Centre for Cancer Biomarkers

Norwegian Centre of Excellence – University of Bergen

Norwegian Centre of Excellence

The Research Council of Norway

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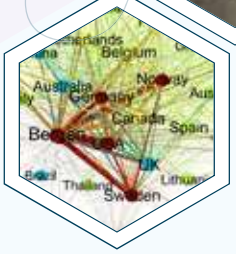

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Director's comments

In the beginning of 2016, CCBIO was struck by the tragic loss of Professor Helga B. Salvesen, group leader and co-director of our center. During the last years, Helga established a strong and prolific research group at the Department of Clinical Science (UiB) and the Department of Gynecology and Obstetrics (Helse Bergen), with a focus on genetic and protein biomarkers in gynecologic cancers. She made important contributions in this field and received international recognition. At the same time, Helga was a dedicated scientist and mentor with high standards and a remarkable working capacity, in addition to being a warm and caring person. The CCBIO family, with all her colleagues and friends, will miss her. She leaves behind an impressive and inspiring legacy.

CCBIO is now moving steadily from the establishing phase to meet a range of challenges in the ambitious areas of precision medicine. The biomarker field is an important nexus between basic studies and the open range of diagnostic and therapeutic advancement, including initiatives by "movers and shakers" with biomedical expertise to big pharma representatives and politicians. The recent PD-L1 story is just one national example. Time will tell whether these processes can speed up and become more transparent and even more predictable and precise.

At the conclusion of 2016, CCBIO´s trajectory is very promising. Within the center, several projects are becoming more mature, with increasing international collaboration and interaction. We are actively recruiting younger faculty members to strengthen our future potential. In medical oncology, immunotherapy is moving centre stage, and we recently launched an investigator-based clinical trial of metastatic melanoma, using anti-Axl therapy (BGB324) developed by our collaborator BerGenBio, in combination with immunotherapy. The study is based on the emerging role of Axl regulation for immune evasion. This clinical trial includes an ambitious program of biomarker analyses at baseline and throughout treatment and follow-up, as well as economic profiling, thus highlighting the cost-effectiveness and societal perspectives. At present, Axl related projects range from basic discovery studies to clinical application, with extensive collaboration within CCBIO. In other areas, studies on matrix and vascular biology are going forward, as well as projects on drug repurposing. We have increased the use of mass cytometry and proteomics profiling to account for complexity in biomarker expression patterns, and liquid biomarker projects are being further developed.

We are continuously trying to enrich and reinvent our activities to create an inspiring science culture. The CCBIO Research School for Cancer Studies is an important tool, with basic courses, seminars, junior scientist symposia and our annual international symposium. As two other examples, CCBIO last year initiated a Nordic biomarker network with focus on tissue analysis, and we organized the first Nordic meeting on translational pathology. Also, we co-organized a meeting in Bergen with Oslo Cancer Cluster on the topic of drug repurposing.

Inspiration is a cornerstone in scientific work, and we try to stimulate our colleagues to widen the perspective and search for ideas and inputs across all research areas, and even outside the fields of science. ••

Lars A. Akslen, Director of CCBIO

Vision and Research Areas

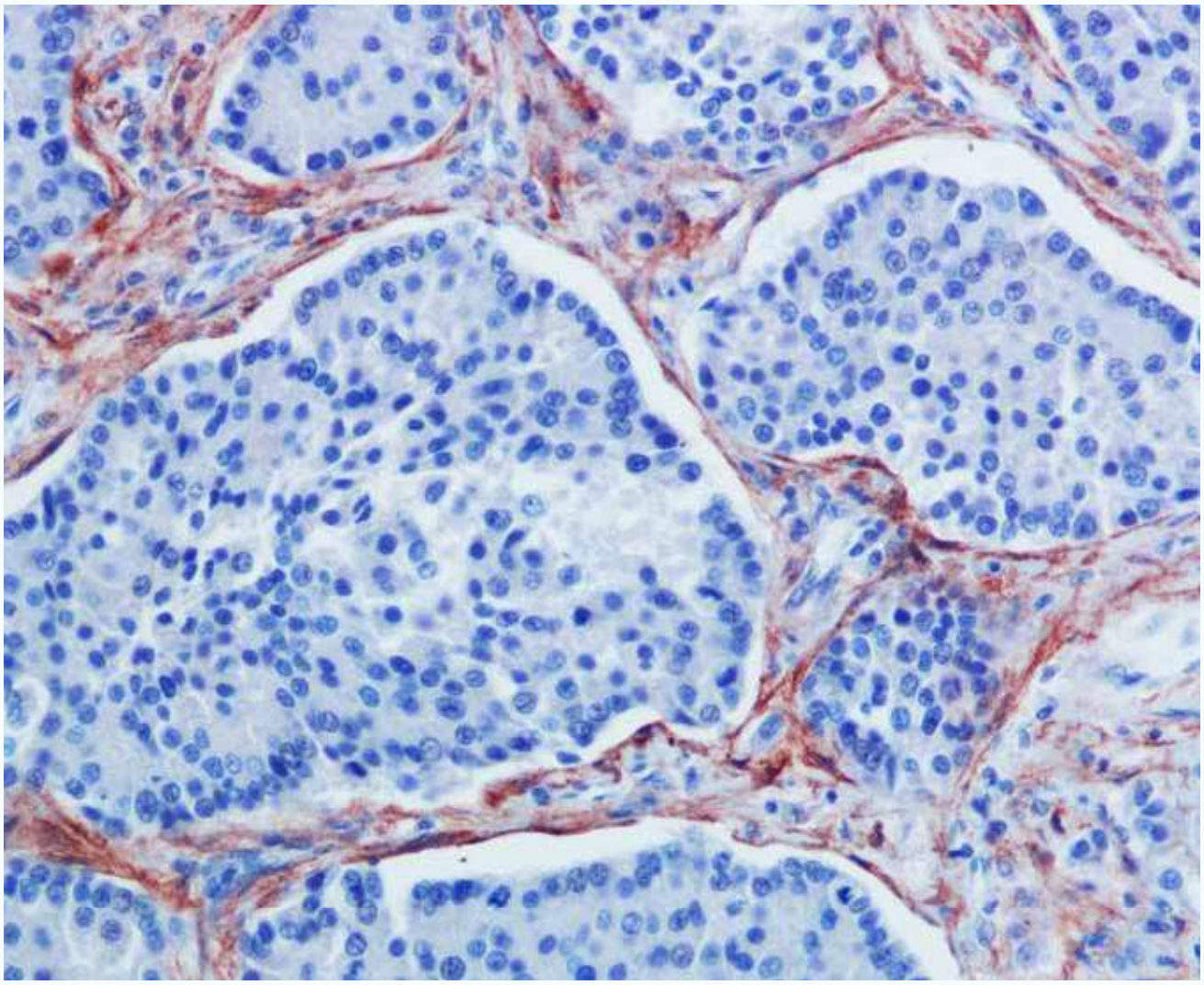
CCBIO aims to discover, validate and translate functional cancer biomarkers to improve biological understanding, early diagnosis of aggressive phenotypes, and cost-effective and responsible treatment of cancer.

CCBIO is focusing on tumor-microenvironment interactions in primary and metastatic lesions, and how tissue context can educate and define aggressive tumor features and predict cancer progression patterns. The center is studying how cross-talk between tumor cells and components in the tumor microenvironment reflect cancer complexity and heterogeneity and determine cancer prognosis, beyond what is given by description of genetic alterations in tumor cells.

CCBIO concentrates on the following overlapping and fully integrated programs:

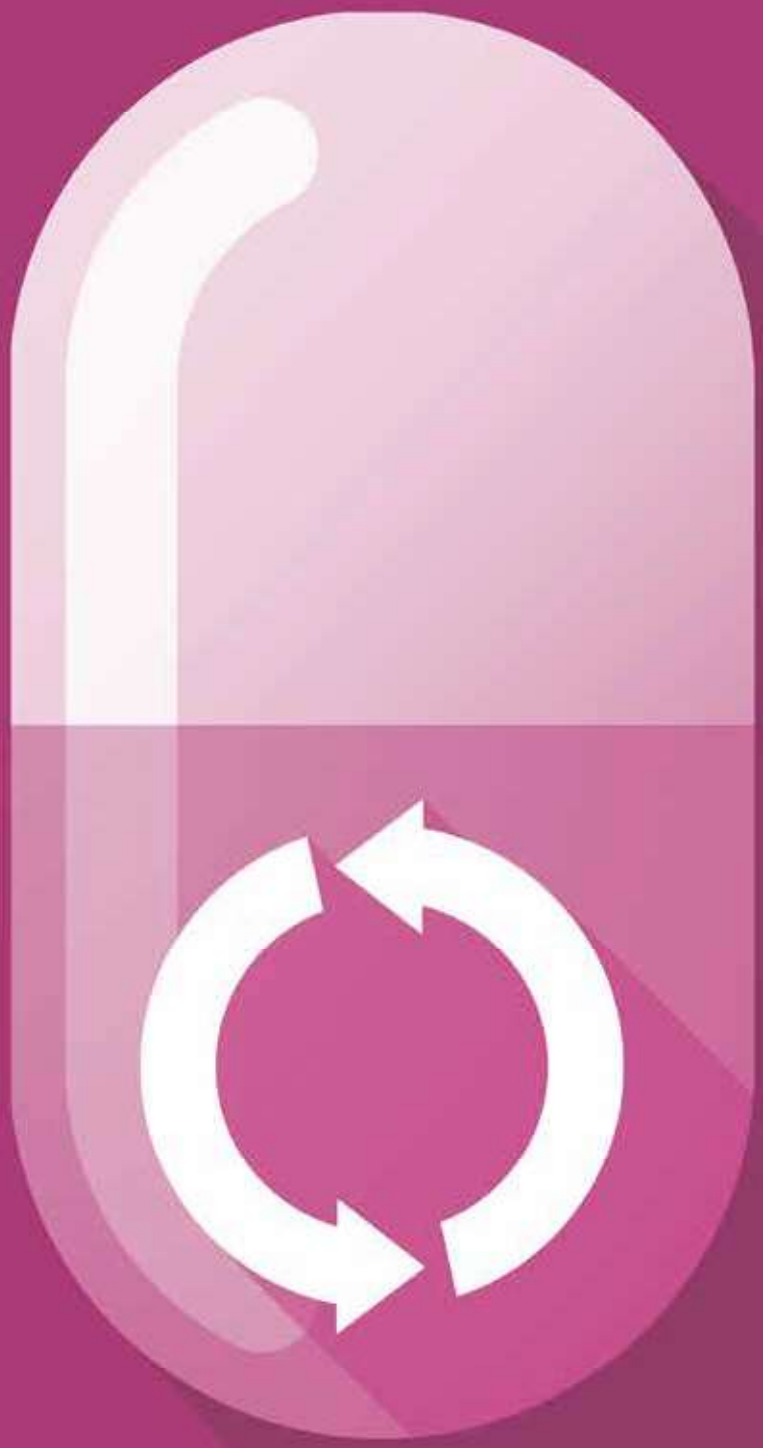
1. **Mechanisms of Tumor-Microenvironment Interactions (Preclinical Studies)**
2. **Exploration and Validation of Cancer Biomarkers (Biomarker Validation)**
3. **Clinical Applications and Trial Studies (Clinical Studies)**

Biomedical project areas are supplemented with integrated ethics and economics projects, focused on how to prioritize and fund expensive cancer treatment in the era of expanding and costly personalized medicine. New collaboration partners, both national and international, have been included to support our efforts. ••



CCBIO Opinion

Text: Bjørn Tore Gjertsen and Karl-Henning Kalland



Repurposing Drugs for Cancer Therapy

Repurposing is a recognized strategy in drug discovery and development where a drug already approved for human use, is screened for new effects and new targets. Repurposing is potentially fruitful because we already know that these drugs are introduced to and distributed in the organism with acceptable and known side effects. It is also often the case that "new substances" which are promising in cell culture, and even in animal models, fail the requirements for absorption, distribution, acceptable side effects and efficiency when they are later tested in the human body.

Based on 1578 FDA-approved (Food and Drug Administration, USA) drugs and drugs in late clinical development, the number of druggable molecules is estimated to 667 among more than 21 000 genes and 1.5 million proteins and isoforms expressed. If an optimal use of these drugs could be exploited across a wider range of diseases, this would expand the therapeutic toolbox considerably. There are several examples of useful repurposing internationally and in our groups.

Thalidomide presents one interesting example. This drug was developed as an anti-emetic and sleeping pill in the late 1950s, resulting in catastrophic occurrence of birth defects when used during pregnancy. Promoted by patient advocacy groups, thalidomide was tested nearly 50 years later with effect against multiple myeloma and stimulated research into thalidomide analogs. One such analog, lenalidomide, was particular effective in myelodysplasia lacking one copy of the 5q chromosome and provided an example of so-called synthetic lethality with 5q deletion. Cereblon, an E3 ubiquitin ligase, was identified as the molecular target of lenalidomide.

In a different approach, our group tested the anti-leukemic effect of the old anti-convulsant and mood stabilizing agent valproic acid in combination with all-trans retinoic acid and theophylline in acute myeloid leukemia, aiming for a combined effect that resulted in increased differentiation and programmed cell death of tumor cells. Novel low-toxic combinations with valproic acid are in development for evaluation in clinical trials.

Our research group employed a fluorescent reporter to screen FDA-approved drug panels for compounds that could inhibit WNT/β-catenin signaling, a pathway that is commonly aberrantly activated in cancer. Several small molecular candidate compounds were found to inhibit activated β-catenin signaling and were next characterized using a method called DARTS. This is a method to identify the molecular target of the compound. The compound axitinib, previously approved as a VEGFR inhibitor against kidney cancer, was found to bind and stabilize the E3 ubiquitin ligase SHPRH, leading to subsequent degradation of activated β-catenin in the cell nucleus. Further testing revealed that axitinib could selectively inhibit WNT/β-catenin signals in both zebrafish and mouse models with reduced tumor development in the mice. Repurposing is not, however, straightforward. Careful design of the screening and evaluation assays is important. Small molecule substances might have more than one molecular target in the cells. The drug concentration required to achieve a desired pharmacological effect can vary strongly between targets. Consequently, if a substantially higher drug concentration is required for a new pharmacological effect, a new preclinical evaluation will be necessary in addition to a new clinical evaluation of toxicity and side effects. At one end of the spectrum, repurposing has the potential to bring old drugs rapidly into new use. At the other end of the spectrum, repurposing could serve to discover leading compounds that could be chemically modified in order to increase target affinity and reduce necessary dosing and toxicity.

The major challenge of cancer therapy today is therapeutic effect in metastatic cancer and surgically non-resectable tumors. A deeper understanding of tumor cell clonal evolution has followed increasing understanding of disease heterogeneity. Therapy of advanced cancer urgently needs a greater toolbox. Repurposing may be one important strategy to increase the number of therapy responders in cancer.

Repurposing may need regulatory steps to move forward, securing approved indications, safety data and allowing insurance reimbursement. An effective moderate cost clinical development plan may be needed to collect sufficient documentation to allow approval of old drugs for new indications. ••

CCBIO Opinion
Text: Eirik Tranvåg and Ole Frithjof Norheim

Prioritization

An increasingly older population, new and expensive treatments and higher public expectations will make fair priority setting essential to maintain a sustainable and just health care system. Through the work of CCBIO, functional cancer biomarkers can evolve to play an important role in this process.

Precision medicines that target specific immune responses or signaling pathways give new hope and treatment options for a range of advanced cancers. However, the price is literally high. Costs per quality adjusted life year (QALY) gained is pushing towards 1 000 000 NOK and beyond, and the demand from patients, physicians and the general public for implementing new drugs is strong. But despite talks of a paradigm shift in cancer treatment, documented treatment benefits remain marginal for some.

Tailoring treatment so that the appropriate medicine is given to the appropriate patient, can increase treatment benefits, reduce side effects and unnecessary treatment, and also potentially reduce treatment costs. It is not controversial to assign biomarkers a central role in this scenario of clinical priority setting, but exactly how biomarkers best can be used is still to be explored. How will biomarker test results influence the physician's decision making? How will average-based calculations of cost and effect be affected by the more detailed and individualized stratification of cancer disease using biomarkers? How will society accept that seemingly identical cancer patients are given different priority and therefore completely different treatments?

The 2016 White Paper on priority setting, "Values in patient health care", and the subsequent political discourse, demonstrated a broad support for the overall goal of the health care system: the greatest number of healthy life years for all, fairly distributed. This will be achieved through three criteria for priority setting: the priority of an intervention increases with the expected utility from the intervention; the priority of an intervention increases the less resources it requires; and the priority of an intervention increases with the severity of disease in the absence of such an intervention.

Cancer biomarkers have the potential to influence all priority decisions: they can help predict the benefit of a selected treatment, save resources through better selection of patients, and give prognostic guidance to evaluate disease severity. Therefore, cancer biomarkers have the potential to influence health care priority setting at all levels.

There are hundreds of new drugs in the pipeline, not only for cancer, but also for common and often chronic diseases like cardiovascular diseases, diabetes, autoimmune and rheumatic diseases. Vaccines, antibodies, stem cell treatment and gene therapy will provide a range of new treatment options that certainly will generate more health. However, without guidance and reliable tools for priority setting, our health care system will not be able to maximize health and distribute it fairly.

CCBIO's work on developing better biomarkers can not only contribute to better treatment for each individual cancer patient, but also inform and facilitate the priority setting processes. This may benefit both individual patients and society as a whole. ••

CCBIO Opinion
Text: Roger Strand and Lars A. Akslen

What is Responsible Cancer Research?

The concept of ELSA - Ethical, Legal and Societal Aspects of Science and Technology - which has been central to the profile of CCBIO since its inception, is gradually becoming supplemented and replaced in Europe by the concept Responsible Research and Innovation (RRI). Originally a European Commission invention, RRI was introduced as a so-called crosscutting principle of Horizon 2020, EU's largest funding program for research and innovation. The Research Council of Norway is currently developing its own RRI framework and implementing it in their biotech, nanotech and ICT research programs. RRI is similar to ELSA but places more emphasis on public engagement with science and the ambition to align research agendas with citizens' needs and concerns.

Recently, Strand and Akslen co-authored a "perspectives" piece for the Journal of the Norwegian Medical Association in which they presented key ethical and social dilemmas on the interface between cancer research and policy. In this piece, they introduced the theory on socio-technical imaginaries and discussed how it may be implemented in RRI frameworks. The piece presents and exemplifies the ELSA/RRI profile of CCBIO for a Norwegian medical audience.

The publication process became interesting in itself as the journal argued that we as authors should "take a stance" in the sense of either fully embracing or fully rejecting technology optimism on behalf of cancer research. The search for a balanced position - an optimistic but critical and reflexive point of view - appeared to be challenging. A very short abstract follows below.

New opportunities in cancer treatment provide health benefits but also risks of higher costs and more prioritization dilemmas. Critical discussion of how cancer research imagines the future can contribute to more responsible research and health policies. Frameworks for responsible research and innovation provide useful concepts for such a discussion. ••


EAST
WEST

CCBIO Opinion

Text: Jean Paul Thiery (affiliated professor at CCBIO)

The Decathlon of the Young Researcher

Performing a Pubmed search is an important daily activity for a scientist; however, not everyone realizes that we now have access to more than 26 million publications following the quasi-exponential increase in the number of indexed papers in this database over the last 10 years. Even in our own research focus, we struggle to select appropriate articles to read. Theoretically, we should be reading more than 10 to 50 papers a day! Review articles are indeed a very helpful way to get a broader picture of our own (or a related) field of interest. However, reviews are not always easy to read if you are not already an expert in the field, and many are redundant or confusing, some written by non-experts that are neither informative nor accurate, and often tainted by a degree of plagiarism of another recent review. For young investigators, the array of information available in the literature becomes so overwhelming that most cannot really triage what is relevant for their research. Artificial intelligence-based categorization has not yet been established to rationalize the results or provide advanced mechanistic insight or a robust platform upon which we can engage in new projects. Mentors need to organize brain-storm sessions to help young researchers formulate new strategies to overcome some of these formidable issues.

Another major concern for the young scientist is career planning. Finding a tenured position in a competitive research institution is a major challenge. The CNS (Cell/Nature/Science) syndrome has spread worldwide, and so, constructing a curriculum vitae with a list of publications in high impact factor journals is a real nightmare for most young academics. Obviously, one should try to attain a very good postdoctoral fellowship in a reputable laboratory that frequently publishes in these high-profile journals. The temptation is indeed to do everything possible to provide the head of the laboratory with an exciting manuscript, sometimes needing to cosmetize the results so that they are supported by the boss and in line with the tone of the journal. In rare cases, cosmetics are insufficient, and some resort to fabricating part of their results. The next challenge for the young investigator is then to assemble a team and secure sufficient funding for a quick start.

How to train these young scientists at CCBIO is a challenge; but, clearly, there are good opportunities in this non-stressful environment. The visiting professors have certainly a role to play in this important mission. ••

Organization of the Center

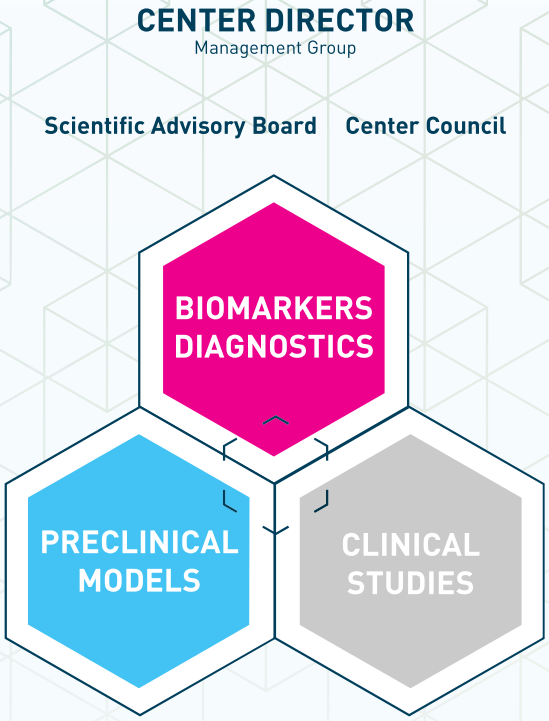
CCBIO is organized across seven departments and four faculties at the University of Bergen (UIB). Its main activities, eight PIs and most of the other staff are located at the Faculty of Medicine and Dentistry´s departments (MOF) the Department of Clinical Medicine (K1), the Department of Clinical Science (K2), and the Department of Biomedicine (IBM)

The majority of CCBIO´s PIs also hold positions and funding at the regional health authorities Helse Bergen and Helse Vest. In addition, CCBIO has activities and employees at the three Departments of Informatics, Economics and Global Public Health and Primary Care, the Center for the Study of the Sciences and the Humanities at the University of Bergen and at the London School of Hygiene and Tropical Medicine.

Research Management
In terms of science management, CCBIO is organized in three integrated research areas and programs (preclinical studies, biomarkers and clinical studies) and four associate programs (prioritization, ethics, economics and bioinformatics) that support the three main research areas (see organizational chart). Lab space and core facilities are available for CCBIO, as is the Clinical Trials Unit at Haukeland University Hospital. The eight principal investigators have monthly meetings to discuss administrative and scientific issues and update each other on development and progress. In addition to taking part in some of the monthly meetings, CCBIO's associate investigators together with the principal investigators take part in a full day strategy seminar bi-annually. The monthly meetings and the bi-annual strategy seminars are important platforms for increased collaboration within CCBIO.

Management group
In 2016, CCBIO was initially managed by the director, Professor Lars A. Akslen, the co-director, Professor Helga B. Salvesen and the administrative leader, Geir Olav Løken. Due to Salvesen´s tragic and unexpected passing in January

Organization Chart of the Center



2016, Professor Bjørn Tore Gjertsen was appointed as co-director. The management group is assisted by four finance officers, a web and newsletter editor, a journalist and a wide range of other administrative staff allocated to CCBIO in parts of their positions. The co-located offices for the management group are in the main building of Haukeland University Hospital (Sentralblokken, second floor).

Integration with the Host Institution and Administrative Support

In terms of administrative support, CCBIO aims to use its funds as efficiently as possible, ensuring excellent administrative services for its scientists and a good climate for collaboration with its departmental and institutional partners. Consequently, CCBIO is organized to retain full control over resources while the day-to-day administration is delegated to the involved departments. As a main principle, funds and positions are located at the respective department where the research takes place. This enables researchers to interact with their familiar support staff, thereby minimizing resources used on day-to-day administration and also gives CCBIO common interests with the departments. This model has been successful as it has proved to be efficient and robust, and has ensured excellent collaboration with the involved departments. ••

Scientific Advisory Board

The CCBIO Scientific Advisory Board (SAB) consists of Professors Carl-Henrik Heldin, Bruce Zetter and Ate van der Zee, all three being internationally leading researchers in CCBIO-relevant fields. The SAB's mandate is to give the center director and center staff advice on science and scientifically relevant matters. The SAB has convened once a year for a full day meeting with the CCBIO PIs and associate PIs, following the CCBIO Annual Symposium.

In its 2016 report, the SAB stated that it was impressed with the progress made during the last year and particularly CCBIO's quick and substantive responses to comments made by the SAB. This especially applies to CCBIO's efforts on improving the bioinformatics infrastructure, initiation of clinical trials, integration of imaging modalities into the work of the center, increased emphasis on liquid biopsy in cancer management, and acquisition of supplemental funding.

In the SAB's opinion, CCBIO displays excellence and scientific rigor in its commitment to translate discoveries to a clinical setting and is rapidly becoming one of the world leaders in the study, discovery, application and translation of cancer biomarkers. It sees CCBIO's basic biomarker research as a core strength and finds it encouraging that the new clinical trials are now in the process of accruing patients. The SAB found it especially promising that two of the trials are in collaboration with industry partners and that CCBIO is closely integrated with the Clinical Trials Unit at Haukeland University Hospital. The SAB encouraged the continued exploration of biomarkers associated with immunotherapy efficacy as well as research on biomarkers associated with drug sensitivity and with the acquisition of chemo resistance in solid and liquid tumors. CCBIO's effort within economics and Ethical Legal and Societal Aspects (ELSA) was characterized as unique and valuable and the SAB recommended a continued expansion of these programs and further integration into CCBIO's medical research effort.

The 2016 SAB report also stated that CCBIO continues to display excellence in its scientific and administrative management, pointing out that the matrix based governance and functioning of CCBIO can provide a model for other similar Norwegian scientific centers. Further, CCBIO's educational effort through the courses of its Research School for Cancer Studies as well as outreach towards the scientific audience through its symposium, research seminars and meetings were characterized as truly outstanding. CCBIO's Junior Scientist Symposium was mentioned as a seminal effort that should be exported to other centers. CCBIO's general dissemination effort in terms of website, newsletters, reports and public dissemination media outlets, the SAB felt was highly professional and represented CCBIO particularly well.

Further, CCBIO's efforts in recruiting international collaborators was characterized as excellent, especially CCBIO's program of 10% adjunct positions as it has given very good collaborative ties both in terms of scientific quality and range. The SAB encouraged further recruitment of adjunct researchers, e.g. with leaders within the related fields of cell-free DNA studies and exosome-associated biomarkers. The SAB was also pleased with CCBIO's efforts to improve the gender balance in its PI group by recruiting female junior- and associate investigators. ••

Carl-Henrik Heldin is the chairman of CCBIO's SAB and is professor and director at the Ludwig Institute for Cancer Research, Uppsala University, Sweden, and chairman of the Nobel Foundation.

Ate van der Zee is professor of gynecological oncology and member of the Board of Directors at the University Medical Center Groningen, the Netherlands.

Bruce Zetter is the Charles Nowiszewski Professor of Cancer Biology at Harvard Medical School and Boston Children's Hospital, Boston, MA, USA.

Center Council

The Center Council's mandate is to provide advice to the CCBIO management team, mostly on administrative and some strategic issues, and to contribute towards ensuring that the activity at the center is in accordance with the contract with the Research Council of Norway (RCN). The Center Council has its focus mainly on potential local synergies, whereas the CCBIO Scientific Advisory Board addresses the scientific and international perspective. The Council is composed of the MOF dean (chair) and vice-dean for research, the heads of department from IBM, K1 and K2, the head of research from Haukeland University Hospital and the CCBIO and MOF directors as observers and the CCBIO administrative leader as council secretary. During the establishing phase in 2013 and 2014, the Center Council met twice a year and has thereafter, by its own choosing, met annually. ••

Highlights From the First Four Years

During its first 3.5 years, CCBIO has established promising scientific activities with increased internal and international collaboration as well as industry interaction and is now a well-organized CoE with robust organization and administrative support.

Nine research groups focus on the following core questions: *How does the cancer microenvironment interact with and support tumor cells to promote cancer progression, and how can various drivers be blocked? Which novel biomarkers can predict tumor aggressiveness and response to therapy?* Studies aim at a refined understanding of tumor complexity and plasticity, especially related to the microenvironment, followed by biomarker and therapy development. To support these aims, basic studies, translational projects, and clinical trials have been established. Integrated studies in ethics and economics are also performed.

Basic projects have focused on the importance of tyrosine kinase Axl for tumor-stroma interactions. One study demonstrates a unique requirement for Axl-dependent tumor plasticity in aggressive pancreatic cancer (Kirane et al., Cancer Res 2015). Additional findings in the Lorens and Brekken (adjunct professor at CCBIO) groups have formed the basis for clinical translation of Axl inhibitors. Collaborating with BerGenBio, Axl-inhibitor BGB324 is now included in many clinical trials with extensive tissue and liquid based biomarker programs. Importantly, a trial combining BGB324 and immunotherapy has been initiated by CCBIO.

Kalland´s Group has developed a new in-house prostate tumorigenesis model and initiated new treatment by cryoimmunotherapy of aggressive prostate cancer (NCT02423928). Cell lines from mice tumor tissue revealed a novel autocrine IL6/STAT3 mechanism present in tumor-initiating cells (Qu et al., Cancer Res 2013). By screening biologically active compounds and FDA-approved drugs according to repurposing, compounds with the novel attribute to block WNT/β-catenin and STAT3 signaling and tumor formation in mice have been identified (Qu et al., PNAS 2016). WNT/β-catenin and STAT3 signaling play essential roles in immune evasion, and it is hypothesized that WNT/β-catenin/STAT3 inhibition can be used to enhance immuno-therapy. The Gullberg Laboratory concentrate on the extracellular tumor matrix. The team characterized integrin α11β1, which is expressed on subsets of normal and cancer-associated fibroblasts. It was demonstrated for the first time that stromal integrin α11 expression in vivo is important for tumor progress by alterations of stroma stiffness (Navab et al., Oncogene 2015). Generation of novel α11 monoclonal antibodies have been performed, with a potential for translational studies. In collaboration with Reed´s Group, the influence of α11β1 on xenograft tumor growth (breast and prostate cancer) has been studied in mice (Reigstad et al., PLoS One 2016). Gullberg is also collaborating with Johannessen´s Group on the role of α11β1 in oral cancer.

The Akslen Group concentrates on the tumor vascular system and how novel biomarkers can predict aggressive disease and response to treatment. In one key study, tissue-based microvascular proliferation could be predicted by a 32-gene RNA-based expression signature and linked to 6p21 amplification (Stefansson et al., Oncotarget 2015). Further studies aim to explore novel angiogenesis drivers in this chromosomal region. In a collaborative study with Dr. Watnick, Boston (adjunct researcher at CCBIO), the role of stromal regulators prosaposin and thrombospondin-1 was reported for ovarian cancer progression (Wang et al., Sci Transl Med 2016). The Salvesen Group has performed studies on genetic and protein biomarkers in gynecologic cancers. In a landmark paper from 2014, genomic alterations of cervical carcinoma were mapped (Ojesina et al., Nature 2014). Data on novel mutational changes and potential treatment targets in this HPV-related and frequent cancer type were reported. In a study of endometrial cancer, genomic alterations in primary tumors and metastases were presented with novel observations (Gibson et al., Nat Genet 2016). The Gjertsen Group focus on the design of novel biomarker intense clinical trials at an early stage, using modalities such as single cell protein analysis, liquid biopsy and mass cytometry, with longitudinal data. Several clinical trials with companion biomarker programs have been initiated. In collaboration with Straume´s Group and Lorens´ Group, a national investigator-based study of metastatic melanoma was initiated, using a combination of anti-Axl treatment (BGB324) and immunotherapy (PD-1) (PI: Straume; NCT02872259). Straume´s Group also reported a role of the tissue based biomarker HSP27 in predicting response to anti-angiogenesis therapy in metastatic melanoma (Schuster et al., PLoS One, 2016). In terms of impact on treatment, studies from Akslen´s Group, on tumor proliferation and lymph node metastases in breast cancer, have influenced new national guidelines on diagnostic procedures from the Norwegian Breast Cancer Group.

CCBIO has created a stimulating science culture for young investigators and future group leaders. The CCBIO Research School for Cancer Studies (RSCS) is the first cancer-based research school in Norway and includes basic courses, junior scientist symposia (four times a year, organized by postdocs), visiting faculty and mentoring sessions. The RSCS includes CCBIOs monthly research seminars, special seminars and CCBIO's annual symposium, the latter is now an established international meeting with well above 200 participants. Networks have been initiated, such as the Nordic Biomarker Network, originating from the First Scandinavian Pathology Symposium in Bergen 2016, focusing on advanced tissue marker studies.

Importantly, CCBIO has initiated projects in ethics and economics related to biomarkers and cost-effective practice. Two books are soon to be published: Lars A. Akslen & Randolph S. Watnick (Eds.) Biomarkers of the Tumor Microenvironment. Springer 2017 (in press); Anne Blanchard & Roger Strand (Eds.) (2017): Social and economic aspects of cancer biomarkers. Bergen: Megaloceros Press 2017 (in preparation).

CCBIO is actively engaging with the society, through participation in public meetings, in social media, and through mass media, with stories and reports in newspapers and on prime-time television, communicating new developments in the field and commenting on research findings and oncology politics. ••

Scientific Activities and Progress

CCBIO has a focus on tumor-microenvironment interactions and plasticity programs in primary and metastatic lesions and how these can define aggressive tumor phenotypes and predict cancer progression and treatment response. CCBIO has three overlapping and well integrated research areas: basic studies of cancer mechanisms, discovery and validation of cancer biomarkers, and clinical studies. An ambition is to obtain rapid transfer of knowledge to practical medicine. Since the opening of CCBIO in 2013, several research projects have been initiated and are now running in different teams, with increased internal collaboration and external networking.

In the area for basic studies, projects are focusing on how tumor cells interact with the surrounding microenvironment, by epithelial-mesenchymal transition, plasticity and transdifferentiation, angiogenesis induction and matrix dynamics, leading to growth and metastatic spread.

In **Kalland´s Group**, one key activity has been the generation and characterization of a new experimental model of stepwise prostate tumorigenesis, comprising benign cells (EPT1), pre-malignant mesenchymal type cells (EPT2), tumorigenic (EPT3-N04/EPT3-PT1) and metastatic (EPT3-M1) cells in mice, with different phenotypes and behavior, and applied in studies of transcriptional reprogramming and drug discovery. This is the first experimental prostate cancer model that derived tumorigenic prostate cells by using physiological selection pressure only. Epithelial-to-mesenchymal transition (EMT) was an early feature of the model, and tumor initiating cell (TIC) subpopulations have been characterized among the tumorigenic cells. Work on the experimental tumorigenesis model has resulted in increased insight into the potential of gene expression reprogramming as a source of cell heterogeneity. Subpopulations of TICs show activation of the WNT pathway and an autocrine IL6/STAT3 feedback loop associated with tumorigenesis. Recently, this model has been used in a drug discovery and development program, resulting in 5 WNT/β-catenin inhibitor candidates (with patents pending). Kalland´s team, in collaboration with Gjertsen and others, have initiated an ongoing phase I clinical trial of cryoimmunotherapy for advanced prostate cancer, including an intensive biomarker program with liquid biopsy projects and collaboration with Dr. Pantel, tissue-based biomarker analysis, and mass cytometry profiling. Within CCBIO, Kalland is collaborating with Gjertsen, Lorens and Akslen.

Gullberg´s Group has studied how different connective tissue cells interact with tumor cells and the extracellular matrix, a process that is similar to wound healing and scarring. In particular, integrins are important regulators of these processes. The group has established a model using A549 lung cancer cells to study tumor-stromal interactions, recently reporting that integrin α11 from fibroblasts is important to stimulate tumor cells to secrete soluble factors influencing immune cell recruitment and tumor growth. Also, integrin α11 was found to be important for stromal stiffness and tumor spread in non-small cell lung cancer. Gullberg and co-workers have found that integrin α11β1 is the receptor on fibroblasts that mediates contraction of wounds, and that this mechanism is mediated via c-jun N-terminal kinase (JNK). This is an important step forward in the efforts to delineate the molecular mechanism of cell-collagen interactions. The team is now also working to generate and

characterize novel integrin α11 blocking antibodies with potential use as robust biomarkers in tissue analyses, and work is ongoing to establish and characterize an α11 promoter-Cre mouse strain. Within CCBIO, Gullberg is collaborating with Reed, Akslen, Johannessen, and Gjertsen.

In collaboration with Gullberg and others, **Reed´s Group** has a focus on the dynamic extracellular matrix and on interstitial fluid pressure (Pif) in tumors and how this can be modified. This is relevant for imaging technologies and for distribution of drugs. Tumors have an elevated Pif that acts as a functional barrier towards transcapillary fluid flux that can block the distribution of cytostatic anti-cancer agents. The group has reported that integrin α11 has an influence on the interstitial pressure, and subsequently on tumor growth patterns in mice lacking this integrin (breast and prostate cancer models). The results point to important biophysical features of the tumor microenvironment and their importance for cancer progress. Reed´s group has also been working on the use of improved imaging techniques (DCE-MRI) in determining tumor vasculature and transcapillary transport in preclinical models. Lately, the team is studying the interaction between the genetic background of integrins (using various mouse strains) and growth of breast cancer models. Studies on the effect of hyperbaric oxygen on experimental tumor growth are ongoing. Within CCBIO, Reed is collaborating with Gullberg and Akslen.

Gullberg's group has identified integrin α11 as a key regulator in stroma-endothelial cross talk.

Johannessen´s Group has worked on basic and translational aspects of oral cancer with focus on cancer-host interactions, particularly between the surface epithelium and the underlying connective tissue. The team has established novel in vitro assays of human tissue-based 3D cell culture models of normal mucosa and oral cancer tissue, and a new rodent oral cancer model. In collaboration with Gullberg´s group, integrin α11 has been identified as a key regulator in stroma-endothelial cross talk. Johannessen´s team now aims to develop a diagnostic and prognostic biomarker profile that can stratify patients with oral premalignant and malignant lesions for a more individualized therapy, and they have reported a "malignancy index" signature which is now being validated. The group identified two distinct fibroblast (CAF) subgroups in oral squamous cell carcinoma based on transcriptome analysis of primary cells from human cancers: a CAF subgroup with a gene expression profile closer to normal fibroblasts, having a more motile phenotype and deeper carcinoma cell

Studies on the progenitor cell marker Nestin indicated an ability to identify BRCA-1 related breast cancer and the aggressive basal-like phenotype

invasion; and a CAF subgroup with a more divergent gene expression profile, having a more stationary phenotype, with less tumor formation and invasion. This study points to functional heterogeneity within tumor associated fibroblasts. Within CCBIO, Johannessen collaborates with Gullberg, as well as Junior Investigator Costea.

The Lorens Group works on cellular plasticity, such as stem cell differentiation and transdifferentiation, a critical prerequisite for adult tissue homeostasis and injury repair. Using comparative functional approaches, the team is investigating the regulation of tumor cell plasticity and maintenance of normal adult stem and progenitor cells. Recent results highlight the Axl receptor tyrosine kinase as a key regulator of both normal adult epithelial stem/progenitor cells and a determinant of carcinoma cell plasticity. The studies on Axl signaling have provided new insights into the regulation of tumor phenotypic heterogeneity and form the basis for the recent clinical translation of novel Axl inhibitors (e.g. BGB324). Importantly, it was recently also reported that Axl-activity could be blocked by low-dose warfarin. The group continues to study how microenvironmental factors and immune cell challenge illicit tumor cell phenotypic plasticity that engenders acquired resistance to both chemo- and immunotherapeutic agents. On this background, a national investigator-sponsored trial on metastatic melanoma with BGB324 anti-Axl therapy and anti-PD-1 (PI Straume) has been launched, with an intensive biomarker-program included. Within CCBIO, Lorens is collaborating with Gjertsen, Straume and Akslen.

Akslen´s Group has focused on the use of biomarkers for improved molecular classification and grading of malignant tumors, as a better guide for targeted treatment. Studies of human tumor samples (primary and metastatic lesions) are combined with experimental cell and animal models to improve translation. The team is concentrating on studies of the tumor microenvironment, especially tumor-vascular interactions and angiogenesis markers, and the use of precise indicators for tumor proliferation with clinical applications. The team has reported novel tissue-based angiogenesis biomarkers. As examples, microvessel proliferation was studied in several human tumor types and provides better prognostic information than vascular density. This marker proved valid also in xenograft models of breast cancer. Further, a 32-gene RNA-based expression signature for microvessel proliferation gives prognostic information in endometrial and breast cancer, and was linked to 6p21 amplification. An 18-gene signature was identified for vascular invasion by tumor cells, pointing towards novel mechanisms involved in early metastatic spread, and this signature was strongly prognostic in breast cancer. Studies on the progenitor cell marker Nestin indicated an ability to identify BRCA-1 related breast cancer and the aggressive basal-like phenotype. During the last year, the team has reported on tumor proliferation markers in breast cancers and how these change from primary tumors to metastases. Data on proliferation is currently used in definition of Luminal B breast cancer and treatment decisions. Whereas 15% of the cases changed from low (primary tumors) to high proliferation (metastases), treatment consequences are currently not clear in guidelines but are being discussed. Further, a paper on improved definitions of extra-nodal growth in lymph node metastases of breast cancer has led to new national guidelines. In a collabora-

tive study with Dr. Watnick (Boston), the importance of prosaposin (PSAP) and thrombospondin-1 (TSP-1) for ovarian cancer progression was reported (Wang, 2016), expanding on previous findings from this collaboration. Within CCBIO, Akslen is collaborating with Kalland, Gullberg, Reed, Lorens, Straume and Gjertsen, as well as Junior Investigators Wik and Krakstad.

Gjertsen´s Group, supported by the Early Phase Clinical Trial Unit at Haukeland University Hospital, has been the initial center for a phase I trial (BGBC003; clinicaltrials.gov) in AML using the novel anti-Axl drug BGB324 (per oral formulation) in collaboration with BerGenBio. The trial is now also recruiting in Houston (Texas) and Germany. In parallel, more focused small trials in chronic myeloid leukemia has been performed and completed in collaboration with the Nordic CML Study Group, providing a unique material for proof of principle testing of how to monitor signaling in cancer cells as biomarkers for risk and therapy response. Importantly, new instrumentation funded by Bergen Research Foundation in 2015, a mass cytometer, allows multiparametric analysis of single tumor cells. Through CCBIO and the Helse Bergen Clinical Trials Unit, the team will address clonal evolution in AML through mass cytometric analysis. The team has performed extensive studies of signaling patterns in CML cases. There is a need for more direct biomarker analyses for early kinase inhibitor therapy, based on increasing reports of adverse events. The group has demonstrated that the drug target can be monitored in the actual cancer cells, and suggests that cellular signal systems involved in signaling of BCR-ABL outline the long time response. This single cell analysis of cellular signaling fit with the blood levels of the drug, and is likely to be a preferred method for future precision medicine with signaling targeted therapy. In the phase I trial with BGB324, the concepts of single-cell biomarker profiling are tested. Different analysis methods and read-out panels have been developed during 2016. The possibility to employ single cell biomarker technology in drug development is very promising. The strategy is also to move these concepts beyond blood cancers to metastatic solid cancers, based on strong collaborations within CCBIO, and several trials are now prepared. In collaboration with Kalland, a phase I clinical trial of cryoimmunotherapy has been initiated for patients with metastatic castration resistant prostate cancer. The trial is based upon a dendritic cell based immunotherapy protocol in collaboration with the Haakon Ragde Foundation in Seattle (USA). The associated biobank is used for development of advanced immune-monitoring and circulating tumor cell enumeration as well as organoid cell culture isolation. Within CCBIO, Gjertsen is collaborating with Lorens, Kalland, Straume, Akslen and Gullberg, as well as Associate PIs Bjørge and McCormack.

Straume´s Group is focusing on the identification of predictive biomarkers for therapy response in academic trials of patients with metastatic melanoma and kidney cancer. In melanoma, previous results of a clinical trial with the anti-VEGF antibody bevacizumab documented that ~30 % of the patients experienced clinical benefit of the treatment. Based on a screen of multiple candidate markers in tissues of primary tumors and metastases, as well as serum markers, HSP27 tissue expression in metastatic lesions was able to predict therapy response. The team continues to screen for serum-based biomarkers of therapy response, to anti-angiogenesis treatment (bevacizumab) and immunotherapy (ipilimumab). Due to the recently reported role of Axl in immune evasion, a national investigator-sponsored trial on metastatic melanoma with BGB324 anti-Axl therapy and anti-PD-1, directed by Straume, has been launched, with an intensive biomarker-program included. Focus will be on predictive markers of response. In a collaboration with national centers, 150 patients with metastatic melanoma were treated with ipilimumab, a CTLA-4 antibody (phase IV clinical trial). Blood and tissue samples are being studied to identify predictive markers of response. In a trial series of 45 cases with metastatic clear cell renal carcinoma treated by VEGF-inhibition (sunitinib), the team is now working on a set of candidate biomarkers for their predictive value. In a study that could be of major clinical significance, the Straume Group reported that breast cancer recurrence can be influenced by the timing of surgery. The finding might lead to increased awareness about the role of surgery in high risk patients and

increased use of immediate surgery. Within CCBIO, Straume collaborates with Lorens, Gjertsen and Akslen.

The Bergen Gynecologic Cancer Group (previously led by Salvesen) has made significant efforts in biomarker discovery and validation in gynecologic cancers, at the genetic and protein levels, with special focus on endometrial cancer and hormone receptor regulation and impact. For both estrogen receptor (ER) and progesterone receptor (PR), loss of expression is linked to aggressive disease and poor survival. ATAD2, a cofactor for ER, was strongly linked to aggressive signatures, while FOXA1, another ER cofactor, showed an unexpected switch in expression from primary tumors to metastatic lesions. Loss of both ER and PR predicted lymph node metastases, and this finding led to determination of ER/PR status for endometrial cancer as a stratifier for lymphadenectomy in a phase 4 implementation trial (MoMaTEC2). Stathmin expression was found to predict clinical response to taxane treatment in endometrial cancer, both in preclinical and clinical settings. This finding has been taken to a phase 2 integrated biomarker trial for paclitaxel treatment in endometrial and ovarian cancer (MoMaTEC2). The team continues studies on genetic alterations in gynecologic cancer, in collaboration with the Broad Institute (Boston). In particular, data from an extensive molecular profiling of genomic alterations in cervical carcinomas were presented (published in Nature). Similar studies on endometrial cancer, also in collaboration with several other teams, are ongoing. Further, the team has studied different imaging modalities in preclinical and clinical settings in relation to angiogenesis and clinical characteristics. The findings are relevant for preoperative patient stratification.

In summary, several efforts and initiatives within CCBIO, with increased internal and external collaboration, are now up and running. The projects are spanning from matrix biology and plasticity programs, through discovery and validation of biomarkers and signatures, to clinical trials with targeted biomarker panels using liquid biopsy and single cell analysis. In this context, the programs on ethics and economics of biomarker based therapy, are also expanding and are being integrated in the recently established clinical trials. ••

Societal Impact, Innovation and Industrial Impact

CCBIO performs research on cancer biomarkers along the entire chain from studies of biological mechanism to clinical trials. Our main societal impact resides in this sense in medical innovation and the improvement of cancer diagnostics and therapies. The main measure of this impact is ultimately its effect on the quality and cost-effectiveness of cancer treatment; it cannot be precisely measured on the short-term. By cost-effectiveness we refer to the challenges of the increased cost of medical services and notably of cancer treatment, which also raise difficult ethical issues of which conditions and patients to prioritize in the public health services. Better knowledge of cancer biomarkers is likely to affect the prioritization dilemmas; however, the nature of that effect depends on the nature of the knowledge to be discovered.

The question of the societal impact of CCBIO is accordingly also a question about the process of caring for and reflecting upon the societal impact. A specific feature of CCBIO is that it integrates research on its ethical, societal and economic aspects into the cancer research proper. A substantial part of the research budget is devoted to economists, ethicists and social scientists who continuously interact with cancer researchers at all levels in the consortium through workshops, informal meetings, PhD courses, conferences and co-authored papers, including an upcoming anthology of the ethical, economic and societal aspects of cancer biomarkers.

Another feature integral to CCBIO's strategy of anticipation and reflection upon its societal impact is its continuous and extensive dissemination towards and interaction with civil society. As documented by our annual reports, we have invested a major effort into communicating prospects and challenges of cancer biomarkers in a number of media channels (including national and regional TV and newspapers), and we participate in public dialogue events, interacting with citizens, experts, authorities and non-governmental organisations such as the Norwegian Cancer Society. For instance, in 2015 we co-organized public meetings together with the Norwegian Academy of Science and Letters and the Philosophical Polyclinic (NGO), respectively, on politically contested issues of expensive cancer treatments. In this way, we wish to practice what currently is being introduced into European and Norwegian research policies as the principle of Responsible Research and Innovation (RRI).

The research environment at CCBIO comprises a high degree of innovation. The European Commission defines innovation as "change that speeds up and improves the way we conceive, develop, produce and access new products, industrial processes and services. Changes that create more jobs improve people's lives and build greener and better societies." Since its inception, CCBIO has endeavored to translate discoveries and facilitate the industrial and job-creating impact of research discoveries. An embodiment of this principle is the biotechnology company BerGenBio AS (www.bergenbio.com). Based on research from the Lorens group on the Axl receptor, and developed via support of Bergen life science innovation support mechanisms and venture capital, BerGenBio has grown into a top-tier biotechnology company developing first-in-class cancer treatments in world-wide clinical trials. Currently employing more than 30 people, many recruited from the UiB/HUS biomedical research community, BerGenBio demonstrates the ability of the Bergen research environs to drive innovation. Several CCBIO principle investigators (Gjertsen, Straume, Akslen, Lorens) have contributed to the successful clinical translation of the BGB324 Axl inhibitor, providing new basic research insights, novel clinical trial design and development of new biomarker strategies for patient stratification through specific R&D collaborations and mentoring of shared industrial PhD candidates. These efforts have gained national and international recognition as BerGenBio expands its clinical trial portfolio and results are presented at key cancer meetings in 2016 (AACR, ASCO, ASH, ENA, ESMO). CCBIO continues to benefit from this strategic alliance that attests a high level of biomedical innovation. A CCBIO investigator-initiated clinical trial (Straume) with the Axl kinase inhibitor BGB324 in combination with targeted and immunotherapeutics for melanoma has attracted collaborators from renowned US biomedical research centers (Harvard Medical School, MIT, Vanderbilt) to conduct in-depth biomarker studies. CCBIO supports national innovation initiatives through board memberships and active participation in dialogue with policy and funding institutions. ••

Research Groups with Princial Investigators (PIs)

During 2016, research efforts have been increasing in the core groups, as reflected in the list of publications. Many of the studies demonstrate an increased collaboration within CCBIO, but also exemplify how local teams can collaborate successfully with international environments and networks.

« Musical landscapes represent a source of continuous energy and inspiration »

CANCER BIOMARKERS

LARS A. AKSLEN GROUP

About the group and its research focus
The Tumor Biology Research Group was established in 1995 at The Gade Institute, later the Department of Clinical Medicine, (UIB). The main purpose has been to explore and validate novel biomarkers for more biologically based classification and grading of cancers, as a better guide for precise treatment. The group has focused on tumor-vascular interactions and how to determine tumor proliferation for clinical applications.

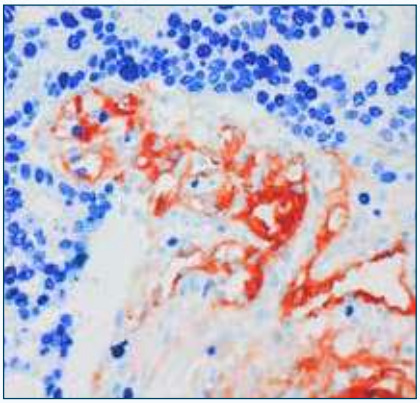
The group´s projects
The aim of the individual studies is to provide better biological understanding and improved markers which can assist in prediction of aggressive tumor behavior and be clinically helpful. The group has concentrated on tissue-based biomarkers examined in cohorts of various human cancers (breast cancer, malignant melanoma, prostate cancer), in combination with cell and animal models to improve translation. The team is currently targeting the following projects:

- *Proteomic profiling and tissue deconvolution of luminal (receptor positive) and non-luminal (receptor negative) breast cancer*
- *Expression of Nestin (NES) as a marker of BRCA1-related, basal-like and aggressive breast cancer*
- *Precision markers of tumor proliferation and clinical applications in breast cancer*
- *Biomarkers of stromal characteristics and tumor-vascular interactions in aggressive cancers*

Research results
The team reported that increased microvascular proliferation was associated with certain gene expression patterns and 6p21 amplification (Stefansson, et al.). Data indicated that there is a difference in blood vessel and lymphatic tumor invasion across subtypes of breast cancer (Klingen, 2016). Findings indicate that tumor proliferation in metastases might be important to predict tumor behaviour (Aziz, 2016). This is relevant for treatment guidelines. Importantly, 15% of the cases changed from low (primary tumors) to high proliferation (metastases), but treatment consequences are currently not clear. Further, a paper on improved definitions of extra-nodal growth in lymph node metastases of breast cancer has led to new national guidelines (Aziz, et al.). In melanoma studies, and for the first time, a tissue-based biomarker (HSP27) significantly predicted the response to bevacizumab treatment of metastatic disease (Schuster, 2016). BRAF-V600E protein expression was found to represent a novel marker of melanoma progression, better than mutation status (Hugdahl, 2016). In a collaborative study with Dr. Watnick (Boston), the importance of prosaposin (PSAP) and thrombospondin-1 (TSP-1) expression for ovarian cancer progression was reported (Wang, 2016), expanding on previous findings from this collaboration.

Plans for the future
The team will continue to combine studies of tumor tissue from patients (primary and metastatic), with experimental cell and animal models. In particular, the following areas will be concentrated on:
Proteomic profiling and tissue deconvolution of luminal (receptor positive) and non-luminal (receptor negative) breast cancer. Human breast cancers (matched luminal and non-luminal cases) are studied in parallel with hormone receptor positive and negative cell lines. Networks reflecting tumor-stroma signalling are being focused in this search for novel biomarkers and targets (Birkeland, 2016). A novel tool for in silico tissue deconvolution has been developed (Dimitrakopoulou, et al.). Expression of Nestin (NES) as a marker of BRCA1-related, basal-like and aggressive breast cancer. The team is working on NES-based algorithms for BRCA1-prediction, and for improved delineation of basal-like tumors. NES expression is associated with stemcell phenotypes (Kruger, et al.).

Biomarkers of tumor stromal characteristics and vascular interactions in aggressive cancers. In a collaboration with Oslo University Hospital, the team is exploring the value of angiogenesis markers in predicting the response of locally advanced breast cancer to bevacizumab anti-angiogenesis treatment (Kruger, et al.). The predictive value of stroma-related serum markers is explored in trials of metastatic melanoma and renal cancer. ••



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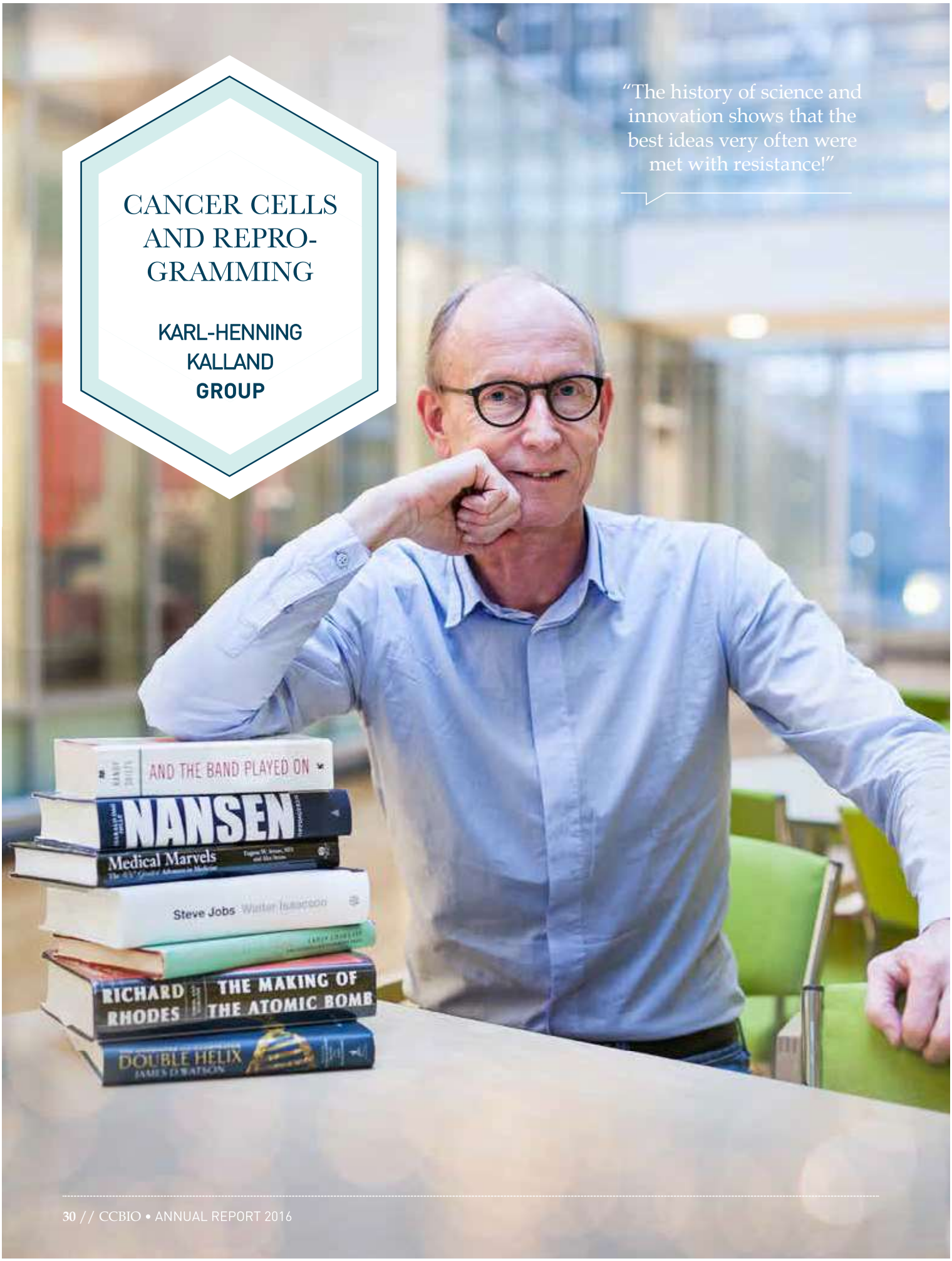
CANCER CELLS AND REPRO-GRAMMING

KARL-HENNING KALLAND GROUP

"The history of science and innovation shows that the best ideas very often were met with resistance!"



About the group and its research focus
The Prostate Cancer Therapy Research Group is located at the Department of Clinical Science, University of Bergen. It aims to take advantage of recent achievements in order to develop immunotherapy enhanced with molecular targeting and with advanced monitoring of treatment effects, including liquid biopsies and immunoassays.

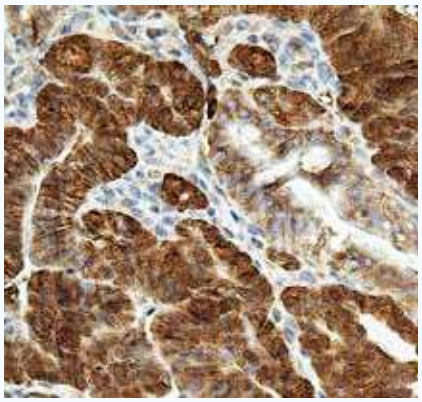
The group's projects
Kalland's research group is engaged in translational cancer research with the focus on molecular mechanisms and regulatory principles underlying reprogramming plasticity that may be exploited by aggressive cancer cells, such as epithelial to mesenchymal transition (EMT), stem cell and neuroendocrine differentiation of prostate cells and asymmetric cell division. The idea is that research using appropriate experimental cell culture and animal models and relevant patient materials will provide insights that may guide innovative cancer therapy and identify useful molecular targets.

One approach is based on the group's experimental model of stepwise prostate tumorigenesis. This model has been developed by the group starting with a benign human prostate epithelial cell with basal cell features. Using only physiological selection, i.e. different growth conditions and selection over time, gene expression reprogramming gave rise to a series of progeny cells with an accumulating number of malignant features. The model encompasses cells that underwent EMT, acquired ability to grow anchorage independently and eventually formed tumors in mice models. Human prostate tumor cells have been recovered from the animal tumors. All these cell types seem to be relatively stable and can be passaged indefinitely in subconfluent cultures. The passage history is carefully recorded.

The experimental model has generated detailed molecular insight into reprogramming plasticity of prostate derived cells, including EMT, as published in a series of publications. The model was next exploited in a drug discovery and development program. The insight into reprogramming plasticity as one basis of cancer cell heterogeneity has stimulated the initiation of a Phase I Clinical immunotherapy trial that theoretically can confront cancer cell heterogeneity.

Research results
The group's recent publication in PNAS has been broadly covered in scientific commentary journals internationally. Several drugs that inhibited WNT/β-catenin signaling were discovered according to a repurposing strategy. The PNAS manuscript describes a novel mechanism by which one of the leading compounds, the drug axitinib, targets the ubiquitin ligase SHPRH and thereby increases degradation of nuclear β-catenin followed by a shift of malignant symmetrical cell division to asymmetrical cell division. Another recent publication reports context dependent target genes of the androgen receptor in prostate cells with epithelial versus mesenchymal features with clinical relevance for androgen deprivation therapy, which is the current first line treatment of invasive prostate cancer.

Plans for the future
The drug discovery and development program will continue with follow-up of several leading compounds. By happenstance, evidence has recently emerged that the WNT-β-catenin pathway is important not only for malignant signaling of cancer cells, but additionally for decisions of dendritic cells to react with immune activation or tolerance against neo-antigens. Plans are ongoing to test compounds for combined activity to inhibit cancer cells, to inhibit cancer cell immune evasion and to stimulate immune activation. This work will be used to enhance the ongoing dendritic cell based cryoimmunotherapy and as the basis for development of a vaccination booster strategy. ••



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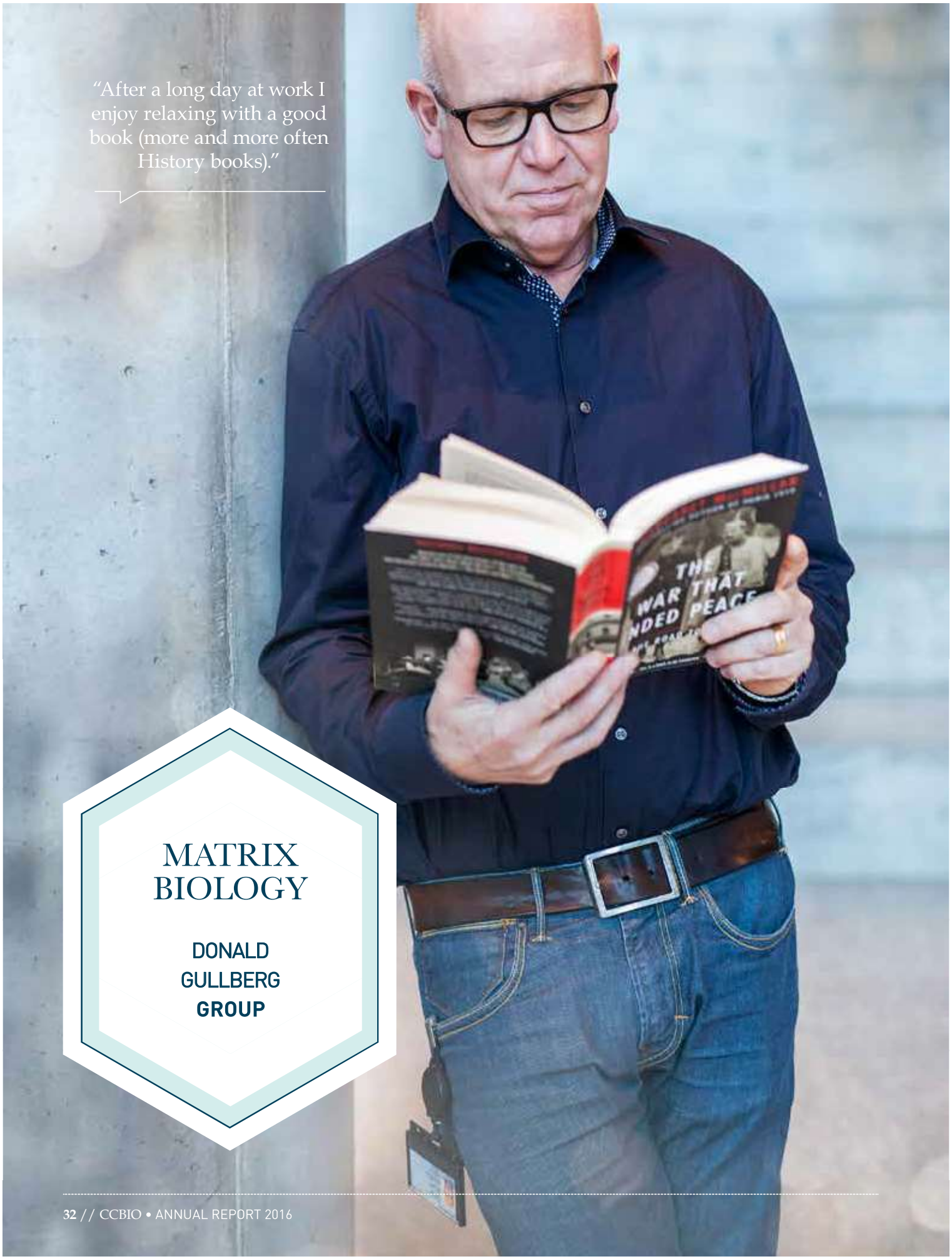


MATRIX BIOLOGY

DONALD GULLBERG GROUP

About the group and its research focus
The Gullberg laboratory has characterized the integrin α11β1, which is expressed in subsets of normal fibroblasts and on carcinoma-associated fibroblasts. Cells lacking α11β1 display disturbed cell-collagen interactions, altered metalloproteinase synthesis and reduced cell proliferation. Major projects within the group aim to further understand the role of this collagen receptor and other fibroblast integrins during health and in disease.

The group's projects
The main focus in the Gullberg lab is firmly anchored in basic science projects. The two major projects in CCBIO have been: 1) Generation and characterization of integrin α11 blocking antibodies; 2) Generation and characterization of α11 promoter -Cre mouse strain.

Project 1): As a first approach to develop blocking, potentially anti-fibrotic reagents, we have developed Mabs against human α11 integrin chain by immunizing NRM mice with recombinant human α11β1. As a result of this project, we have subcloned 25 hybridomas which all are specific for human α11, and out of which three appear to block α11 function. All of the 25 hybridomas react with α11 in fluoresecence activated cell sorting (FACS), work in immunostaining of cryosections and react with α11 in Western blotting.

Project 2): An α11 promoter-driven Cre transgenic mouse strain has successfully been generated. To map the expression pattern and determine if it replicates the endogenous α11 expression, mice have been bred with Cre-dependent lacZ ROSA 26 reporter strain (R26R) (Soriano, 1999). Preliminary data demonstrate that the Cre recombinase is expressed in embryos in an α11-specific pattern.

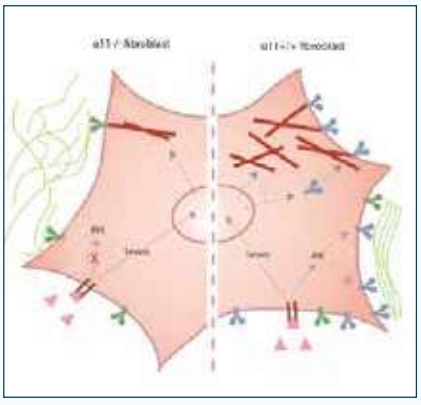
Research results with focus on excellent results/publications
The group's data based on integrin α11 blocking antibodies has the potential to generate interesting results. Preliminary data from the α11-Cre mouse strain indicate that this transgenic mouse strain might offer a unique opportunity to delete genes in a fibroblast-specific manner and is thus of high general interest the tumor stroma research field.

Plans for the future
For the remainder of the period, the group has three major projects: 1) Continued work with integrin α11 blocking reagents (antibodies and small molecules); 2) Continued work with α11-Cre mouse strain, and 3) Exploring the role of integrin α11 in mouse tumor models.

Project 1): Based on earlier identified α2 integrin modulators, a list of existing small molecules has been selected to be tested for α11 blocking function. Candidate molecules will be tested for their ability to block α11-dependent fibrosis. The fibrosis model relates to Fra-2 transgenic mice as a genetic model for systemic sclerosis. The Fra-2 transgenic mice spontaneously develop skin fibrosis prior to succumbing to the effects of pulmonary fibrosis at 4 months of age. The plan is to start breeding Fra-2 mice in 2017 and to cross these with Itga11-/- mice in 2018. Provided an attenuated fibrosis is seen in this genetic model (Fra-2 tg//α11-/-), α11 inhibitors will be supplied via osmotic pump at different time points in different regimes (early time point before fibrosis has developed as well as starting treatment at later time points when fibrosis has been established) in a manner similar to what has been done in other models.

Project 2): Based on the results with α11-Cre mice, the group will continue a systematic characterization of internal tissues by performing lacZ staining on tissue sections. They also plan to perform skin wounding and bleomycin-induced fibrosis in these mice to analyze α11-driven Cre expression in these pathological conditions including tumor fibrosis.

Project 3): The hypothesis is that α11 regulates collagen assembly in pancreatic ductal adenocarcinoma (PDAC). Pdx1-Cre; KrasG12D mice that develop PDAC with prominent fibrosis will initially be crossed with floxed Itga11 mice (breeding in Bergen since spring 2016) to evaluate possible role of α11 in the prominent collagen production.This project will be performed in collaboration with V.Weaver UCSF. ••



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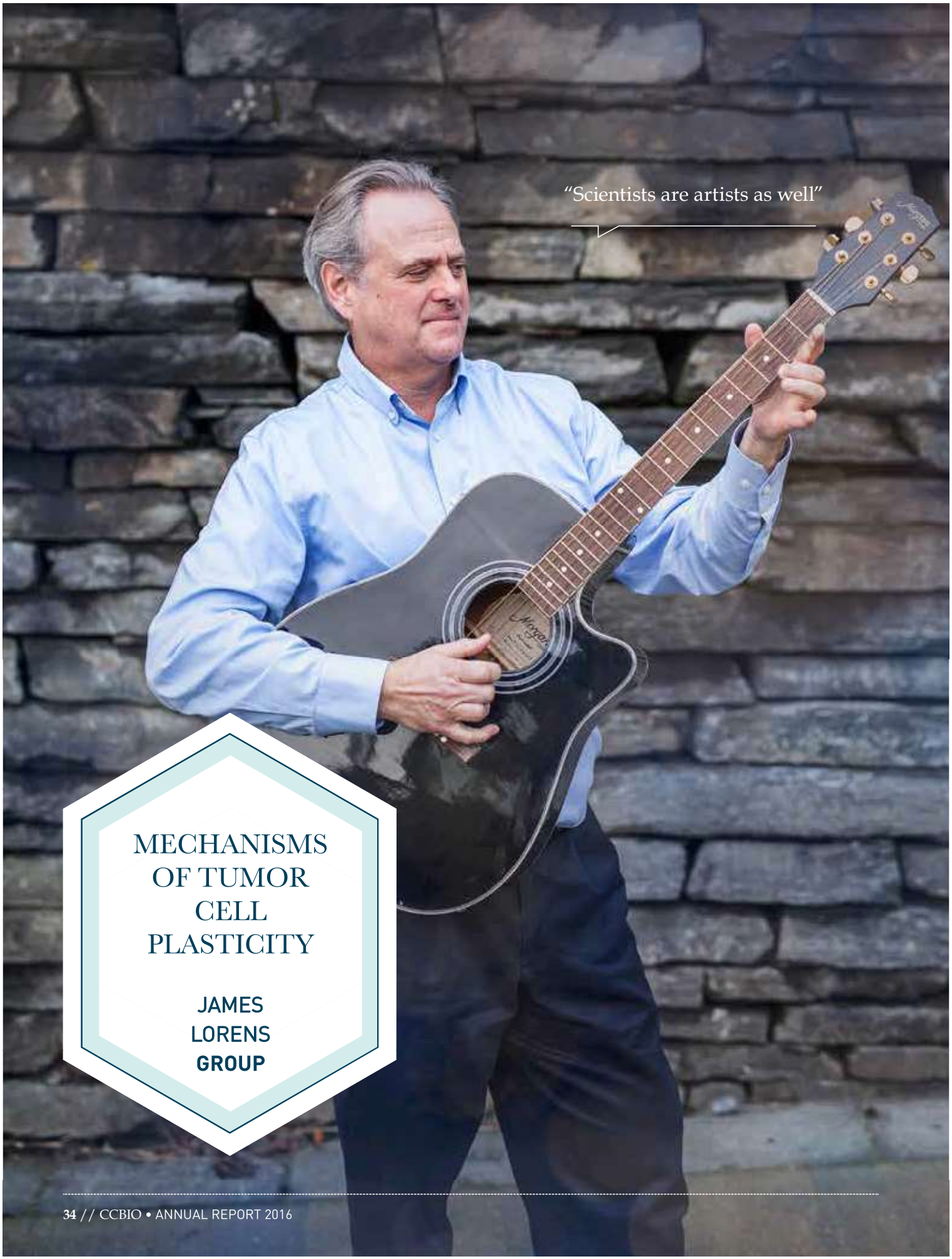


MECHANISMS OF TUMOR CELL PLASTICITY

JAMES LORENS GROUP

About the group and its research focus
The major challenge for current cancer treatments is the remarkable heterogeneity of tumors. This is the result of selective forces acting on evolving and genetically unstable tumor cells during cancer progression. The breakdown of normal tissue structure exposes tumor cells to numerous biophysical challenges, nutritional deprivation and a hostile non-native microenvironment comprising different matrix proteins and a variety of stromal and immune cells. In response, tumor cells trigger cellular plasticity reprogramming characteristic of adult tissue homeostasis and repair. This endows tumor cells with astonishing functional flexibility that allows adaptation to different niches within the dynamic tumor microenvironment. This "hallmark" of cancer, tumor cell plasticity, is a central feature of cancer spread and treatment failure. The group's research focuses on understanding the molecular mechanisms that endow tumor cells with adaptive cellular plasticity in the context of acquired drug resistance. The goal is to determine new avenues of therapeutic intervention to improve our ability to treat aggressive cancers.

Recent findings
The group's recent results highlight how carcinoma cells coopt cellular plasticity programs that normally regulate adult tissue responses to injury, to achieve resistance to current anti-cancer therapies. They discovered that the Axl receptor tyrosine kinase is a common regulator of both normal adult epithelial stem cells and aggressive carcinoma cells. Cancer cells utilize Axl signaling to support phenotypic plasticity, activate cell survival mechanisms and achieve resistance to anti-cancer therapies. The group's studies on Axl provide new insight into the how tumors become more heterogeneous in response to microenvironmental factors and effector immune cell challenge. In particular, the results reveal an unexpected commonality between acquired resistance to chemo-, targeted and immunotherapeutic agents that is related to Axl activity.

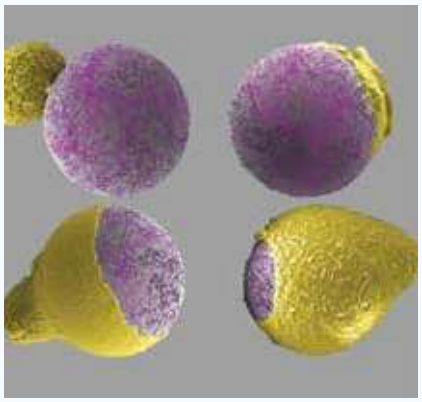
Research results
The Axl receptor is effectively targeted by the clinical stage small molecule kinase inhibitor BGB324. The group's studies demonstrate that selective Axl inhibition improves the efficacy of different cancer therapeutics in several preclinical models. Clinical translation of these results is ongoing in current Phase I/II clinical trials in acute myeloid leukemia and non-small cell lung cancer. The first results from these trials reported earlier this year are encouraging and further trials are planned.

Lie et al., Inhibition of Axl in erlotinib-resistant NSCLC cells abrogates autophagic flux and induces immunogenic cell death. Poster presentations at the 28th EORTC-NCI-AACR Symposium (Munich), 2016 CCBIO Symposium (Bergen); manuscript in preparation. First description of a novel Axl-dependent cell survival mechanism underpinning cross-resistance to multiple anti-cancer treatments. This project is the foundation for an RCN Mobility Grant to CCBIO Postdoc Agnete Engelsen to work with CCBIO Associate Professor J.P. Thiery at the Gustave Roussy in Paris.

Terry et al., Hypoxia-induced EMT drives non-small cell lung cancer cell phenotypic plasticity and immune resistance oncoimmunology, in press. First report of Axl-dependent cancer cell resistance to NK-mediated cytotoxicity. Collaboration with Professor S. Chouaib and with CCBIO Associate Professor J.P. Thiery at the Gustave Roussy in Paris.

Ertsås et al., Microsphere cytometry to interrogate microenvironment-dependent cell signaling. Integrative Biology, in press. This describes new flow cytometry-based technology to study microenvironment-dependent cell signaling. Collaboration with CCBIO Associate Professor M. LaBarge (LNBL and City of Hope) and Professor Garry Nolan (Stanford).

Plans for the future
The group is exploring the role of Axl signaling in resistance to the new class of cancer immunotherapies (immune checkpoint inhibitors). Their results show that Axl inhibition sensitizes cancer cells to the anti-tumor immune response and can be used to improve immune checkpoint inhibitor efficacy. In collaboration with leading international cancer researchers they are studying the mechanistic basis for this observation. They hope to shed new insight into how cancer cells interact with the immune system that can be used to improve cancer immunotherapy. ••

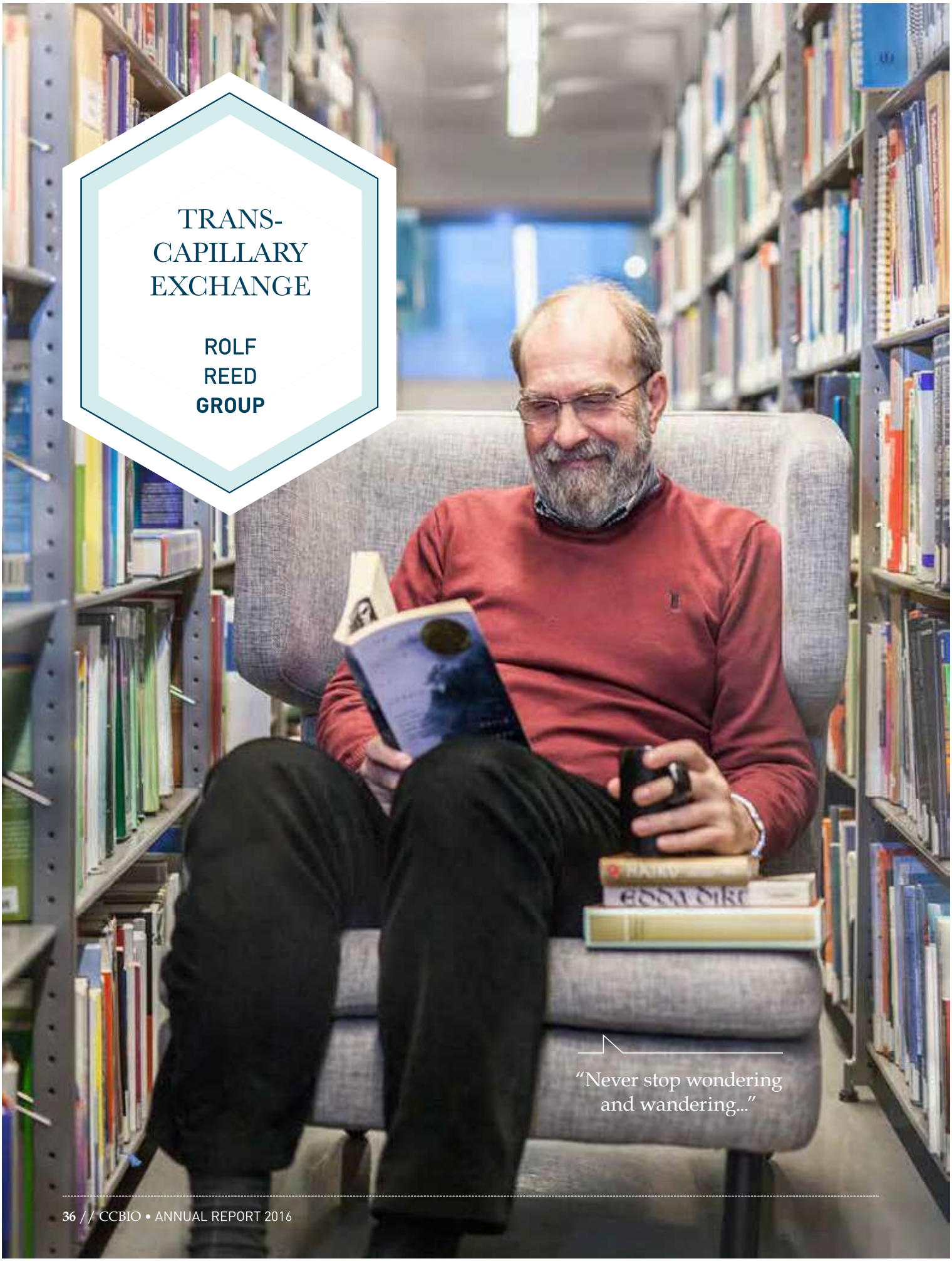


RESEARCH GROUP:

Lorens, James, MS, PhD, professor
Bougnaud, Sebastien, postdoc, PhD
Davidsen, Kjersti, PhD candidate, MD
Engelsen, Agnete, postdoc, MS, PhD
Ertsås, Henriette, PhD candidate, MS
D'Mello, Stacey, researcher, PhD
Haaland, Gry, PhD candidate, MD
Hinz, Stefan, industrial PhD candidate, MS
Jokela, Tiina, postdoc, MS, PhD
Kang, Jing, PhD candidate, MD
Lie, Maria, PhD candidate, MS
Pelissier, Fanny, PhD candidate, MS
Vik Berge, Sissel, staff engineer

TRANS-CAPILLARY EXCHANGE

ROLF REED GROUP



"Never stop wondering and wandering..."

About the group and its research focus
The group studies the role of the collagen matrix and its role as a determinant for the biophysical properties on experimental cancers. These ongoing studies originate from a long-term collaboration with Professor Kristofer Rubin at Lund University, Sweden. More recently, the collaboration also includes Professor Donald Gullberg at CCBIO. The studies have demonstrated that the connective tissue in general, including experimental tumors, can modify the interstitial fluid pressure via an interaction between cellular tension in the fiber networks in the tissue and the cellular collagen binding integrin receptors. The raised interstitial pressure and "interstitial hypertension" constitutes a functional barrier towards the movement of substances across the tumor microcirculation. The long term goal is to provide insight into how the interstitial hypertension can be modified by the tumor microenvironment and potentially give insight towards potential means by which it can be attenuated and thereby possibly pave the way for improved therapy.

The group's projects
The specific focus for ongoing studies is on the role of the collagen binding integrin α11 and αVβ3 since the latter is taking over for the former when integrin α11 is lacking. It has been demonstrated that carcinomas from integrin β(3)-deficient mice have denser and coarser collagen network compared to controls and with elevated interstitial pressure in experimental carcinomas. The studies are extended to more tumor types and also to study the effect on tumor stroma when the stromal cells are lacking integrin α11.

An extension of the above studies involves collaboration with Professors Gullberg and Akslen in CCBIO to investigate integrin α11 in human cancers. This collaboration now also includes Professors Trine Bjøro and David Warren at the University of Oslo and testing of antibodies towards the human integrin α11 with the specific aim to investigate whether it can serve as a biomarker in human cancers.

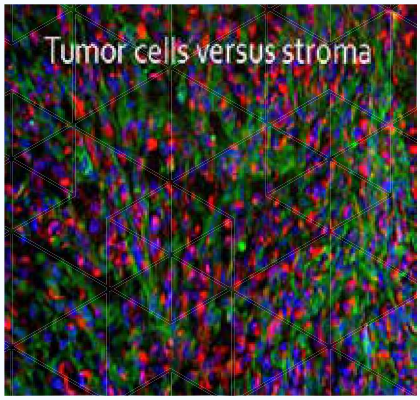
Furthermore, the CCBIO projects involve studies with Professors Donald Gullberg and Marion Kusche Gullberg in the Matrix Biology Group using tumor-fibroblast heterospheroids as a 3D model system to understand communication between the tumor cells and fibroblasts. Regarding the role of integrins α11 and αVβ3 in the tumor stroma, a long-term goal is to develop a vitro system to screen for compounds targeting integrins/integrin signaling and with the potential to inhibit tumor growth and spread.

Collaboration on transcapillary exchange with Professors Kathy Ferrara and Fitz-Roy Curry at the University of California Davis, and Professor Torfinn Taxt at UiB, focuses on methods for its measurement in genetically modified mice with subsequent use for studies in experimental tumors using dynamic contrast enhanced magnetic resonance (DCE-MRI) to study transcapillary exchange. The aim of the research is to understand the tumor stroma and its dynamic properties, and how this insight can be used to alter therapeutic principles of solid tumors.

Research results
Inga Reigstad, Hilde Ytre-Hauge Smeland, Trude Skogstrand, Kristina Sortland, Caroline Schmid, Rolf Kåre Reed, Linda Stuhr: Stromal Integrin α11β1 Affects RM11 Prostate and 4T1 Breast Xenograft Tumors Differently, PLoS One. 2016 Mar 18;11(3).

Inga Reigstad, Kristina Sortland, Trude Skogstrand, Rolf K. Reed and Linda Stuhr: The Effect of Stromal Integrin β3-Deficiency on Two Different Tumors in Mice. Cancers 2016, 8(1), 14.

Plans for the future
The above projects will have natural extensions into the future as they develop further. ••



RESEARCH GROUP:

Reed, Rolf Kåre, MD, PhD, professor
Lu, Ning, PhD, senior laboratory engineer
Stuhr, Linda, professor
Skogstrand, Trude, PhD, postdoc
Schmid, Caroline, PhD, postdoc
Reigstad, Inga, MD, PhD candidate
Smeland, Hilde, PhD
Salvesen, Gerd, engineer
Tveitarås, Maria, engineer

ORAL CANCER

ANNE CHRISTINE JOHANNESSEN GROUP

About the group and its research focus
Research at the Bergen Oral Cancer Group aims to identify molecules of importance for oral cancer development, in order to identify patients at risk for developing oral cancer from premalignant lesions, and to reveal potential targets for more efficient, individualized therapy of oral cancer.

The group's projects
The major scientific results and research projects of the center:

1. Importance of the heterogeneity of CAFs in OSCC.
Bidirectional tumor-stroma interactions have been shown by many to have tumor-promoting effects, but the group focused on the cell interactions within stroma and the functional relevance of heterogeneity of carcinoma-associated fibroblasts (CAFs) for tumor development and invasion. Two distinct CAF subgroups were identified in oral squamous cell carcinoma (OSCC) based on transcriptome analysis of primary cells grown in 3D collagen gels and on the functional analysis of CAF strains derived from several patients with OSCC: 1) a CAF subgroup with a gene expression profile closer to normal fibroblasts, having a more motile phenotype and supporting higher tumor formation and deeper carcinoma cell invasion; and 2) a CAF subgroup with a more divergent gene expression profile, having a more stationary phenotype, secreting very high levels of transforming growth factor-β1 to maintain the activated phenotype, but supporting less tumor formation and invasion. This study also shows that CAFs heterogeneity and the co-operation between different subsets of CAFs are important factors for tumor promotion in OSCC.

2. Role of integrin α11 in progression of OSCC.
The work showed that integrin α11 was overexpressed in the stroma of head and neck cancer compared with normal mucosa and correlated positively with the expression of α-SMA. Using an animal model of chemically induced oral carcinogenesis, the group also showed an important role for α11 in the transition from a hyper-proliferative stage to a malignant, invasive stage. Other experiments also showed that α11 expressed by the fibroblasts in the tumor stroma plays a biological role for tumor progression both by directly affecting the invasive properties of oral cancer cells and by providing a pro-angiogenesis microenvironment.

Research results
Collaboration between the Oral Cancer Group and the Matrix Biology Group.
Research project: Role of integrin α11 in oral carcinogenesis.
PhD thesis: Role of integrin α11 in oral carcinogenesis. In vitro and in vivo studies. Himalaya Parajuli, 2016, ISBN: 978-82-308-3342-1

Plans for the future
Ongoing and further work will focus on combining identification of biomarkers in both the epithelial and stromal compartments, including the inflammatory infiltrate and blood- and lymph vessels, in a comprehensive analysis towards a malignancy index that can be used as a diagnostic and predicitive tool for oral cancer.

In 2015, the Oral Cancer Group started planning a common research project between the Gynaecological Cancer Group and the Oral Cancer Group. A PhD position was allocated for the project. Due to the sudden loss of the PI of the group, Helga Salvesen, the project has been delayed, and focus switched from comparing oral and cervical cancers to comparing oral and vulva cancers. ••

RESEARCH GROUP:

Senior researchers:
Johannessen, Anne Christine, DDS, PhD, professor
Costea, Daniela Elena, professor, DDS, PhD
Neppelberg, Evelyn, associate professor, DDS, PhD

Technicians:
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Sandnes, Dagny Ann, engineer

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Suleiman, Salwa, researcher, DDS, PhD
Nginamau, Elisabeth Sivy, researcher, MD, PhD

PhD candidates:
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Gafaar, Nuha, DDS
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Rajthala, Saroj, MSc
Nazar, Mohamed, DDS

Pre-PhD projects:
Ali, Hassan, MPhil candidate, DDS
Birkeland, Eivind, MSc
Konstantinova, Victoria, MPhil, DDS
Jacobsen, Martha Rolland, student

ANTI-ANGIOGENIC TREATMENT

ODDBJØRN STRAUME **GROUP**

About the group and its research focus
Straume's research group focuses on clinical cancer research. The group's main research goal is to identify biomarkers, predictive biomarkers in particular, in clinical materials. They analyze clinical materials such as population based patient series, clinical trial series as well as single cancer patients treated in the clinic. They use a wide variety of analyses in close collaboration with the other research groups at the CCBIO. The group's view is that it's efforts is very relevant and representative for CCBIO studies with the final and ultimate goal of improving cancer treatment.

The group's projects
1) Clinical trial: A Phase Ib/II randomised open label study of BGB324 in combination with pembrolizumab or dabrafenib/trametinib compared to pembrolizumab or dabrafenib/trametinib alone, in patients with advanced non-resectable (Stage IIIc) or metastatic (Stage IV) melanoma. The main objective is to analyze safety and efficacy of BGB324 in combination with MAPK inhibitors and immunotherapy as well as to identify predictive markers of response. Inclusion starts January 2017. (Schuster/Straume/Lorens/Jing.)

2) Clinical trial: A National, Multicenter, Interventional Study in Patients with Unresectable or Metastatic Melanoma (IPI4). The aim is to identify predictive value of VEGF related biomarkers in the trial. Inclusion ended in 2015. (Schuster/Akslen/Straume.)

3) Clinical trial: Efficacy of bevacizumab monotherapy in treatment of metastatic melanoma and predictive value of angiogenic markers. The group's goal is to analyze predictive markers of response in liquid biopsies. (Schuster/Straume.)

4) Clinical trial: Predictive markers of response to sunitinib in treatment of metastatic renal cell carcinoma. The aim is to analyze predictive markers of response in liquid biopsies and biopsies. (Pilskog/Straume.)

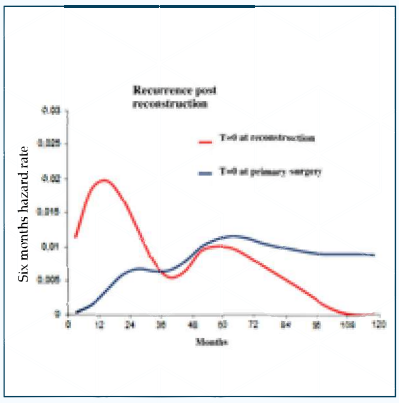
5) Research project: Importance of physical trauma on time to recurrence after primary treatment of breast cancer. Can surgical or traumatic tissue trauma synchronize growth of dormant micrometastases? Here the group analyses patient series as well as blood samples from patients undergoing different types of breast surgery as well as burn injury patients. They also examine the relation between postoperative complications and survival in breast cancer and melanoma. The project is based on the hypothesis that dormant micrometastases can initiate tumor growth following a systemic burst of growth factors after surgery or trauma. (Dillekås/Straume/Jensen.)

6) Research project: The Role of the Epithelial-to-Mesenchymal Transition (EMT) and Cancer Stem Cell Traits in Breast Cancer Metastasis. The group analyses the role of activation of the EMT associated Axl receptor in initiation and progression of breast cancer. They found that warfarin, which also has an Axl inhibitory role, is associated with reduced incidence of different cancers in a large registry based study of the Norwegian population. (Haaland/Straume/Lorens.)

7) Research project: Targeting Cancer Stem Cells with Axl Receptor Inhibitors to Improve the Treatment of Cancer. The group uses different preclinical models to study efficacy of the Axl inhibitor BGB324 in cancer. The combinations of BGB324 with immune check point inhibitors are particularly promising. (Davidsen/Straume/Lorens.)

Research results
All of the above mentioned projects have the potential of generating excellent results and publications. In particular, the results from projects 5 and 6 look very promising.

Plans for the future
The group plans to continue the above mentioned projects. Especially, data from the clinical trial in project 1 need time to mature, and results cannot be expected before 2020. The plan is to continue the group's close collaborations within CCBIO, as well as with the group's international and national collaborators. The group's goal is to deliver high quality tissue and blood samples from relevant patients series. ••



RESEARCH GROUP:

Straume, Oddbjørn, MD, PhD
Schuster, Cornelia, PhD candidate, MD, PhD
Pilskog, Martin, PhD candidate, MD
Haaland, Gry, PhD candidate, MD
Davidsen, Kjersti, PhD candidate, MD
Dillekås, Hanna, PhD candidate, MD

SIGNALING-TARGETED THERAPY

BJØRN TORE GJERTSEN GROUP

"We band of brothers and sisters are needed to fight this war on cancer"

About the group and its research focus
The Signaling-Targeted Therapy Group has its background in the study of intracellular signal transduction by protein phosphorylation in regulation of cell death (apoptosis). Early works included the first proof-of-principle concept of apoptosis-resistance mechanism in myeloid leukemia through point mutation in protein kinase A and indicated the therapeutic potential of small molecule activators and inhibitors of signaling.

The group sees CCBIO as an ideal platform for extensive biomarker and functional sensitivity testing for individualized signal transduction therapy.

The group's projects
During treatment, the clonal repertoire of acute myeloid leukemia is usually highly remodeled, and the most dangerous clones may be hardly detectable at diagnosis but strongly amplified during the intensive chemotherapy. The group is currently analyzing sensitivity screens, exome sequencing and functional signaling analyses from patients in the phase I trial BGBC003 testing the per-oral AXL inhibitor BGB324 (Hellesøy M. et al. ASH Meeting Abstract 2016). This is an exciting trial where the group contributed with the first of 24 dosed patients, and has fortunately been able to follow two long-term survivors.

Signaling-targeted therapy is the cornerstone in treatment of chronic myeloid leukemia. The group has developed a method for monitoring leukemia cells and immune cells early after start of chemotherapy. Material collected from one of several small clinical trials in chronic myeloid leukemia (Nordic CML Study Group) has been analyzed and is prepared for publication in 2017. This experience is applied in analyses of patients treated with AXL inhibitor and conventional chemotherapy of acute myeloid leukemia.

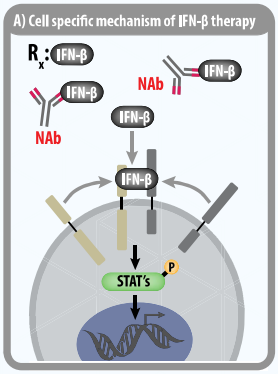
Research results
Intercellular communication in the leukemic bone marrow participates in disease development, progression and chemo resistance. Tunneling nanotubes (TNTs) are intercellular communication structures, and in 2016, the group published that the NF-kB pathway was involved in the regulation and formation of TNTs in AML cells (Omsland M et al. Oncotarget 2016). Standard AML therapy downregulated TNTs and inhibited NF-kB. Interestingly, the widely used chemotherapy daunorubicin was found to be transported through TNTs connecting AML cells indicating a novel function of TNTs as drug transporting devices. TNT communication in the bone marrow compartment could reflect important biological features of AML representing a target for future therapy development.

Plans for the future
In autum 2016, the group was able to test a novel low-toxic combination therapy towards NFkB, a prosurvival pathway in AML. The combination is carefully selected based on in vitro and in vivo experiments. Two patients are dosed at increasing level and a wider inclusion is planned if these pilot patients tolerate the drug combination and possibly indicate response.

The AXL inhibitor BGB324 will likely have to be part of a combination therapy regimen. In addition to test selected anti-metabolite combinations within the clinical trial, the group is also performing a wider combination screen in vitro. The small molecular inhibitor combinations are examined in view of the single cell signaling profile observed in treated patients. The goal is to develop effective combinations that may respond to detrimental clonal evolution.

Development of single cell signaling and immune profiling allow monitoring of immune responses in signaling targeted therapy, and a combination of real time monitoring of clonality and immune state may be central for future determination of responders versus non-responders.

The CCBIO Annual Symposium and the joint CCBIO and Oslo Cancer Cluster meeting on repurposing and in vitro drug screens have been important venues for development of future projects. Together with the CCBIO Junior Scientist Symposia, this creates an active environment for training of young scientists. ••



RESEARCH GROUP:

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Hjelle, Sigrun Margrethe, MS, PhD
Rane, Lalit Shirish, MS, PhD
Jebsen, Nina Louise, MD, PhD

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Gullaksen, Stein Erik, MS
Aasebø, Elise, MS
Bischof, Katharina, MD
Shafiee, Sahba, MS
Ha, Trung Quang, MD, MS
Hajjar, Ehsan, MS
Dowling, Tara, MS

Pre-PhD projects:
Tislevoll, Benedicte Sjo
Fagerholt, Oda Helen Eck

Technicians:
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Sabir, Misbah, MS
Kopperud, Reidun, MS, PhD

Administrative support:
Scarlett, Samantha, MS

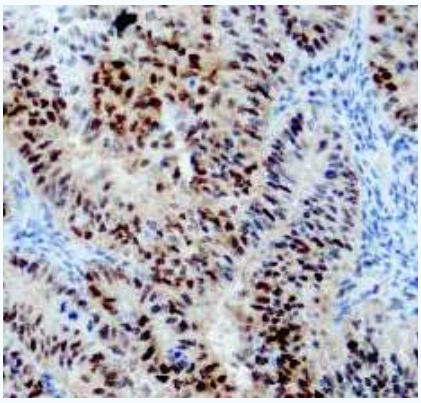
BERGEN GYNAECOLOGIC CANCER RESEARCH GROUP

About the group and its research focus
The Bergen Gynaecologic Cancer Research Group is currently headed by Professor Jone Trovik. The group suffered a huge loss early on in 2016 when group leader Helga B. Salvesen passed away. A clear aim in 2016 has been to continue and to further develop the great research Professor Salvesen had established. The group focuses on identifying molecular alterations underlying cancer initiation and progression in gynecologic cancers, aiming to improve knowledge on disease development and progression. In addition, to improve disease detection and diagnosis, the group seeks to identify and validate both imaging and molecular biomarkers in close collaboration with the clinic.

The group's projects
Together with collaborators at the Broad Institute in Boston, USA, extensive molecular profiling of paired primary and metastatic lesions has been performed, providing increased insight into the underlying mechanisms of disease spread. This is highly motivated by the fact that most cancer deaths are caused by development of metastases, and currently few treatment options are available for metastatic gynecologic cancers. Results were published in Nature Genetics in 2016 (Gibson, Hoivik et al Nat.Gen 2016). The group has also identified recurrent hormone-binding domain truncated ESR1 amplifications in primary endometrial cancers (Holst et al, 2016). The gained molecular knowledge from these studies will contribute to improved future clinical trials on molecularly targeted therapies. During the past few years, the group has done extensive work to identify more potent biomarkers for gynecologic cancers, with special focus on hormone receptors in endometrial cancer. Recently, they identified Androgen receptor (AR) as a promising biomarker and identified a patient group that might benefit from AR-targeting therapy (Tangen et al, 2016). The group have launched the MOMATEC2 study (ClinicalTrials.gov Identifier: NCT02543710), a phase 4 implementation trial for validation of ER/PR status as a stratifier for lymphadenectomy in endometrial cancer. The research group has explored the utility of imaging markers like 18F-FDG PET through meta-analysis of literature (Bollineni et al 2016) and in relation to hypoxia (Berg et al 2016). Both imaging and molecular biomarkers are further explored in endometrial cancer orthotopic mouse models, based on cell lines or patient derived xenograft (PDX) models. These models are also used for drug testing and validation of predictive biomarkers. In addition, the research group is an active partner in several international consortiums, resulting in a number of high-impact publications.

Research results
The group published the below article with both joint first (Gibson and Hoivik) and senior (Beroukhim and Salvesen) authorship:
Gibson WJ, Hoivik EA, Halle MK, Taylor-Weiner A, Cherniack AD, Berg A, Holst F, Zack TI, Werner HM, Staby KM, Rosenberg M, Stefansson IM, Kusonmano K, Chevalier A, Mauland KK, Trovik J, Krakstad C, Giannakis M, Hodis E, Woie K, Bjorge L, Vintermyr OK, Wala JA, Lawrence MS, Getz G, Carter SL, Beroukhim R, Salvesen HB. The genomic landscape and evolution of endometrial carcinoma progression and abdominopelvic metastasis. Nat Genet. 2016 Aug;48(8):848-55.

Plans for the future
The Bergen Gynaecologic Cancer Research Group will continue to explore genetic alterations linked to progression of endometrial cancer from primary tumor to metastasis, including a higher focus on epigenetic traits. Validation and exploration of single targets will also be included for investigations towards potentially new biomarkers in endometrial cancer. For cervical cancer they have initiated an international collaboration with focus on biomarkers of tumor recurrence and relationship between genomic alterations and clinicopathological phenotypes. Alongside the molecular characterization, they will continue the MoMaTEC2 trial with the goal of implementing molecular biomarkers to identify low risk patients to undergo surgical treatment without lymphadenectomy. The group will also implement use of an electronic platform collecting extensive patients' self- reported Quality of Life (QOL) aspects during follow-up of endometrial cancer patients to complement the group's data. They will continue exploring the endometrial cancer patient-population for biomarkers, with a stronger focus on early detected biomarkers for cancer development and metastatic spread. They plan to perform functional studies related to hormone receptor alterations in endometrial cancer with a goal of exploring effects of drugs that are already approved for other cancer indications. ••



RESEARCH GROUP:

Senior staff:
Trovik, Jone, professor, MD, PhD, group leader
Krakstad, Camilla, associate professor, MS, PhD
Haldorsen, Ingfrid, adjunct professor, MD, PhD

Clinical staff:
Valen, Ellen, study nurse
Enge, Elisabeth, study nurse

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Høivik, Erling, MS, PhD
Werner, Henrica, MD, PhD
Bollineni, Vikram, MD, PhD
Onyango, Therese Bredholt, MS, PhD
Holst, Frederik, MS, PhD

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Mauland, Karen, MD
Ytre-Hauge, Sigmund, MD

Technical support:
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Madissoo, Kadri, MS
Sortland, Kristina, engineer

Medical students:
Engerud, Hilde
Mjøs, Siv


ASSOCIATE
INVESTIGATORS
"Listening to music, allows my mind to wander and find new angles on research – and life"

BIOINFORMATICS
– INGE JONASSEN

About the group and its research focus
Professor Inge Jonassen and part of his team from the CBU (Computational Bioinformatics Unit, Department of Informatics, UiB) are working on the development and application of bioinformatics methods for analysing data descending from high-throughput measurement technologies applied to cancer samples.

The primary focus of the group, in collaboration with the Akslen group, is the development and application of computational deconvolution methods for decomposing transcriptome data from samples composed of a combination of tumor cells and the surrounding and supporting microenvironment. The research aims to decompose computationally the signal into that originating from the tumor cells and those originating from other tissues/cell types in the sample. This will be an enabling step towards studying the interactions between tumor cells and the environment and integrating them into the research along the continuum from diagnosis to treatment and outcome.

The group's projects
The group's first objective was to analyse several public benchmark transcriptome datasets (microarray and RNA-Seq) with a variety of deconvolution methods, test their performance and find out which of the mathematical assumptions reflect biological reality to a sufficient degree and can lead to more robust results. On second level, they developed a new computational method that addresses several computational challenges and they show extensively the performance of the group's method relative to other state-of-the-art methods (manuscript under preparation) based on the benchmark data. The group's proposed approach on breast cancer data was further tested and biologically consistent results were found. In this framework, they also developed SelGenes, a tool for selecting marker genes (i.e. genes highly specific for a tissue/cell type) for the cell types included in heterogeneous samples (published in master thesis). The performance of the group's approach was tested both on the benchmark data and on cancer data and biologically consistent results were found.

Another focus of the group is the development and application of systems biology integrative approaches. In collaboration with the Akslen group, they applied a subpathway enrichment analysis approach to reveal mechanisms that change between tumor samples with high and low Nestin expression, associated with the basal-like phenotype in breast cancer (the results are part of the analysis of a submitted manuscript). Moreover, in collaboration with the Biosignal Lab (Professor Anastasios Bezerianos, Deptartment of Medical Physics, School of Medicine, University of Patras, Greece), the group developed a time-varying method for microRNA-mediated subpathway enrichment analysis. The tool was tested on interferon-gamma (IFN-g) stimulated melanoma cells.

Research results
One manuscript (submitted), in collaboration with the Akslen group.
One manuscript (in preparation), in collaboration with the Akslen group.
Master thesis, "SelGenes: a tool for selecting marker genes in heterogeneous samples", Kristian Samdal.
Conference abstract: Konstantina Dimitrakopoulou, Elisabeth Wik, Lars Akslen, Inge Jonassen. Gene expression deconvolution in complex tissues via particle swarm optimization. EMBL Cancer Genomics, 1 - Nov 4 2015, Heidelberg, Germany.
Conference abstract: Konstantina Dimitrakopoulou, Elisabeth Wik, Lars Akslen, Inge Jonassen. Deconvolution of transcriptome data from heterogeneous tissue samples. 15th European Conference on Computational Biology, Sept 3-7 2016, Hague, Netherlands.
Journal publication: Vrahatis AG, Dimitrakopoulou K, Balomenos P, Tsakalidis AK, Bezerianos A. CHRONOS: a time-varying method for microRNA-mediated subpathway enrichment analysis.Bioinformatics. 2016 Mar 15;32(6):884-92.

Plans for the future
In the longer perspective, the Jonassen group intends to apply network-based approaches on the deconvoluted expression data to explore the interactions involved in different tumor types and their microenvironments. Furthermore, they intend to integrate other omics data like DNA methylation, copy number variation and protein expression, and also to explore utlisation of single-cell omics data, to improve the group's comprehension of the mechanisms underlying tumor development and treatment response. Furthermore, the group intends to be more involved in applied work including data sets generated within the center. ••

RESEARCH GROUP:

Jonassen, Inge, professor
Dimitrakopoulou, Konstantina, postdoc
Samdal, Kristian Brakstad, master student
Kjørsvik, Øystein, master student

"I often say sociology is a martial art, a means of self-defense (Pierre Bordieu)."

ASSOCIATE INVESTIGATORS

INTEGRATING ELSA INTO CCBIO

– ROGER STRAND

About the group and its research focus
CCBIO's ELSA team is a dedicated research group on the ethical, legal and social aspects of cancer biomarkers. The group's model is that of "integrated ELSA", namely to build ELSA awareness and capacity throughout the CCBIO by interaction both in the scientific venues and the governance bodies of the center, including a dedicated PhD course.

The group's projects
The ELSA team pursues three main lines of inquiry: 1) Issues of social justice and public legitimacy in priority decision-making in public health care, and how biomarkers and personalized cancer medicine affect these ethical issues by providing increased scientific knowledge but also changed business models for the pharmaceutical industry; 2) The tension between the need for universal rules and values in public health decision-making and the ethical relevance of biological and clinical understanding of individual cancer patients (or small subgroups); and 3) The ethical aspects of the challenges of reproducibility and clinical (ir)relevance in biomarker research. These three lines are interrelated and also closely related to the economic aspects studied by economist colleagues in CCBIO.

Additionally, considerable research and policy-advising effort has gone into the issue of Responsible Research and Innovation (RRI). This was not anticipated in the original application as the RRI concept came to the academic and policy forefront only in 2013. Notably, the team leader Roger Strand has inter alia chaired a European Commission DG Research and Innovation Expert Group on Indicators for Responsible Research and Innovation and contributed to the revision of the ethical frameworks of the Council of Europe. In 2016, this work has focused mainly on the implementation of RRI in Norway and through the Research Council of Norway.

Research results
Anne Blanchard (2016). Mapping ethical and social aspects of cancer biomarkers. N Biotechnol. 33(6):763-772. While potentially more important publications are in the pipeline for 2017, Blanchard's paper is highly original as it presents the results of a broad-scoped, integrated mapping of ethical and societal aspects of cancer biomarkers performed within and together with a cancer research consortium.
Blanchard, A. (2016). Mouse models: some reflections from the lab. In A. Olsson, S. Araujo & F. Vieira (Eds.), Food Futures: Ethics, Science and Culture (pp. 505-510). The Netherlands: Wageningen Academic Publishers.
F. Wickson, R. Strand & K. L. Kjølberg (2015). The Walkshop Approach to Science and Technology Ethics, Science and Engineering Ethics, 21:241–264. (Comment: This is a paper on the methodology of integrated ELSA research.)
E. Schei & R. Strand (2015). Love life or fear death? Cartesian dreams and awakenings. In: Â. Guimarães Pereira & S. Funtowicz (eds): Science, Philosophy and Sustainability. The End of the Cartesian Dream. London and New York: Routledge, Earthscan, pp.45-57.

Plans for the future
The group's immediate plan for 2017 is to finalize the group's upcoming anthology "Social and economic aspects of cancer biomarkers" in collaboration with the CCBIO Economics team.

For CCBIO's 2nd period, the group plans to keep the original research foci and strengthen the collaboration with the health prioritization ethics team at the University of Bergen. Additionally, they will launch a new research line on RRI and Quality, transcending the idea of attending to specific ethical and societal aspects and attending to the co-production of science, technology and society itself – in the group's case, the co-production of cancer research, treatment and what we broadly may call the politics and political economy of cancer treatment. The group wishes to explore issues such as (i) the reproducibility challenge, (ii) the "relevance" of biomarkers and the challenge of ecological/external validity and (iii) the role of theory and model architecture in preclinical research, including the role of systems biology and the digitalization of biology.

Outreach
The outreach dimension of the ELSA work is highly important. The group has organized two international conferences:

Ethical and Social Aspects of Cancer Research. CCBIO, Bergen, 11 October 2016. http://www.uib.no/en/ccbio/100446/snet-pre-conference-event-ethical-and-social-aspects-cancer-research
S.Net Annual Meeting 2016, co-organized with Senter for vitenskapsteori (SVT), Bergen, 12-14 October 2016. http://www.uib.no/en/svt/92313/S-NET-Conference-2016. ••

RESEARCH GROUP:

Strand, Roger, professor, group leader
Blanchard, Anne, postdoc
Nygaard, Ina Hannestad, research assistant
Mille Sofie Stenmarck, medical student
Karoline Huse, medical student


ASSOCIATE
INVESTIGATORS
«Investigating health economy and cost-effectiveness of biomarkers might help us give **a strike** to all cancers!»


"Holding on to your health without losing all your money"

HEALTH ECONOMICS

– JAN ERIK ASKILDSEN AND JOHN CAIRNS

About the group and its research focus
Health economics at CCBIO is concerned with two major research problems: what is the cost-effectiveness of biomarkers, and how does the interplay between the diagnostic market and the pharmaceutical market affect incentives to invest in R&D for cancer biomarkers, termed the industrial organization of biomarkers. The Health Economics Research Group is located at the Department of Economics, University of Bergen, in close cooperation with the London School of Hygiene and Tropical Medicine (LSHTM) in the UK.

The group's projects
Research into the industrial economics of biomarkers is conducted in close cooperation with the Bergen Center for Competition, Law and Economics (BECCLE) at the University of Bergen. A starting point for this research is the interesting observation that the development of diagnostic tests that make it possible to predict whether a patient is likely to have beneficial response to a certain drug, has been slower than expected. One factor that may explain the lack of progress is limited transparency and sharing of knowledge between the drug companies and the developers of biomarker tests.

The research group will investigate different possible mechanisms explaining this outcome, and look at possible regulatory mechanisms to mitigate adverse social affects. Ana Beatriz Mateus D'Avó Luís has recently been granted a 3 year grant for a PhD project which will constitute the main output from this line of research. Professor Tommy Staahl Gabrielsen at the Department of Economics and BECCLE and Associate Professor Julie Riise at the Department of Economics will be her supervisors. The first study, deriving a theoretical basis for regulation mechanisms, will investigate conditions for the development of patented drugs. The focus will be on both regulated and unregulated markets, and with consideration to possible mechanisms that may affect the incentives to bring patented drugs together with biomarkers to the market. A further intention is to use quality register data available in Norway to investigate actual use and consequences of biomarkers. Ana Beatriz Mateus D'Avó Luís will cooperate with John Cairns and Mikyung Kelly Seo at the LSHTM in investigating whether there has been a positive relationship between the utilization of cancer biomarkers and the improvement of health and productivity outcomes in recent years.

Mikyung Kelly Seo started her PhD on the economic evaluation of cancer biomarkers in January 2016 under the supervision of Professor John Cairns. She presented her review of the impact of biomarkers on the cost-effectiveness of targeted therapies for metastatic colorectal cancer at the 4th CCBIO Symposium in May. Her detailed PhD plans were approved by an independent assessment committee in October 2016. John Cairns gave several lectures as part of the PhD course CCBIO903 - Cancer Research: Ethical, economic and social aspects, in May and June 2016. ••

RESEARCH GROUP:

Cairns, John, professor, associate investigator
Askildsen, Jan Erik, professor, associate investigator
Gabrielsen, Tommy Staahl, professor
Riise, Julie, associate professor
Seo, Mikyung Kelly, PhD candidate
Luís, Ana Beatriz Mateus D'Avó, PhD candidate


ASSOCIATE
INVESTIGATORS
"Biomarkers will play an important role for future health care priority setting".

GLOBAL HEALTH PRIORITIES

- OLE-FRITHJOF NORHEIM

About the group and its research focus
Global Health Priorities is an interdisciplinary research group situated at the Department of Global Health and Primary Care at the University of Bergen. The group consists of a team of cross-disciplinary researchers and professionals dedicated to study the ethics and economics of priority setting in global health.

The group aims to better understand substantial ethical dilemmas, priority setting processes and fairness in resource allocation in low-, middle- and high-income countries. Key topics for Global Health Priorities are; the ethics of decisions at a clinical and population level, local implications of global/national health policies, equity-efficiency trade-offs, and standard and extended health economic evaluations. The main emphasis is on priority setting in global health, but the group also does substantial work on priority setting at the national level.

The group's projects
The current focus is on the new era of personalized cancer diagnostics and therapy: seeking new roles for age and biomarkers in clinical decision making. The group is investigating three issues in particular:

- Todays use of patient age in clinical decision making
- How biomarkers and age will affect treatment decisions for new expensive drugs
- Assess how biomarkers and age best can be used in clinical decision making

Plans for the future
PhD project started August 2016, UiB financing until 2020.

Cancer, NCDs and global health
Cancer is the second largest non-communicable disease group (NCD), and is now the third largest cause of mortality and morbidity in the world (DALYs). NCDs have risen on the global agenda the last years. Traditionally linked to ageing, affluence and lifestyle in high-income countries, it has now been evident that NCDs have a large global impact, typically with a disproportional effect in low- and middle-income countries. The majority of both future cancer cases and cancer deaths will come in low- and middle- income countries. This means that providing access to new and better cancer diagnostics and treatment must have a global ambition. In the literature on ethics and priority setting, higher priority to the worse off is considered relevant. The launch of the Lancet NCDI Poverty Commission, with contributions from GHP, is an effort to address the negative link between poverty and health, and to rethink priority setting for NCD and injuries for the poorest billion. ••

RESEARCH GROUP:

Norheim, Ole Frithjof, MD, PhD, professor
Tranvåg, Eirik Joakim, MD, PhD candidate

Newly Recruited Associate Investigators

// LINE BJØRGE

Professor Line Bjørge is currently head of the Gynecologic Oncology Unit at the Women's Clinic, Haukeland University Hospital, a European Training Center in Gynecological Oncology and professor at the University of Bergen. Bjørge received her medical degree and PhD degree from the University of Bergen and her MBA degree from the Mannheim Business School and ESSEC, Paris. She performed her residency in Obstetrics and Gynecology at Haukeland University Hospital and her postdoc-research training in Bergen, Helsinki and Innsbruck. She serves on the boards of Onkologisk Forum and the Nordic Society of Gynaecological Oncology (NSGO) and is member of the translational research group in the Gynecologic Cancer Inter-Group (GCIG).

The focus of her early research work was immune therapy of ovarian cancer with the use of complement activating monoclonal antibodies. Together with her Finnish mentor, Professor Seppo Meri, she discovered resistance mechanisms and developed methods to overcome them. The last decade, her research portfolio has been more translational and she has developed a large multidisciplinary research portfolio, entitled "Precision Medicine in Ovarian Cancer" where the aim is to translate data from comprehensive molecular profiling into clinical meaningful strategies to improve prevention and individualized patient care. The main focus for the translational research portfolio is biomarker studies, preclinical models and early phase clinical studies. Bjørge is also principal investigator for two projects funded by the European Commission and is national coordinator for different international phase II and III studies focusing on treatment of gynecological cancer.

The group's current main interest is surgical management of ovarian cancer. Based on improved understanding of how the extent of cytoreduction is influenced by inherent tumor biological characteristics as well as the aggressiveness of the surgical approach, the group aims to better define the value of cytoreduction and to use this knowledge to develop more individualized therapy. This project has recently received funding from the regional health authorities, Helse-Vest HF. ••

// EMMET Mc CORMACK

Professor Emmet McCormack is PI of the research group Translational Molecular Imaging in Cancer. His main motivation is the development and effective translation of novel therapies

and imaging strategies for the treatment of cancer, particularly cancers with limited therapeutic options. It is the group's belief that the current dogma of rushing novel pharmaceuticals through inappropriate preclinical models is one of the major reasons for their limited clinical penetration. This can only be solved through multidisciplinary development of preclinical surrogates, models and diagnostic tools that more accurately mimic clinical conditions. Subsequently, the group has lead the development of patient derived xenograft models in hematological malignancies (in collaboration with Professors Øystein Bruserud and Bjørn Tore Gjertsen), gynecological cancers (in collaboration with Professor Line Bjørge and Dr. Camilla Krakstad) and pancreatic cancer (in collaboration with Professor Anders Molven and Dr. Dag Hoem) in Bergen.

The group now has multimodal imaging of over 40 personalized cancer models, spanning most cancer phenotypes in addition to lab-on-a-chip scaffolds for greater in vitro understanding of the bone marrow microenvironments. The group's work has featured in high impact journals such as Cell Stem Cell, PNAS, Leukemia, Blood, Cancer Res etc., been awarded substantial independent grants , and been recognized both nationally (Best Young Investigator 2014 – Norwegian Oncology Society) and globally (Best Young Investigator – World Molecular Imaging Society).

Current projects include, SonoCURE (funding through NFR, NIH and Helse Vest) exploring the application of Sonoporation (the transient formation of pores in cells by microbubbles activated by ultrasound) in the treatment of pancreatic ductal adenocarcinoma. The application aims to elucidate, evaluate, and potentiate a new era of sonoporation theranostics for PDAC through application of innovative biomarker mining, organoid models and preclinical modelling. Clinical collaboration with researcher Kotopoulis, Professor Dimcevski and Professor Gilja are planned for a Phase II trial follow up from a very successful Phase I trial (Dimcevski et al. J Control Release 2016). A second major focus is the development of novel preclinical models of leukemia and lymphomas for novel targeted and immune- therapies (Li et al. Cell Stem Cell 2014), with exploration of microenvironmental factors critical to disease development. Finally, the group is developing the application of image-guided surgery (Helland et al. PLoS One 2016), whereby fluorescent dyes will target biomarkers on surgically amenable cancers to aid their greater resection. This is particularly relevant to gynecological cancers and sarcomas. ••

// DANIELA ELENA COSTEA.....

Professor Daniela Elena Costea and her team are focusing on characterizing the interactions between epithelial (stem) cells and their microenvironment in normal conditions and during carcinogenesis. The group's research interest stems from their early findings showing that the tight control exerted by mesenchyme on epithelial differentiation and cell death is gradually lost during neoplastic progression (Costea et al, J Invest Dermatol, 2003 & Differentiation, 2005) and changes from a restrictive to a dedifferentiating and invasive stimulating factor (Costea et al, Am J Pathol, 2006). The group is proposing the concept of cancer as a deregulation of the developmental and homeostatic processes that govern how cells organize into tissues and organs. This histogenetic perspective implies that (1) both epithelium and the microenvironment co-evolve during carcinogenesis, (2) both provide biomarkers for prediction of aggressive tumor behavior, (3) epithelial –microenvironment interactions are essential to the carcinogenic process, and (4), their disruption can be therapeutically used to change the natural course of cancer. The group's recent and current studies support this view by demonstrating that activated tumor stroma is a prerequisite for carcinoma invasion and that the vicious epithelial –microenvironment interactions in carcinomas can be disrupted by targeting either the stromal or the epithelial compartment by use of nanoparticles (Costea et al, Cancer Res. 2013 & Suliman, Biomaterials 2016). For being able to perform pertinent studies on cell-to-cell interactions, the group has developed human skin and mucosal (oral, tonsillar, bladder and cervical) 3D organotypic in vitro model systems as well as a humanized, microenvironmentally-induced bioluminescence mouse model of cancer (Suliman, Nead and Neck 2016). In addition to basic research, the group is working on translational research projects on biomarkers in head and neck, skin, kidney and bladder cancer, and use of stem cells and nanoparticles for targeting the carcinogenesis process. The group is partner in several EU and Eurasia research projects and has a wide research network including research groups from Europe, Asia, Australia, Brazil and the US. ••

Junior Associate Investigators

// CAMILLA KRAKSTAD.....

Associate Professor Camilla Krakstad has her background from research on signal transduction, and during her PhD she studied cAMP signaling in apoptotic cell death in both normal and cancer cells. She is also well trained in the use of animal models in medical research and was involved in development and characterization of a mouse knock out model for the cAMP receptor EPAC. In 2010 she joined the translational research team focusing on gynecologic cancers, previously headed by Helga B. Salvesen. Combining her background from signal transduction with valuable patient samples inspired more clinical focused research with a particular interest in improving treatment of endometrial cancer patients.

Krakstad has been involved in the identification and validation of several potent biomarkers for endometrial cancer, among others several members of the hormone receptor family have been studied (Br J Cancer 2012, E J Cancer 2015, Oncotraget 2016). The team has pointed to important molecular alterations underlying development of aggressive, hormone receptor negative disease and will further explore these observations in preclinical model systems, including both cell and animal models.

State-of-the-art animal models and advanced molecular imaging of endometrial cancer has been established (PlosOne 2015). These models are currently used for drug testing and validation of predictive value of specific biomarkers. As an example, the biomarker Stathmin is currently being tested as a predictive biomarker for drug response based on previous work. Drug testing in mouse models is also part of a strong collaboration with Professor Ingfrid Haldorsen to identify functional imaging parameters of tumors in patients and mice related to clinically relevant biomarkers.

In ongoing and future projects, the group will continue to combine genetic and molecular studies of precursor, primary and metastatic lesions with registry data to identify new biomarkers and further define the development and progression of gynecologic cancers. The group's findings in experimental cell and animal models will be further explored. The future goal is that novel potential targets and biomarkers will be validated in the human setting through collaborations with both local (CCBIO) and international partners. ••

// ELISABETH WIK.....

Postdoc Elisabeth Wik has been a member of the Tumor Biology Research Group (directed by Akslen) since 2013, in combination with a position as resident at the Department of Pathology, Haukeland University Hospital.

Wik focuses her research on prognostic and predictive biomarkers in breast cancer. She mainly works on integrating large-scale omics data and clinico-pathologic information, in particular describing biologic characteristics of the different molecular subtypes of breast cancer. Aiming to capture biologic complexity and diagnostic relevance, signature biomarkers have been of major interest since her PhD studies. Also, morphologic tumor features are of interest and viewed as highly relevant when exploring markers with diagnostic relevance. Following up on previous work on markers of angiogenesis in the Akslen Group, one axis in Wik's projects presently relates to an angio-immunogenic profile in breast cancer. Further, Wik has initiated studies of young breast cancer patients, supervising one medical student in this field (Amalie A. Svanøe). The surgeons Turid Aas and Benedicte Davidsen from the Department of Surgery, Haukeland University Hospital, are collaborating on this study. One aim is to extend population based biobanking and databases with clinico-pathologic information from breast cancer patients, along with follow-up data.

Wik has been involved as a lecturer at courses provided by the CCBIO Research School since its opening, and has been coordinating the CCBIO Junior Scientist Symposium (CCBIO901) from the start in June 2014, and also as scientific coordinator since 2015. She has coordinated the CCBIO Bioinformatics group (CCBIO-BIG). Wik has been awarded several prizes for oral presentations at international conferences, and in 2016 she received the Professor Kreyberg Prize for her PhD thesis.

Elisabeth Wik is the main supervisor of medical research student Amalie A. Svanøe, and co-supervisor for PhD students Sura Aziz, Kristi Krüger, Tor Audun Klingen and Ying Chen. She also collaborates with candidates involved in pre-PhD studies. ••

Research Collaboration
Across Groups in the Center

When CCBIO was established in July 2013, several of the PIs already had extensive and long-standing collaborations which strongly supported the concept already from the beginning. For example, the director had for many years been collaborating and publishing with Salvesen, Straume, Kalland, and Lorens. Similar collaborations apply to some of the other PIs. To date, 211 papers have joint authorships between two or more principal investigators.

During CCBIO's first 3,5 years, additional collaborations have developed, also across the three main project areas. We would like to highlight the following examples of projects in progress:

• Gullberg and Reed have initiated collaboration with Akslen to work on potential translational use of CCBIO-supported novel non-commercial integrin α11 antibodies. These will be examined for possible use in clinically related projects (e.g. breast and lung cancers).

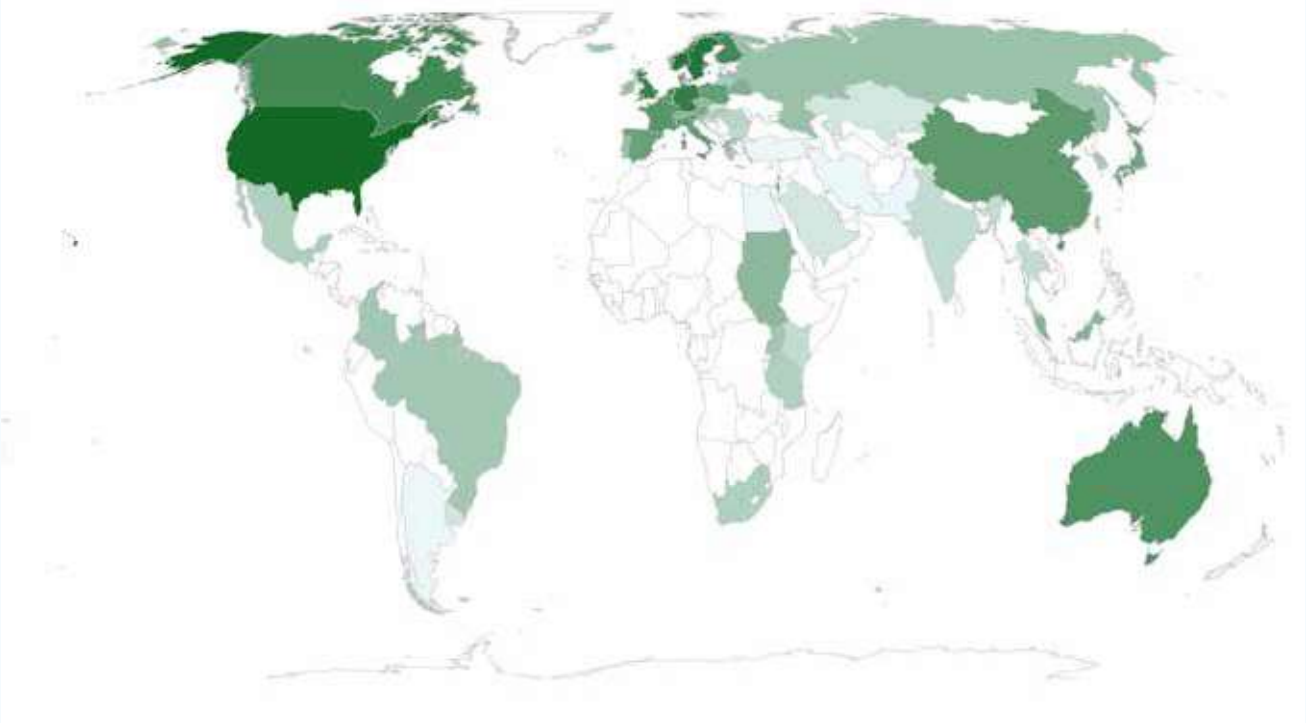
• Kalland has initiated collaboration with Gjertsen on the CCBIO-supported trial of dendritic-cell based cryo-immunotherapy treatment of advanced prostate cancer. The trial has an extensive biomarker program.

• Straume has initiated collaboration with Lorens and Gjertsen to organize the recently launched trial using a combination of the anti-Axl drug BGB324 and immunotherapy in metastatic melanoma. This trial has an extensive biomarker program including circulating and tissue-based biomarker analyses. The trial is an example of translation within CCBIO. The basic studies were performed by the Lorens team including close collaboration with BerGenBio. The drug BGB324 has been made available for this trial.

• Akslen has initiated collaboration with CCBIO Associate PI Inge Jonassen (bioinformatics) to develop novel approaches on in silico deconvolution of microarray based omics-data derived from whole sample tumor tissues, potentially to segregate signaling networks from the tumor stroma and to explore the possibility of novel and useful information for translational purposes.

• Akslen and Straume have initiated collaboration with CCBIO Associate PI John Cairns at the London School of Hygiene and Tropical Medicine to perform economics evaluations and profiling for biomarker-based cost-effectiveness data derived from clinical trials at CCBIO and others. ••

International Collaboration



In CCBIO, we have extensive and increasing external collaboration. Regarding international contacts and projects, such activities have been well established by all PIs. In addition to standard project collaboration, CCBIO has organized a panel of 13 international affiliated researchers in the form of adjunct positions at CCBIO, for project support, advisory roles, participation in activities organized by the CCBIO Research School for Cancer Studies (basic courses, research seminars, annual symposium), and for mentoring inititatives (see details below in Chapter 17). The first adjunct researchers recruited in 2015 (Arne Östman, Jean Paul Thiery) have interacted very well with the CCBIO environment with bilateral visits and project participation. Östman has received funding from the Norwegian Cancer Society for a postdoctoral fellow, establishing his own activity at CCBIO. Of the 11 researchers recruited in 2016, most of them have been actively engaged in various projects, primarily with a main link to one of the principal investigators and we expect these formalized international collaborations to yield ample results in the years to come.

As a measure of the importance of external collaborations for CCBIO, we had international participation in 58% of the papers published in 2016. In comparison, we had national collaborators outside of Bergen in 31% of the papers. Of the international collaborators and co-authors, we have a significant over all participation from North America, EU countries, Australia and Asia.

Over several years, the PIs and research groups have had close collaborations with teams at top-ranking institutions abroad, such as Harvard Medical School, Stanford University, Massachussetts Institute of Technology, McGill University, and Scandinavian universities such as Karolinska Institute, Uppsala University and Lund University. Also, we have a close collaboration with the London School of Hygiene and Tropical Medicine, through our associate PI at CCBIO, John Cairns.

Regarding individual projects, Kalland has for many years collaborated with teams at the University of Seattle (USA) and Zhejiang Iniversity, Hangzhou (China), in the studies of prostate cancer biology. Others include Thorsten Schlomm, Martini-Klinik (Hamburg), and Klaus Pantel, University of Hamburg (Germany). Schlomm and Pantel have been appointed as affiliated researchers at CCBIO. Also, Kalland has collaborated with the Weizman Institute, Rehovot (Israel). Gullberg has for many years collaborated with B. Eckes, University of Cologne, in studies of the role of integrin a11 in fibrosis. Two other long-term collaborations have been running, one on tumor-stroma interactions in lung cancer with M-S Tsao, University of Toronto, and one on heart fibrosis with C. McCulloch, University of Toronto. More recently, Gullberg has established collaboration with Valerie Weaver at UCSF, and with Ritva Heljasvaara at the University of Oulu. Dr. Heljasvaara has been recruited as an affiliated researcher at CCBIO. Reed has for a long time been collaborating with the University of California at Davis and with Uppsala University, on the physiology of interstitial fluid pressure and its regulation in tumors and other processes. Johannessen has been collaborating with teams at the University of London. The group has an ongoing collaboration on biomarker validation in oral cancer with TATA Memorial Hospital and the Advanced Centre for Treatment, Research and Education in Cancer, Mumbai (India) and the Koirala Memorial Hospital (Nepal). Further, the group has collaboration with the University of Maastricht, University of Khartoum and the eNose Company from the Netherlands, to develop an electronic nose device for detection of specific patterns of volatile organic compounds (VOC) in oral cancer patients.

Lorens has developed active collaboration with many teams worldwide, especially in the US after having worked in the pharma industry in California. In the Axl projects, he has collaborated more recently with Mark LaBarge and Garry Nolan at Standford University, Rolf Brekken at the University of Texas – Southwestern, and with S. Chouaib and J.P. Thiery at the Gustave Roussy in Paris. LaBarge and Brekken have been recruited as affiliated researchers at CCBIO. In addition to project collaboration, Lorens is also coordinating the collaboration between the Bergen-based pharma company BerGenBio and CCBIO, also with respect to international involvement and trial related projects. Akslen has for many years been collaborating with Harvard Medical School and the Vascular Biology Program at Boston Children's Hospital. This collaboration first included the late director, Judah Folkman, followed by Randolph Watnick, Diane Bielenberg, and the current director, Marsha Moses. Projects have been focusing on micro-environmental biology in progressing tumors, especially related to prosaposin and thrombospondin-1 and have resulted in multiple joint papers. Akslen has collaborated for a long time with William Foulkes at McGill University (Canada) on genetic factors and biomarkers in breast cancer subtypes. More recently, collaboration with Arne Östman at the Karolinska Institute has been established, on the peri-vascular niche and related paracrine loops in malignant tumors. Akslen has also been collaborating with Rameen Beroukhim at the Broad Institute (MIT) on genetic factors in cancer. Watnick, Östman and Beroukhim have been recruited to CCBIO as affiliated researchers. The Bergen Gynecologic Cancer Group (previously led by Salvesen) has been collaborating closely with the Broad Institute (MIT) for many years, especially with Matthew Meyerson and Rameen Beroukhim. Also, the group has collaborated extensively with many translational and clinical networks. Gjertsen has been collaborating e.g. with FIMM (Finnish Institute of Molecular Medicine – EMBL Node) and with Nordic and international networks studying leukemia. Straume has been collaborating with Romano Demicheli and Elia Biganzoli (Milano) on the impact and timing of breast surgery related to disease recurrence. Straume also collaborates with Jonathan Irish at Vanderbilt University, Nashville (USA) on CYToF (mass cytometry) analyses of patient derived plasma and tissue collected in clinical trials, and with Miles Miller at Massachusetts General Hospital/Harvard/ MIT on analyses of soluble Axl as a biomarker in patient derived plasma and tissue collected in clinical trials.

As we see it, CCBIO has an extensive international collaboration and networking to support our aims in individual projects as well as our educational and science culture efforts. In addition to the existing collaborative relations, we expect to benefit strongly form CCBIOs network of adjunct positions in the years to come. ••

International Network and Affiliated Investigators

Throughout 2016, CCBIO was in the process of formalizing its international network, mainly in the form of employing high ranking researchers within various fields of cancer research in 10% adjunct professor and researcher positions. CCBIO's rationale with this network is to establish an array of experienced advisors on scientific projects, collaboration, networks, and research strategy, as well as to perform joint research in the forefront and facilitate the transfer of knowledge. Another important aim is to enable CCBIO's Research School to have research-based courses on the highest level and to enable co-supervision and exchange of research- and postdoctoral fellows. By the end of 2015, Professors Arne Östman and Jean Paul Thiery had commenced their positions. During 2016, we have added another 11 highly ranked international affiliated investigators to our network, and have already experienced good results in terms of fruitful collaboration and exchange of knowledge.

// FRÉDÉRIC AMANT.....

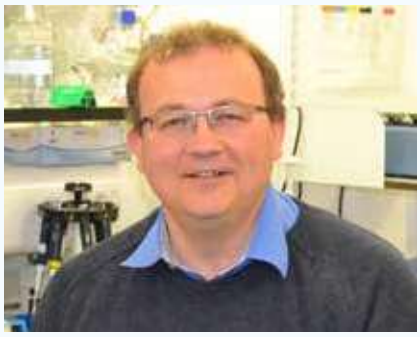
Professor Frédéric Amant, born 1967, PhD and MD, received his medical degree from the University of Leuven (KU Leuven), Belgium in 1992, completed his specialty training as an obstetrician/gynecologist in 1998, and his subspecialty training in gynecologic oncology in 2000. He is professor at the KU Leuven, Belgium, and a specialist in gynecologic oncology at the University Hospitals Leuven (UZ Gasthuisberg), Belgium and at Antoni van Leeuwenhoek – Netherlands Cancer Institute (Center for Gynecologic Oncology Amsterdam). At KU Leuven he heads the scientific section of this specialty.

Professor Amant is an author on more than 400 peer-reviewed scientific papers, has contributed to 20 books and is a highly sought-after guest lecturer worldwide. He chairs the Endometrium Tumor Site Committee of the European Organization for Research and Treatment of Cancer (EORTC), Gynecologic Cancer Group. He chairs the European Network for Individualized Treatment of Endometrial Cancer (ENITEC), a task force within the European Society of Gynecologic Oncology (ESGO). Professor Amant also heads the International Network on Cancer, Infertility and Pregnancy (INCIP), also within ESGO, and is recognized as a world authority on the topic cancer in pregnancy. Furthermore, he chairs the Patient Derived Tumor Xenograft Platform (Trace) at KU Leuven and is a member of the European consortium on xenografts EurOPDX.

// RAMEEN BEROUKHIM.....

Rameen Beroukhim, born 1969, got his PhD at the University of Cambridge in 1996 and his MD at the University of California in 2000. He is currently a physician in the Department of Medical Oncology at the Dana-Farber Cancer Institute, an associate physician in medical oncology at Brigham and Women's Hospital and an assistant professor of medicine at Harvard Medical School. Dr. Beroukhim co-chairs the International Cancer Genome Consortium effort to characterize structural alterations across 2800 cancer whole genomes. He is also the lead principal investigator of a multi-investigator R01 grant and of individual and multi-PI foundation- and industry-funded grants. His administrative roles include numerous committees, working groups and grant review activities, such as admissions committees for the HMS Bioinformatics and Integrative Genomics (BIG), MD-PhD programs and the MGH/DFCI neurooncology fellowship program, the Ethics Advisory Committee at DFCI, and the Broad Institute Cancer Program Steering Committee. He has been ad hoc reviewer of 31 well-renowned scientific journals, and is at the editorial review board of Neurooncology since 2013.

Dr. Beroukhim's scientific focus is on the genomic features of oncogenesis and cancer progression in brain and other cancers, and the implications of these in identifying novel cancer dependencies, therapeutic strategies, and biomarkers. He has 154 peer-reviewed articles, including 16 last- or co-last author papers, of which four were published in Nature Genetics and Cell.



//JEAN-CHRISTOPHE BOURDON

Dr. Jean-Christophe Bourdon, born 1967, earned his PhD in cellular and molecular biology in 1997 at the Paris XI University, France. He is currently senior lecturer at the College of Medicine at Dundee University. He became co-director of the Inserm-European Associated Laboratory (Toulouse University, France) in 2006 and was awarded the prestigious fellowship from Breast Cancer Campaign in 2012.

Dr. Bourdon is author on 66 articles in peer-reviewed journals (5 book chapters, 6 review and editorial letters). He is regularly invited to give keynote lectures at international institutes and conferences. He sits at the Scientific Advisory Boards of Breast Cancer Now and is a member of the British Breast Group. Dr. Bourdon has organized several international conferences and is the principal organizer of the International p53 Isoform Conference. He reviews for several top-high impact Journals such as Cell, Nature and eLife and for major international funding agencies.
Dr. Bourdon's expertise is particularly in the human p53 gene. His research group has demonstrated that p53 isoforms are associated with cancer patient prognosis. The aims of his research group are: 1) to characterize the biological activities of the p53 isoforms in cancer, particularly in breast cancer; 2) to establish regulation of p53 isoforms expression at the mRNA (splicing, internal promoter) and protein levels (proteasome degradation); 3) to define p53 isoform as predictive treatment biomarkers (personalized treatment) and 4) to develop new drugs that modulate p53 protein isoform expression in order to control cell response to cancer treatment.

// ROLF A. BREKKEN.....

Professor Rolf A. Brekken, born 1969, received his BA in biology from Luther College in Decorah, IA and his PhD from UT Southwestern Medical Center. His graduate studies were focused on developing novel therapies that target the vascular compartment of tumors. He was a postdoctoral fellow in the Department of Vascular Biology at the Hope Heart Institute in Seattle, WA where he studied how the extracellular matrix (ECM) contributes to vascular function in tumors. He joined the Department of Surgery at UT Southwestern as faculty in 2002 and was promoted to associate professor with tenure in 2009 and to professor in 2015. His laboratory is located in the Hamon Center for Therapeutic Oncology Research.

Dr. Brekken is the Effie Marie Cain Scholar in Angiogenesis Research and Deputy Director of the Hamon Center for Therapeutic Oncology Research. His laboratory receives funding from the ACS, NCI, DOD, CPRIT and biopharmaceutical companies. He is an author on over 150 peer-reviewed scientific papers and a senior editor at Cancer Research. Two therapeutic antibodies Dr. Brekken helped develop are in clinical trial and he recently co-founded a company, Tuevol Therapeutics, which is focused on the development of novel therapies for cancer.

Dr. Brekken's laboratory studies the tumor microenvironment. In particular his group is focused on three areas: 1) ECM signaling in tumors; 2) therapeutic immune reactivation; 3) how immune cells contribute to the metastatic cascade.

// HANI GABRA.....

Professor Hani Gabra, born 1963, took his medical degree at Glasgow University in 1987 and his PhD at Edinburgh University in 1996. After 5 years as clinical scientist and head of the ICRF Ovarian Cancer Cell and Molecular Genetics Laboratory in Edinburgh, he moved in 2003 to his current position as professor of medical oncology, head of the Molecular Therapeutics Unit and director of the Ovarian Cancer Action Research Centre at the Imperial College London.

Professor Gabra is the founding president of the European Translational Ovarian Cancer Network (EUTROC), a consortium of 70 centers conducting translational studies and clinical trials in ovarian cancer. He led the Ovarian Cancer Section of the Scottish Gynaecological Cancer Trials Group (SCOTROC) and was the Scottish representative to the Gynaecological Cancer Intergroup (GCIG) 2004-9. He has served on CRUK's CTAAC national clinical trials funding committee, and currently sits on the INCa French Translational Research Funding Committee. He is a member of the editorial board of several journals.
Professor Gabra's basic science research interests are in tumor-suppressor biology and cancer multiplatform molecular profiling and integrative OMICS. He has translational research interests in the molecular basis of ovarian cancer platinum resistance as well as all phases of clinical research in gynecological cancer.

// JEAN PAUL THIERY.....

Professor Jean Paul Thiery, born in 1947, is a well-known researcher within the field of cancer therapeutics. Until July 2015 he was professor and head of the Department of Biochemistry of the Yong Loo Lin School of Medicine at the National University of Singapore (NUS). He also held a research director position at IMCB A*STAR and has been director of research at the Center National de la Recherche Scientifique (CNRS), Paris. Later, from 1995 to 2003, he established and headed the Cell Biology Department of the Institut Curie (200 people, 11 research units).

In terms of advisory boards and advisory panels, Professor Thiery has been part of more than 40 different scientific, advisory and grant giving panels worldwide. In terms of academic evaluation, Thiery has been on the editorial board of well-known journals, including the Journal of Cell Biology. He is currently science magazine scientific advisor for Science Translational Medicine.

Professor Thiery has made seminal contributions in the fields of cell adhesion, cell migration, morphogenesis and cancer, publishing more than 400 peer-reviewed articles in different areas of the life sciences.

// RANDOLPH WATNICK.....

Dr. Watnick, born 1971, received his PhD in biochemistry and molecular biophysics from Columbia University in 1999. Dr. Watnick is currently assistant professor at the Department of Surgery, Harvard Medical School and research associate in the Vascular Biology Program at Boston Children's Hospital.

Dr. Watnick is author on 20 peer-reviewed articles and has received several awards, such as the Samuel and Lewis Rover Award for outstanding research in Biochemistry and Molecular Biophysics and a Damon Runyon post-doctoral fellowship. He has also co-edited one text book in collaboration with Professor Lars A. Akslen on Biomarkers of the Tumor Microenvironment. Dr. Watnick has served as a grant reviewer for the Italian Ministry of Health and is an ad hoc reviewer for Nature, Cancer Research, Molecular and Cellular Biology, and Science Translational Medicine.
Dr. Watnick's expertise is in tumor stromal interactions, regulators of metastasis and gene regulation in epithelial and mesenchymal cells. His research group studies the regulation of angiogenesis, proliferation and motility in both epithelial cells and fibroblasts. They have identified a novel suppressor of metastasis, Prosaposin, which acts both locally and distally by stimulating the expression/activity of p53, which then stimulates the expression of Tsp-1. Significantly, Prosaposin also inhibits both primary tumor growth and metastasis when administered in a systemic fashion thus making it a potential therapeutic agent to stem the metastatic dissemination of human tumors. Dr. Watnick's group has also developed a therapeutic peptide derived from Prosaposin, which is in late stage pre-clinical studies.

// THORSTEN SCHLOMM.....

Dr. Schlomm, born 1973, received his MD at the Georg-August University Göttingen, Germany in 2001, and finished his habilitation thesis in 2009 at the University Medical Center Hamburg-Eppendorf. He is currently full professor in urology and scientific director of the Martini-Clinic, Prostate Cancer Center at the University Medical Center Hamburg-Eppendorf (UKE).

Clinical validation of molecular prostate cancer markers are central topics of Dr. Schlomm's research. In 2003, he established a prostate cancer biobank at the UKE, now consisting of over 20 000 prostate cancer samples, ready to use for molecular diagnostics. Together with Guido Sauter´s group, Dr. Schlomm developed a prostate cancer TMA including over 17 000 fully annotated prostate cancers. This TMA is one of the main resources for many translational research programs.

Dr. Schlomm has published more than 200 peer-reviewed scientific articles and received several honorary awards, among other the ASCO Merit Award and the Peter-Bischoff-Award Urology. His clinical expertise is underlined by his status as a high-volume surgeon, having performed more than 2000 radical prostatectomies, recently leading to the development of a new surgical technique, which now is becoming an international standard in prostate cancer surgery. At present, he is the clinical coordinator of the German ICGC (International Cancer Genome Consortium) and the TCGA (The Cancer Genome Atlas) prostate cancer genome sequencing projects.

// MARK LABARGE.....

Mark LaBarge, born 1974, studied genetics at the University of California, Davis, and then earned his PhD in molecular pharmacology at Stanford University in 2004. He is currently professor at the Department of Population Sciences, City of Hope National Cancer Center, California.

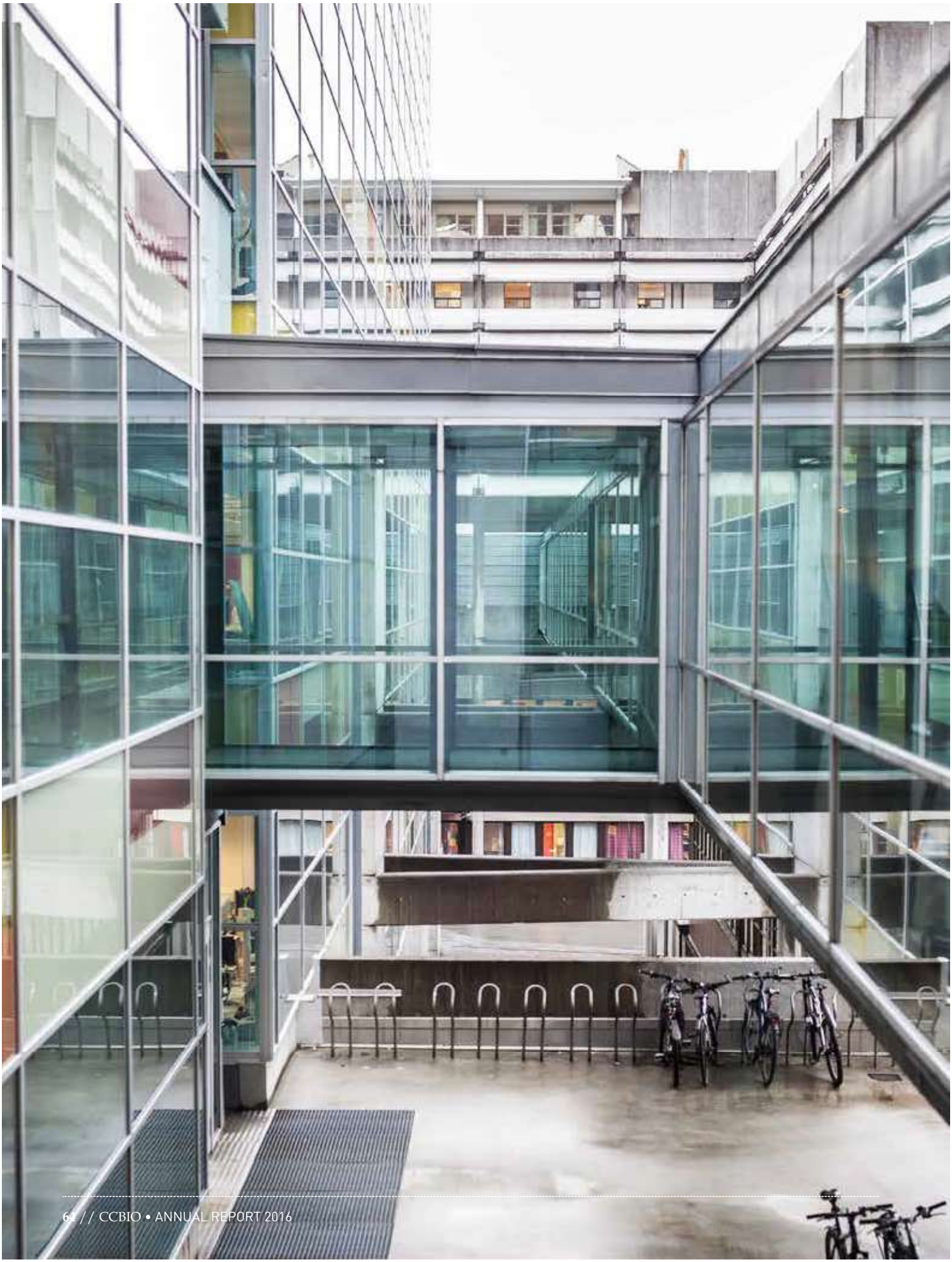
He is author on 30 articles in peer-reviewed journals and 6 book chapters that mainly address the biology of the microenvironment and stem cells in the breast, and is currently on the editorial board of the Frontiers in Cell and Developmental Biology (associate editor) and the Journal of Breast Cancer Survival. He is also grant reviewer for NIH, NSF, US Department of Defense, the European Research Council, Human Frontiers, Breast Cancer Campaign UK and other international organizations. He has received several awards, among them the US National Institute of Health Pathway to Independence Award, and the Era of Hope Scholar Award (CDMRP Breast Cancer Research Program).

Professor LaBarge's principle interests are to understand the role of microenvironment in mammary stem cell fate decisions in the context of aging and breast cancer. The objective of his research is to generate a comprehensive understanding of the effects of aging on the human mammary gland and how the resulting processes may contribute to tumorigenesis. His team is actively engaged in developing strategies to delay the biological effects of aging in the breast as a means of cancer prevention.

// RITVA HELJASVAARA .....

Senior Researcher Ritva Heljasvaara, born 1960, received her PhD in 1996 in molecular biology at the University of Oulu, Finland. In 1998 she joined one of the world's leading extracellular matrix (ECM) and collagen research groups led by Professor Taina Pihlajaniemi at the University of Oulu, and is currently the co-director of the group. Together with five other teams at the University of Oulu, their research group forms the Finnish Centre of Excellence in Cell-Extracellular Matrix Research of Academy of Finland for 2012-2017.

Dr. Heljasvaara obtained her post-doctoral training in molecular biology and cell biology at the National Institute of Biotechnology, CSIC, Madrid, Spain (1997-1998), and in tumor biology at the University of Oviedo, Spain (2006-2007). She is recognized for her expertise in extracellular matrix and tumor biology and for her work on experimental mouse tumor models. Since 2003 she has supervised/co-supervised five completed PhD theses, and is currently supervising four PhD/MD-PhD students. She has published almost 50 original peer-reviewed scientific articles with important contributions in clarifying the roles of ECM components and angiogenesis regulators in tumorigenesis. Her current research focuses on understanding the functions of the ECM components in skin and breast cancer microenvironments.



// KLAUS PANTEL.....

Professor Pantel, born 1960, did his MD at the University of Cologne in 1986, Dr.Med. at the University of Cologne in 1987 and Dr.med.habil. at the Ludwig-Maximillians-Universitaet in 1995. He is currently director of the Institute of Tumor Biology at the University Medical Center Hamburg-Eppendorf.

The pioneer work of Professor Pantel in the field of cancer micrometastasis, circulating tumor cells and circulating nucleic acids (ctDNA, microRNAs) is reflected by more than 400 publications in high ranking biomedical and scientific journals and has been awarded the AACR Outstanding Investigator Award 2010, the German Cancer Award 2010, and the ERC Advanced Investigator Grant 2011. Moreover, Professor Pantel coordinates the European TRANSCAN group "CTC-SCAN", the European IMI consortium CANCER-ID (www.cancer-id.eu) on blood-based "Liquid Biopsies" and serves on the editorial boards of international cancer journals (e.g., Clin. Cancer Res., Breast Cancer Res., Cancer Res.). Professor Pantel has established a clinical micrometastasis research network at the University Cancer Center Hamburg with a clear focus on diagnosis and treatment of solid tumors. Moreover, their laboratory for CTC analyses serves as central diagnostic center in various large-scale national and international clinical trials. Professor Pantel's expertise is particularly on disseminating tumor cells as biomarker of treatment efficacy. This work provides new insights into the biology of early tumor cell dissemination in cancer patients with particular emphasis on the identification of the putative metastatic founder cells ("stem cells") and the regulation of cancer dormancy responsible for late relapses in breast cancer patients.

// THERESE SØRLIE.....

Therese Sørlie, born 1967, got her PhD at the University of Oslo in 2000. She is currently adjunct professor at CCBIO and researcher and group leader at the Department of Cancer Genetics, Institute for Cancer Research at Oslo University Hospital.

She has over the years served in several scientific boards and committees, currently at the EACR Board, the Advisory Board for Research at the Cancer Clinic (KRE) at Oslo University Hospital (OUS), and the ESMO 2018 Scientific Committee. She is author on 52 articles in peer-reviewed journals and 16 reviews, book chapters and editorials, is a sought-after invited speaker, reviewer of manuscripts for several journals and peer reviewer of proposals for the European Research Council.

Sørlie's group investigates breast tumor initiation and progression; from the cell of origin in which the first oncogenic events take place, the specific pathways and processes that are deregulated in the further progression of the tumors, to the specific events that are essential for the transition from in situ to invasive cancer. The aim is to identify the cellular origins of breast tumors and the mechanisms behind tumor initiation and further development into the heterogeneous molecular subtypes.

// ARNE ÖSTMAN.....

Professor Arne Östman, born 1956, received his PhD in 1990 on Platelet-derived growth factor from the Ludwig Institute for Cancer Research, Uppsala University. He is currently an internationally renowned researcher within the field of molecular oncology and a full professor at the Karolinska Institute (KI).

Professor Östman is the coordinator of STARGET, a center-of-excellence network on tumor stroma based at the Karolinska Institute, with 10 year funding from the Swedish Research Council of 10 million SEK/year (2006-), vice-coordinator of STRATCAN, a government funded initiative for development of excellent cancer research at KI (2010-), and deputy head of department (2010-13).

In terms of academic evaluation, he is or has been on the evaluation committees of the Swedish Cancer Society (2007-) and the Swedish Child Cancer Society (2003-14), grant evaluation boards for EU, ERC, CRUK, ANR, DKH and Israeli and US/Canadian research agencies.

Professor Östman has unique expertise in the biology of tumor microenvironment regulation with special focus on tumor associated fibroblasts and their role in cancer progression, and he has made important contributions in this field.

Research School for Cancer Studies: Courses at CCBIO

The CCBIO Research School for Cancer Studies (RSCS) focuses on translational cancer research and innovation, including international exchange and mobility as well as ethical-, legal- and societal aspects of cancer research and treatment.

The research school courses are available for all interested students within the field of cancer research. The RSCS is directed by Professor Anne Christine Johannessen in collaboration with CCBIO's director.

In accordance with its aims, the RSCS is now well established as a scientifically stimulating and inclusive meeting place for junior researchers within various areas of cancer research and related ELSA fields with a common focus on translational studies of cancer biomarkers. PhD candidates and postdocs have an opportunity to meet each other and deliberate upon their research projects across the established

research groups and diciplines. CCBIO has successfully integrated the RSCS into its strategic activities like the CCBIO Annual Symposium, CCBIO Junior Scientist Symposia and CCBIO Seminars. In conjunction with lectures and seminars, CCBIO makes sure to use the opportunity for younger and more senior researchers to have targeted meetings with the invited speakers where potential points of common interest are mapped out. In combination with CCBIO's strategy of inviting external speakers also for the other courses and its recruitment of an international network of adjunct positions, this ensures that the center's younger researchers have access to renowned national and international researchers from outside CCBIO.

In 2016, CCBIO held courses that run continuously, reflecting that they are integral parts of CCBIO's continuous strategic activities, as well as the ethics and economics course CCBIO903. The more methods specific courses will be held again in 2017 and 2018 when CCBIO's next batch of PhDs and postdocs have been recruited.

CCBIO901 and CCBIO902
- Courses Integrated into CCBIO's Strategic Activities
CCBIO's Junior Scientist Symposium, where PhDs and postdocs organize their own seminars and present their results four times a year, forms the PhD Course CCBIO901. CCBIO's monthly seminars and the CCBIO Annual Symposium form the PhD course CCBIO902. Both are described in detail in separate articles.

CCBIO903
- Cancer Research: Ethical, Economic and Social Aspects
The CCBIO903 course started up in 2015 and was held again in 2016. This course is highly interactive and aims to address current issues that researchers and clinicians face every day, such as how to prioritize research questions or how to choose between treatments for a patient; involving both ethical, social and economic considerations. These issues have been strongly present in the media in the last couple of years, adding further pressure on the researchers and clinicians to address these dilemmas. In this context, the objective of the course is to help PhD candidates to find ways to systematically reflect on the broader social and ethical context of their own research, as well as to introduce them to methods of cost-benefit analysis of health measures and treatment options.

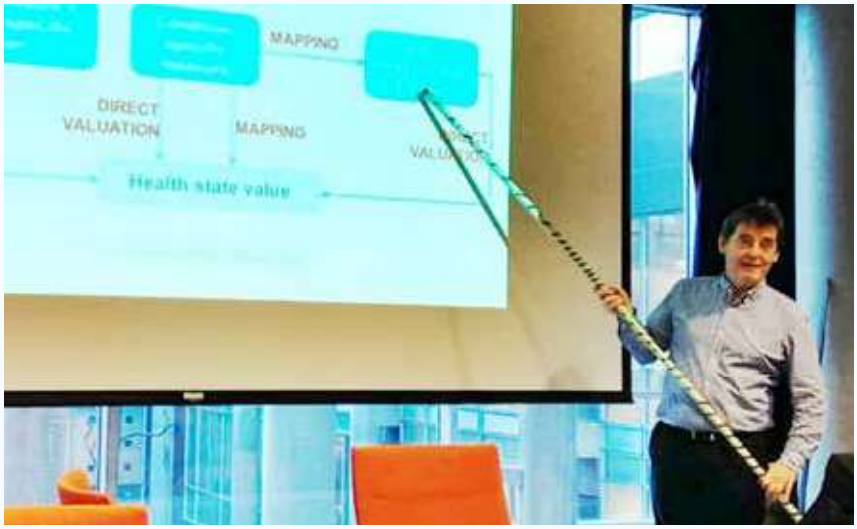
Some of the questions addressed during the course were:
How can your reserch contribute to debates on what is good for society? Should everyone have access to the newest cancer therapy? How should we assess the cost-effectiveness of cancer biomarkers? How can economic models help guide health care resource allocation? How do we make medical

decisions when surrounded by risks, uncertainties and even ignorance? What can the 'good life' actually mean? What may the future hold for cancer research?

In 2016, the course took place over two weeks, the 23-26th of May and the 14-17th of June, and was structured around lectures and open discussions with a high degree of interaction. The candidates were asked to write a term paper that included an analysis of the ethical, economic and social aspects of a specific field or topic, preferably related to their own PhD project. The candidates were also required to give an oral presentation during the course, based on their own term paper in order to receive feedback from the whole group and the lecturers.

In 2017, CCBIO903 will take place in the fall. CCBIO903 is open to PhD candidates affiliated with the Centre for Cancer Biomarkers (CCBIO), to other PhD candidates and to students at the Medical Student Research Program. PhD candidates from medical fields of research from all over Norway can also attend.

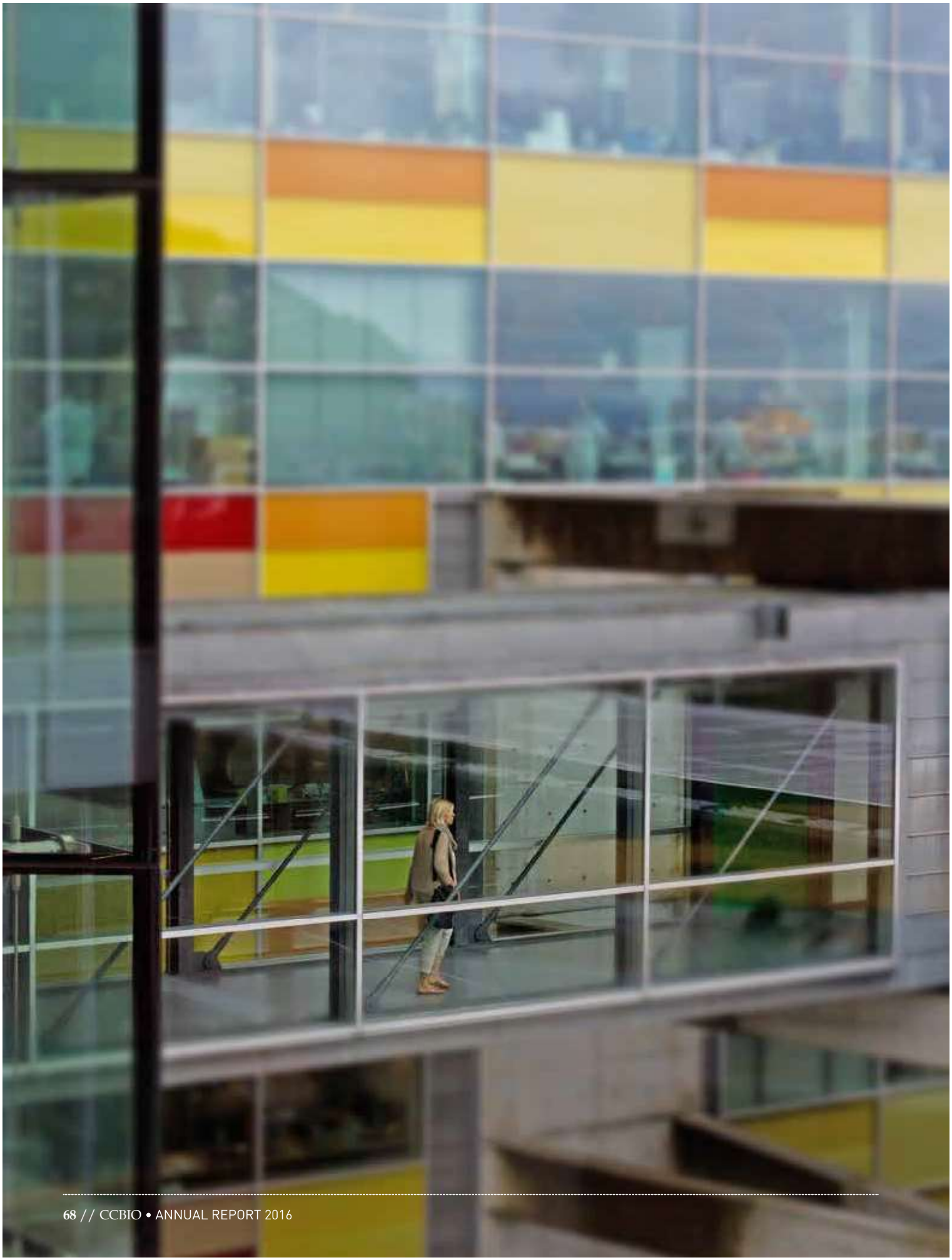
CCBIO903 is led by Roger Strand, John Cairns and Anne Blanchard.



CCBIO904
- Biomarkers and Tumor Biology in Clinical Practice
CCBIO904 was held for the first time 4-6th of November 2015, with 15 participants signed up for the course and more attending for individual lectures. The students were active in discussions of cases presented by the lecturers. Participants were required to prepare 15 minutes presentations at the last day of the course.

The main goal of this course is to illustrate how basic cancer research and knowledge about tumor biology have substantial impact on patient outcomes and lives. Lectures cover tumor biological aspects important for the understanding of why cancer develops and which mechanisms are important for tumor growth, metastases and morbidity in patients. In 2015, twelve highly dedicated lecturers from several research groups at Haukeland University Hospital and the University of Bergen presented 15 different topics, including cellular signaling, tumor invasion and metastasis, the immune system in cancer, mutations in cancer and tumor biology. There was a special focus on biological alterations that are of importance for personalized therapies as well as clinical cancer research. The next CCBIO904 course will be in the spring of 2018. Oddbjørn Straume and Bjørn Tore Gjertsen have the academic responsibility, and Reidun Kopperud is the course coordinator.

CCBIO905
- Methods in Cancer Biomarker Research
CCBIO905 was held for the first time in September 2015 as a three-day course geared towards students with an interest in methods relevant for cancer biomarker research. Around 30 students signed up, and several more attended individual lectures. The participants displayed a high level of interest and were very active during the lectures, asking questions and discussing applications for the different methods. The lecture on next



generation sequencing (NGS) turned out to be of special interest with more than 80 participants and especially lively discussions.

CCBIO905 presents a broad range of topics, and in order to cover it all, the 2015 course had 15 thematic parts, including several methods ranging from basic techniques on nucleotides and proteins to more advanced and modern techniques as well as bioinformatics, biobanking and components of ethics and economy. As an integral part of the course, the students are acquired to band together and prepare group presentations on important scientific papers describing results from clinical trials that have led to approval of new cancer treatments. The presentations addressed topics like the studies' background, the impact of the biomarkers in terms of predictive power and the trials' clinical results as well as methods used and drug mechanisms. The course was concluded with a three-hour multiple-choice examination. The next CCBIO905 course will be in the autumn of 2017.

Lars A. Akslen and Jim Lorens have the academic responsibility and Monica Mannelqvist is the course coordinator.

BMED904 - Matrix Biology

BMED904 is a well-established course from the Bergen Biomedical Research School (BBRS) that has been included into CCBIO's course portfolio. In June 2015, the course was arranged jointly with CCBIO's RSCS for the first time as a five day course that included lectures from local researchers and a number of internationally well-known researchers within the field of matrix biology as well as practical laboratory training. Fifteen students signed up for the course and up to 70 attended individual lectures.

The course focused on basic molecular mechanisms pertaining to the biological role of the extracellular matrix. Three of the lecture highlights were John Couchman (Copenhagen), Cathy Merry (Manchester, UK) and Ulrich Valcourt (Lyon). In addition to attending lectures, the students read relevant articles, worked on articles group-wise and presented their articles for the rest of the group. All students also spent time in the Matrix Biology Lab, where microscopy of integrin-tagged cells as well as culture in 3D collagen matrices was demonstrated.

The course worked well, feed-back was positive, and several attendants commented that the course should have been advertised also in the rest of Norway as well as Scandinavia. The next course will be June 12-15, 2017, and will cover various aspects of extracellular matrix (ECM) biology, including the structure and function of the main classes of ECM molecules and the composition of the ECM in different tissues and cellular receptors for ECM molecules and their signaling. A recurring theme will be the roles of the various ECM molecules and their functions in health and disease.

The course is organized and executed by Marion Kusche-Gullberg and Donald Gullberg.

International Collaboration and Further Development of Courses

CCBIO has strong emphasis upon internationalization and most of the CCBIO groups have a research focus that is inherently international. In addition, CCBIO aims to move beyond the usual internationalization measures. Accordingly, CCBIO received in 2015 funding from the Research Council of Norway (RCN) and The Norwegian Center for International Cooperation in Education (SIU)'s effort towards Partnerships for Excellent Education and Research (INTPART). This funding mechanism is geared towards forwarding a stronger integration of excellent research with excellent teaching, in collaboration with international partners. Hence, CCBIO is now, with ample resources at its disposal, in the process of elaborating the existing course portfolio together with its partners at Harvard Medical and Kennedy Schools. Courses that cannot be linked to the INTPART effort will also experience improved access to resources through the freeing up of funds. ••

Researcher Training

The centrally organized part of CCBIO's researcher training is centered around the CCBIO Research School for Cancer Studies (RSCS). The RSCS is a scientifically stimulating and inclusive meeting place for junior researchers within various areas of cancer research with a common focus on translational studies of cancer biomarkers and also serves as a bridge to CCBIO's ELSA efforts. Through RSCS and its embedment into CCBIO's other strategic activities (see chapter on RSCS), PhD candidates and postdocs get ample opportunity to meet each other and deliberate upon their research projects across the established groups. CCBIO strives to stimulate its PhDs and postdocs to independence and encourages the formation of subgroups where experienced postdocs provide guidance to younger researchers within their CCBIO research group. Throughout 2016, CCBIO had a total of 48 PhD students, of which 65% were female and 35% were male. Slightly more than half of the PhD students were of Norwegian origin and among the remainder, Africa and Asia was particulary well represented with a third of all PhDs. CCBIO prides itself with being an international CoE.

Doctoral Defenses

2016 proved to be a good year for CCBIO when it comes to doctoral defenses affiliated to CCBIO. Several candidates from different groups defended their work ranging from basic to translational and clinical studies. Lavina Ahmed was the first industrial PhD student from CCBIO, with a combination of industrial and academic work in her thesis.

2016

Jenny Hild Aase Husby: "Functional imaging to promote individualized and targeted therapy in endometrial cancer." Supervisors: Professors Ingfrid S. Haldorsen and Helga B. Salvesen.

Himalaya Parajuli: "Integrin Role of integrin α11 in oral carcinogenesis. In vitro and in vivo studies." Supervisors: Professors Daniela Elena Costea, Anne Christine Johannessen and Donald Gullberg.

Fanny Pélissier: "The Role of Age in Cellular Responses to Microenvironmental Cues as a Breast Cancer Susceptibility Factor." Supervisors: Professor James B. Lorens and Dr. Mark LaBarge.

Hengshuo Liu: "Expression and mechanosensitivity of integrin α11 in the tumor microenvironment." Supervisors: Professor Donald Gullberg and Professor Rolf K. Reed.

Ingvild Løberg Tangen: "Hormone signaling related factors as biomarkers in endometrial cancer." Supervisors: Associate Professor Camilla Krakstad and Professor Helga Salvesen.

Gøril Knutsvik : "Biomarkers in breast cancer, with special focus on tumor cell proliferation." Supervisors: Professor Lars A. Akslen and Associate Professor Ingunn M. Stefansson.

Lavina Ahmed: "Axl as a Biomarker in Breast and Lung Cancer." Supervisors: Professor Lars A. Akslen, Dr. David Micklem and Dr. Hawa Nalwoga.

Elise Aasebø: "Mass spectrometry-based proteome quantification in leukemic cells from acute myeloid leukemia patients." Supervisors: Professor Frode S. Berven, Professor Frode Selheim, Dr. Marc Vaudel and Bjørn Tore Gjertsen.

Cornelia Schuster: "Investigation of predictive markers in patients with metastatic melanoma treated with bevacizumab." Supervisors: Dr. Oddbjørn Straume and Professor Lars A. Akslen.

André Sulen: "Leukocyte p38 and p53 proteins after environmental exposure; variation, associations and applicability." Supervisors: Professor Bjørn Tore Gjertsen, Jörg Aβmus and Bjørg Eli Hollund.

2015

Lene Elisabeth Myhren: "Cell death induction by free and encapsulated cancer drug candidates." Supervisors: Stein Ove Døskeland, Lars Herfindal and Bjørn Tore Gjertsen.

Katarzyna Wnuk-Lipinska: "The role of Axl signaling in phenotypic plasticity in normal and neoplastic epithelial cells." Supervisors: Professor James B.Lorens and David Micklem.

Ida Wiig Sørensen: "Molecular Characterisation of Integrin a 11 Function." Supervisors: Professor Donald Gullberg and Professor Marion Kusche-Gullberg.

2014

Crina Elena Tiron: "The Role of the Axl Receptor Tyrosine Kinase in Breast Cancer." Supervisor: Professor James B. Lorens.

Tarig Al-Hadi Osman: "Cancer stem cell-related markers in normal and neoplastic oral mucosa". Supervisors: Professor Daniela Elena Costea and Anne Christine Johannessen.

Øystein Helland: "Ovarian Cancer: A clinical challenge requiring basic answers." Supervisors: Professor Line Bjørge, Professor Bjørn Tore Gjertsen and Professor Emmet McCormack.

Henrica Maria Johanna Werner: "Clinical and molecular markers in endometrial cancer. " Supervisors: Professor Helga Salvesen and PhD Candidate Jone Trovik.

Amani Hamza Ali Osman: "Characterization of the tumor stroma and stem cell niche in oral squamous cell carcinoma." Supervisors: Professor Anne Christine Johannessen and Professor Daniela Elena Costea.

Åshild Lunde: "Tensions in Practice, Knowledge and Regulation: Genetic Counseling in Norway". Supervisors: Professor Roger Strand and Professor Karin Nordin.

2013

Hanne Eknes Puntervoll: "Molecular studies of sporadic and hereditary cutaneous malignant melanoma." Supervisors: Professor Lars A. Akslen and Professor Anders Molven.

Hanne Haslene-Hox: "The microenvironment in human ovarian carcinoma". Supervisors: Professor Helge Wiig, Professor Helga Salvesen and Professor Olav Tenstad.

Elisabeth Wik: "Endometrial carcinoma: a step closer to individualized therapy?." Supervisors: Professor Helga Salvesen and Professor Lars A.Akslen.

Even Birkeland: "Mutations and gene amplifications in endometrial carcinomas." Supervisors: Professor Helga Salvesen and Associate Professor Camilla Krakstad.

Jørn Skavland: "Risk stratification and therapy response monitoring by phosphoprotein profiles in acute myeloid leukaemia." Supervisors: Professor Bjørn Tore Gjertsen nd Professor Øystein Bruserud.

CCBIO
Bioinformatics Group

The CCBIO Bioinformatics Group (BIG) was established to facilitate work on bioinformatics analyses, and to increase cooperation in these matters across CCBIO research groups. David Fredman and Kjell Petersen from ELIXIR/CBU teamed up with representatives from several CCBIO research groups.

Kjell Petersen from the ELIXIR/CBU service group has been the main responsible for running the workshops, and Elisabeth Wik (CCBIO Junior Associate Investigator and postdoc in the group of Professor Akslen) has been coordinating the group.

The workshops have alternated between being structured with a lecture on the "topic-of-the-day", followed by individual analysis work and support, and as plain analysis workshops. Topics covered in the structured parts of the workshops have been analyses of metadata (introduction and practical examples) and introduction to and suggestions for self-studies of the programming language R. Several workshops have covered NGS Data Analysis on NeLS Galaxy.

The seminars have been run by Kjell Petersen and Charitra Kumar Mishra from the ELIXIR/CBU support team, joint with the support workshops they run. There have been in total 6 seminars this year. Which researchers or groups from CCBIO that has taken part in the workshops has varied according to the need for this kind of support in the various CCBIO research groups.

CCBIO-BIG is aiming partly for joint workshops together with open CBU seminars (e.g. seminars and workshops on general bioinformatic topics). The group plans to do a short assessment of the estimated needs for bioinformatic support within CCBIO the coming year, and will plan its activities accordingly. Additionally, CCBIO BIG has ongoing discussions with NORBIS (the National Research School in Bioinformatics, Biostatistics and Systems Biology) about developing workshops and/or courses (3-5 days) on cancer related bioinformatics, aiming to combine lectures on specific topics, and possibilities to in-depth learning of specific tools, along with hands-on training with the researcher's own data. ••

CCBIO Junior Scientist Symposium

In 2016, CCBIO901, the CCBIO Junior Scientist Symposium (JUSS), was organized and chaired by the postdocs Agnete Engelsen and Elisabeth Wik. Researcher Erling A. Høivik co-chaired the December symposium.

Also this year, four symposia took place, with 30-45 registered attendants per meeting. The seminar format includes talks by four to six PhD candidates and postdocs to present their research, followed by a short discussion after each presentation. Each seminar lasts four hours in total. Starting in 2015, an "inspirational lecture" has also been part of each seminar. These are sessions where a senior researcher gives a presentation with a particular emphasis on sharing experience from the many different and often under-communicated aspects that make up a research career. Throughout 2016, Professor Daniela Costea and Associate Professor Nils Halberg were amongst the younger seniors who shared glimpses from their professional and private journeys that brought them where they are today, as experienced and skilled researchers at the University of Bergen. Costea presented interesting views on how to be a research leader, and Halberg brought interesting perspectives on various aspects of a life in science, comparing experiences from his research periods in Denmark, USA and Norway. At the December seminar, Professor Curtis C. Harris, Head of the Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, NIH, USA, visited Bergen and shared his vast experience in combined medical oncology and cancer research. Wisely, as we could hope from a person with his experience, he advised the young, aspiring scientists to learn early how to collaborate.

One of the novelties of 2016 was the introduction of themes covering transferable skills, constituting an important part of the PhD education. The national winner of Forsker Grand Prix in 2015, Cecilie G. Gjerde, was invited to present tools and tips for good research presentations (her presentation entitled "Research communication - business or pleasure?"), in addition to presenting her research project on stem cell based bone culturing. At the December seminar, Professor Arild Raaheim presented the lecture "Supervision: Challenges and opportunities." He pointed out important elements for deep learning, and opportunities for improved supervision. This was an important lecture for the juniors under supervision today, and with key issues to remember to do good jobs as future supervisors.

The rest of the 2016 program covered cancer research in a broad perspective. The topics ranged from molecular and mechanistic studies, through bioinformatics and clinical research and to socio-ethical considerations in biomarker research. One seminar focused on immuno-oncology, also with an excellent broader introduction to the field by one of the PhD candidates (K. Davidsen). Further, proteomics in cancer research was presented with a dedicated joint session at the April seminar. ••

Centre for Cancer Biomarkers

PROGRAM - CCBIO Junior Scientist Symposium

February 25th 2016 - Auditorium 2, BBB

Symposium Chairs: Agnete Engelsen and Elisabeth Wik

10.00-10.20: Maria Ramnefjell:
Vascular invasion and vascular proliferation are adverse prognostic factors in non-small cell lung carcinoma

10.20-10.40: Saroj Rajthala:
Micro-RNA profiling of oral cancer stroma

10.40-11.00: Konstantina Dimitrakopoulou:
Gene expression deconvolution in complex tissue samples

11.00-11.15 BREAK

11.15-12.00: Cecilie Gudveig Gjerde,
the winner of 'Forsknings Grand Prix' 2015: Research communication - business or pleasure?

12.00-13.00 LUNCH

13.00-13.20: Mahdi Hassan-Olive:
Thioridazine sensitizes glioblastoma cells to temozolomide by impairing autophagy

13.20-13.40: Henriette Ertsås Christie:
Microenvironment- contextual cell signaling is attenuated with age

13.40-14.00: Jessica Furriol:
IL8 gene polymorphisms in combination with clinical factors predict disease free survival in breast cancer

Centre for Cancer Biomarkers

PROGRAM - CCBIO Junior Scientist Symposium

April 28th 2016 - Auditorium B301

Symposium Chairs: Agnete Engelsen and Elisabeth Wik

10.00-10.05 Welcome and introduction to the PhD course CCBIO 901

10.05-10.25: Katharina Bischof:
Prognostic and predictive markers in high grade serous ovarian carcinoma

10.25-10.45: Deusdedit Tusubira:
Repression of mitochondrial respiration is an important step in epithelial to mesenchymal transition (EMT)

10.45-11.00 BREAK

11.00-12.00: Nils Halberg:
Inspirational lecture

12.00-13.00 LUNCH

Proteomics session:

13.00-13.20: Frode Selheim:
PROBE: A core facility for mass spectrometry based proteomics

13.20-14.00: Even Birkeland and his master student Silje Kjølle:
Secreted proteins in breast cancer, a proteomics approach

Centre for Cancer Biomarkers

PROGRAM - CCBIO Junior Scientist Symposium

August 25th 2016, - Auditorium B301

Symposium Chairs: Agnete Engelsen and Elisabeth Wik

10.00-10.50: Inspirational lecture' by Professor Daniela Elena Costea (K1)

10.50-11.00 BREAK

11.00-11.20: Øystein Eikrem (K1):
New methods clear dust off old biopsies - RNA sequencing of FFP Etissues

11.20-11.40: Kjersti Davidsen (IBM):
Introduction to cancer immunotherapy

11.40-12.00: Kjersti Davidsen (IBM):
Enhancing the effect of immune checkpoint inhibition by targeting Axl

12.00-13.00 LUNCH

13.00-13.20: Maria Kolnes Lie (IBM):
Inhibition of Axl in erlotinib-resistant NSCLC cells abrogates autophagic flux and induces immunogenic cell death

13.20-14.00: Kjell Petersen (Department of Informatics):
Integrated dataanalysis of proteomics and transcriptomic data from brain cancer model

Centre for Cancer Biomarkers

PROGRAM - CCBIO Junior Scientist Symposium

December 8th 2016 -Auditorium, Hudbygget

Symposium Chairs: Agnete Engelsen, Erling A. Høivik and Elisabeth Wik

10.00-10.45: Inspirational lecture: Professor Arild Raaheim (Department of Education, UIB):
A supervisor's view on supervision. Challenges and possibilities

11.45-11.00 BREAK

11.00-11.20: Karen Mauland (K1):
High proportion of visceral fat is linked to poor endometrial cancer outcome

11.20-11.40: Gry Sandvik Haaland (IBM):
Warfarin use and cancer incidence

11.40-12.00: Trung Ha (K2):
Preclinical Activity and Molecular Mechanisms of Resazurin in Acute Myeloid Leukemia

12.00-12.40 LUNCH

12.40-13.00: Hanna Dillekås (K1):
Recurrence of breast cancer in relation to delayed reconstruction

13.00-14.00: Inspirational lecture: Professor Curtis C. Harris (Center for Cancer Research, National Cancer Institute, NIH):
Integration of "OMIC" Biomarkers: A Precision Medicine Strategy for Lung Cancer

CCBIO Research Seminars

In 2016, CCBIO's monthly research seminars focused almost exclusively on speakers of international interest. The seminars have been very well visited by the local scientific audience, far outnumbering similar seminar series in terms of attendance, the available auditorium often being filled to the rim with up to 120 participants. Through active marketing and recruitment of students and younger researchers to the seminars, it fulfills the aim of conveying relevant biomarker research to the local scientific community and students and younger researchers in particular, readying the ground for future recruitment. Students and younger researchers are especially frequent participants as the seminar series is included into the master level course BMED380 and the PhD-level course CCBIO902. Last, but not least, each seminar is followed by an informal pizza get-together that is an important catalyst for interaction on all levels. In most cases, targeted meetings with the speakers are arranged before or after the lectures so that CCBIOs researchers, in particular the younger ones, get the opportunity to discuss projects and collaboration with the invited lecturers.••

CCBIO Seminars in 2016

28.01.2016

Jean-Christophe Bourdon, Division of Cancer Research, Jacqui Wood Cancer Centre, University of Dundee, United Kingdom. Title: A decade of research on p53 sumarised.

25.02.2016

Olivier De Wever, Laboratory of Experimental Cancer Research, Ghent University, Belgium. Title: Communication in the tumor environment: diagnostic and therapeutic opportunities.

17.03.2016

Lutz P. Müller, MD; Clinic for Internal Medicine IV - Hematology / Oncology, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany. Title: Growth promotion of colorectal cancer by mesenchymal stromal cells – when and how?

28.04.2016

Krister Wennerberg, Institute for Molecular Medicine Finland, University of Helsinki, Finland. Title: Targeting cancers using individual systems medicine.

26.05.2016

Anne Blanchard, CCBIO, **John Torgils Vaage,** Oslo University Hospital, **Jim Lorens**, CCBIO and **Richard Godfrey**, BerGenBio. Title: Pharma and public cancer biomarker research in the transition from a blockbuster model to personalised medicine.

16.06.2016

Gwendalyn J. Randolph, Division of Immunology, School of Medicine, Washington University in St. Lois, USA. Title: The Lymphatic vasculature in immunity and inflammatory disease.

25.08.2016

Jonathan M. Irish, Department of Cancer Biology, Vanderbilt University, Nashville, TN, USA. Title: Decoding human tumor microenvironments and healthy tissues using high dimensional single cell mass cytometry.

29.09.2016

Herbert Schiller, Comprehensive Pneumology Center, Institute of Lung Biology and Disease, Helmholtz Zentrum München, Neuherberg, Germany. Title: Multi-dimensional proteomics of the extracellular matrix in regeneration and fibrosis.

10.11.2016

Caroline Heckman, FIMM, Helsinki. Title: In vitro drug screen in acute myeloid leukemia.

01.12.2016

Jean-Paul Thiery, CCBIO, Yong Loo Lin School of Medicine National University of Singapore, University Paris Denis Diderot, Paris, France and Comprehensive Cancer Center Institut Gustave Roussy, Villejuif, France. Title: Epithelial cell plasticity in carcinoma: Harnessing mechanisms controlling biomechanics and progression of malignancy for the design of new therapeutic strategies.

15.12.2016

Kenneth Hugdahl, Department of Biological and Medical Psychology, University of Bergen. Title: Excellence in science: Experience with ERC Advanced Grants.

CCBIO Special Seminars and Meetings

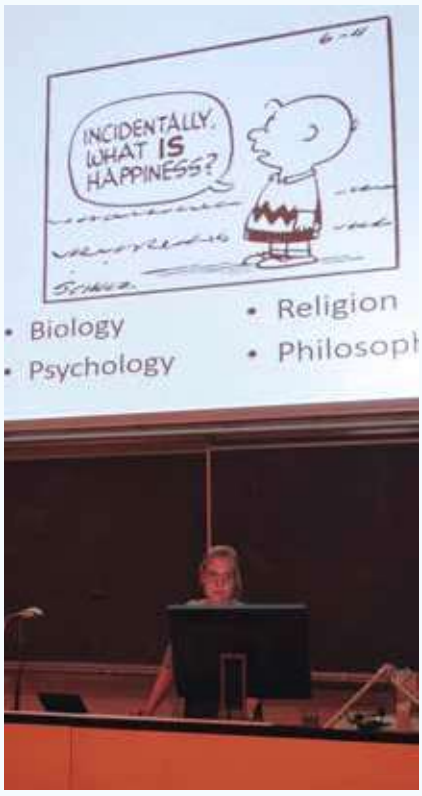
CCBIO Special Seminars
Whenever CCBIO's PIs have separate symposia with interesting lecturers, senior researchers visiting outside of the annual symposium and the CCBIO seminars, or the opportunity arises to invite an especially interesting lecturer, CCBIO encourages them to arrange talks under the umbrella of the CCBIO Special Seminars. In this way, the special seminars are integrated into CCBIO's seminar series, while at the same time making them stand out. The special seminars have typically been very well visited with 100 to 140 participants.

Pharma and Public Cancer Biomarker Research in the Transition from a Blockbuster Model to Personalized Medicine
May 26th, Roger Strand and Anne Blanchard invited to a CCBIO Special Seminar where the focus was on the transition from a "blockbuster" drug model to the delivery of cancer therapies that are tailored to ever-smaller subgroups of patients that share some common biological and genetic characteristics.

Researchers with broad experience from biomedicine, industry, government and social science shared their views and reflections on the challenges and opportunities of personalized cancer medicine. Speakers and panelists were **Anne Blanchard,** CCBIO, **John Torgils Vaage,** Oslo University Hospital, **Jim Lorens,** CCBIO/Department of Biomedicine, University of Bergen and **Richard Godfrey,** BerGenBio. Moderator was **Roger Strand,** CCBIO/ Centre for the Study of the Sciences and the Humanities (SVT), University of Bergen.

The panel discussed the three main actors that face challenges in this transition: pharmaceutical companies who may fear market fragmentation; public research who encounters challenges of validating cancer biomarkers; and governmental agencies who are confronted with the question of how to achieve a fair and sustainable allocation of cancer care. Cooperation and collaboration between industry, public research and the government is clearly needed to meet the challenges. At the same time, the choice of collaborative model shapes the trajectory of drug development, cancer research and ultimately how society will understand cancer and organize its cancer care.

S.Net Pre-Conference Event: Ethical and Social Aspects of Cancer Research
This special seminar October 11th aimed at bringing together young researchers from the fields of oncol-



ogy, medical ethics, priority setting in health care, and science and technology studies, in order to discuss topics ranging from the ethics of personalized medicine, the role of cancer biomarkers in clinical practice, cancer and

extraordinary treatments that lead to ever longer lives, and issues of privacy in biobanks. The seminar was also a pre-event to the 8th annual S.Net meeting, which took place 12-14 October in Bergen. CCBIO's **Roger Strand** was the initiator. After opening words by the Director **Lars A. Akslen,** presentations on various topics were given by local speakers such as **Eirik Tranvåg, Caroline Engen, Karoline Huse, Anne Blanchard, Gry Wester** and **Kjetil Rommetveit,** and also the international speakers **Alessandro Blasimme,** University of Zurich: «Towards precision medicine: oncology and the search of a new ethics of medical discovery» and **Pankaj Sekhsaria**, Hyderabad, India: «How (non) users matter - A case of study of nanotechnology for Retinoblastoma treatment in India».

Scandinavian Pathology Seminar
CCBIO organized the Scandinavian Pathology Seminar 2016 August 30-31, with the intention to create a Scandinavian (or Nordic) network for researchers within tissue based research fields. CCBIO Director **Lars A. Akslen** and CCBIO affiliated investigator **Arne Östman** from the Karolinska Institute initiated and chaired the meeting, which was the first of its kind. Approximately 50 invited cancer researchers gathered in the wild west of Sotra at Panorama Hotel outside of Bergen. The symposium had talks by senior and junior researchers, company

presentations and also a poster session. Among several exciting presentations, **Octavian Bucur** from Harvard Medical School talked about the new technique of expansion pathology, and the Vice Program Director of The Human Protein Atlas **Fredrick Pontén** (Uppsala) presented the publicly available database and its vision to include all human proteins. **Monica Nistér** from the Karolinska Institute presented her pediatric tumor biobank, and work done on brain tumors trying to identify genomic aberrations. **Olli Carpén** from the University of Turku discussed prognostic biomarkers in endometrial cancer and melanoma. **Johan Hartman** (Karolinska Institute) discussed the phylogenetic reconstruction of metastatic breast cancer, whereas **Johan Lundin** (Helsinki) covered aspects of image analysis and deep learning. The response during and after the meeting was very positive, and a follow-up network meeting is now being planned for 2017, aiming to further connect Nordic researchers engaged in tissue based research. ••

Centre for Cancer Biomarkers

Norwegian Centre of Excellence
The Research Council of Norway

Scandinavian Pathology Seminar

August 30 - 31, 2016 - Bergen - Norway

SCIENTIFIC PROGRAM

Day 1: Tuesday - August 30, 2016

09:00-10:00 REGISTRATION AND COFFEE

10:00-10:15 Welcome and Introduction:
Arne Östman and Lars A. Akslen

Chair: Arne Östman
10:15-10:45 Fredrick Pontén: The Human Protein Atlas: implications for pathology and clinical medicine.
10:45-11:15 Octavian Bucur: Expansion Pathology: physical tissue expansion in diagnostic pathology
11:15-11:45 Therese Sørlie: Molecular analysis of breast cancer progression
11:45-12:15 Johan Lundin: Deep learning for tissue analytics and outcome prediction in cancer
12:15-12:25 Company presentation: Perkin Elmer

12:25-13:25 LUNCH

Chair: Elisabeth Wik
13:25-13:55 Anna Bofin: Molecular subtypes of breast cancer: Exploiting archival tissue samples to solve the problems of today
13:55-14:25 Patrick Micke: The specificity of lung cancer; targets beyond targeted therapy
14:25-14:55 Olli Carpén: Novel prognostic biomarkers in endometrial cancer and melanoma
14:55-15:25 Monica Nistér: The Pediatric Tumor Biobank
15:25-15:35 Company presentation: Definiens

15:35-16:00 COFFEE

Chair: Therese Sørlie
16:00-16:20 Artur Mezheyeuski: Image analysis of histo-morphological complexity predicts CRC prognosis and treatment response
16:20-16:40 Elisabeth Wik: An angio-immunogenic profile of basal-like breast cancer; relevance of cancer testis antigens
16:40-17:00 Teijo Pellinen: Multi-parametric immunohistochemistry
17:00-17:20 Marit Valla: Molecular subtypes of breast cancer: Trends in incidence and prognosis
17:20-17:30 Company presentation: Visio Pharm
18:00-19:00 Posters

19:15 DINNER

Day 2: Wednesday - August 31, 2016

Chair: Even Birkeland
09:00-09:30 Arne Östman: Perivascular cell subsets predicts prognosis and response to treatment

09:30-10:00 Hege Russnes: Intra-tumor heterogeneity in breast carcinomas - a clue to treatment resistance?

10:00-10:30 Johan Hartman: Phylogenetic reconstruction of metastatic breast cancer

10:30-11:00 Lars A. Akslen: Tissue derived markers of tumor-vascular interactions

11:00-11:10 Company presentation: Offspring Biosciences

11:10-11:30 COFFEE

Chair: Lars A. Akslen
11:30-11:50 Monica Engstrøm: HER2 gene copy number in breast cancer. Is CEP17 redundant?

11:50-12:10 Even Birkeland: Proteomic analysis of paraffin embedded breast cancer tissue

12:10-12:30 Per-Henrik Edqvist: The U-CAN biobank initiative; perspectives from first five years

12:30-12:35 Closing remarks

12:35 LUNCH

HELGA B. SALVESEN

Memorial Symposium

On September 14th, CCBIO invited to a one day symposium in the memory of Helga B. Salvesen, with the title "Biomarkers in Female Cancer". The aim of the symposium was to honor the late CCBIO Principal Investigator Helga Salvesen's memory by focusing on the state of the art within research on gynecologic cancer as well as younger researchers efforts within the field. People came from far and near to be together at this scientific gathering. The 150 participants were provided with much scientific refill during the day. Several top names in cancer research had come to Bergen this September day, among others **Ate van der Zee** from Groningen University in the Netherlands, **Hani Gabra** from Imperial University London and **Inger Thune** from the University of Oslo. The scientific program focused on new biomarker studies in gynecologic and breast cancers. There was also a combined lunch and poster session where younger researchers presented their work. The day turned out to be very inspirational for the participants. Through her work Helga had been a role model for many young researchers, and this was reflected during the entire day. Opening remarks were given by **Lars A. Akslen, Per Bakke** and **Line Bjørge.** Presentations were given by **Toni Hurtado, Erling Høivik, Ingunn Stefansson, Anna Berg, Even Birkeland, Elisabeth Wik** and **Erica Werner.** ••

R&D Network: Personalized Cancer Therapy

Repurposing and in Vitro Drug Screens

CCBIO and Oslo Cancer Cluster (OCC), of which CCBIO is an active member, held a joint R&D Network meeting in Bergen on November 10th. International and Norwegian experts presented and discussed trends and examples in oncological drug repurposing (also sometimes called drug repositioning) and in vitro drug screening. In vitro drug screens have been used as a research tool for therapy development in decades, but robotics and bioinformatics has made it feasible to test more agents and even combinations. The culture conditions of these screens have improved to better reflect the tumor environment. Therefore, several groups have started small clinical trials for selecting the

therapeutic agent through screens of cells from refractory/relapsed cancers.

Repurposed therapeutics have increasingly emerged as experimental options, sometimes based on high-end in vitro drug screens. Both approaches can address existing unmet patient needs and provide new treatment options for specific cancers and individual patients. The program, organized by CCBIO Co-Director Bjørn Tore Gjertsen, featured speakers with complementary backgrounds and expertise from academia and industry. These were:

Per Øyvind Enger, UiB and Haukeland University Hospital, who discussed clinical considerations and novel insights regarding repurposing in glioblastoma.

Pan Pantziarka, AnticancerFund, UK gave the talk Repurposing and clinical trials in cancer – academic trials from a charity perspective.

Eva Wessel Stratford, Oslo University Hospital focused on sarcoma therapy development, particularly next gen sequencing and implications for drug choice.

Jorrit Enserink, Oslo University Hospital, discussed drug screening for acute myeloid leukemia patients.

Kjetil Taskén, Norwegian Center for Molecular Medicine (NCMM), Oslo, presented in vitro drug screen in B-cell malignancies.

Emmet McCormack, Kinn Therapeutics and the University of Bergen, gave a biotech perspective and presented a case study.

Caroline Heckman, FIMM, Helsinki, was the invited international keynote speaker. She gave a most interesting talk on in vitro drug screen in acute myeloid leukemia.

Anna Eriksson, Uppsala University, Dept. of Medical Sciences, presented a case study on repurposing of Quinacrine for treatment of acute myeloid leukemia.

Cesare Spadoni, Chairman aPODD (accelerating Paediatric Oncology Drug Development) talked about drug repurposing as an opportunity for developing better drugs for children with cancer.

The program also included a patient's perspective, with speaker Lars Haakon Søraas who gave a thought-provoking view of his experience with the Norwegian health care system.

The program included time for networking, allowing the audience to connect to the speakers and meet with other colleagues in an informal setting. This was the second joint CCBIO/OCC meeting in Bergen, the first being held in 2015, and it is obvious that this will be an annual autumn mini-symposium for the years to come. ••

The 4th Annual Symposium

10th-11th May 2016
at Solstrand Hotel & Bad








Similarly to the previous years, the 2016 CCBIO Annual Symposium proved to be a very valuable meeting point where new networks were established and new research collaborations formed, in addition to receiving updates on the latest in cancer research. The symposium served as a strategy meeting in the war against cancer and a breeding ground for sharing knowledge on biomarkers. More than 200 participants filled Solstrand Hotel to the rim during the two days they spent together, under great conditions for networking with a fjord view in the sunshine. The symposium offered a broad program, ranging from biomarkers and immunotherapy via health budgets to cancer testing through urine samples. In addition to leading international and national cancer researchers, CCBIO also this year made room for up and coming local researchers as speakers as well as two long poster sessions for the younger researchers to present their work and discuss their projects with senior researchers and internationally leading scientists. ••

Centre for Cancer Biomarkers

4th CCBIO Symposium 2016

Solstrand, May 10-11, 2016 - Bergen - Norway

Norwegian Centre of Excellence
The Research Council of Norway

SCIENTIFIC PROGRAM

Day 1: Tuesday May 10, 2016

09:00-10:00 REGISTRATION AND COFFEE

10:00-10:15 Lars A. Akslen (Director of CCBIO): Introduction to CCBIO Symposium 2016.

Chair: Lars A. Akslen

10:15-11:00 Marsha A. Moses: Mining the Human Proteome: Biomarker Discovery for Human Cancer and Its Metastases

11:00-11:45 Meenhard Herlyn: Tumor microenvironment and drug resistance

11:45-12:30 Brunangelo Falini: NPM1-mutated acute myeloid leukemia: biological and clinical features

12:30-14:30 LUNCH AND POSTER SESSION I
Young investigators (Chair: Randy Watnick)

14:30-14.50 Elisabeth Wik: An angio-immunogenic profile of basal-like breast cancer; relevance of cancer testis antigens

14:50-15:10 Siver Moestue: Imaging-based biomarkers in breast cancer

15:10-15:30 Guro Lind: Identifying and developing DNA methylation cancer biomarkers for clinical use

15:30-15:50 Kelly Seo: Impact of cancer biomarkers on the cost-effectiveness of targeted therapies, focusing on mCRC/metastatic colorectal cancer

15:50-16:45 COFFEE

Chair: Donald Gullberg

16:45-17:15 Ritva Heljasvaara: Collagen XVIII in breast cancer - a regulator of growth factor receptor-integrin crosstalk and a therapeutic target

17:15-17:45 Anne Blanchard: Cancer biomarkers looking for patients

19:00 DINNER

Day 2: Wednesday May 11, 2016

Chair: Jim Lorens

09:00-09:30 Karl Johan Malmberg: Allogeneic Natural Killer Cell Therapy Against High-Risk Myeloid Dysplastic Syndrome

09:30-10:00 Rolf Brekken: Phosphatidylserine signaling and immune suppression in the tumor microenvironment

10:00-10:30 Salem Chouaib: Hypoxia and the anti-tumor response

10:30-11:00 Michael Curran: Hypoxia is an essential driver of immune suppression in the tumor microenvironment

11:00-11:30 COFFEE

Chair: Oddbjørn Straume

11:30-12:15 Thorsten Schlomm: Diversity of Prostate Cancer: Implication for Translational Research

12:15-12:45 Hani Gabra: OPCML, a Negative Regulator of Receptor Tyrosine Kinases in Ovarian Cancer: New Biology, New Therapy?

12:45-14:30 LUNCH AND POSTER SESSION II
Young investigators (Chair: Bjørn Tore Gjertsen)

14:30-14.50 Emmet McCormack: Avatars and imaging in cancer therapy development

14:50-15:10 Camilla Krakstad: Exploring biomarkers for endometrial cancer

15:10-15:30 Dana Costea: Effects of nanodiamond modified copolymer scaffolds on tumor progression

15:30-15:50 Ingfrid Haldorsen: Imaging biomarkers relevant for angiogenesis in endometrial cancer

15:50-16:05 Xisong Ke: Cancer therapy: Identification of novel targets

16:05-16:15 Bjørn Tore Gjertsen (Co-Director of CCBIO): Closing remarks.

DISSEMINATION AND COMMUNICATION

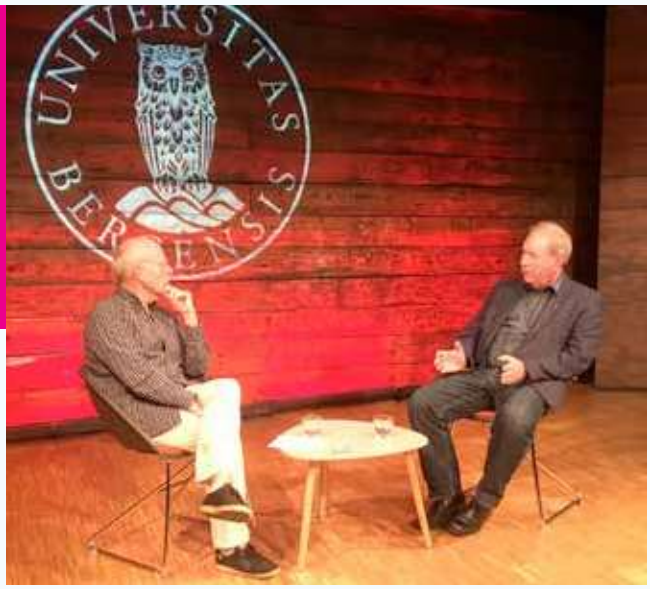
2016

Dissemination and Communication

CCBIO aims to communicate novel findings to the public in a timely and informative way. In 2016 our research could be viewed, read and listened to both in national mainstream media and publications with more specific audiences. We are also actively using our web pages, keeping them updated at all times and presenting big and small news stories from our research community.

Social media has grown to be the inbound marketing tool and connector for organizations, businesses and individual users alike. It is a global tool to stay in touch, meet, greet, communicate, network and market. CCBIO promotes our researchers, scientific findings, happenings, media appearances and behind-the-scenes glimpses via the faculty Facebook, Twitter and Instagram accounts. The hashtag is of course #CCBIO.

A typical social media story would be when the CCBIO director met with the Norwegian national broadcast character Trond Viggo Torgersen at Litteraturhuset in Bergen to discuss cancer in a public meeting. This will also be part of a national radio program. CCBIO's photo and comment was published at Facebook, Twitter and Instagram.



CCBIO offers schools a unique way of learning about cancer cells in the form of a play, or a highly entertaining presentation for other audiences. Since 2016, we have offered a choice between the play "Stop the cancer cell Gloria Glutton!" which is appropriate for children in the age of 4 to 13, or the lecture/stand-up routine "Christine the Cancer Cell – A sociopath in the body", suitable for youth and adults. Both are free of charge, and performer is Henriette Christie Ertsås, PhD Fellow at the Department of Biomedicine and CCBIO. During 2016, 5 shows were booked at schools and events, and proved to be a success both with the children and the teachers and parents.

CCBIO is every year present at the national Research Days Festival in Bergen, with an interactive stand where people, and children in particular, can do a little research themselves. This is always very popular, and of course well covered in the social media.

CCBIO in the Media

In 2016, CCBIO had a total of 31 mass media appearances.
Links to each news story can be found at **www.ccbio.no**, submenu CCBIO in the media.

04.02.16 – DAGBLADET
"Fremtidens kreftbehandling kan bli langt mer målrettet enn i dag" - Lars A. Akslen


8 KREFTINFORMASJON.NO

NYHETER

Lars A. Akslen
Professor ved Universitetet i Bergen og senterleder for Center for Cancer Biomarkers (CCBIO)

FOTO: KIM ANDREASEN (UIB)

04.03.16 - TV2
"Britiske forskere mener de har funnet kreftens akilleshæl" - Bjørn Tore Gjertsen

09.03.16 - TV2 NYHETSKANALEN
"Revolusjon i kreftbehandlingen" - Lars A. Akslen

10.03.16 – EUREKALERT AND MEDICALXPRESS.COM
"Small peptides attack ovarian cancer on two fronts, research shows" - Lars A. Akslen

21.03.16 - ABC NYHETER
"Bør forske mer i Norge på gamle medisiner som ny kreftbehandling" - Bjørn Tore Gjertsen


– Bør forske mer i Norge på gamle medisiner som ny kreftbehandling

– Min påstand er at kombinasjoner av gamle medisiner, repurposing, kan ha vel så god effekt som nye medisiner, sier professor Bjørn Tore Gjertsen.

04.04.16 - TV2
"Denne musa får menneskekreft for at du skal få bedre behandling" - Bjørn Tore Gjertsen

05.04.16 – TIDSSKRIFT FOR DEN NORSKE LEGEFORENING
"Nye prognosemarkører ved brystkreft" - Lars A. Akslen


FRA ANDRE TIDSSKRIFTER

MIN FØRSTE PUBLIKASJON

Nye prognosemarkører ved brystkreft

17.04.16 – KHRONO
"570 nominerte til å verta beste formidlar"
- Roger Strand

25.04.16 - TV2
"Sier ja til ny behandling for pasienter med føflekkreft"
- Oddbjørn Straume


LIVET TIL KREFTSYKE KAN FORLENGES:

Sier ja til ny behandling for pasienter med føflekkreft

Nye medisiner for pasienter med føflekkreft med spredning kan bety forlenget levetid for mange pasienter.

08.06.16, BERGENS TIDENDE
"Lovende nytt for bergensk kreftmedisin"
- Bjørn Tore Gjertsen and James Lorens


NYHETER

GODE RESULTATER – Nå traver jeg rundt på golfbanen med trallen på slep, sier Jan Helge Johannessen fornøyd. Han er en av flere kreftpasienter som har god effekt av medisin fra bergensk bioteknologiselskap.

Lovende nytt for bergensk kreftmedisin

27.06.16 – BROAD INSTITUTE
"Thwarting cancer's spread"
- Particular mention of Helga Salvesen

30.06.16 – BERGENS TIDENDE
"Større kreftrisiko for overvektige"
- Camilla Krakstad and Karen Mauland


Større kreftrisiko for overvektige

07.07.16 - NRK RADIO
"Sløvåg revolusjonerer helseforskning"
- Bjørn Tore Gjertsen and André Sulen

07.07.16 - NRK HORDALAND
"Ny Forskning; Folk fikk endringer i kroppen av Sløvåg-gassen"
- Bjørn Tore Gjertsen and André Sulen

26.07.16 - NRK RADIO
"Forstadia til livmorkreft kom tilbake"
- Jone Trovik

26.07.16 - NRK HORDALAND
"For halvparten kom forstadia til kreft tilbake"
- Jone Trovik


Hordaland

For halvparten kom forstadia til kreft tilbake

26.08.16 – DAGENS MEDISIN
"Sen rekonstruksjon kan trigge tilbakefall"
- Hanna Dillekås

08.09.16 – DAGBLADET PLUSS
"Brystrekonstruksjon gir mindre tilbakefall"
- Hanna Dillekås

08.09.16 - P4 RADIO
"Brystrekonstruksjon gir mindre tilbakefall"
- Hanna Dillekås

28.09.16 - UIB NEWS
"Recycling approved drugs for cancer treatment"
- Yi Qu, Xisong Ke and Karl-Henning Kalland

29.09.16 – ALPHAGALILEO
"Recycling approved drugs for cancer treatment"
- Yi Qu, Xisong Ke and Karl-Henning Kalland

30.09.16 – HEALTH MEDICINE NETWORK
"Recycling existing drugs may help fight several types of cancer"
- Yi Qu, Xisong Ke and Karl-Henning Kalland

04.10.16 – SCIENCENORDIC
"Recycling approved drugs for cancer treatment"
- Yi Qu, Xisong Ke and Karl-Henning Kalland

10.10.16 – HELSE BERGEN INNSIDEN
"Fikk pris for presentasjon" - Amalie Svanøe

11.10.16 – FIRDAPOSTEN
"Forskar på kreft" - Amalie Svanøe

11.10.16 – DAGENS MEDISIN
"Ny behandling utsatte tilbakefall"
- Line Bjørge

11.10.16 – DAGENS MEDISIN
"Gammel kreftmedisin kan brukes på ny"
- Yi Qu, Xisong Ke and Karl-Henning Kalland

15.11.16 - NBS-NYTT
"Technologies for digital life"
- Inge Jonassen and Roger Strand

01.12.16 – DAGENS MEDISIN
"Presenterte ny studie"
- Oddbjørn Straume

08.12.16 – PÅ HØYDEN
"Sju unge UiB-forskarar får Fripro-støtte"
- Agnete Engelsen

31.12.16
The Norwegian Prime Minister's New Year's Address, where she highlighted CCBIO PI James Lorens and his company BerGenBio as an example of excellent cancer research.

FACTS AND FIGURES 2016

31

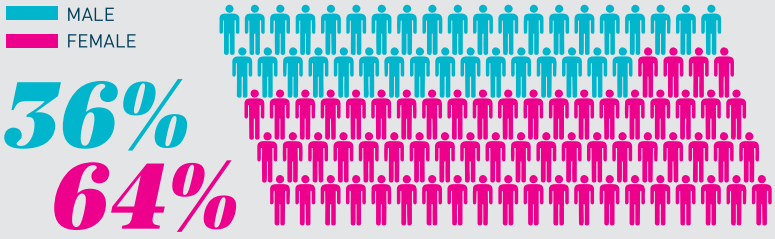
The 31 mass media stories in 2016 shows that CCBIO emphasizes public dissemination of its research results.

PERFORMANCE INDICATORS

	2013	2014	2015	2016	TOTAL
PUBLICATIONS	76	71	77	85	309
COMPLETED PHDS	5	6	3	10	24
EXTERNAL FUNDING MNOK	7,2	21,9	22,5	36,0	88
MEDIA APPEARENCES	39	11	32	31	113

CCBIO's scientific production is high and as expected it is now rising as the first round of CoE financed PhDs and postdocs conclude their projects. The influx of external funding is very good and increasing. Numbers illustrated are for external funds consumed in 2013-2016.

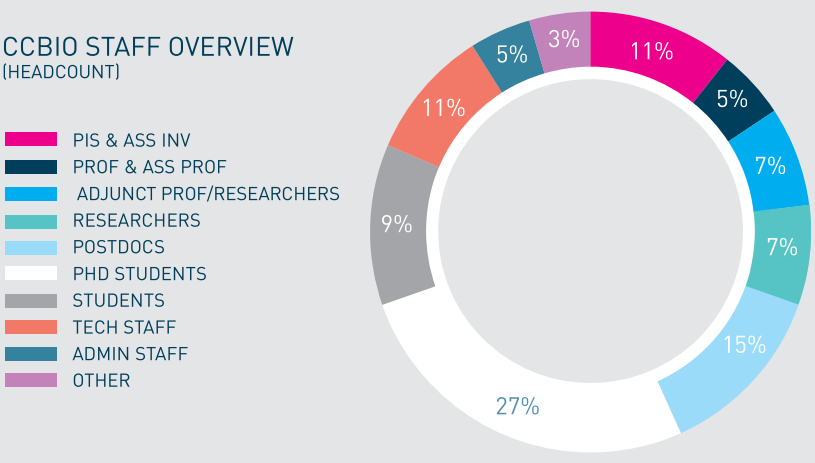
GENDER DISTRIBUTION
(HEADCOUNT)



TOTAL: 176 PERSONS

Of the 176 persons involved in CCBIO, 64 % are female. This tendency holds true for junior staff like PhDs and postdocs as well as for technical and administrative staff. For professors and associate professors, the gender composition is exactly balanced with 50% women and men respectively. Due to the recruitment of mainly female talent to enlarge CCBIOs group of investigators, this group is now considerably less male dominated with 36% females in 2016 as compared to 20% in 2015. This is in line with CCBIO's aim to put all available talent to its best use, e.g. by attaining a more balanced gender distribution in its top tire. Hence, gender balance can be achieved without compromising on excellence.

CCBIO STAFF OVERVIEW
(HEADCOUNT)

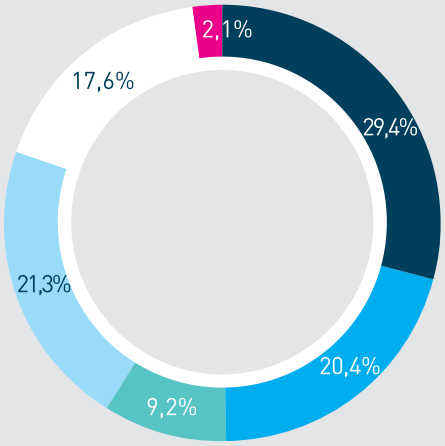


TOTAL: 176 PERSONS

The breakdown of CCBIO's headcount shows a rather balanced composition of senior researchers and "researchers to be" in the form of PhD students and master students as well as technical and administrative support staff. However, in accordance with the RCNs policy of a 1-to-1 relation between PhDs and postdocs, CCBIO aims to increase the amount of CoE-financed postdoctoral positions and other positions for younger researchers. This will increase the chance of high impact publications and major breakthroughs originating from CCBIO's recruitment positions and thereby increase the level of excellence. It will also improve the scope for recruiting future excellent researchers. In 2016, CCBIO enlarged its group of investigators by recruiting five associate and junior associate investigators, four of them female. This is part of CCBIO's effort to ensure continuation after 2023 and has also improved gender balance within the CCBIO investigator group. The basis of CCBIOs international network of 13 adjunct professor and researchers is now complete, ensuring excellent access to high-level collaboration, advice and tuition for CCBIOs researchers, younger researchers and PhDs respectively.

FUNDING
(FUNDS USED IN 2016)

- UIB
- RCN CoE
- RCN PROJECTS
- OTHER PUBLIC FUNDING
- PRIVATE FUNDING
- INTERNATIONAL FUNDING

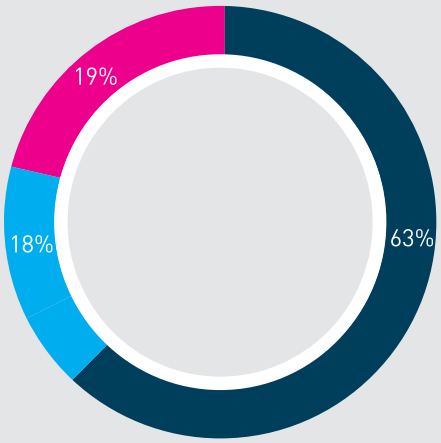


TOTAL = 71,7 MILL NOK

Total funds used in 2016 were 71.7 MNOK, of which less the 50% is RCN CoE funding and own funding from the UiB, down from 60% in 2016. The total of 36 MNOK in external funding is three times the budgeted amount and illustrates a high success rate with public and private funding agencies. CCBIO's research effort is resource intensive and more funding is needed. We expect to see a further increase in funds used as CCBIO gears up its research effort while at the same time ensuring that funding is used to the best possible effect.

INTERNATIONALIZATION
(STAFF COUNTRY OF ORIGIN)

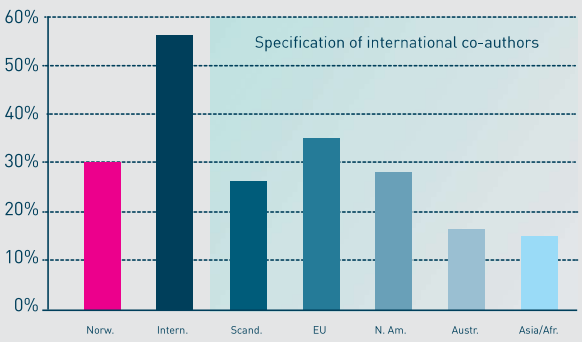
- NORWAY
- OTHER WESTERN COUNTRIES
- AFRICA & ASIA



CCBIO's inherently international nature is illustrated by the fact that in 2016, 58% of CCBIO's publications have international co-authorship and that 37% of CCBIO's staff are foreign nationals. If subdividing country of origin, 45 % of PhDs and 50 % of postdocs originate from outside of Norway and, due to CCBIO's recruiment of a predominantly international network of top tire researchers to adjunct positions, foreign nationals now represent 39% of CCBIO's senior researchers. International co-authorship has stronger prevalence than co-authorship by researchers from other Norwegian universities. If subdividing the international co-authorships into regions, we can conclude that CCBIO collaborates with institutions from most major world regions. The figure illustrates that many of CCBIO's international publications have co-authors from more than one region, being true multilateral collaboration across world regions.

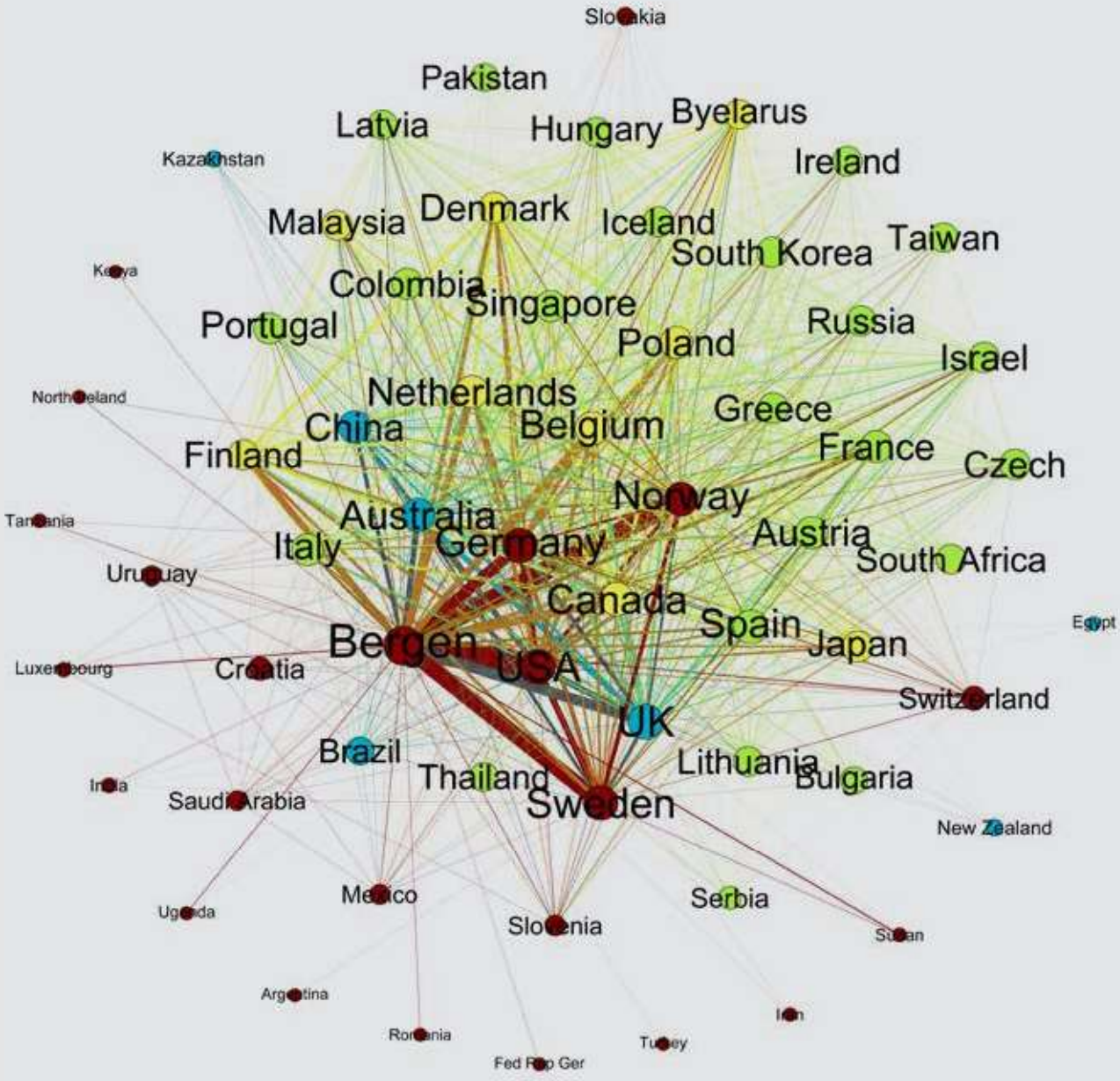
INTERNATIONALIZATION
(STAFF CO-AUTHORSHIP)

- NORWAY, NON-BERGEN
- INTERNATIONAL, OVER ALL
- SCANDINAVIAN
- EUROPEAN UNION
- NORTH AMERICA
- AUSTRALIA
- ASIA & AFRICA



CCBIO'S COLLABORATIVE CLOUD

The figure reflects a bibliometric analysis of author nationality on CCBIO's publications during the period 2013-2016. The thickness of the lines illustrate the frequency of co-authorships. The distance between various nationalities illustrates the relative frequency of co-authorships between these nationalities. Countries with few co-author relations among CCBIO's publications are placed at the periphery. CCBIO's home region Bergen is separated from the rest of Norway. As can be noticed, CCBIO published with authors from all continents during the period, somewhat broader than in 2016 alone; the latter is illustrated on page 93.




CCBIO
CAPTURING CANCER COMPLEXITY
AND CLINICAL CHALLENGES
th
CCBIO
ANNUAL SYMPOSIUM
2018
MAY 23-24
SOLSTRAND // BERGEN // NORWAY
UNIVERSITAS BERGENSIS
Norwegian
Centre of
Excellence
The Research Council of Norway

Complete list of personnel at CCBIO

NAME	POSITION	ACADEMIC TITLE	GROUP
Aasebø, Elise	PhD student	MS, PhD	Gjertsen
Aass, Håvard Hoel	Senior Executive Officer	MA	Administration
Ahmed, Israa	PhD student	DDS	Johannessen
Akslen, Lars A.	Professor, Director, Principal Investigator	MD, PhD	Akslen
Amant, Frédéric	Adjunct Professor	MD, PhD	CCBIO
Andresen, Vibeke	Researcher	MS, PhD	Gjertsen
Arnes, Jarle	Senior Consultant	MD, PhD	Akslen
Askildsen, Jan Erik	Professor, Associate Investigator	MA, PhD	Askildsen
Azeem, Waqas	PhD student	MS	Kalland
Aziz, Sura Muhammed	PhD student	MD	Akslen
Bachmann, Ingeborg M.	Professor	MD, PhD	Akslen
Bakke, Ragnhild Maukon	Student		Kalland
Bedringaas, Siv Lise	Chief Engineer	MS	Gjertsen
Berg, Anna	PhD student	MD	Gyn-Cancer
Berge, Sissel Vik	Chief Engineer		Lorens
Beroukhim, Rameen	Adjunct Researcher	MD, PhD	CCBIO
Birkeland, Eivind Salmorin	Student	MS	Johannessen
Birkeland, Even	Postdoc	MS, PhD	Akslen
Bischof, Katharina	PhD student	MD	Gjertsen
Bjørge, Line	Professor, Associate Investigator	MD, PhD	Gjertsen
Blanchard, Anne	Postdoc	MA, PhD	Strand
Bollineni, Vikram	Postdoc	MD, PhD	Gyn-Cancer
Bougnaud, Sébastien	Postdoc	MS, PhD	Lorens
Bourdon, Jean-Christophe	Adjunct Researcher	MS, PhD	CCBIO
Brekken, Rolf	Adjunct Professor	MD, PhD	CCBIO
Brodal, Hans Petter	Staff Engineer	MS	Gjertsen
Børretzen, Astrid	Senior Consultant	MD	Akslen
Cairns, John	Adjunct Professor, Associate Investigator	MA, PhD	Cairns
Chen, Ying	PhD student	MD	Akslen
Costea, Daniela Elena	Professor, Junior Associate Investigator	DDS, PhD	Johannessen
Davidsen, Kjersti	PhD student	MD	Lorens/Straume
Dillekås, Hanna	PhD student	MD	Straume
Dimitrakopoulou, Konstantina	Postdoc	MS, PhD	Jonassen
D'Mello, Stacey Ann	Researcher		Lorens
Dowling, Tara Helen	PhD student	MS	Gjertsen
Dyrkolbotn, Kjetil	Higher Executive Officer	MA	Administration
Edelmann, Reidun Jetne	Postdoc	MD, PhD	Akslen
Edvardsen, Britt	Chief Engineer		Gyn-Cancer
Enge, Elisabeth	Study Nurse		Gyn-Cancer
Engelsen, Agnete	Postdoc	MS, PhD	Lorens
Engen, Caroline Benedicte	PhD student	MD	Gjertsen
Engerud, Hilde	Student		Gyn-Cancer
Ertsås, Henriette	PhD student	MS	Lorens
Erusappan, Pugazendhi	PhD student	MS	Gullberg
Eskender, Mariamawit	Student		Akslen
Fagerholt, Oda Helen Eck	Student		Gjertsen
Finne, Kenneth	Postdoc	MS, PhD	Akslen
Fonnes, Tina	PhD student	DVM	Gyn-Cancer
Forthun, Rakel Brendsdal	Researcher	MS, PhD	Gjertsen
Freds, Larry	PhD student	MS	Gullberg
Furriol, Jessica	Postdoc	MS, PhD	Akslen
Gabra, Hani	Adjunct Professor	MD, PhD	CCBIO
Gabrielsen, Tommy Staahl	Professor	MA, PhD	Askildsen
Gafaar, Nuha	PhD student	DDS	Johannessen
Gavasso, Sonia	Researcher	MS, PhD	Gjertsen
Gjertsen, Bjørn Tore	Professor, Co-Director (Feb 2016-), PI	MD, PhD	Gjertsen
Grønning, Mona	Chief Engineer		Gullberg
Gullaksen, Stein Erik	PhD student	MS	Gjertsen
Gullberg, Donald	Professor, Principal Investigator	MS, PhD	Gullberg
Ha, Trung Quang	PhD student	MD, MS	Gjertsen
Haaland, Gry	PhD student	MD	Lorens/Straume
Hajjar, Ehsan	PhD student	MS	Gjertsen
Haldorsen, Ingfrid Salvesen	Professor	MD, PhD	Gyn-Cancer
Halle, Mari Kyllesø	PhD student	MS	Gyn-Cancer
Hallseth, Gerd Lillian	Chief Engineer		Akslen
Halvorsen, Ole Johan	Professor	MD, PhD	Akslen
Hassan, Ali	Student	DDS	Johannessen
Heljasvaara, Ritva	Adjunct Researcher	MS, PhD	CCBIO
Hellesøy, Monica	Researcher	MS, PhD	Gjertsen
Hinz, Stefan	PhD student	MS	Lorens
Hjelle, Sigrun Margrethe	Postdoc	MS, PhD	Gjertsen
Hoang, Hua My	Staff Engineer		Kalland
Holst, Frederik	Postdoc	MS, PhD	Gyn-Cancer
Hove, Elisabeth	Senior Executive Officer		Administration
Hua, Yaping	PhD student	MS	Kalland
Hugdahl, Emilia	PhD student	MD	Akslen
Huse, Karoline	Student		Strand
Høgås, Mildrid Bønes	Senior Executive Officer		Administration
Høivik, Erling André	Postdoc	MS, PhD	Gyn-Cancer
Jacobsen, Martha Rolland	Student		Johannessen
Jahedul, Alam	PhD student	MS	Gullberg
Jebsen, Nina Louise	Postdoc	MD, PhD	Gjertsen
Johannessen, Anne Christine	Professor, Principal Investigator	DDS, PhD	Johannessen
Jokela, Tiina	Postdoc	MS, PhD	Lorens
Jonassen, Inge	Professor, Associate Investigator	MS, PhD	Jonassen
Kalland, Karl-Henning	Professor, Principal Investigator	MD, PhD	Kalland

NAME	POSITION	ACADEMIC TITLE	GROUP
Kalvenes, Mai Britt	Senior Engineer	MS, PhD	Akslen
Kang, Jing	Staff Engineer	MD	Lorens
Katta, Kirankumar	Postdoc	MS, PhD	Gullberg
Ke, Xisong	Researcher	MS, PhD	Kalland
Kjølle, Silje	PhD student	MS	Akslen
Klingen, Tor Audun	PhD student	MD	Akslen
Knutsvik, Gøril	Researcher	MD, PhD	Akslen
Konstantinova, Victoria	Student	DDS, MA	Johannessen
Kopperud, Reidun	Senior Engineer	MS, PhD	Gjertsen
Krakstad, Camilla	Associate Professor, Junior Associate Investigator	MS, PhD	Gyn-Cancer
Krüger, Kristi	PhD student	MD	Akslen
Kusche-Gullberg, Marion	Professor	MS, PhD	Gullberg
Labarge, Mark	Adjunct Professor	MS, PhD	CCBIO
Ladstein, Rita Grude	Associate Professor	MD, PhD	Akslen
Leitch, Calum	PhD student	MS	Gjertsen
Lie, Maria Kolnes	PhD student	MS	Lorens
Litlabø, Hanne Bjelland	Student		Akslen
Lorens, James B.	Professor, Principal Investigator	MS, PhD	Lorens
Lu, Ning	Senior Engineer	MS, PhD	Gullberg
Luís, Ana Beatriz Mateus D'Avó	PhD student	MA	Askildsen
Løken, Geir Olav	Administrative Leader	MA	Administration
Madissoo, Kadri	Staff Engineer	MS	Gyn-Cancer
Mannelqvist, Monica	Senior Engineer	MS, PhD	Akslen
Marvyin, Kristo	Student		Kalland
Mauland, Karen Klepsland	PhD student	MD	Gyn-Cancer
Mc Cormack, Emmet	Professor, Associate Investigator	MS, PhD	Gjertsen
Mjøs, Siv	Student		Gyn-Cancer
Nalwoga, Hawa	Researcher	MD, PhD	Akslen
Nazar, Mohammad	PhD student	DDS	Johannessen
Neppelberg, Evelyn	Associate Professor	DDS, PhD	Johannessen
Nginamau, Elisabeth Sivy	Researcher	MD, PhD	Johannessen
Norheim, Ole Frithjof	Professor, Associate Investigator	MD, PhD	Norheim
Nygaard, Ina Hannestad	Research Assistant		Strand
Olsen, Jan Roger	PhD student	MS	Kalland
Omsland, Maria	PhD student	MS	Gjertsen
Onyango, Therese Bredholt	Postdoc	MS, PhD	Gyn-Cancer
Pantel, Klaus	Adjunct Professor	MD, PhD	CCBIO
Parajuli, Himalaya	PhD student	DDS, PhD	Johannessen
Pelissier, Fanny	PhD student	MS, PhD	Lorens
Pilskog, Martin	PhD student	MD	Straume/Akslen
Puntervoll, Hanne Eknes	Senior Engineer	MS, PhD	Akslen
Qu, Yi	Postdoc	MS, PhD	Kalland
Rajthala, Saroj	PhD student	MS	Johannessen
Ramnefjell, Maria	PhD student	MD	Akslen
Rane, Lalit Shirish	Postdoc	MS, PhD	Gjertsen
Reed, Rolf K.	Professor, Principal Investigator	MD, PhD	Reed
Reigstad, Inga	PhD student	MD, PhD	Reed
Riise, Julie	Associate Professor	MA, PhD	Askildsen
Sabir, Misbah	Staff Engineer	MS	Gjertsen
Salvesen, Gerd Signe	Staff Engineer		Reed
Salvesen, Helga B.	Professor, Co-Director, PI (-Jan 2016)	MD, PhD	Gyn-Cancer
Sandnes, Dagny Ann	Staff Engineer		Johannessen
Sapkota, Dipak	Postdoc	DDS, PhD	Johannessen
Scarlett, Samantha	Research Coordinator	MS	Gjertsen
Schlomm, Thorsten	Adjunct Professor	MD, PhD	CCBIO
Schmid, Caroline	Postdoc	MS, PhD	Reed
Schuster, Cornelia	PhD student	MD, PhD	Straume
Seo, Mikyung Kelly	PhD student	MA	Cairns
Shafiee, Sahba	PhD student	MS	Gjertsen
Skavland, Jørn	Postdoc	MS, PhD	Gjertsen
Skogstrand, Trude	Postdoc	MS, PhD	Reed
Smeland, Hilde Ytre-Hauge	PhD student	MS, PhD	Reed
Solheim, Marion	Advisor		Administration
Sortland, Kristina	Staff Engineer		Gyn-Cancer
Stefansson, Ingunn	Associate Professor	MD, PhD	Akslen
Stenmarck, Mille Sofie	Student		Strand
Strand, Roger	Professor, Associate Investigator	MS, PhD	Strand
Straume, Oddbjørn	Professor, Principal Investigator	MD, PhD	Straume
Stuhr, Linda	Professor	MS, PhD	Reed
Suleiman, Salwa	Researcher	DDS, PhD	Johannessen
Sulen, André	PhD student	MS, PhD	Gjertsen
Svanøe, Amalie	Student		Akslen
Svendsen, Henrik Løvendahl	Senior Consultant	MS, MD	Akslen
Sørlie, Therese	Adjunct Professor	MD, PhD	CCBIO
Tangen, Ingvild Løberg	PhD student	MS, PhD	Gyn-Cancer
Thiery, Jean Paul	Adjunct Professor	MD, PhD	CCBIO
Tislevoll, Benedicte Sjo	Student		Gjertsen
Tranvåg, Eirik Joakim	PhD student	MD	Norheim
Trovik, Jone	Professor	MD, PhD	Gyn-Cancer
Tveiterås, Maria	Staff Engineer		Reed
Valen, Ellen	Study Nurse		Gyn-Cancer
Vidhammer, Eli Synnøve	Senior Executive Officer		Administration
Watnick, Randolph	Adjunct Researcher	MD, PhD	CCBIO
Werner, Henrica Maria Johanna	Postdoc	MD, PhD	Gyn-Cancer
Wik, Elisabeth	Postdoc, Junior Associate Investigator	MD, PhD	Akslen
Ytre-Hauge, Sigmund	PhD student	MD	Gyn-Cancer
Zeltz, Cedric	Researcher	MS, PhD	Gullberg
Øijordsbakken, Gunnvor	Chief Engineer		Johannessen
Östman, Arne	Adjunct Professor	MD, PhD	CCBIO
Øyan, Anne Margrethe	Researcher	MS, PhD	Kalland

CCBIO LIST OF PUBLICATIONS

2016

CCBIO - List of Publications

Publications are listed in the order they appear in PubMed with the most recent publications first.

Mauland KK, Wik E, Hoivik EA, Kusonmano K, Halle MK, Berg A, Haugland HK, Øyan AM, Kalland KH, Stefansson IM, Akslen LA, Krakstad C, Trovik J, Werner HM, Salvesen HB. Aneuploidy related transcriptional changes in endometrial cancer link low expression of chromosome 15q genes to poor survival. *Oncotarget.* 2016 Dec 25 (publication online).

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Qu Y, Kalland KH, Ke X. Small molecule induces Wnt asymmetry in cancer. *Cell Cycle*. 2016 Sep 29:1-2.

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Parajuli H, Teh MT, Abrahamsen S, Christoffersen I, Neppelberg E, Lybak S, Osman T, Johannessen AC, Gullberg D, Skarstein K, Costea DE. Integrin α11 is overexpressed by tumour stroma of head and neck squamous cell carcinoma and correlates positively with alpha smooth muscle actin expression. *J Oral Pathol Med*. 2016 Oct 4 (publication online).

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Klingen TA, Chen Y, Stefansson IM, Knutsvik G, Collett K, Abrahamsen AL, Aase H, Aas H, Aas T, Wik E, Akslen LA. Tumour cell invasion into blood vessels is significantly related to breast cancer subtypes and decreased survival. *J Clin Pathol*. 2016 Sep 9 (publication online).

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Bojan A, Berindan-Neagoe I, Ciurea S, Dima D, Fuji S, Ghiaur G, Grewal R, McCormack E, Tanase A, Trifa A, Tomuleasa C. Proceedings from Proceedings from the 1st Insights in Hematology Symposium, Cluj-Napoca, Romania March 11-12, 2016. *Rom J Intern Med.* 2016 Sep 1;54(3):157-160.

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van der Putten LJ, Visser NC, van de Vijver K, Santacana M, Bronsert P, Bulten J, Hirschfeld M, Colas E, Gil-Moreno A, Garcia A, Mancebo G, Alameda F, Trovik J, Kopperud RK, Huvila J, Schrauwen S, Koskas M, Walker F, Weinberger V, Minar L, Jandakova E, Snijders MP, van den Berg-van Erp S, Matias-Guiu X, Salvesen HB, Amant F, Massuger LF, Pijnenborg JM. L1CAM expression in endometrial carcinomas: an ENITEC collaboration study. *Br J Cancer*. 2016 Sep 6;115(6):716-24.

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Annual Symposium

10th-11th May 2016

CCBIO Investigators and Invited Speakers

From left to right: *Xisong Ke, Siver Moestue, Anne Christine Johannessen, Ola Myklebost, Mikyung Kelly Seo, Randolph Watnick, Roger Strand, Meenhard Herlyn , Marsha A. Moses, Frédéric Amant, Oddbjørn Straume, Line Bjørge, Lars A. Akslen, Rolf Brekken, Guro Lind, Elisabeth Wik, Thorsten Schlomm, Anne Blanchard, John Cairns, Ritva Heljasvaara, Emmet Mc Cormack, Donald Gullberg, Daniele Elena Costea, Brunangelo Falini, Camilla Krakstad, Michael Curran, James B. Lorens, Bruce R. Zetter, Therese Sørlie, Arne Östman, Ingfrid Haldorsen, Karl Johan Malmberg, Hani Gabra, Mark LaBarge, Bjørn Tore Gjertsen, Karl-Henning Kalland, Rolf K. Reed, Inge Jonassen*

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