with the highest International reputation in the Cancer field. Yearly a seminar in the Academy of Sciences is organised with the support of Thoresen Foundation with researchers from all walks of medical science, and where the Center also is profiled with several speakers.

In 2013 the Center was represented at the Forskningsdagene at the University Square in front of the University Aula downtown. The stand was very well visited and got a lot of attention.

The director of the Center has been invited to give a large number of presentations at various International Meetings highlighting the Center and presenting work based on all the projects in the Center. Media attention of the work ongoing in the Center has also been extensively. A list of major talks at international meetings, together with a list of media exposure and public talks, in 2012 and 2013 are attached.

In summary, how to communicate the results through popular publications; scientific audiences, scientific journalism; posters with project information; press contacts; use of media and interactive web pages is a priority in the centre at all levels.

11. Self-evaluation summary and plans for the remaining project period

Accomplishments due to funding from K.G. Jebsen

The K.G. Jebsen Center for Breast Cancer Research grew on the background of the OSBREAC (The Oslo Breast Cancer Research consortium), which provided the initial collaborations necessary for the collection of a constitutive series of breast cancer from Oslo and Akershus area. In this group, researchers, surgeons and oncologists from the Oslo University Hospital (Norwegian Radium Hospital, Ullevål), Akershus University hospital and later also from Drammen and Fredrikstad joined forces to

collect the sample material using fragmented funding from the Norwegian Cancer Society and Helse SørØst as well as local hospital grants. Only with the funding from the K.G. Jebsen Foundation it became possible to melt these separate studies into a common study of the molecular profiling of breast cancer, which in size and depth of the analyses can be compared to the two largest and highly profiled similar studies on world basis (the TCGA, funded by the NCI, NIH and METABRIC, funded by Cancer Research UK), with whom we extensively collaborate. Profiled world wide as the Norwegian Breast Cancer study (NBCS) funded by the K.G. Jebsen Center, our study consists at present of close to 2000 cases and 2000 controls, characterised at different molecular levels, a core of which (approximately 700 cases) is profiled at every level. With this we participate in large EU funded consortia such as the Breast Cancer Research Consortium (BCAC), the BASIS, the EUROCAN, the GlycoHit and most recently the TRANSCAN project. Several calls of Horizon 2020 will be attended.
More importantly, we have in the first half of the project period performed and published promising results from the analyses of our own patient cohorts, and have developed important analytical tools on our pilot dataset (described in Activity 5). These results and methodology we are exporting, in a collaborative setting, to the large international consortia. This generation of molecular data and high level of integration analyses has only been possible with the funding from the K.G. Jebsen Foundation, and will affect the strategy of how to perform analyses of both the primary tumors as well as single disseminated tumor cells (DTC) in the benefit of the best treatment for the patients.

Our DTC research has identified high risk patients with an especially poor prognosis after completion of standard adjuvant chemotherapy and that the change in DTC status by alternative treatment can affect the prognosis. The establishment of methods for detailed characterisation of the DTCs/CTCs and circulating tumour DNA, will be used to analyse a larger number of patients, with comparison to the primary tumor profiles and outcome. The results from these analyses will be used to identify therapeutic targets and candidate patients for alternative treatment approaches (either as secondary adjuvant treatment or as metastatic treatment). Such approaches are planned to be tested in new clinical trials, facilitated by our described experience in running DTC studies.

At the present moment we have finalised the accumulation and analyses of the first freeze of the data and the published papers illustrate good progress on the first two of our initial goals: develop validated stratification criteria based on phenotypic/genotypic profiling of breast tumors and use validated phenotypic and genotypic stratification criteria for assessing individual response and prognosis in patients with breast cancer. The main challenge for us now is to identify with sufficient certainty the biological pathways responsible for the observed stratification and prognosis and interpret those also in terms of response to treatment (goal 3 from our initial plan). We have a great body of data (unpublished and in manuscript form) on treatment response to conventional chemotherapy, but a great challenge and breakthrough will be to identify markers of response to targeted treatment longitudinally (the last goal of our initial proposal). This and the synthesis of our results in translatable molecular and imaging biomarkers from preclinical models into clinical trials such as the described above MetAction and I-BCT-1 spinning off the K.G. Jebsen Center will be the focus of the next half of the project term and a starting point for its eventual continuation.

Adjustments from the initial plan needed to be made

From December 2011 until ultimo 2012 a postdoctoral fellow was working with characterization of disseminated tumor cells (DTC) isolated from bone marrow (BM) of early breast cancer patients. BM DTCs were found in very low numbers and in order to facilitate their characterization attempts were made to propagate the cells in vitro by co-cultivating with feeder cells, acknowledging the crucial impact of the microenvironment. BM samples from 25 Oslo2 patients were included in a pilot study. Unfortunately, we were not able to provide evidence of DTC expansion in the co-cultures. According to an oncogenic theory called epithelial-mesenchymal transition, DTCs may acquire a mesenchymal-like phenotype during invasion and extravasation. Such transition will obscure their identification by phenotype characteristics (due to down-regulation of epithelial markers) and putative malignant cells will thereby resemble normal mesenchymal cells present in the BM. Realizing that it will be challenging to characterize the DTC based on these criteria we decided to re-prioritize the postdoctoral project and the focus has been shifted to characterizing tumor stroma interactions during metastatic dissemination by the use of in vitro and in vivo model systems (see activity 3).

Other main adjustments to the initial plan come from the changing environment of new technologies, availability of novel approaches and the evolving state of the field. The development of

the digital PCR technology allows the detection of single copies of molecules and together with ctDNA will potentially revolutionize diagnostics. In collaboration with the leading laboratory of Carlos Caldas in Cambridge UK, we have started to explore these potentials. Single cell sequencing is anther cutting edge technology that became to us available after the initiation of the project due to collaboration with the laboratory of Kevin White of University Chicago and Thierry Voet of University of Leuven and Cambridge. Cheaper and more available next generation sequencing (Iontorrent and Miseq) allows us to initiate deep re-sequencing for the first mutations identified in breast cancer, as well as to embark on new and unexplored territories as those of MtDNA sequencing. Circular RNA sequencing, which we have initiated with our collaborators at Mt Sinai, New York. The development of methodology for tumor clonality changes after treatment as well as the monitoring and importance of immunological profiles will be other priorities.

Future plans opportunities for translation or innovation

The initiation of a new study exploring how to reduce the use of adjuvant systemic treatment to low risk breast cancer patients has recently started (RAST study). The study will include low risk patients, based on traditional clinicopathological parameters from several cohorts (Oslo1, Oslo2, OsloVal), with ability for genomic profiling and molecular analyses, aiming to identify characteristics of excellent outcome patients with no need of adjuvant systemic treatment (or adjuvant chemotherapy). About 1500 patients will be analysed within the study, including a large group of adjuvant un-treated patients, and followed up to 10 years. The Ki67 expression analysis (which will be used as a part of the analyses in this study) has been performed, including analysis of Ki67 on whole sections from patients in the Oslo1 study. The Nanostring System is now in place at our Institution, and the PAM50/ROR score will be used for subtyping and risk classification with comparison to other primary tumor analyses (including those analyses performed in the Oslo2 study). Our collaborators at The Cancer Institute of New Jersey (CINJ) have also developed a technique based on outlier analysis which can identify amplicons associated with progression, recurrence, metastasis from gene expression data. Such analyses are also planned to be performed at the Center in the next translational phase of the project.

Conclusion

A more fundamental understanding of the biological dynamics of cancer will enable us to better identify risk factors, refine cancer diagnosis, predict therapeutic effects and prognosis and identify new targets for therapy. We are seeing a paradigm shift from large randomized clinical trials towards treatment modalities tailored for stratified patient groups (the NeoAva trial), down to N of 1 trials (the Metaction project), where a single patient is the entire trial, a single case study. This will fundamentally alter the way we statistically model and evaluate treatment strategies, from identifying patient groups that respond to treatment above random, to identifying pathways and biological entities that are druggable and altered above random; from evaluating the response in randomized arms, using the other arm as a control, to evaluating response of experimental and control interventions in each individual using the same individual as a control. The real challenge would be to develop statistical models to identify critical, rate-limiting molecular targets for intervention out of the wealth of information that next generation sequencing uncovers, on the background of great redundancy of pathways and heterogeneity of tumors. Since we are moving towards an era in which the amount of data produced every year is increasing exponentially, the biomedical community needs to “embrace the complexity” and find new ways of shared analysis. We need to learn from physicists and mathematicians and transform our way of working, making data available on a hub so that everyone interested in it can work on it. New ideas can then be picked up by anyone instantly, rather than waiting for publication. This was essential in the success of the DREAM breast cancer competition, and is an example of the one of the many computational challenges set by DREAM with the goal of catalyzing the interaction between theory and experiment, specifically in the area of cellular network inference and quantitative model building in systems biology. An enormous challenge is also the functional validation of the *in silico* findings in relevant living biological systems and the development of adequate *in vitro* functional studies (like siRNA screens, knock in and knock out systems) to keep up with the increasing throughput with which candidates for validation are generated. In the remaining years we will fully benefit from the K.G. Jebsen financial support to explore functions of thousands of candidate cancer genes and proteins in order to ascertain their value as risk factors, as predictive factors for therapy response and as therapeutic targets.

The K.G. Jebsen Center for Breast Cancer Research

LIST OF RELEVANT PUBLICATIONS

Group leaders in the Center: underlined, bold
* publication where The K.G. Jebsen Foundation is acknowledged

Original Papers

2012

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Scientific articles in Nordic journals and books and popular articles.

C33. Ikdahl, T., **Børresen-Dale, A.-L**., Helland, Å. and Haakensen, V.: Tumorbiologi. In: Kreftsykdommer *Eds: Kåresen, R and Wist, E. , Rev. 4. .Gyldendal Norsk Forlag, in press 2012*

Key abstracts at the last San Antonio Breast cancer Symposium

***Engebråten, Olav**; Vaske, Charles J.; Krohn, Marit; Silwal-Pandit, Laxmi; Vollan, Hans Kristian Moen; Møller, Elen Kristine; Nord, Silje; Fleischer, Thomas; **Borgen, Elin**; Edvardsen, Hege; Garred, Øystein; Fangberget, Anne; Holmen, Marit Muri; Schlichting, Ellen; Skjerven, Helle; Lundgren, Steinar; **Wist, Erik; Naume, Bjørn; Børresen-Dale, Anne-Lise; Kristensen, Vessela N..**
Molecular response in breast cancer tumors treated with neoadjuvant chemotherapy with and without bevacizumab: Results from NeoAva - A randomized study.
SABCS 2013; 2013-12-10 - 2013-12-13

Flote, Vidar Gordon; Frydenberg, Hanne; Ursin, Giske; Wilsgaard, Tom; Iversen, Anne June; Ellison, Peter; **Wist, Erik;** Egeland, Torstein; Thune, Inger; Furberg, Anne-Sofie. High-density lipoprotein cholesterol is associated with mammographic density in premenopausal women.
SABCS 2013; 2013-12-10 - 2013-12-13

* Mathiesen, Randi R.; **Borgen, Elin;** Sætersdal, Anna Barbro; Fangberget, Anne; Schirmer, Cecilie; Stav, I; Fagerland, Morten; **Wist, Erik; Engebråten, Olav; Naume, Bjørn.**
Detection and monitoring of circulating endothelial cells, circulating tumor cells and disseminated tumor cells during neoadjuvant breast cancer treatment including bevacizumab.
SABCS 2013; 2013-12-10 - 2013-12-13

*Møller, Elen Kristine; Vollan, Hans Kristian Moen; Nord, Silje; von der Lippe Gythfeldt, H; Edvardsen, Hege; Silwal-Pandit, Laxmi; Krohn, Marit; Fleischer, Thomas; Schlichting, Ellen; **Borgen, Elin;** Garred, Øystein; Fangberget, Anne; Holmen, Marit Muri; Skjerven, Helle; Lundgren, Steinar; **Wist, Erik; Naume, Bjørn; Børresen-Dale, Anne-Lise; Kristensen, Vessela N.; Engebråten, Olav.**
A time course study of genomic instability in breast cancer patients receiving neoadjuvant chemotherapy with or without bevacizumab. SABCS 2013; 2013-12-10 - 2013-12-13

Scientific consortium papers (BCAC of whicVNK and ALBD is a key member of the consortia)

BCAC consortium: Fine-scale mapping of the FGFR2 breast cancer risk locus: putative functional variants differentially bind FOXA1 and E2F1. *Am J Hum Genet. 2013 Dec 5;93(6):1046-60. PMID:24290378*

BCAC consortium: A large-scale assessment of two-way SNP interactions in breast cancer susceptibility using 46 450 cases and 42 461 controls from the breast cancer association consortium. *Hum Mol Genet. 2013 Nov 28. PMID:24242184*

Bojesen SE, Pooley KA, Johnatty SE, Beesley J, Michailidou K, Tyrer JP, Edwards SL, Pickett HA, Shen HC, Smart CE, Hillman KM, Mai PL, Lawrenson K, Stutz MD, Lu Y, Karevan R, Woods N, Johnston RL, French JD, Chen X, Weischer M, Nielsen SF, Maranian MJ, Ghoussaini M, Ahmed S et al. and the **BCAC Consortium** (2013) *Nat Genet, 45 (4), 371-84, 384e1-2PubMed 23535731*

French JD, Ghoussaini M, Edwards SL, Meyer KB, Michailidou K, Ahmed S, Khan S, Maranian MJ, O'Reilly M, Hillman KM, Betts JA, Carroll T, Bailey PJ, Dicks E, Beesley J, Tyrer J, Maia AT, Beck A, Knoblauch NW, Chen C, Kraft P, Barnes D, González-Neira A, Alonso MR, Herrero D et al. and the **BCAC Consortium** Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. *Am J Hum Genet*, (2013), *92 (4), 489-503 PubMed 23540573*

Garcia-Closas M, Couch FJ, Lindstrom S, Michailidou K, Schmidt MK, Brook MN, Orr N, Rhie SK, Riboli E, Feigelson HS, Le Marchand L, Buring JE, Eccles D, Miron P, Fasching PA, Brauch H, Chang-Claude J, Carpenter J, Godwin AK, Nevanlinna H, Giles GG, Cox A, Hopper JL, Bolla MK, Wang Q et al. and the **BCAC Consortium** Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nat Genet*, (2013), *45 (4), 392-8, 398e1-2 PubMed 23535733*

BCAC consortium: Genome-wide association study identifies 25 known breast cancer susceptibility loci as risk factors for triple-negative breast cancer. *Carcinogenesis. 2014 Jan 23. PMID:24325915*

List of major Scientific Presentation of the PI, where the K.G. Jebsen Center is profiled

2012

1. EMBL Conference on Personalised Health, Heidelberg, 16-18 February, 2012
2. 6th Scientific Workshop of the International Cancer Genome Consortium (ICGC), Cannes, March 20-22, 2012
3. Keynote lecture at CROATIAN ONCOLOGY CONGRESS, Dubrovnik, Croatia, 28 March- 1 April, 2012
4. Global Academic Program Meeting, Oslo , 14-16 May, 2012
5. Nobel Conference on Breast Cancer, Stockholm, June 14-17, 2012
6. International Symposium: Controversies in Endocrine Surgery and Translational Research, Bergen, Norway, August 23rd – 24th, 2012**.**
7. International Symposium on Personalized Cancer Care, Oslo, 7-9 September, 2012 **,** *The center was co-organizer of this Symposium*
8. ESMO 2012 Congress, Vienna, 28 September - 2 October, 2012
9. Workshop on Cancer bioinformatics: methods and applications, Paris, France, October 4-5, 20128
10. Cancer Crosslinks Sweden 2012, Lund, October 11, 2012
11. The 43rd International Symposium of The Princess Takamatsu Cancer Research Fund, Tokyo, November 14 -16, 2012

2013

12. Wiseman Institute, Israel, invited speaker. March 9-17, 2013
13. XXII Porto Cancer Meeting, invited speaker, April 10-14, 2013
14. p53 Workshop, Toronto, invited speaker, June 14-19, 2013
15. EACR Genomics, Cambridge, invited speaker, June 25-27, 2013
16. FEBS, St.Petersburg, invited speaker, July 7-12, 2013
17. Progess towards individual cancer treatment, London, invited speaker. September 26-27, 2013
18. Ecco 17, Amsterdam, invited speaker. September 27- October 1. 2013.
19. IMBL/EMBL Science and Society Conference, Heidelberg,invited speaker. November 7-8,2013.
20. 50 års jubileum Prekliniske instituttet, Bergen, September 19, 2013.

Media exposure and lectures for the public
2012-2013

Når	Hvor	URL	Overskrift
2012-03-19	Radiumhospitalets legater	http://www.radiumhospitaletslegater.no/artikler/nyhetsartikler/legatpengene-var-avgjoerende.aspx	Legatpengene var avgjørende
2012-03-20	Radiumhospitalets legater	http://www.radiumhospitaletslegater.no/artikler/nyhetsartikler/moldejenta-som-fikk-kjemisett-til-jul.aspx	Moldejenta som fikk kjemisett til jul
2012-03-19	Radiumhospitalets legater	http://www.radiumhospitaletslegater.no/artikler/nyhetsartikler/personlig-og-tilpasset-,-intervju-med-anne-lise-boerresen-dale.aspx	Personlig og tilpasset, intervju med Anne-lise Børresen-Dale
2012-09-25	TV2, Din Helse	http://webtv.tv2.no/webtv/?progId=653438	Din Helse skal handle om brystkreft: Hva slags liv får man etter endt behandling? Årets Rosa sløyfe-aksjon. Vi har besøk av Anne-Lise Børresen-Dale, kreftforsker, Institutt for klinisk medisin ved Ous, Beate Wilhelmsen, brystkreftrammet i 2008, godhelsetips.com og Anne Lise Ryel, generalsekretær, Kreftforeningen.
2012-04-19	ABC Nyheter	http://www.abcnyheter.no/nyheter/helse/2012/04/19/brystkreft-er-ikke-en-men-ti-sykdommer	Brystkreft er ikke én, men ti sykdommer
2012-04-12	forskning.no	http://www.forskning.no/artikler/2012/april/318866	Vi vil aldri utrydde kreft
2012-04-21	videnskab.dk	http://videnskab.dk/krop-sundhed/vi-far-aldrig-udryddet-kraeft?page=1	Vi får aldrig utryddet kræft (Oversatt versjon av artikkel fra forskning.no)
2012-04-28	VG	http://arkivet.vg.no/index.php?page=show&urlId=05501620120428doc64mqptd0k0319x9yzlsx&preview=aHR0cDovL3d3dy5yZXRyaWV2ZXltaW5mby5jb20vcHJveHkvP2lkPTA1NTAxNjIwMTIwNDI4MnFMN2E1MkNPZDcwMU5pSHhoNGZWN01RMTAwMjAxMDEwODFvJng9NzhmNTgwZWQwNWQ5NjIyNWY0YWJhOTgyZDQ1YzY1MDEmcHJldmlldz0x&part=&product=R	Fremtidens krefthåp: Flere vil reddes
2012-06-20	Forskningsrådet	http://www.forskningsradet.no/prognett-kreft/Nyheter/Brystkreft_er_mange_ulike_sykdommer/1253978236671/p1253968049675	Brystkreft er mange ulike sykdommer
2012-06-07	OUS nyheter	http://www.oslo-universitetssykehus.no/aktuelt/nyheter/sider/genkartlegging-gir-ny-kunnskap-om-brystkreft.aspx	Genkartlegging gir ny kunnskap om brystkreft
2012-07-27	forskning.no	http://www.forskning.no/artikler/2012/juni/325481	Hver kreftsvulst sin historie
2012-09-24	TV2, God Morgen Norge	http://www.tv2.no/gmn/nettprat/-brystkreftpasienter-faar-unoedvendig-toeff-behandling-3884385.html	Brystkreftpasienter får unødvendig tøff behandling
2012-09-24	TV2, God Morgen Norge	http://www.tv2.no/gmn/nettprat/-viktig-med-godt-kosthold-gode-tanker-og-mosjon-3884559.html	NETTREFF OM BRYSTKREFT: Viktig med godt kosthold, gode tanker og mosjon
2012-09-05	Dagsavisen	http://www.dagsavisen.no/samfunn/flere-kan-slippe-c-ellegift/	Flere kan slippe cellegift
2012-09-25	hegnar.no	http://www.hegnar.no/kvinner/article705991.ece	Vil slå brystkreften uten cellegift
2012-09-26	TV2, Nyheter	http://www.tv2.no/nyheter/innenriks/helse/norske-forskere-med-paa-brystkreftgjennombrudd-3884846.html	Norske forskere med på brystkreft-gjennombrudd
2012-10-00	Athene	Intervju i medlemsblad for brystkreft opererte, Kreftforeningen	Håper flere kan leve med kreft

Når	Hvor	URL	Overskrift
2013-09-25	Apollon	http://www.apollon.uio.no/artikle	Molekylært kaos i kreftsvulstene
2013-03-01	Forskningsrådet	http://www.forskningsradet.no/p	Tester skreddersydd kreftbehandling
2013-05-23	Norsk Golf	http://norskgolf.no/node/4702#1	For Bente – og alle de andre
2013-10-01	Rosa Sløyfe	https://kreftforeningen.no/rosasl	Dette går pengene til
2013-11-26	Apollon	http://www.apollon.uio.no/artikle	Persontilpasser brystkreftbehandlingen
2013-09-02	Diagnose:Brystkreft (bok, Solveig Bøhle)	ref aftenposten-saken	
2013-12-12	Aftenposten	http://www.aftenposten.no/meni	En mer skånsom behandling
2013-04-23	Scientific American Worldview	http://www.saworldview.com/ww/	Not just a number
2013-05-30	Kreftregisteret	http://www.kreftregisteret.no/no/	Nye dødelighetstall i tråd med tidligere europeiske studier
2013-11-01	1.6millionerklubben	http://1.6millionerklubben.no/ku	Kunstkalender 2014
2013-09-02	Dagens medisin	http://www.dagensmedisin.no/n	60 legers råd til den neste helseministeren
2013-03-01	Foredrag for Bryst Cancer Foreningen, Gardermoen		
2013-11-11	Foredrag for kreftforeningen, Radiumhospitalet	Hva betyr kreftforeningens tildeling for kreftforskning	