Centre for Cancer Biomarkers

Norwegian Centre of Excellence – University of Bergen

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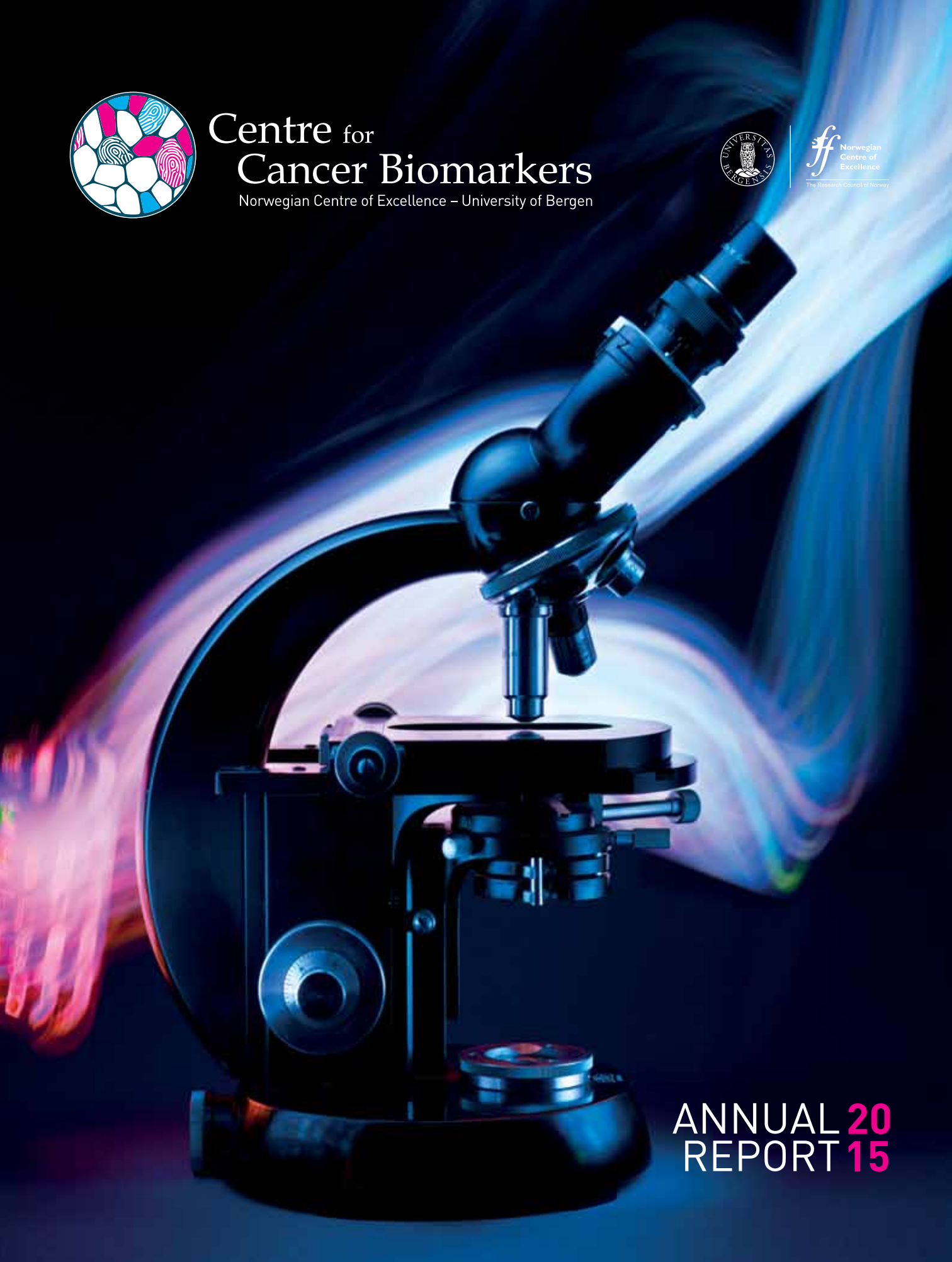

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CONTENTS

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Director´s Comments

During 2015, CCBIO as a research center and a newly established organization across several departments has gained significant momentum. The challenge in today's basic and translational cancer research is huge. There are a lot of activities going on in different areas, and we have much information on how cancers develop and progress. However, there is a gap in the transfer of knowledge to practical medicine. This phase is very time-consuming, with complex regulatory mechanisms and long-lasting clinical trials of new treatments as part of today's set-up. Biomarkers have yet to be fully included in trial design.

The development of a stimulating and encouraging scientific environment is an important pathway towards excellence. The establishment of the CCBIO Research School for Cancer Studies is crucial in this context. In 2015, a full program of integrated courses and seminars was conducted on various topics: Matrix biology; Cancer Research: Ethical, Economic and Social Aspects; Biomarkers and Tumor Biology in Clinical Practice; Methods in Cancer Biomarker Research; CCBIO Junior Scientist Symposium (JUSS); monthly research seminars with external visitors, and the CCBIO Annual Symposium. The half-day JUSS meetings are arranged four times a year, and these are organized by our postdocs. This has been a successful series with a suitable format for training of our young investigators in how to present data, discuss the findings, and chair scientific meetings.

Another important component of CCBIO is our many international collaborations and networks, allowing for scientific input in different areas and mobility of students as well as faculty. We have during 2015 continued our recruitment of international collaborators and advisors who are hired in part-time positions. In 2016, this network will be complete with 15 positions. Of further importance, CCBIO in 2015 received an INTPART grant from SIU and RCN to increase our international efforts towards education, as an integrated part of the research school.

Several promising research projects are now running in different teams, with increased collaboration and networking within CCBIO itself. A key area has been to better understand how tumor cells interact with and influence their surrounding microenvironment and the multiple facets of tumor plasticity. The enormous challenge in our field is to not only integrate the vast amount of information into a "unifying model of cancer biology", but also to move this knowledge towards clinical practice without delay. We believe that smart use of individual or complex biomarkers is a necessary and cost-effective tool.

curiosity and excitement are two of the most striking hallmarks of excellence.

Scientific work is challenging, often difficult, and very time-consuming, but also a lot of fun. It is important to ask "stupid" and "out-of-the-box" questions all the time, and try to answer them. Unexpected findings should be followed up on, these might represent the most novel observations. And not the least, curiosity and excitement are two of the most striking hallmarks of excellence. ••

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 treatment of cancer.

CCBIO has a focus on tumor-microenvironment interactions in primary and metastatic lesions and how they can 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.

By three overlapping research areas, CCBIO will re-focus its cancer research into the following main 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 have been 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. ••

TEXT: James B. Lorens

CCBIO on Tumor Microenvironment

Cancer is a leading cause of death worldwide and a major health challenge; over half of current adults under the age of 65 years will be diagnosed with cancer at some point in their lifetime. Encouragingly, our understanding of the molecular basis of cancer has evolved remarkably during the past two decades. The Cancer Genome Atlas (TCGA) program, following on the coattails of the Human Genome Project, has sequenced thousands of cancer cell genomes. TCGA has identified a broad range of recurrent gene mutations and genomic rearrangements that contribute to tumorigenesis. In concert with this, the pharmaceutical industry, following the success of imatinib (a small molecule targeting the BCR-ABL protein) for chronic myeloid leukemia (CML), and erlotinib (an EGF receptor inhibitor) for non-small cell lung cancer (NSCLC), has developed scores of molecularly targeted therapeutics, including many against specific protein mutations. In spite of this remarkable progress, most cancer patients still do not experience durable clinical responses, due to acquired drug resistance and subsequent relapse; and the War on Cancer continues.

The confounding reality for cancer treatment is the heterogeneity of tumors. This is a reflection not only of the intrinsic genetic instability of tumors but also of the extrinsic selective forces acting on an evolving tumor cell. The breakdown of normal tissue structure during malignant progression exposes tumor cells to numerous biophysical challenges, nutritional deprivation and a hostile non-native microenvironment comprising different matrix proteins and a variety of stromal cells. Philosophers refer to a confrontation that causes us to become aware of our own weaknesses as a "boundary situation". A key outcome of the boundary situation is a realization of the necessity to communicate. Indeed, tumor cells that encounter a reactive stroma engage in reciprocal interactions that trigger adaptive, cellular plasticity related to stem cell differentiation and transdifferentiation, characteristic of adult tissue homeostasis and repair. This endows tumor cells with a remarkable phenotypic and functional flexibility, as evidenced by tumor vascular mimicry, epithelial-to-mesenchymal transition, and acquired drug resistance. This ability to assume different phenotypic states ("shape-shifting") allows adaptation to different niches within a dynamic tumor microenvironment. This new "hallmark" of cancer, tumor cell plasticity, is central to cancer progression and treatment failure. Indeed, tumor cell plasticity represents a unifying theme, reconciling different models of carcinogenesis (i.e. stochastic vs hierarchical) and is an important target for future cancer therapeutic development.

With the knowledge that an entire human being is derived from a single genome, we shouldn't be surprised that multigenomic tumors are phenotypically diverse. Hence, deeper mechanistic insight into how the interaction between extrinsic microenvironmental and intrinsic genomic factors activates phenotypic plasticity programs in tumor cells is required to understand the tumor heterogeneity that undermines current treatments and to develop new therapeutic concepts to treat cancer. The investigators at CCBIO endeavor to better understand the molecular basis of tumor-stroma interactions that can inform improved treatment decisions and new therapeutic concepts. ••

TEXT: Bjørn Tore Gjertsen

CCBIO on Targeted Treatment

Two major challenges seem to limit contemporary targeted treatment of cancer: i) mapping of tumor clonality at diagnosis and during therapy, and ii) identification of patients responding to immunological check-point inhibitors.

Targeted therapy in metastatic cancer has proved to be challenging, and blind spots in diagnostics need likely to be unblinded to improve therapeutic results. Biomarkers may provide the information needed for successful precision medicine. The nature of these biomarkers include a wide range of modalities, including clinical and imaging features, tissue morphology through histopathology, gene aberrations, messenger RNA expression, and proteins. Mutation analysis by next generation sequencing has dominated recent biomarkers studies, maybe without the striking importance in therapy response prediction as initially expected.

Immunotherapy represents a rejuvenated therapy concept through immunological check-point inhibitors. Decades of immunostimulatory therapy have indicated the potential. Both interleukin-2 and interferon alpha has been used in cancer therapy with striking effect in a few cases, but with problematic adverse effects. Now the concept of stimulation is left for a concept of inhibitory mechanism release, using targeted therapeutic antibody to alleviate the immunological blockage caused by cancer cells. This seems to be far more potent than stimulating the immune system.

However, response to immunological check-point inhibitors is extremely divergent, from more than 80% in Hodgkin's lymphoma to 10-20% in gynecological cancer. Strikingly, amplification of the gene for PD-1 is frequently present in Hodgkin's lymphoma, maybe not surprising based on the immune cell domination in the tumor environment of Hodgkin's lymphoma. From the patient's perspective, 10% response rate is low but at the same time data indicate that these responders are long term stable. It will therefore be of huge value to identify these responders before or early after start of therapy.

Other cancers may only be accessible for immunological check-point inhibitors if microsatellite instability is present and a high number of mutations are characterizing the tumor genome. Clear biomarker strategies beyond these are lacking. No biomarkers have indicated therapy response or the possibility for adverse effects. With the immunological check-point inhibitors, receptor blocking between T-cells, particularly PD-1 and CTLA-4, has been identified.

Tumor cells often have significant phenotypical plasticity and may hide in different environments. This plasticity is probably epigenetically directed, meaning that permanent changes in the genome is lacking. Such plasticity appears in tumors that also show clonal heterogeneity, implicating that various mutations with various phenotypical properties are present in large tumors. Finally, some of the most effective chemotherapeutics may induce damages in DNA. This urges the use of biomarker panels that comprise of both mutational information and protein expression. Such multi-parametric panels will likely be needed both for primary diagnostics and later follow-up.

Small molecule inhibitors are key therapy in care of subsets of sarcoma, in renal cancer, in melanoma and in leukemia. These targeted therapies are followed by simple diagnostics, not taking into consideration mechanism of action. A specific mutation is identified at diagnosis, and the muted gene may be used to quantify tumor load in the patient along therapy. Treatment responses are routinely followed by imaging modalities like computer tomograms and magnetic resonance imaging. In these cases the sensitivity is low, and typically it takes 6 to 12 weeks before any meaningful change in disease can be measured. When these small molecule inhibitors fail –because most will sooner or later fail in solid cancers – various escape mechanism may have been trigged. These escape mechanisms include the simple point mutation of the binding site of the therapeutic molecule target, parallel compensatory signaling pathways and unrelated mechanisms like cell death rheostat systems that are retuned to cell survival.

Therefore, we need biomarkers to identify the repertoire of possible escape mechanisms at diagnosis, and follow these escape mechanisms under therapy. This implicates integration of more complex biomarkers in clinical trials, addressing the tumor microenvironment. CCBIO is now actively designing biomarker programs in small academic and academic-industry initiated trials. Within 1-2 years we will see the first results of these trials, and the goal is to contribute in the shift of paradigm needed for more effective clinical trials in cancer. • •

TEXT: Anne Blanchard

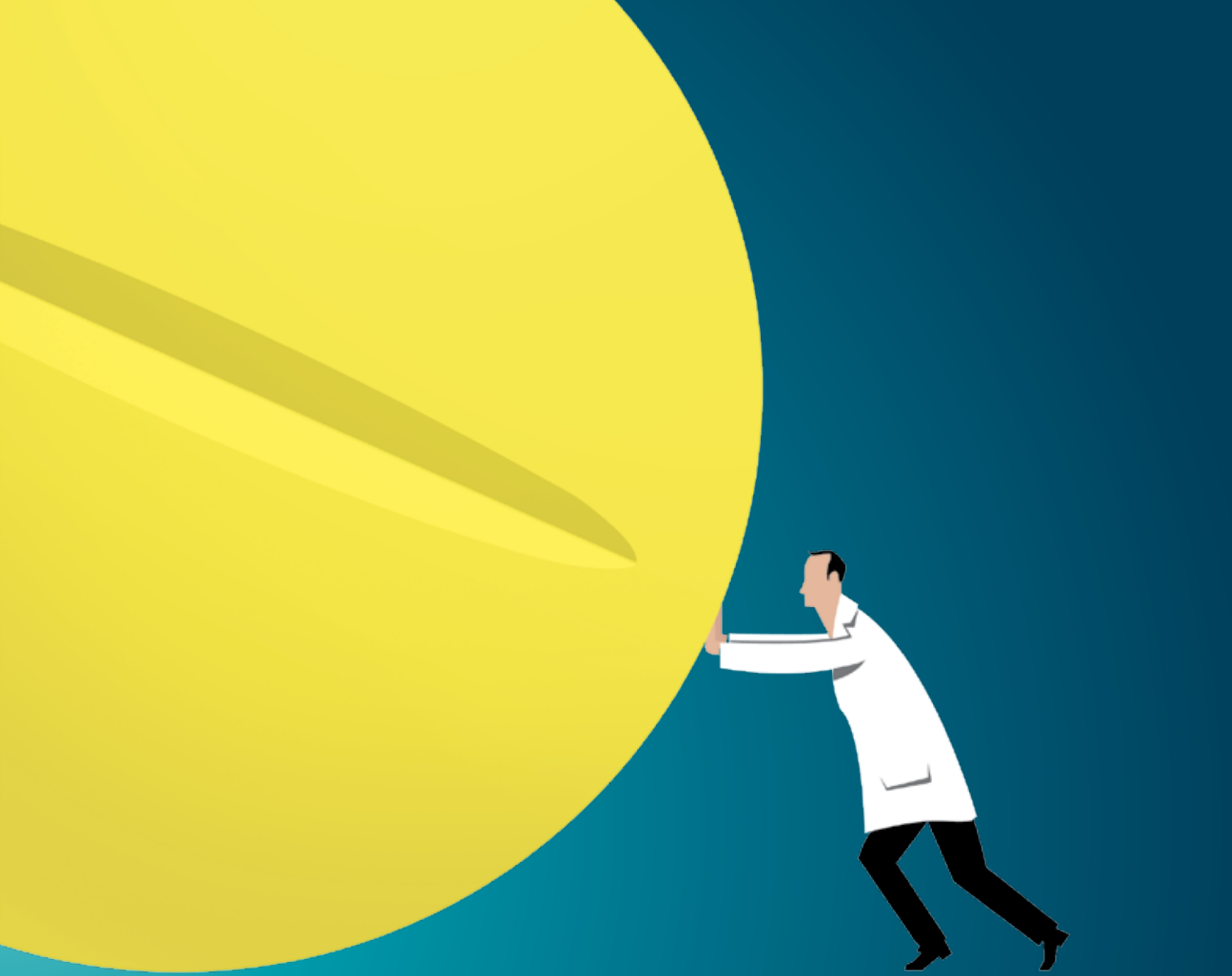
CCBIO on Ethics

Today, less than 1% of researched cancer biomarkers make it to clinical practice. There are several reasons for this, ranging from the complexities and uncertainties characterizing this field, to methodological shortcomings, or indeed the complicated relationship between Big Pharma and public cancer biomarker research.

Big Pharma can be an efficient incubator for innovative ideas from public research, and help bring cancer biomarkers to their commercial end, and to the patient's side. While public research is about scientifically discovering biomarkers, Big Pharma, with its financial resources, its 'pharmaceutical manpower' and its large-scale platforms, is more about testing and validating biomarkers on tens of models and on hundreds of thousands of samples. In this way it provides a solid basis to move on to clinical trials, and then, to governmental approval for clinical practice.

But this relationship is complicated. Indeed, the interests, values and underlying principles of Big Pharma, as a for-profit industry, are often different from the values of medical practitioners and researchers who are close to the clinical reality of the patients. While the research community may see a particular biomarker as indispensable for a sub-group of patients, Big Pharma must weigh this up against economic considerations and risks.

This relationship is also complicated by the different specificity at which public research and Big Pharma operate. As a cancer biomarker becomes more specific in its application and its role, it will likely be more scientifically robust and efficient for a particular subgroup of patients. But, in parallel, there is a



risk that this biomarker becomes an orphan test. However, a number of pharmaceutical industries prefer to focus on tests that are done on a large number of people, such as diabetes or asthma tests, and very specific cancer biomarkers would not be fitted to their large-scale validation platforms.

There are also incompatibilities related to timelines. While academics want to publish, Big Pharma often wants to keep the research secret as long as possible. There are no standard procedures for such cooperation; it works through negotiations to arrive at a legal contract.

Finally, the question of power and influence also remains a bone of contention between these groups. In entering into a relationship with Big Pharma, it becomes more likely that public research will be influenced by external agendas. Interests such as profit, patentability, marketability, or the image of the pharmaceutical company can distort the objectivity of the research, without necessarily making it 'bad science'. The relationship is not one between two equal parties; there is a significant asymmetry in power. Though the public research community can claim some power over the knowledge of biomarkers, Big Pharma can draw on deep reserves of political and economic power.

In the field of cancer biomarkers, the relationship between public research and Big Pharma is quite new. Like all new relationships, it is both exciting and frightening, and both partners should be clear about what they bring to, and want from, this relationship; whether just a marriage of convenience or something more profound. ••

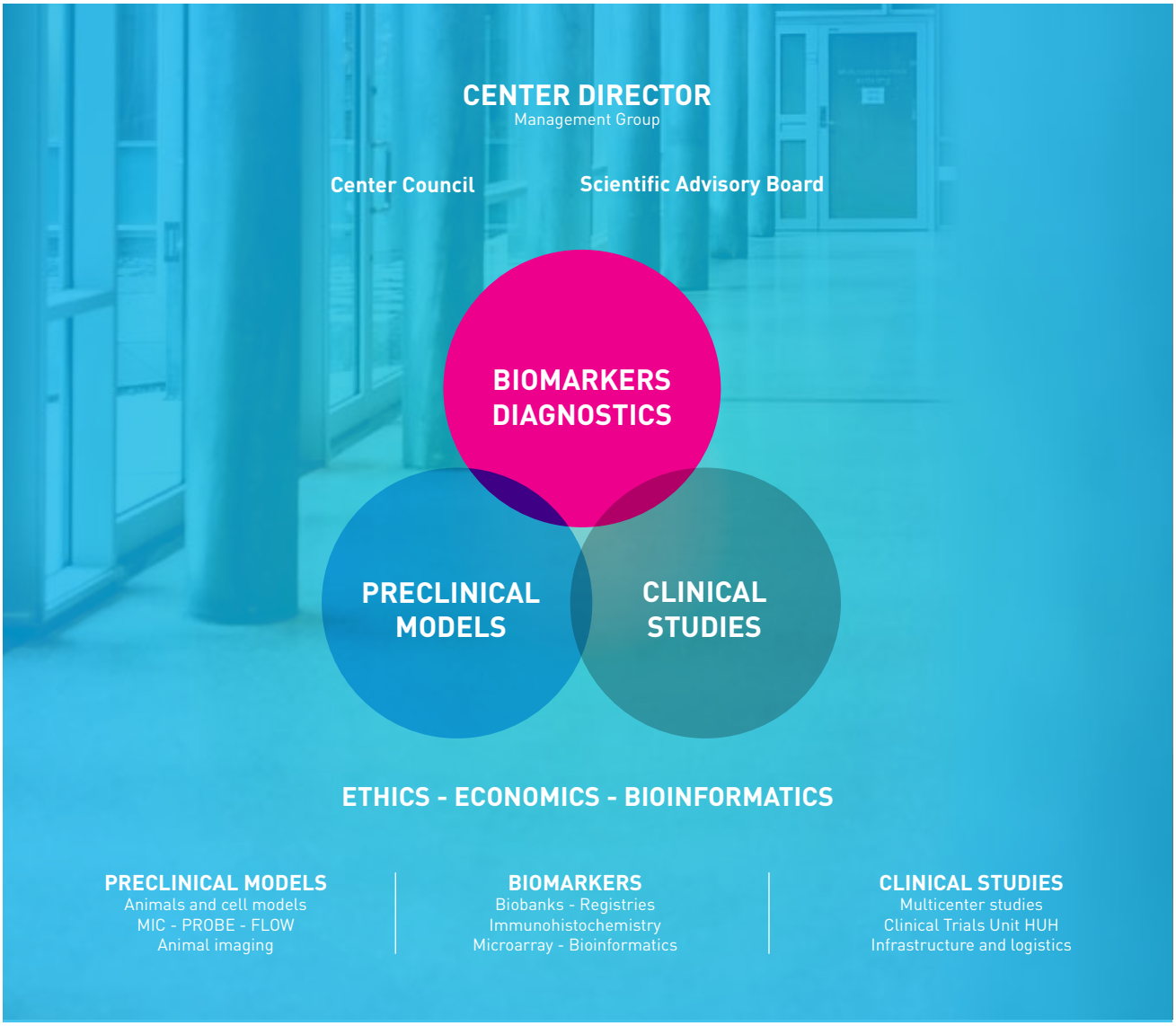
Organization of the Center

CCBIO is organized across six departments and four faculties. In 2015, its main activities, nine PIs and most of the other staff are located at the Faculty of Medicine and Dentistry (MOF) departments, Department of Clinical Medicine (K1), Department of Clinical Science (K2), and Department of Biomedicine (IBM).

The majority of CCBIO´s PIs also hold positions and funding at Helse Bergen and Helse Vest. In addition, CCBIO has activities and employees at the Departments of Informatics and Economics, 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, clinical studies) and three associate programs (ethics, economics and bioinformatics) that support the three main research areas (see figure). Lab space and core facilities are available for CCBIO, as is the Clinical Trials Unit at Haukeland University Hospital. The team of nine principal investigators have monthly meetings to discuss administrative and scientific issues and update each other on developments 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 2015, CCBIO was managed by the director, Professor Lars A. Akslen, co-director, Professor Helga B. Salvesen and the Administrative Leader, Geir Olav Løken, assisted by five finance officers and other administrative staff allocated to CCBIO in parts of their positions. The co-located offices for the CCBIO Management Group are in the main building of Haukeland University Hospital (Sentralblokken, second floor).



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.

Integration with 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 department 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 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

From left: Ate van der Zee, Carl-Henrik Heldin and Bruce Zetter

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 convenes once a year for a full day meeting following the CCBIO Annual Symposium. In 2015, the SAB provided an overall favorable review of CCBIO as well as advice on how to proceed with improving CCBIO´s research performance, cohesion and gender balance.

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

Professor Heldin was born in 1952 and obtained a PhD degree in medical and physiological chemistry in 1980 at the University of Uppsala, where he continued to work until 1985 in a position sponsored by the Swedish Cancer Society. Since 1986 he has been the branch director of the Ludwig Institute for Cancer Research in Uppsala, Sweden, and since 1992 also professor in molecular cell biology at Uppsala University.
Professor Heldin is a member of several learned societies, including the European Molecular Biology Organization, the Royal Swedish Academy of Sciences and Academia Europea, and he is an honorary doctor at the universities of Patras, Helsinki, Turku and Heidelberg.

He serves or has served on the scientific advisory boards for several companies and academic institutions, including the German Cancer Center, Heidelberg, the Max Planck Institute for Biochemistry, Martinsried, the European Institute for Oncology, Milan, and the European Molecular Biology Laboratory, Heidelberg and now also CCBIO. Professor Heldin was vice president of the European Research Council until 2014 and is currently an associate editor for the journals Molecular Biology of the Cell, Genes to Cells and Growth Factors.

Professor Heldin has received several scientific awards, including the Prix Antoine Lacassagne (1989), K. Fernströms Large Medical Prize (1993) and the Pezcoller-American Association for Cancer Research Award (2002). ••

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

Professor van der Zee was born in 1960 and obtained a PhD focused on targeted gynecologic oncology from the Faculty of Medical Sciences at the University of Groningen in 1994, where he has also been head of the Department of Gynecologic Oncology.

Professor Van der Zee serves and has served on various national and international advisory and program committees, including the Dutch Cancer Society, NCRN UK, IGCS, and ESGO. He is senior editor of the International Journal of Gynecological Cancer and leads a world-wide consortium (GROINSS-V-II) that performs landmark clinical studies in vulvar cancer.

Professor Van der Zee is past president of the European Society for Gynecologic Oncology (2009 – 2011) and past president of the Dutch Working Party for Gynecologic Oncology. Further, he has recently initiated and established a managed clinical network for ovarian cancer for all hospitals in the north-east of the Netherlands, in which gynecologists and medical oncologists collaborate to improve the care for ovarian cancer patients and which forms a unique platform for translational research.

Professor Van der Zee combines his management position with clinical research, performing surgery in gynecological oncology, seeing patients during consulting hours, academic research and mentoring PhD students. ••

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

Professor Zetter was born in 1946 and obtained his PhD from the University of Rhode Island in 1974. He has been vice president of research and chief scientific officer at Boston Children's Hospital.

Professor Zetter is frequently sought as an advisor on science and business practice to industry executives and scientists. He has served as consultant or scientific advisory board member to more than 30 biotechnology and pharmaceutical companies, venture firms and investment firms and academic institutions. Further, he also serves on several grant review boards for public agencies such as the American Heart Association and the American Cancer Society, and currently also serves on the editorial board of 8 peer-reviewed journals. In addition, he is often called on as an expert witness in court cases involving health and biotechnology.

As a frequent lecturer, he has given over 300 lectures to universities, conferences and businesses. He has also won numerous national and international awards for his work in the field of cancer research including a Faculty Research Award from the American Cancer Society and the prestigious MERIT award from the US National Cancer Institute and a Creativity Award from the Prostate Cancer Foundation. He has also received three teaching awards from the students at Harvard Medical School for excellence as a teacher and as a course director. ••

International Network and Affiliated Investigators

CCBIO is 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. The aim of this network is for CCBIO to establish a team of experienced advisors regarding scientific projects, collaboration and 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 a high 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. Thirteen other candidates are set to commence in early 2016 and will be presented in the 2016 annual report.

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.

ARNE ÖSTMAN

Professor Arne Östman, born in 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 Activities and Highlights

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

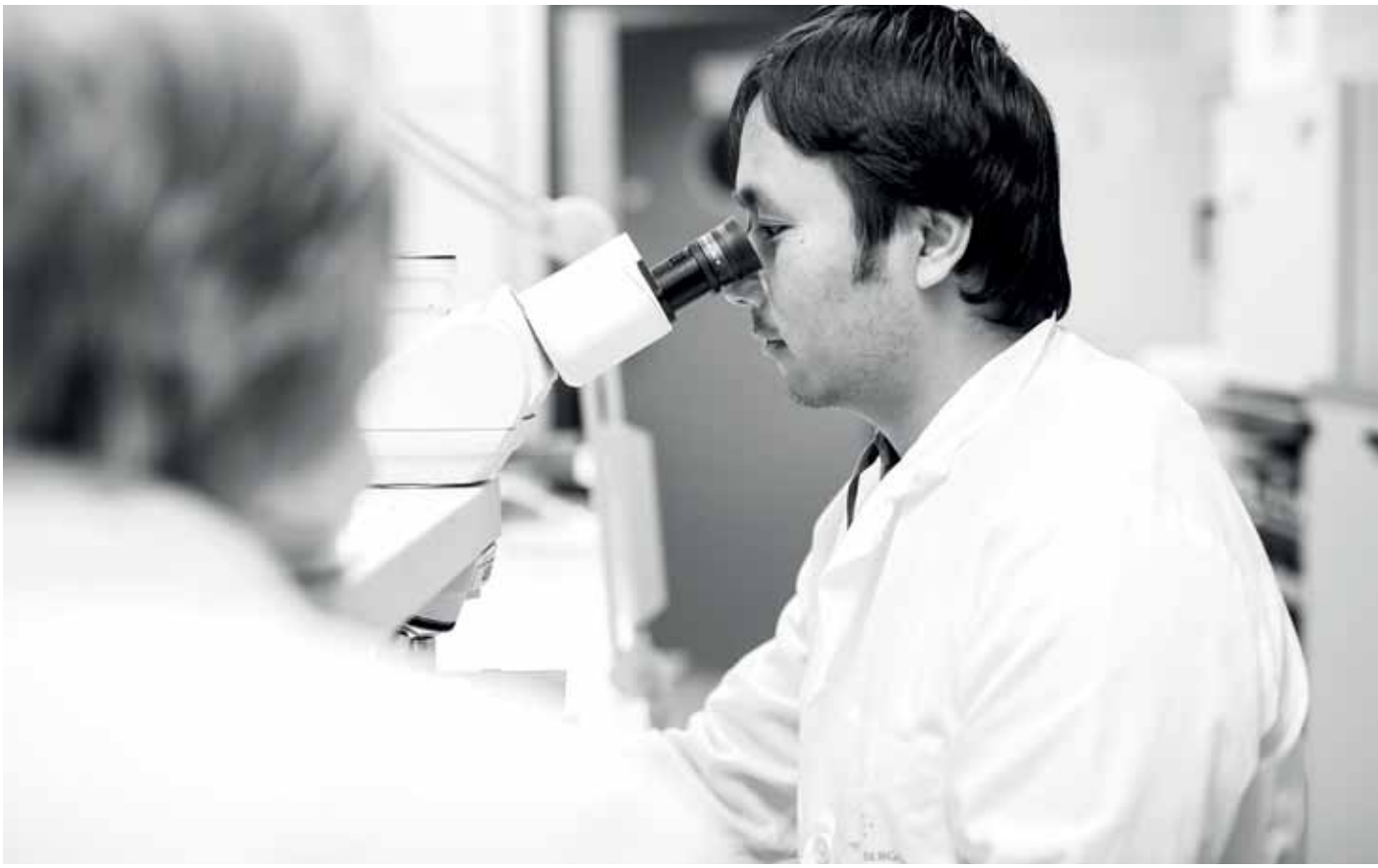
CCBIO has a focus on tumor-microenvironment interactions and plasticity programs in primary and metastatic lesions and how these can define aggressive tumor features and predict cancer progression patterns. CCBIO has three overlapping and well integrated research areas: basic studies of cancer mechanisms, discovery and validation of cancer biomarkers, and clinical studies. An ambition for CCBIO 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 collaboration and networking within the center.

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 the initiation of 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. Each of the different cell types can be passaged indefinitely. 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 ROS/IL6/STAT3 loop with increased resistance to apoptosis and anoikis. Recently, this model has been used in a drug discovery and development program, resulting in 5 WNT/beta-catenin inhibitor candidate (with patents pending).

Gullberg´s group has studied how different connective tissue cells interact with tumor cells and the extracellular matrix, a process which 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 alpha-11 from fibroblasts is important to stimulate tumor cells to secrete soluble factors influencing immune cell recruitment and tumor growth. Also, integrin alpha-11 was found to be important for stromal stiffness and tumor spread in non-small cell lung cancer.

In collaboration with Gullberg and others, **Reed´s group** has a focus on interstitial fluid pressure (Pif) in tumors and how this can be modified. 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 alpha-11 has an influence of 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.

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 alpha-11 has been identified as a key regulator in stroma-endothelial cross talk. Johannessen´s team also aims to develop a diagnostic and prognostic tool that can stratify patients with oral premalignant and malignant lesions for a more individualized therapy of oral cancer patients, and they have published a "malignancy index" signature which is now being validated.

Axl is a key regulator of cancer cell plasticity.

The group of Lorens 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. These 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 continue to study how microenvironmental factors and immune cell challenge illicit tumor cell phenotypic plasticity that engenders acquired resistance to both chemo- and immunotherapeutic agents.

Salvesen´s group has made significant efforts in biomarker discovery and validation in gynecologic cancers, with special focus on endometrial cancer and hormone receptor regulation and impact.

Akslen´s team has focused on the use of biomarkers for improved molecular classification and grading of malignant tumors, as a better guide for targeted and precise 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 two main programs: first, studies of the tumor microenvironment, especially tumor-vascular interactions and angiogenesis markers; second, genetic and molecular markers of aggressive tumors, especially related to tumor cell proliferation.

The team has reported novel tissue-based angiogenesis biomarkers. Microvessel proliferation was studied in several human tumor types and provide better prognostic information than vascular density. This marker also proved valid in xenograft models of breast cancer. By supervised analysis, a 32-gene RNA-based expression signature for microvessel proliferation was prognostically significant in endometrial cancer and is now explored in other tumor types. An 18-gene signature was identified for vascular invasion by tumor cells, pointing towards novel mechanisms involved in early metastatic spread, and was significant in endometrial and breast cancer. The progenitor cell marker Nestin has been found to identify subgroups of aggressive tumors in breast cancer and malignant melanoma. In breast cancer, proliferation markers in primary tumors and metastatic lesions have been reported to improve molecular classification, as a basis for more precise treatment. Correlations between vascular biomarkers and imaging features have been performed on breast and endometrial cancers in collaboration with other teams. Genetic markers are being explored in melanoma, like CDK4 and BRAF as well as others.

Salvesen´s group has made significant efforts in biomarker discovery and validation in gynecologic cancers, 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 will be taken to a phase 2 integrated biomarker trial for paclitaxel treatment in endometrial and ovarian cancer (MoMaTEC2). The team also continues studies on genetic alterations in gynecologic cancer, in a collaboration with the Broad Institute. 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 with angiogenesis and clinical characteristics. The findings are relevant for preoperative patient stratification.

Gjertsen´s group, supported by the Early Phase Clinical Trial Unit at Hauke-

land University Hospital, has been the initial center for a phase I trial (BGBC003; clinicaltrials.gov) with the novel anti-Axl drug BGB324 (per oral formulation) from BerGenBio. The trial is now also recruiting in Houston (Texas) and Germany. The trial will likely conclude at the end of 2016. 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 units, 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 analysis 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 suggest 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 a preferred method for future precision medicine with signaling targeted therapy. In contrast to the nearly monogenic BCR-ABL positive chronic myeloid leukemia, acute myeloid leukemia (AML) usually comprise 4-5 mutations. In the phase I trial with BGB324, the concepts of single cell biomarker profiling is tested. Analysis methods and read-out panels have been developed during 2015. 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.

The possibility to employ single cell biomarker technology in drug development is very promising.

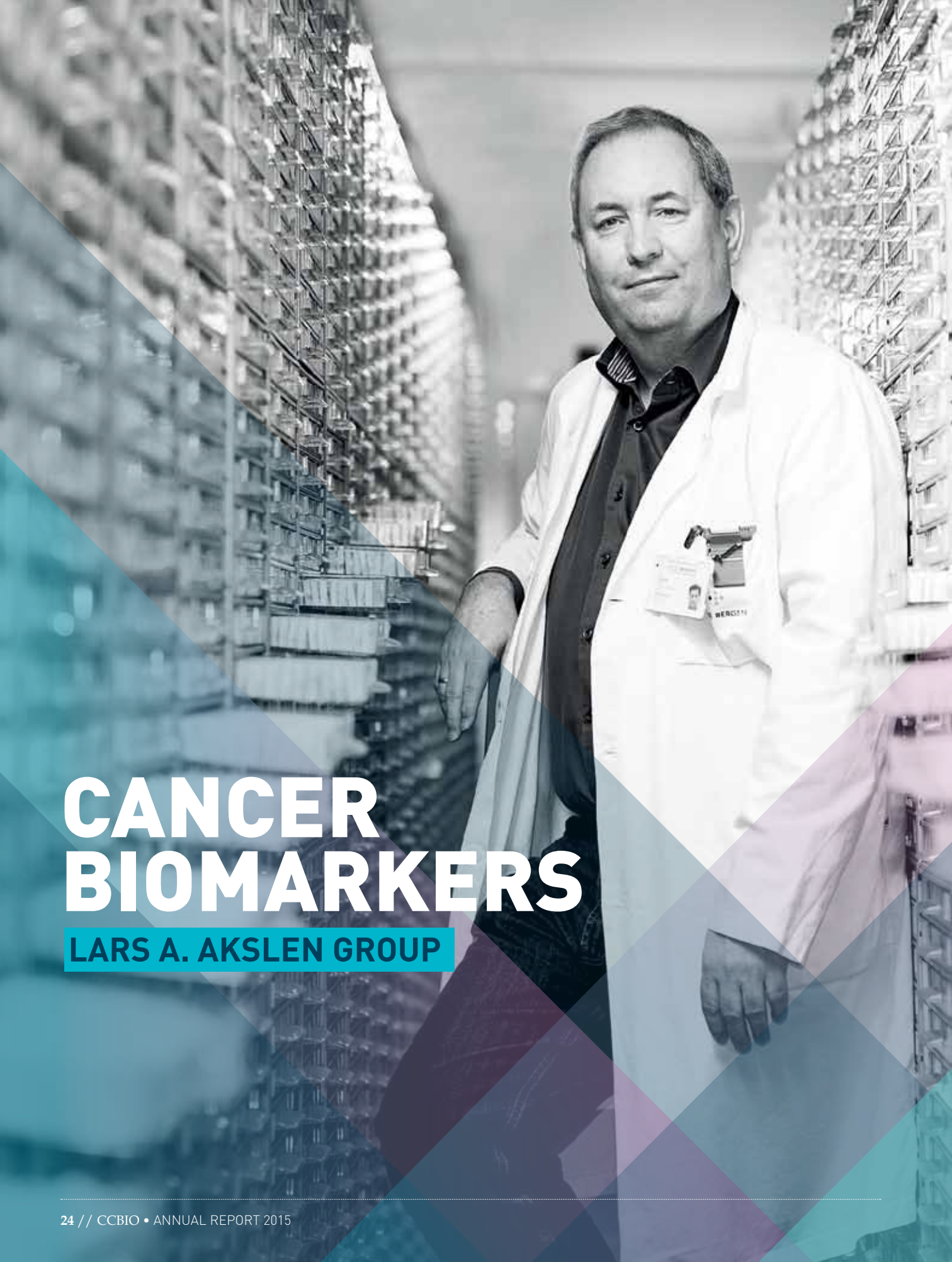
In collaboration with Kalland (PI), a phase I clinical trial of cryoimmunotherapy at Haukeland University Hospital has been initiated for patients with metastatic castration resistant prostate cancer, so far with around 10 patients recruited. The trial is based upon a dendritic cell based immunotherapy protocol in collaboration with the Haakon Ragde Foundation in Seattle (USA). One important aspect of the research protocol is to overcome tumor cell heterogeneity. The associated biobank is used for development of advanced immune-monitoring and circulating tumor cell enumeration as well as organoid cell culture isolation.

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 expression in metastatic lesions was able to predict therapy response. In metastatic kidney cancer, the VEGF receptor inhibitor sunitinib is first line treatment, and about 50 % of the patients are expected to respond. In a trial series of 45 cases with metastatic clear cell renal carcinoma, the team is now working on a set of candidate biomarkers for their predictive value. 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. Further, in a collaboration between CCBIO and BerGenBio, an investigator initiated randomized phase II clinical trial in metastatic melanoma will be initiated to study the combination of the Axl kinase inhibitor BGB324 with pembrolizumab or the BRAF inhibitor dabrafenib. Focus will be on predictive markers of response.

In summary, several efforts and initiatives within CCBIO, with increased 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. ••

PRINCIPAL INVESTIGATORS AT CCBIO

During 2015, research efforts have been increasing in the core groups, as reflected in the list of publications. Several papers have been published in high-ranking journals during 2015, such as studies on genetic and protein biomarkers in gynecologic cancers, breast cancer, hematologic cancer, and melanoma. Also, a study on how prostate cancers can limit their own spread was published. These studies exemplify how local teams can collaborate successfully with international environments and networks.



CANCER BIOMARKERS

LARS A. AKSLEN GROUP

"We are now starting to use biomarkers in molecular classification and grading of cancers, paving the way for precise therapy."

Lars A. Akslen is an award-winning specialist in surgical pathology and has over the years initiated many research projects - with a focus on breast cancer, malignant melanoma and prostate cancer. He might study tiny biomarkers in the microscope, but the translation to new and better cancer medicine is of great importance.

Akslen knows how to keep busy. He is not only the director of CCBIO, he also directs the Tumor Biology Research Group at the Department of Clinical Medicine at UIB.

What is a biomarker and how can your findings be put to use for cancer patients?

According to the NCI definition, a biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease; a biomarker may be used to see how well the body responds to a treatment for a disease or condition.

In my language, a cancer biomarker (or a biomarker signature) is the biological fingerprint or barcode of a patient´s cancer, telling us how aggressive it is, how it can be treated, and showing that each cancer is different. We are now starting to use biomarkers in molecular classification and grading of cancers, paving the way for precise therapy.

Can you tell us about your main research projects of 2015?

We have realized that malignant tumors not only consist of tumor cells, but they are also dependent on the supporting microenvironment, such as the tumor circulation, to grow and spread. Improved markers of tumor angiogenesis have been identified, and we have discovered novel angiogenesis drivers in aggressive breast cancers. During the last years, we have also been looking at how quantification of tumor cell proliferation may assist in better classification of breast cancer.

In your work, you seem to follow the whole process from basic research to new and improved cancer therapies?

For me, the chain-of-evidence from model studies to mapping of patient tumor tissues and detection of new targets and treatment modalities is a closed circle and an open field at the same time.

What are your goals when it comes to scientific findings?

The ultimate goal is to discover novel and unexpected features of malignant tumors that can eventually be applied in practical medicine. ••

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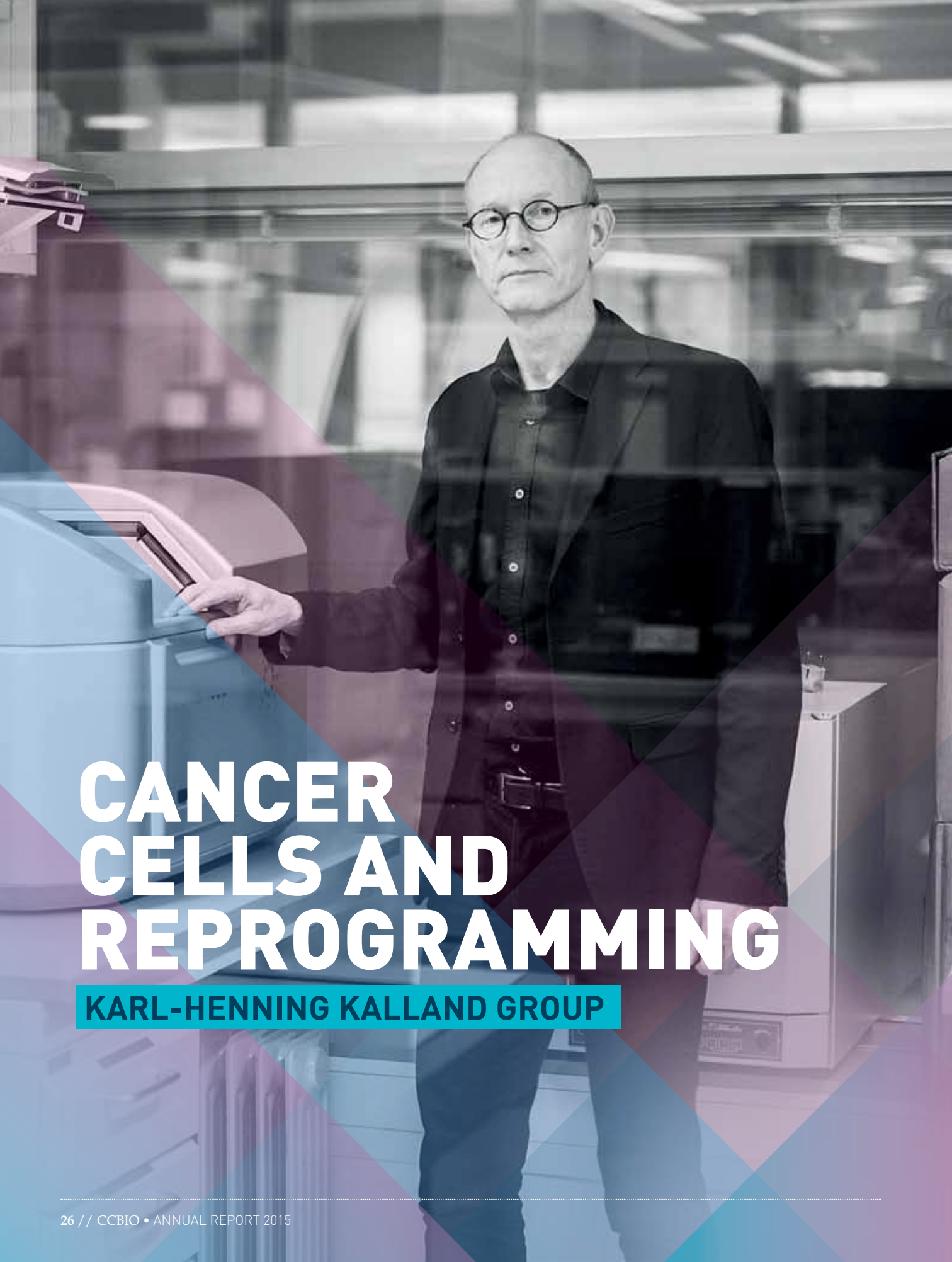

CANCER CELLS AND REPROGRAMMING

KARL-HENNING KALLAND GROUP

«The times are exciting for innovative combinations of immunotheraphy and molecular targeted therapy."

Professor Kalland is directing the Prostate Cancer Therapy Research Group at the Department of Clinical Science, and the group has made encouraging progress during the last couple of years.

You work with cryoimmunotherapy, can you tell us about your findings?

-Cryoimmunotherapy can theoretically confront the big problem that cancer cells exist as multiple subtypes due to mutations and gene reprogramming. Unfortunately, in invasive cancer there almost always exist cancer cell types that are resistant to any single specific therapy and these cells will cause relapse after seemingly successful initial treatment. In cryoimmunotherapy, immune cells derived from the patient, called dendritic cells, are injected in high numbers into the cancer tissue that first is killed by freezing inside the body. The dendritic cells may then "see" all the different subtypes of cancer cells and instruct the patient's immune system to attack all those subtypes. Very recently, we have started a Phase I Clinical Trial of cryoimmunotherapy at Haukeland University Hospital.

Can you tell us about your highlights of 2015?

-One highlight in 2015 was that the Phase I Clinical Trial was started and six patients treated before the New Year. It was a lot of work to assemble the clinical teams, establish the logistics and coordinate and conduct the treatments successfully. Another highlight is that our drug discovery and development program, utilizing an experimental prostate cancer model, identified compounds with the ability to block oncogenic signaling. Patent applications have been filed for several compounds with the ability to block the so-called WNT-beta-catenin pathway, and manuscripts reporting molecular targets of the compounds and novel mechanisms are in the publication process.

What are your plans for further research?

-The research biobank associated with the Phase I Clinical Trial, new methodology for monitoring treatment effects and novel leading compounds, have provided a basis for "next generation" immunotherapy. The times are exciting for innovative combinations of immunotherapy and molecular targeted therapy, and we hope to contribute to the cumulative progress within this field.••

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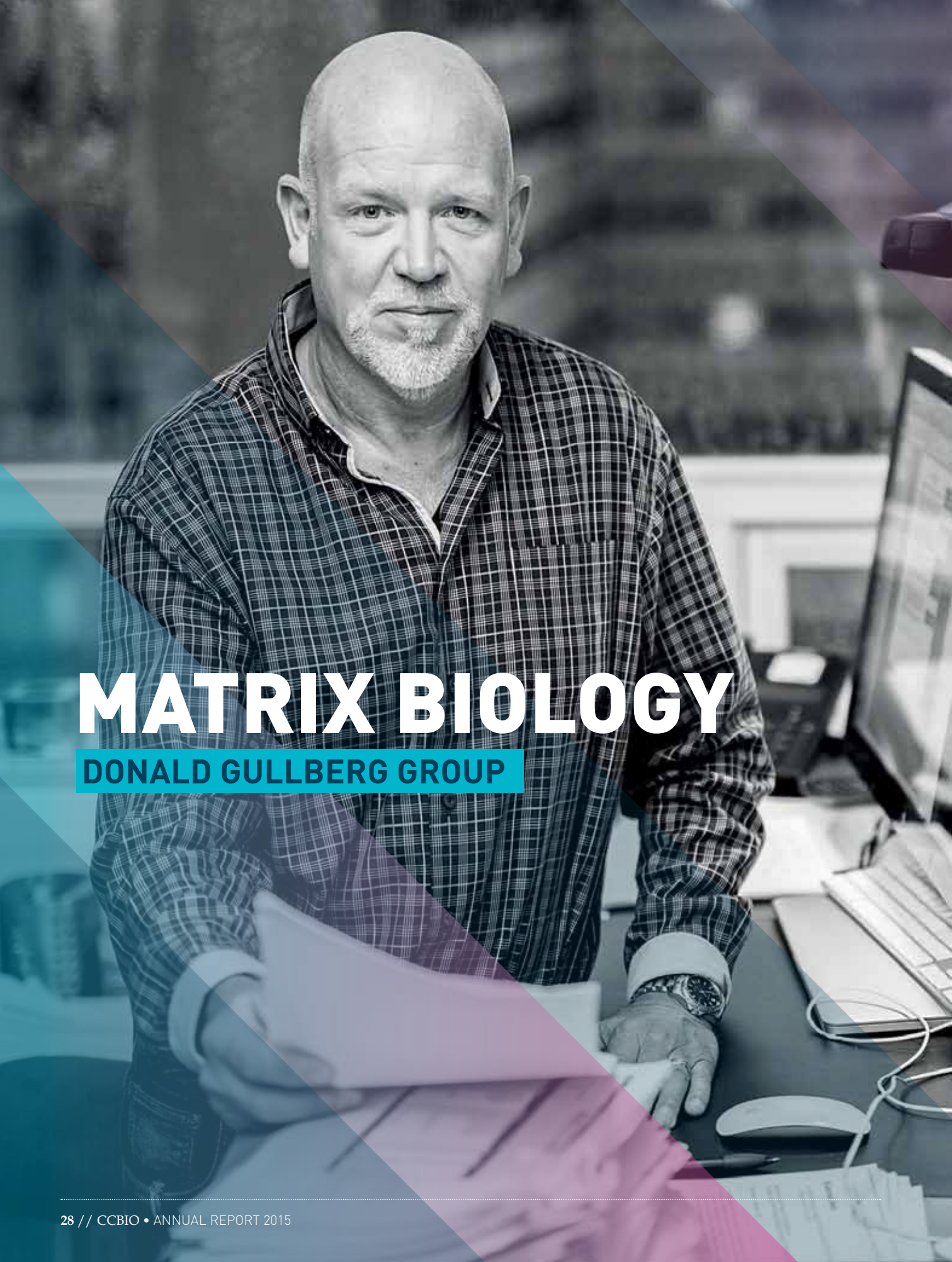

MATRIX BIOLOGY

DONALD GULLBERG GROUP

"We are interested in basic mechanisms of how connective tissue cells interact with the fibrillar protein collagen"

Professor Gullberg is directing the Matrix Biology Group at the Department of Biomedicine at UiB. The Gullberg group was the one to discover integrin α11, and they continue to explore the possibilities in this area.

What is the main emphasis of your research?

-We are interested in basic mechanisms of how connective tissue cells interact with the fibrillar protein collagen. In various projects it has become increasingly clear that both wound healing, scarring and solid tumor growth and spread, share some common mechanisms at the molecular level. We currently have funding to pursue projects related to fibrosis (scarring) and the tumor microenvironment (TME).

Your projects focus on integrin α11, can you tell us more about the significance of this integrin?

-Integrin alpha11 is a collagen receptor that was identified in my laboratory 20 years ago, and amazingly enough it keeps challenging us as we try to understand what it does. We have learned some basic things about this receptor in the time that we have been acquainted. It mediates cell adhesion and cell migration on collagen, and it reorganizes collagen to make it more compact. In certain lung tumors it conditions the TME so that tumors grow and spread more.

Can you describe your 2015 research projects and your findings?

-Within the framework of CCBIO, two major projects have been pursued in 2015. Firstly, generation and characterization of monoclonal antibodies, Moabs, recognizing human integrin alpha 11 together with a German company, Nanotools. Secondly, generation and characterization of a new transgenic mouse strain with the potential to serve as a tool for conditionally deleting cancer-associated fibroblasts (CAFs) in the stroma of experimental tumors.

What is the next step for your research group?

-In the coming year it will be important to characterize the new antibodies to integrin alpha11, and determine a potential commercial strategy in case some are good enough to be commercialized. Also, to characterize the new mouse strain and see if it can be an important contribution to research aimed at understanding what goes on in the TME. ••

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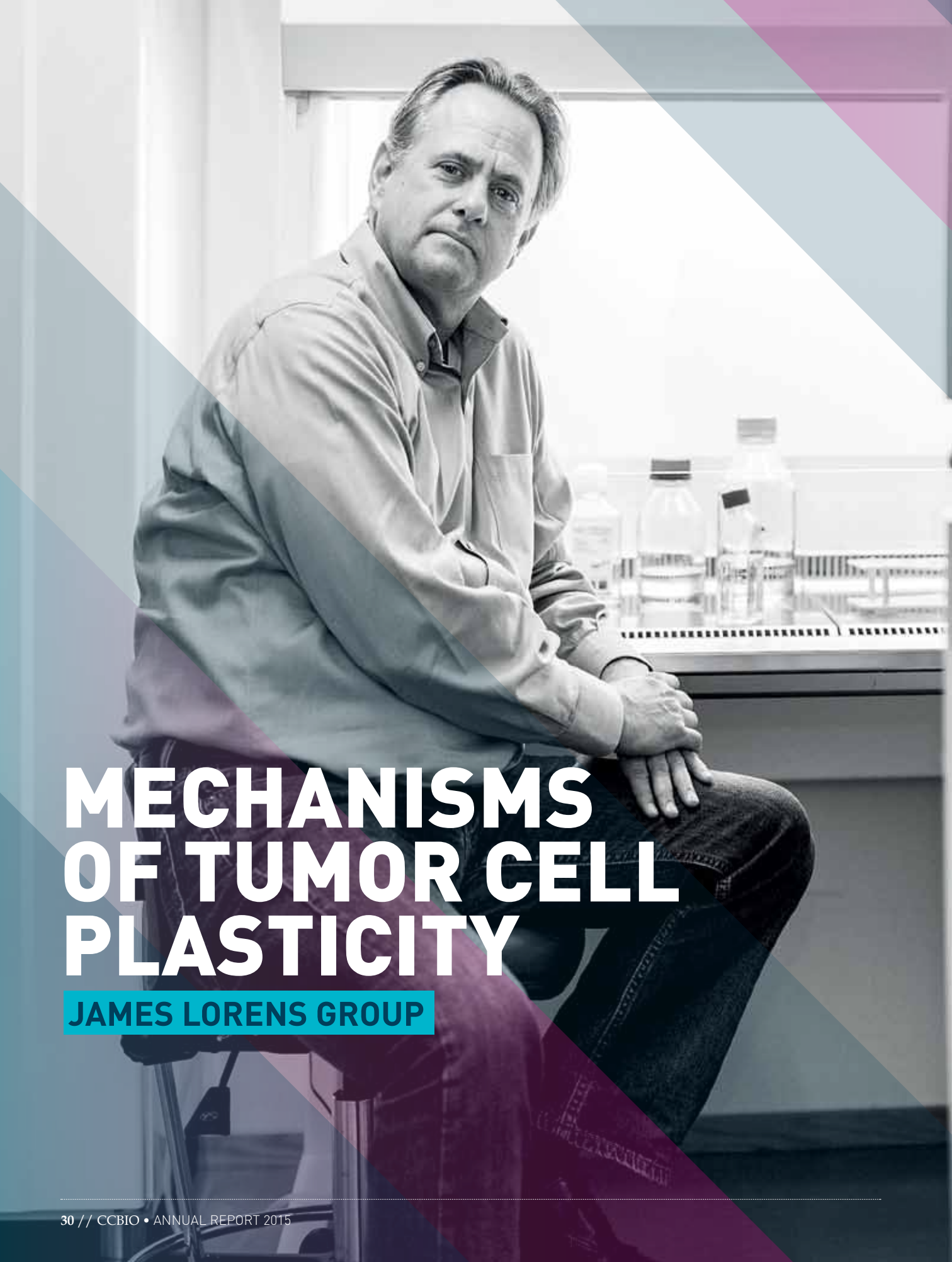

MECHANISMS OF TUMOR CELL PLASTICITY

JAMES LORENS GROUP

"Our insights can be readily translated to address tumor plasticity that contributes to current treatment failures."

In 2015, James Lorens won the Helse Vest Innovation Prize for his work with developing first-in-class drugs for aggressive, immune-evasive, drug-resistant and metastatic cancers. His research has resulted in the company BerGenBio, committed to discovering and developing novel drugs for treating cancer patients.

You work with the mechanisms of tumor cell plasticity. Can you explain what it is and why it is relevant?

-Cellular plasticity describes the ability of cells to change their state. Well studied examples include stem cell differentiation, transdifferentiation, and more recently experimentally induced pluripotent stem cells. Common to these is an epigenetic reprogramming that alters gene expression of hundreds or thousands of genes. Normal cellular plasticity programs are strongly dependent on microenvironmental cues ("niches"). Tumor cells can activate these plasticity programs through interplay between mutations in their genomes and interactions with the tumor microenvironment. This endows tumor cells with enhanced adaptive abilities and new cellular functions that underlie tumor heterogeneity, metastasis and drug resistance. Understanding this is crucial to inform better cancer treatment options.

Are you targeting certain cancer types in your research?

-Most, if not all, cancer types can undergo some form of cellular plasticity under specific conditions. Hence we study this phenomenon in several cancer cell types, including breast, lung and skin cancers.

What is the most important thing that you have learned?

-We have uncovered a novel link between how the Axl receptor tyrosine kinase influences tumor plasticity and how it regulates normal stem cells. This provides a rationale for the wide spread association of Axl with aggressive cancers.

How do you see your findings benefiting future cancer patients?

-The Axl receptor is a target of new therapeutics in clinical trials. Our insights can thus be readily translated to address tumor plasticity that contributes to current treatment failures.
••

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TRANSCAPILLARY EXCHANGE

ROLF REED GROUP

" The aim is to understand basic mechanisms of transport across the microvascular barrier."

The Rolf Reed Group is focusing on research that leads to better insight of the tumor stroma and its dynamic properties, with the goal of altering therapeutic principles of solid tumors.

Could you tell us about your research on transcapillary exchange - what does it really mean?

-Transcapillary exchange describes the transport and transport processes taking place at the smallest blood vessels in the body, the microcirculation. This is where the nutrients are delivered by the arterial blood and then transported across the microvessels to reach the cells of the tissue while waste products are removed from the cells across the microcirculation and leave the tissue via the venous blood. Transcapillary exchange is determined by the pressure across the microvessels as well as the properties of these vessels. Our research has a particular focus on how the tissue via its structural molecules also can influence this transport by altering the biophysical properties of the tissue and thereby the pressures responsible for this transport. An immediate problem in cancers is a high tissue pressure that limits transport across the microvessels which also limits the delivery of cytostatic agents from the blood to the tumor. Our research is aimed at understanding what generates this high pressure and how the tumor microenvironment can be modified to enhance the transport.

How would you describe your findings so far?

-We have especially been working on the role of the collagen binding cellular receptors, the integrins, and how altered integrin-expression, i.e. collagen binding properties, will modify the microenvironment of the tumor and also the biophysical properties involved in transcapillary transport.

What groups of cancer patients is your work concentrated on?

-The research we are performing is not focused on a particular group of cancers. It is better characterized as "underpinning" since the aim is to understand basic mechanisms of transport across the microvascular barrier and its interaction with tissue stroma in general and with specific emphasis on the events that are altered in cancers. ••

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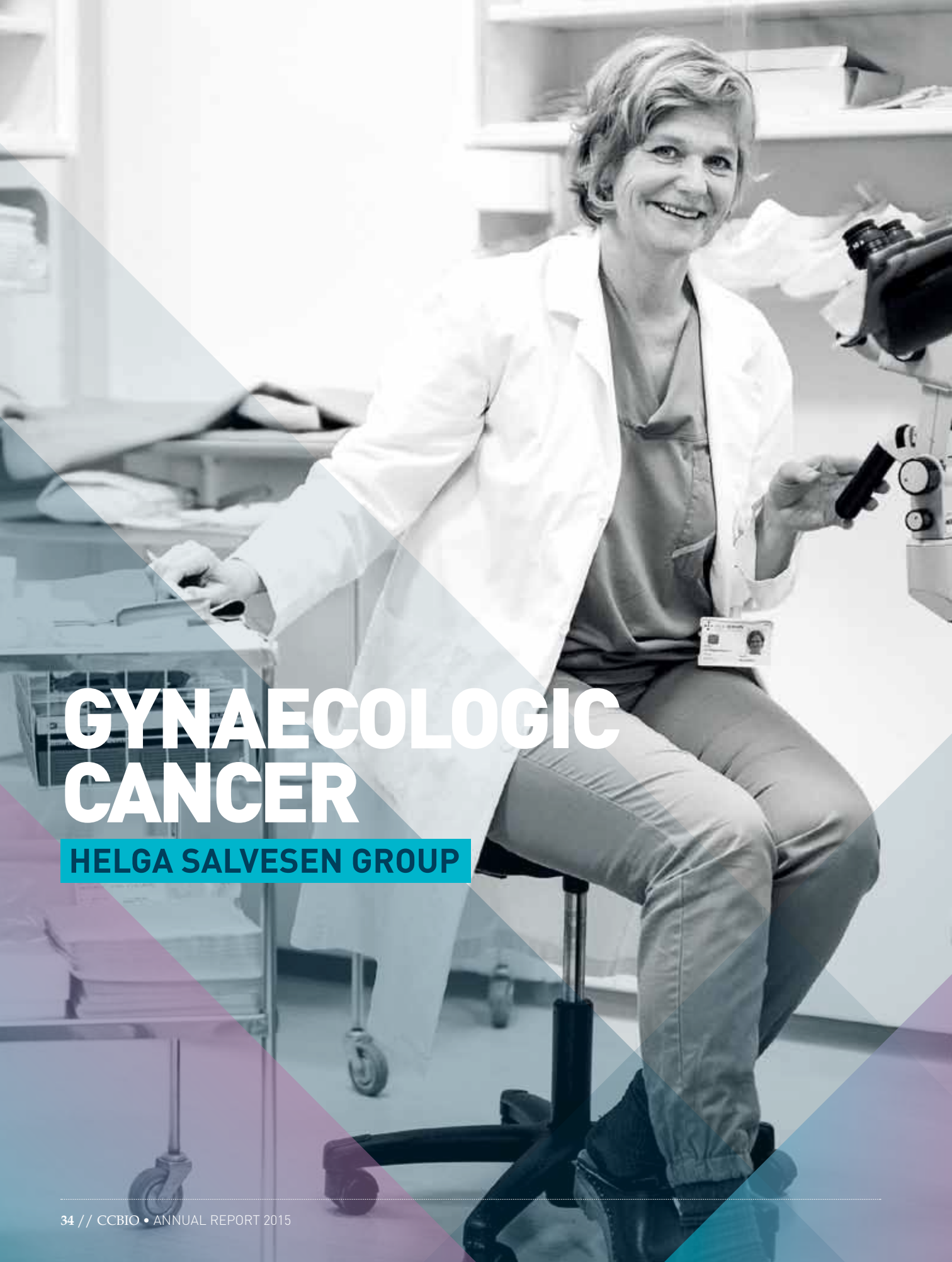

GYNAECOLOGIC CANCER

HELGA SALVESEN GROUP

"The gained molecular knowledge allows us to improve future clinical trials on molecularly targeted therapies."

The Bergen Gynaecologic Cancer Group focuses on molecular alterations in gynecologic cancers to improve the knowledge on cancer initiation and progression and to develop reliable biomarkers for individualized therapy. Through comprehensive molecular profiling of primary lesions from cervical-, endometrial- and ovarian carcinomas, new treatment targets are identified and molecular processes underlying tumor development are explored. As part of an established collaboration with Harvard, The Dana Farber Cancer Institute and MIT, profiling of paired primary and metastatic lesions have been performed, giving better insight into the underlying mechanisms of disease spread. The gained molecular knowledge allows us to improve future clinical trials on molecularly targeted therapies.

To bridge the gap between research and the clinic, our group also works to improve the preclinical models employed for gynecologic cancers. We have developed ovarian and endometrial cancer orthotopic mouse models, both based on cell lines and patient derived xenograft (PDX) models. Currently, these models are used for drug testing and validation of predictive biomarkers. In parallel, a large translational study exploring the value of functional imaging both of animal models and in patients is ongoing. The aim is to identify and validate potential imaging biomarkers that may enable more accurate preoperative staging and better prognostication in order to provide more individualized and tailored gynecologic cancer treatment. In parallel, the mouse models will be used to explore the feasibility of novel PET-tracers and their ability to provide predictive imaging parameters that may be transferable to the clinic. The combined results from both preclinical and clinical projects will be important for designing prospective international trials (MoMaTEC 1 and 2).

Several prognostic biomarkers have been identified and work is ongoing to better understand the molecular mechanisms and altered signaling pathways these biomarkers reflect. We have recently launched a prospective multi-center study (MoMaTEC2) with the goal of implementing the use of biomarker guided treatment. This multicenter trial aims at reducing morbidity, promoting individualized treatment and to facilitate the implementation of molecularly based targeted therapy for women with gynecologic cancer, through collection of primary tumors both regionally, nationally and from multiple European cancer centers. ••

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ORAL CANCER

ANNE CHRISTINE JOHANNESSEN GROUP

"There is a need for a simple clinical tool that can select premalignant and malignant lesions in the oral cavity"

Professor Johannessen is the leader of the Bergen Oral Cancer Research Group, BOCG. The group aims to identify key molecules for oral cancer development.

Your group focuses on oral cancer, could you tell us about your findings so far?

-Oral cancer originates from the surface of the oral mucosa, infiltrating the connective tissue and bone, and thereby leading to destructions of the face, if left untreated. Our research group has focused on the interaction between infiltrating epithelial tumor cells and the host cells in the connective tissue, especially the fibroblasts. We have shown that fibroblasts associated with cancer cells (CAFs) play a crucial role in cancer progression and have characterized at the molecular level how CAFs are actively involved in cancer development and invasion. The group has also identified diagnostic biomarkers implicated in the regulation of cell cycle, genomic stability, chromatin maintenance and stem cell regulation and developed a cancer index system of diagnostic and prognostic value based on this panel of molecular markers.

How do you work in your research?

-We have developed a 3D cell culture model mimicking oral mucosa, with surface epithelium and connective tissue, making it possible to study the interaction between these two compartments. This model has been used to compare growth of normal and malignant mucosa. By manipulating the model, e.g. by changing the growth conditions or by exposing the surface to external factors, we have been able to characterize stepwise tumor progression and regulating factors important for tumor infiltration. We are also using advanced animal models in our research, in addition to patient material from oral cancer. This material is achieved from Norwegian patients, but also from the United Kingdom, India, Nepal and Sudan, in close collaboration with researchers from these countries, opening up for comparative studies on oral cancer from different parts of the world.

What is the ultimate goal of your research?

-There is a need for a simple clinical tool that can select premalignant and malignant lesions in the oral cavity. Today there is no diagnostic tool that can predict which white or red oral pre-cancer lesions that will progress to infiltrative oral cancers. Our goal is to develop such a diagnostic and prognostic tool that can stratify patients with oral lesions for more individualized therapy. ••

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ANTI-ANGIOGENIC TREATMEN

ODDBJØRN STRAUME GROUP

"We set out to identify cancer biomarkers that could be used to guide good clinical decision making."

Oddbjørn Straume and his group are working on several promising projects, including research on melanoma, kidney cancer and breast cancer.

Can you tell us about your work and what drives you?

-Melanoma is my personal favorite among all cancers. The melanoma is a kind of prototype malignancy for many kinds of tumor processes, such as interactions with the immune system and the tumor microenvironment, cellular plasticity as well as angiogenesis. I also have research projects on treatment of metastatic kidney cancer. In addition, we study the relation between physiologic processes, such as wound healing, stress responses or tissue trauma, and breast cancer recurrence. In the clinic, I work with all these three cancer types.

How promising are the results so far?

-We set out to identify cancer biomarkers that could be used to guide good clinical decision making. This is a huge challenge, and I am respectful of how difficult it is to predict the behavior of a disease that by definition is unpredictable, due to tumor cell heterogeneity and complex interactions with the host tissues. Nevertheless, I think that the time spent on building up clinical series with complete follow-up and treatment response endpoints will be worthwhile. Several of the candidate biomarkers studied in the CCBIO groups need validation in these kinds of datasets before they can be introduced in the clinic. In particular, a planned randomized phase Ib/II clinical trial will be specifically designed to validate predictive biomarkers of anti-Axl targeted treatment.

What do you hope for the future regarding coming research?

-I hope that the time invested in our clinical trials so far will pay off by resulting in new promising predictive markers useful for the clinicians when planning individualized treatment. I also hope that our research will increase the understanding of tumor biological processes, and maybe, if we are lucky, lead to new targets for future treatment of cancer. ••

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SIGNALING-TARGETED THERAPY

BJØRN TORE GJERTSEN GROUP

"We are working on development of «liquid biopsies» in cancer diagnostics and follow-up of cancer patients."

Professor Gjertsen and his group have great success with research on the aggressive blood cancer acute myeloid leukemia, AML. Important lessons have also been learned through their exciting research on targeted therapy of chronic myeloid leukemia.

You work with signaling-targeted therapy; can you elaborate on your research?

-Our research group addresses how to understand the signaling inside single tumor cells and we are focusing on biomarkers that may represent future diagnostics. A new machine, a mass cytometer, allows us to pick up more than 50 signals from a single cell. We use this technique to map the various cells in blood cancer. That also includes many normal cells that form essential parts of the immune system. The effects of signaling targeted therapy do not only affect cancer cells, but immune cells as well. Likely, the sum of these effects predicts the outcome of cancer therapy.

What do you hope for in the future when it comes to your research?

-We have two main long-term goals. Firstly, we hope that our new diagnostic tests will increase the precision of leukemia therapy: more correct dose and less adverse effects. Maybe we can tell if a medicine is effective in hours or days, rather than months. Secondly, we currently have, in an early development stage, several molecules that act directly on signaling in cancer cells. The long term goal is that these molecules will be made available for patients, and represent more effective and less toxic therapy compared to contemporary medicines.

What are your coming plans, scientifically speaking?

-We are working on development of «liquid biopsies» in cancer diagnostics and follow-up of cancer patients. Blood samples from cancer patients will be analyzed for small amounts of DNA that has been leaking from tumors and into the blood. This DNA could unravel a spectrum of mutations that are unique to the type of disease, unique for the patients, and unique for the various daughter tumors in metastatic disease. In the future we think this will allow us a more precise picture of the disease, and a better monitoring of therapy effect. For each patient this will implicate more personalized therapy and hopefully better survival. ••

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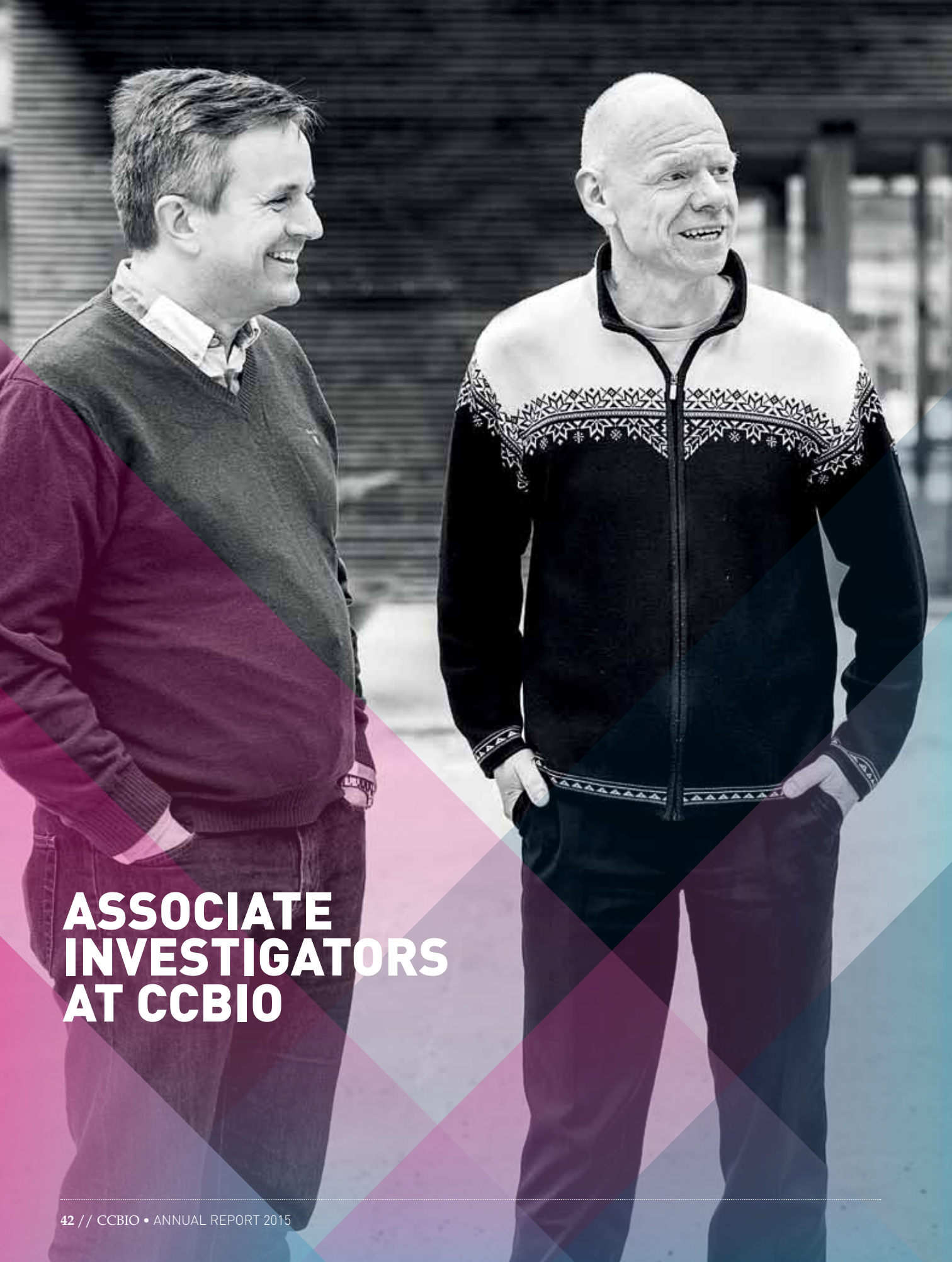
Administrative support:
Scarlett, Samantha, M.S.



ASSOCIATE INVESTIGATORS AT CCBIO

BIOINFORMATICS
INGE JONASSEN

In the context of CCBIO, Professor Inge Jonassen and part of his team from the CBU (Computational Bioinformatics Unit) at the University of Bergen are working on development and application of bioinformatics methods for analysis of data resulting from high-throughput measurement technologies applied to cancer samples. A primary focus is on deconvolution of gene expression data sets, resulting from samples composed of a combination of tumor cells and the surrounding and supporting microenvironment. The research aims to decompose the signal into that originating from the tumor cells and those originating from other tissue and cell types in the sample. This will enable us to study interactions between tumor cells and the environment and to identify relations to choice of treatment, outcome, and prognosis.

In this first phase, we are analyzing public gene expression data sets with a variety of methods to find out if any of the tools can be adapted to suit our needs. Part of this work also involves analysis of earlier published tumor type specific expression signatures. In the longer perspective, we want to perform network and module analysis, using the output from the deconvolution approach to improve our understanding of the networks involved in different tumor types and their microenvironments. We further intend to integrate other omics data on DNA methylation, copy number variation and protein expression to achieve a more holistic view of the underlying mechanisms.

How is bioinformatics useful for cancer research?

- The gene expression data generated from heterogeneous samples that include both tumors and their microenvironments are complicated to analyze. Bioinformatics and biostatistical methods are crucial in order to turn such big data into useful conclusions e.g. about genomic variability between cancer patients and relations to treatment response or prognosis. ••

RESEARCH GROUP:

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

INTEGRATING ELSA INTO CCBIO
ROGER STRAND

In 2015, the CCBIO research group on ELSA, "Ethical, Legal and Social Aspects of Cancer Biomarkers", started with running the course "CCBIO 903 Cancer Research: Ethical, Economic and Social Aspects" over two weeks, with main lecturers Roger Strand and Anne Blanchard from the ELSA group, as well as John Cairns from the London School of Hygiene and Tropical Medicine. Topics such as the economics of health care allocation and decision-making, and uncertainties around cancer biomarkers research and their impacts on broader social issues were discussed.

Anne Blanchard focused her research on the changing business models of pharmaceutical industries, in the transition from 'blockbuster' models to personalized medicine. In particular, Anne was interested in the relationship between public research and Big Pharma in that context. To this aim, she undertook a fieldwork in the United States constituting of interviews with people having experience from working with pharmaceutical companies, with the objective of learning about the challenges and opportunities of this transition. Some of this research was reported to CCBIO during a Junior Scientist Symposium, and will constitute the basis for a special seminar in 2016, as well as for a paper. In addition, on the basis of a literature review and her interactions with CCBIO researchers, Anne also submitted a review paper aiming to map the ethical and social aspects of cancer biomarkers.

Roger Strand's ELSA work in 2015 focused in particular on methodological and institutional aspects. In 2014-15, he chaired a European Commission DG Research and Innovation Expert Group on Indicators for Responsible Research and Innovation. He and Matthias Kaiser also wrote a commissioned report for the bioethics committee of the Council of Europe (DH-BIO) on the ethical issues raised by emerging sciences and technologies. The report was the topic of discussion of a dedicated international conference in Strasbourg, at the Council of Europe, in May 2015. ••

RESEARCH GROUP:

Strand, Roger, professor
Blanchard, Anne, postdoc

THE ECONOMICS OF CANCER BIOMARKERS

JOHN CAIRNS

Professor John Cairns from London School of Hygiene & Tropical Medicine (LSHTM) is an international capacity within health economics and has unique competences in relation to economic evaluation of new types of clinical treatment. In the capacity as adjunct professor and associate PI at CCBIO, Cairns, in collaboration with Professors Tommy Staahl Gabrielsen and Jan Erik Askildsen from the UiB Department of Economics, works on two main CCBIO projects: 1. The industrial economics of biomarkers – how the interplay between the diagnostic market and the pharmaceutical market affects the incentives to invest in R&D for biomarker-based diagnostic tests; 2. How cancer biomarkers change the cost-effectiveness of different therapies and the opportunities for economic models to contribute to optimizing the development of cancer biomarkers.

In 2015, the economics team worked on: an economic model of the relationship between the developers of cancer biomarkers and drug manufacturers, a seminar paper "Assessing the cost-effectiveness of bevacizumab in the treatment of metastatic melanoma", a presentation made at the 3rd CCBIO Symposium "Challenges in valuing the benefits of new cancer therapies", and the development and delivery (with Roger Strand) of the nationally unique PhD course "CCBIO 903 Cancer Research: Ethical, Economic and Social Aspects".

In 2015 Kelly Seo was recruited to a PhD position to conduct research on the cost-effectiveness of different therapies and economic modelling for optimizing the development of biomarkers. Kelly is based at LSHTM. A position as PhD candidate at the Department of Economics, related to the industrial economics of biomarkers, has been posted in cooperation with the Bergen Center for Competition Law and Economics (BECCLE).

A review of economic evaluations to identify how the introduction of cancer biomarkers has changed the cost-effectiveness of treatments for metastatic colorectal cancer is underway. Presentations of models and results will be held during CCBIO seminars and the CCBIO Annual Symposium. The PhD-course on the ethical, economic and social aspects of cancer research is being prepared for a further version to be held in 2016. ••

INVOLVED RESEARCHERS:

John Cairns, professor
Gabrielsen, Tommy Staahl, professor
Jan Erik Askildsen, professor

CCBIO RESEARCH SCHOOL FOR CANCER STUDIES

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 the director of CCBIO.

Activities in 2015

In 2015, the RSCS more than attained its goal of being 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. PhD candidates and postdoctors got ample opportunity to meet each other and deliberate upon their research projects across the established research groups. CCBIO successfully integrated the RSCS into its strategic activities like the CCBIO Annual Symposium, CCBIO Junior Scientist Symposia and CCBIO Seminars. This in combination with CCBIO's strategy of inviting external speakers also for the other courses ensured that our younger researchers had access to renowned national and international researchers. CCBIO made sure to use the opportunity for younger and more senior researchers to have targeted meetings with our invited speakers where potential points of common interest were mapped out.

During 2015, the full range of CCBIO's courses were held, ranging from courses reflecting CCBIO's main focus on relevant biomarker studies to interdisciplinary training in addressing ethical, economic and societal aspects pertaining to cancer research. Mostly, courses will run once a year or every second year, the exemption being courses that run continuously, reflecting that they are integral parts of CCBIOs continuous strategic activities.

CCBIO 901 and 902 - Courses integrated into CCBIO's strategic activities

CCBIO's Junior Scientist Symposium, where PhDs and PDs 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.

CCBIO 903 - Cancer Research: Ethical, Economic and Social Aspects

The first CCBIO 903 course took place over two weeks in early 2015 and was attended by 17 highly motivated PhD candidates and students from the Medical Student Research Program. The course was framed with a very high degree of interactivity, and both participants and lecturers learned a lot over the two weeks. In 2016, CCBIO903 will take place on the 23-26th of May and the 14-17th of June. PhD candidates from medical fields of research from all over Norway can attend.

In CCBIO903, lectures were followed by long time-slots devoted to group discussions in order to offer a unique space for PhD candidates in medical sciences to engage in broader debates that surround their research. PhD candidates were asked to review their own research topic according to the ethical, social and economic perspectives they were introduced to in the

course, and write about this in a term paper. The ideas for term papers were presented to the rest of the group during the second week of the course as a basis for plenary discussions and feedback.

Some of the questions addressed during the course were:

- How can we deal with the complexity and uncertainties around cancer in the lab, while maintaining the quality of our science?
- How can medical science contribute to debates on what is good for society, and what society needs?
- Why is funding for cancer research increasing every year: is it because of hope or despair?
- How can economic models guide health care resource allocation, and what are the limits of such models?

CCBIO 903 was led by Roger Strand, John Cairns and Anne Blanchard.

CCBIO 904 - 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 was to illustrate how basic cancer research and knowledge about tumor biology have substantial impact on patient outcomes and lives. Lectures covered tumor biological aspects important for the understanding of why cancer develops and which mechanisms are important for tumor growth, metastases and morbidity in patients. 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.

Helga B. Salvesen and Oddbjørn Straume had the academic responsibility, and Reidun Kopperud was the course coordinator.

CCBIO 905 - 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.

In order to cover CCBIO905's rather broad topic, the 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 were 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.

Lars A. Akslen and Jim Lorens had the academic responsibility and Monica Mannelqvist was the course coordinator.

BMED 904 - Matrix Biology
BMED904 is an already well established course from the Bergen Biomedical Research School (BBRS) that has now been included also in 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 course was 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 successfully sought funding from the 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, able to further elaborate 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.

Bioinformatics
CCBIO aims to establish the activities of the CCBIO Bioinformatics Group (BIG) into at least one new course within translational bioinformatics, in collaboration with the National Research School in Bioinformatics and Biostatistics (NORBIS). This will contribute towards facilitating a much needed elevation in the level of knowledge and skills in medically relevant bioinformatics. BIG is also covered below. ••

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.

Workshops on relevant issues

Regular workshops have been held, and students and researchers from the majority of the CCBIO research groups have participated. Topics for the meetings have been suggested by the participants and were relevant to the specific projects. Study design, data normalization, data download from public repositories, functional interpretation of analysis output, and application of gene expression signatures have been among the topics elucidated and discussed. Also, introduction to RNA seq analyses was given in two half day seminars in December 2015. In particular from autumn 2015, there was a markedly increased interest in this seminar series from researchers, with many participants from the CCBIO groups.

Open seminars and CCBIO meetings

The future activities of the group will partly be joint ventures together with open CBU seminars (e.g. seminars and workshops on general bioinformatic topics), and part of the meetings will be open only for CCBIO affiliated researchers (e.g. discussing hypotheses, study design and analyses of ongoing projects within CCBIO). BIG is coordinated by David Fredman and Kjell Petersen from the ELIXIR/CBU Service Group and Elisabeth Wik (postdoc in the group of Lars A. Akslen/CCBIO).

Future plans

Seminars and workshops as described above are planned, approximately 4 seminars per semester. To further contribute to the strengthening of the bioinformatic link within CCBIO, the coordinator group is at present discussing how to organize the seminar series as a PhD course, as part of the Research School for Cancer Studies. ••

CCBIO Junior Scientist Symposium

In 2015, "CCBIO901, CCBIO Junior Scientist Symposium" (JUSS) was organized and chaired by the Postdoc Elisabeth Wik, Researcher Camilla Krakstad (spring semester) and Postdoc Agnete Engelsen (autumn semester).

With four symposia in 2015 and 40-50 registered attendants per meeting, they have clearly succeeded in making JUSS reach its aim of being a popular and durable arena for increased scientific and social interaction amongst junior researchers from CCBIO and beyond. JUSS is now an excellent opportunity for PhD candidates and postdocs to gain increased experience with oral presentations and academic discussions as well as in chairing scientific sessions, and also in getting valuable input for potential collaborations in ongoing and future projects.

The standard JUSS format has been to include six to eight PhD candidates and postdocs to present their research, followed by a short discussion after each presentation (lasting 4 hours in total). As a valuable addition in 2015, an "inspirational lecture" was added to the program. 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 2015, Professor Bjørn Tore Gjertsen shared glimpses of his journey from being a hardworking PhD student to becoming a professor and successful group leader, and Professor Roger Strand challenged the audience with discussions on the distinctions of cancer as illness, sickness and disease, and how this influences the research strategies. The inspirational lectures were well received by the audience, and initiated lively discussions.

Throughout 2015, JUSS covered cancer research from a wide range of perspectives, with topics ranging from molecular and mechanistic studies, through bioinformatics and clinical research, to socio-ethical considerations in biomarker research. A particular focus has been dedicated towards implementation of novel technology, and the arrival of the new CyTof mass cytometer this fall was highlighted by presentations from two dedicated PhD students.

Whereas the high sustained number of participants speaks for itself, the level of the presented research and the research communication skills displayed in presentations and the following deliberations, as well as the lively discussions during lunch-break suggest that JUSS contributes both towards better integration as well as new and fruitful research collaborations within and beyond CCBIO. ••

Centre for Cancer Biomarkers

PROGRAM - CCBIO Junior Scientist Symposium

February 12th 2015 - Auditorium 2, BBB

Symposium Chairs: Camilla Krakstad & Elisabeth Wik

10.00-10.40 **Marion Solheim**
Scientists and the media

10.40-11.00 **Break**

11.00-11.20 **Karen Mauland**
Aneuploidy predicts aggressiveness and poor prognosis in endometrial cancer, and is reflected in a 9-gene signature

11.20-11.40 **Sura Aziz**
Assessment of the proliferation markers in lymph node metastasis in breast cancer and their impact on survival

11.40-12.40 **Lunch**

12.40-13.20 **Cecilie Brekke Rygh**
Preclinical PET/CT at UiB

13.20-13.30 **Break**

13.30-13.50 **Lavina Ahmed**
Axl as a biomarker for cancer EMT

13.50-14.00 **Concluding remarks**

Centre for Cancer Biomarkers

PROGRAM - CCBIO Junior Scientist Symposium

April 30, 2015 - Auditorium 4, BBB

Symposium Chairs: Camilla Krakstad & Elisabeth Wik

10.15-11.00 **Gyri Wester**
The moral significance of the social in equalities in health: Some policy implications

11.00-11.15 **Break**

11.15-12.00 **Liv Cecilie Vestrheim**
The immune system's response; a common denominator in preeclampsia and cardiovascular disease

12.00-12.40 **Lunch**

12.40-13.00 **Calum Leitch**
Repositioning Hydroxyurea and Valproic Acid as combination therapy in acute myeloid leukaemia

13.00-13.20 **Caroline Schmid**
Novel uses for small molecule PDGF-Re ceptor β (PDGF-Rβ) inhibitors

13.30-13.40 **Break**

13.40-14.00 **Dipak Sapkota**
S100A16 promotes differentiation and functions as a tumor suppressor in oral squamous cell carcinoma

Centre for Cancer Biomarkers

PROGRAM - CCBIO Junior Scientist Symposium

September 17th 2015 - Auditorium 4, BBB

Symposium Chairs: Agnete Engelsen and Elisabeth Wik

10.00-10.20 **Anne Blanchard**
Big pharma, medicalisation and the good life

10.20-11.05: **BjørnTore Gjertsen**
How to succeed in cancer research (Or how do you define yourself into success...)

11.05-1120 **Break**

11.20-11.40 **Henriette Cristie Ertsaas**
Microsphere cytometry to study microenvi ronment contextual cell signaling

11.40-12.00 **Kristi Kruger**
Nestin expression in breast cancer - a marker for angiogenesis and the basal-like phenotype

12.00-13.00 **Lunch**

13.00-13.20 **Synnøve Yndestad**
The PTEN pseudogene, friend or foe? A Long non Coding RNA that influences breast cancer through ceRNA network and microRNA interactions.

13.20-13.40 **Yaping Hua**
Development of a small molecule for treatment of castration recurrent prostate cancer via androgen receptor and IL6/STAT3 pathway

13.40-14.00 **Tiina Jokela**
Dissection of mammary stem cell and cancer stem cell niche

Centre for Cancer Biomarkers

PROGRAM - CCBIO Junior Scientist Symposium

November 26th 2015 - Auditorium 4, BBB

Symposium Chairs: Agnete Engelsen and Elisabeth Wik

10.00-10.00 **Professor Roger Strand "Cancer: illness, disease and sickness"**
Inspirational lecture with plenary discussion.

11.00-11.10 **Break**

11.10-11.30: **Pugazendhi Murugan Erusappan**
The role of the cytoplasmic tail of integrin alpha 11

11.30-11.50 **Martin Pilskog**
Analysing response of sunitinib treatment in metastatic renal cell carcinoma.

11.50-12.10 **Anna Berg**
Tissue and imaging biomarkers for hypoxia predicts poor outcome in endometrial cancer

12.10-13.00 **Lunch**
(included, please specify upon registration)

13.00-13.20 **Gry Haaland**
Register based cancer research - challenges and opportunities

13.20-13.40 **Stein-Erik Gullaksen**
Mass Cytometry in Bergen

13.40-14.00 **Fanny Pelissier**
High dimensional analysis of age-related phenotypic diversity in human mammary epithelial cells

CCBIO Research Seminars

In 2015, CCBIO's monthly research seminars focused almost exclusively on speakers of national and 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 BMED 380 and the PhD-level course CCBIO 902. Last, but not least, each seminar is followed by an informal pizza get-together that is an important catalyst for interaction on all levels. ••

CCBIO Seminars in 2015

22.01.2015
John Cairns CCBIO & London School of Hygiene and Tropical Medicine: Assessing the cost-effectiveness of bevacizumab in the treatment of metastatic melanoma.

19.02.2015
Anne Christine Johannessen, CCBIO: Oral cancer – ongoing research with special focus on tumour microenvironment.

26.03.2015
Hani Gabra, Imperial College London, UK: OPCML, a tumour suppressor and novel systems regulator of tyrosine kinase signalling in ovarian and other cancers.

08.04.2015
Rik Thompson, Queensland University of Technology: Epithelial Mesenchymal Plasticity and Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer.

08.04.2015
John D. Haley, Stony Brook School of Medicine New York: Epithelial-Mesenchymal Transition in Cancer Progression and Treatment.

30.04.2015
Lorena Arranz, UiT The Arctic University of Norway: Neuroglial dysregulation of the haematopoietic stem cell niche in myeloid leukaemia.

28.05.2015
Neil C. Henderson, University of Edinburgh: Targeting of pericytes and tissue myofibroblasts during organ fibrogenesis

11.06.2015
Robert S. Kerbel, Sunnybrook Research Institute & University of Toronto: Antiangiogenic therapeutics in oncology: Overview, update, and future directions.

27.08.2015
Roya Navab, Princess Margaret Cancer Center, University Health Network: Integrin α11β1 regulates cancer stromal stiffness and promotes tumorigenicity and metastasis in non-small cell lung cancer

24.09.2015
Bruce Baguley, The University of Auckland: The importance of being... a receptor tyrosine kinase.

15.10.2015
Matthew G. Krebs, University of Manchester: Circulating biomarkers in early phase drug development for lung cancer.

22.10.2015
Eric Sahai, The Francis Crick Institute: The role of CAFs in therapy failure. Intravital imaging reveals how stroma dictates heterogeneous responses to targeted therapy.

26.11.2015
Patrick Schöffski, KU Leuven: Modelling mesenchymal malignancies: development of patient-derived xenografts of soft tissue sarcomas and gastrointestinal stromal tumours and in vivo-drug testing with direct implications for clinical research (bedside to bench and back).

17.12.2015
Jarle Breivik, University of Oslo: Cancer and aging: Facing realities and an uncertain future.

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 CCBIOs seminar series, while at the same time making them stand out. The special seminars have been very well visited with 100 to 140 participants.

Special Seminar on: Tumor plasticity and drug resistance. April 8th, James Lorens invited two excellent speakers to hold a joint CCBIO Special Seminar on the topic of tumor plasticity and drug resistance. The seminar was a success with well above 100 participants and an informal gathering afterwards in order to encourage the participants to deliberate upon the talks and interact with the speakers. Professor Rik Thompson from Queensland University of Technology held the talk 'Epithelial Mesenchymal Plasticity and Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer'. Associate Professor/Director, John D. Haley, Stony Brook School of Medicine New York, SBU Cancer Center and SBU Proteomics Center, contributed with the talk 'Epithelial-Mesenchymal Transition in Cancer Progression and Treatment'.

Special Seminar on: Antiangiogenic therapeutics in oncology: overview, update, and future directions.
Robert Kerbel, a leading expert on angiogenesis and professor in the Department of Medical Biophysics at the University of Toronto, senior scientist at the Sunnybrook Research Institute (Toronto), and a Canada Research Chair in tumor biology and angiogenesis, visited Bergen on June 11th to give a talk at a joint BBB-Seminar and CCBIO Special Seminar. The seminar was chaired by Oleg Tsinkalovsky, Department of Biomedicine.

In his talk, Professor Kerbel described the main types of current antiangiogenic drug based therapies and analyzed possible causes of numerous failures of phase III clinical trials that involved antiangiogenic drugs, and summarized the most promising strategies for improving the efficacy of antiangiogenic treatment. At the end of the talk, he presented some of his own studies focused on the development of improved, more translationally relevant preclinical therapy models of advanced metastatic disease for evaluating antiangiogenic drug mechanisms and efficacy. The lecture was followed by an active and long discussion covering a broad range of questions from specific issues of antiangiogenic therapy and its promising combination with immunotherapy, to the general perspectives of winning the war against cancer. The auditorium was completely packed at this occasion.

As a part of his scientific program in Bergen, Professor Kerbel had meetings with senior as well as junior researchers at CCBIO and beyond with the successful aim of establishing collaborations.

OSLO CANCER CLUSTER

-R&D Network: Cancer biomarkers and targeted therapy

CCBIO and Oslo Cancer Cluster (OCC), of which CCBIO is an active member, held a joint R&D Network meeting in Bergen on October 15th. The meeting focused on cancer biomarkers and targeted therapy and entailed talks from OCC, CCBIO and commercial companies as well as Bergen Teknologioverføring (BTO) and a combined poster and networking tapas dinner in the aula of the BB-building. The meeting was a veritable success with about 140 participants from around Norway and will be continued regularly as an autumn mini-symposium for the years to come.

The scientific highlight of the meeting was undoubtedly the keynote lecture by Dr Matthew Krebs, Institute of Cancer Sciences, University of Manchester. He focused upon 'Circulating biomarkers in early phase drug development for lung cancer'. Krebs took his point of departure in modern medicine's call for novel approaches to tumor monitoring and characterization and the invasive nature of biopsies that still remain the gold standard for tumor profiling. With a basis in his home institution's experience of circulating tumor cells and cell-free DNA in lung cancer, he focused on circulating biomarker's potential for bypassing these limitations as well as their inherent challenges. Dr. Krebs specifically discussed how these assays may be applied in the setting of early phase drug development as predictive, pharmacodynamic and resistance biomarkers and as a research tool to understand more about the biology of disease to guide future drug targets and combinations. He also focused upon how circulating biomarkers are starting to be used in routine clinical practice to guide standard-of-care treatment decisions and selection of patients to early phase clinical trials.

CCBIO Special Seminars and Meetings

Health Priorities of the Future
October 26th 2015, The Norwegian Academy of Science and Letters and CCBIO held a public meeting focused on future health priorities at Litteraturhuset in Bergen. Professor Ole M. Sejersted, Vice Preses at the Academy, introduced the topic followed by short talks by five expert panelists, among them CCBIO's Director Lars A. Akslen. Following the presentations, the audience joined in on what became a lively debate. CCBIO's own Communications Advisor Marion Solheim chaired the meeting.

Transparency about public health priorities: The backdrop for the meeting was the report "Open and just - priorities in the Norwegian healthcare services" submitted by Prioriteringsutvalget, the Norwegian governmental expert group on public health prioritization. In the first talk, the leader of Prioriteringsutvalget, Professor Ole Frithjof Norheim, presented the report's main conclusion stating that health prioritization needs to be systematic, transparent, based on general criteria, effective and anchored in the goal of "as many good life-years as possible for everybody, fairly distributed".

People do care, most of all about fairness: Associate Professor Elisabeth Ivarsflaten is the coordinator of Norsk medborgerpanel, a large-scale survey among Norwegian citizens on attitudes to key issues in Norwegian society and politics. The survey showed that health is a very important issue for people, and that the public is divided on whether the resources used on health are sufficient.

Bertil Tungodden, Professor at NHH and co-director of the Choice Lab, stated that Norwegians are more than anything concerned with justice and fairness, i.e. that people need to feel that the distribution of resources is fair. This also raises questions pertaining to personal responsibility for lifestyle related diseases and injuries.

Fairness and personal freedom: The Secretary General of the Norwegian Cancer Society, Anne Lise Ryel, feels that attention to expensive treatment is taking too much of the prioritization debate. She raised the issue of why people who choose to buy expensive cancer drugs that are not covered by the public system must go to private clinics instead of being treated by his or her own doctor.

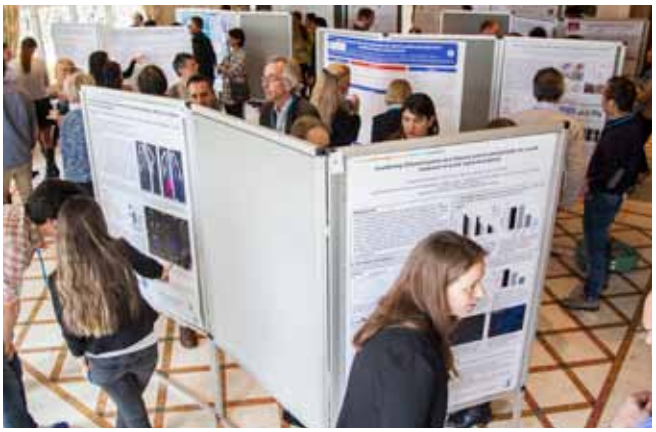
Smart knowledge: CCBIO's Director Lars A. Akslen focused on personalized treatment and prioritization. A researcher today is asked to consider the social role and function of his knowledge before it is produced. There is a new request from society onto science to produce not only knowledge, but smart knowledge that can promote socially robust decision-making. CCBIO's efforts to find biomarkers that can predict which cancer cells that will spread or not, and who might benefit from which treatment, is a direct answer to this challenge. Hence, CCBIO's research results might play an important part in the health priorities of the future. ••

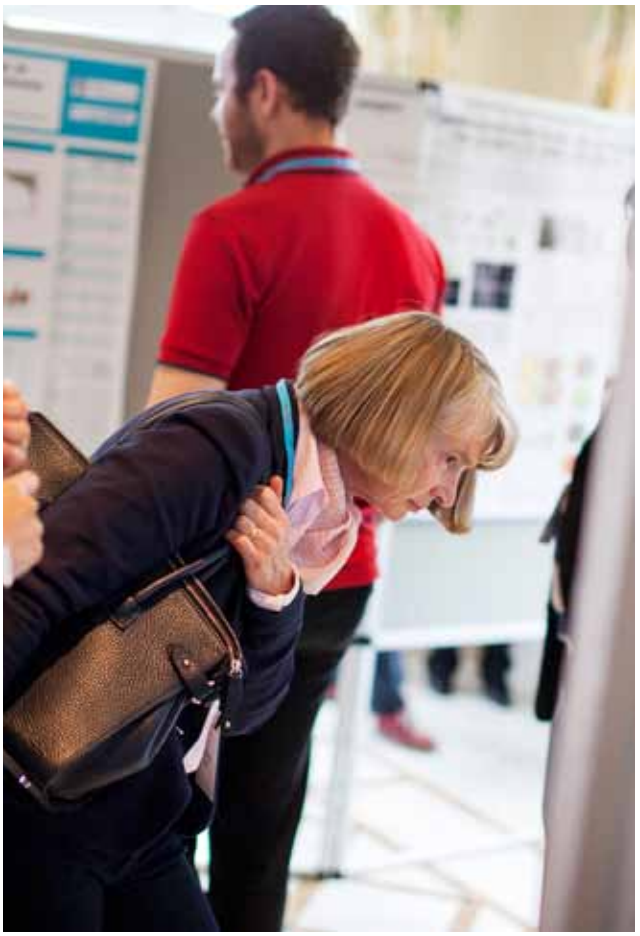
Above: Professor Ole Frithjof Norheim, Leader of Prioriteringsutvalget, Associate Professor Elisabeth Ivarsflaten, Department of Comparative Politics, Professor Lars A. Akslen, Director of CCBIO, Anne Lise Ryel, Secretary General of the Norwegian Cancer Society and Professor Bertil Tungodden, Co-director at the Choice Lab at NHH.

The 3rd Annual Symposium

19th-20th May 2015
at Solstrand Hotel & Bad.

200 participants






CCBIO
4th Symposium
2016
MAY 10-11

Many of the world's top cancer researchers presented the latest in cancer research when the Center for Cancer Biomarkers invited to its annual two-day symposium May 19th-20th 2015. Solstrand Hotel was filled to the rim when about 200 participants spent two days together with cancer research as their main focus. In addition to leading cancer researchers, CCBIO made space for up and coming local researchers as speakers as well as two long poster sessions for the younger researchers to present their work.

The symposium program reflected CCBIO's intention to be excellent in education as well as in research, by facilitating that students and researchers can make new contacts and catch up on the latest research in their field. Also, the symposium setting gave ample opportunity to think out of the box, resulting in new research collaborations and grants being written. ••

Centre for Cancer Biomarkers

3rd CCBIO Symposium 2015

Solstrand, May 19-20, 2015 - Bergen - Norway

SCIENTIFIC PROGRAM

Day 1: Tuesday May 19, 2015

09:00-10:00 Registration and coffee

10:00-10:15 **Lars A. Akslen (Director of CCBIO)**
Introduction to CCBIO Symposium 2015.

Chair: Professor James Lorens
10:15-11:00 **Jean Paul Thiery (Singapore)**
Epithelial-Mesenchymal Transition (EMT)-based Therapeutic Strategies in Cancer

11:00-11:45 **Thomas Brabletz (Erlangen)**
Cellular plasticity in cancer: driving force and therapeutic target

11:45-12:15 **Randolph Watnick (Boston)**
The role of Notch1 and p53 in modulating the cancer stem cell phenotype.

12:15-14:15 LUNCH AND POSTER SESSION I

Chair: Roger Strand
14:15-14.45 **John Cairns (London)**
Challenges in valuing the benefits of new cancer therapies

14:45-15:15 **Ole Frithjof Norheim (Bergen)**
Valuing the benefits of new therapies: recommendations from the third national committee on priority setting in Norway

15:15-15:45 **Roger Strand (Bergen)**
Sociotechnical Imaginaries of Cancer Biomarkers - a Preliminary Analysis

15:45-16:15 COFFEE

Chair: Rolf Reed
16:15-16:45 **Thorarinn Gudjonsson (Reykjavik)**
Cellular processes during breast morpho-genesis and EMT: an approach from 3D culture

16:45-17:15 **James Lorens (Bergen)**
Multipotent mammary stem cell activity requires Axl receptor tyrosine kinase

17:15-17:45 **Karl-Henning Kalland (Bergen)**
Prostate cancer - new therapeutic approaches

19:00 DINNER

Day 2: Wednesday May 20, 2015

Chair: Arne Östman
09:00-09:45 **David Tuveson (New York):**
Pancreatic Cancer Models and Medicine

09:45-10:15 **Arne Östman (Stockholm)**
Cancerassociated fibroblasts and pericytes as sources of prognostic and predictive information

10:15-10:45 **Per Øyvind Enger (Bergen)**
Brain tumor stroma interactions from a translational perspective

10:45-11:15 COFFEE

Chair: Helga Salvesen
11:15-12:00 **Ravi Bhatia (Birmingham, Al)**
Targeting leukemia stem cells in myeloid malignancies

12:00-12:30 **Bjørn Tore Gjertsen (Bergen)**
Biomarkers in individialized cancer trials – hype or future cancer care?

12:30-14:15 LUNCH AND POSTER SESSION II

Chair: Karl-Henning Kalland
14:15-15.00 **Klaus Pantel (Hamburg)**
Liquid biopsy: Implications for cancer therapy

15:00-15:30 **Odd Helge Gilja (Bergen)**
Ultrasound sonoporation applied experimentally and in patients with pancreatic adenocarcinoma

15:30-16.00 **Guttorm Haraldsen (Oslo)**
Interleukin-33 - an important factor in stromal inflammation

16:00-16:30 **Nils Halberg (Bergen)**
A microRNA Regulon that Mediates Breast Cancer Metastasis

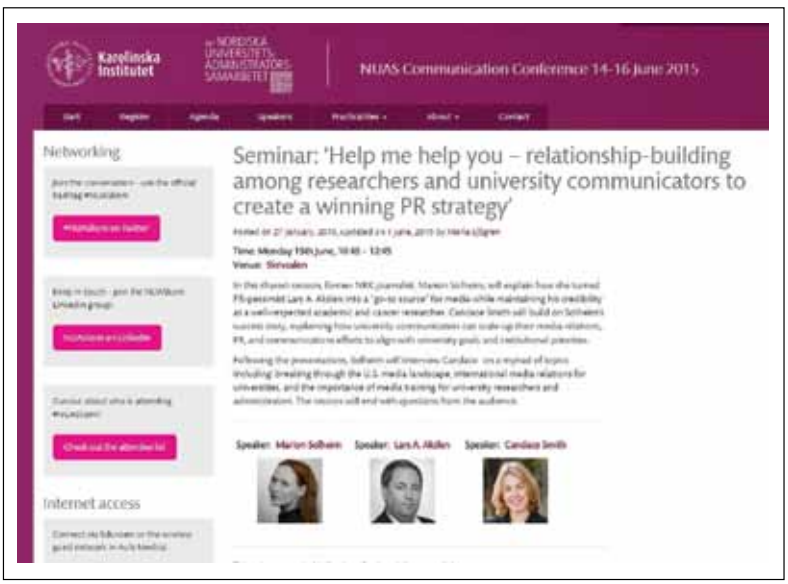
16:30-16:45 **Lars A. Akslen (Bergen)**
Closing remarks

CCBIO AND COMMUNICATION

CCBIO and Communication

CCBIO aims to communicate novel findings to the public in a timely and informative way. In 2015 our research could be viewed, read and listened to in both national mainstream media and publications with more specific audiences.

CCBIO's Director, Lars A. Akslen, and Communications Advisor Marion Solheim were asked to speak at the 2015 NUAS conference (the Nordic Association of University Administrators) about the way they work with the media. The seminar "Help me help you - relationship-building among researchers and university communicators to create a winning PR strategy" went very well.



Also, as a way to get information, findings and facts out to the public, CCBIO and the Norwegian Academy of Science and Letters (Det Norske Videnskaps-Akademi) organized a debate in October, on Litteraturhuset in Bergen. The Health Priorities Debate was open to the public, and the biggest auditorium at Litteraturhuset was filled with people who wanted to hear the experts talk live.

When it comes to media appearances, 2015 was a good year for CCBIO. Here are the stories in which our scientists participated:

04.01.15 – BERGENS TIDENDE
"Gaven til gamlelandet" – Karl-Henning Kalland (http://www.bt.no/nyheter/lokalt/Gaven-til-gamlelandet-3272315.html)

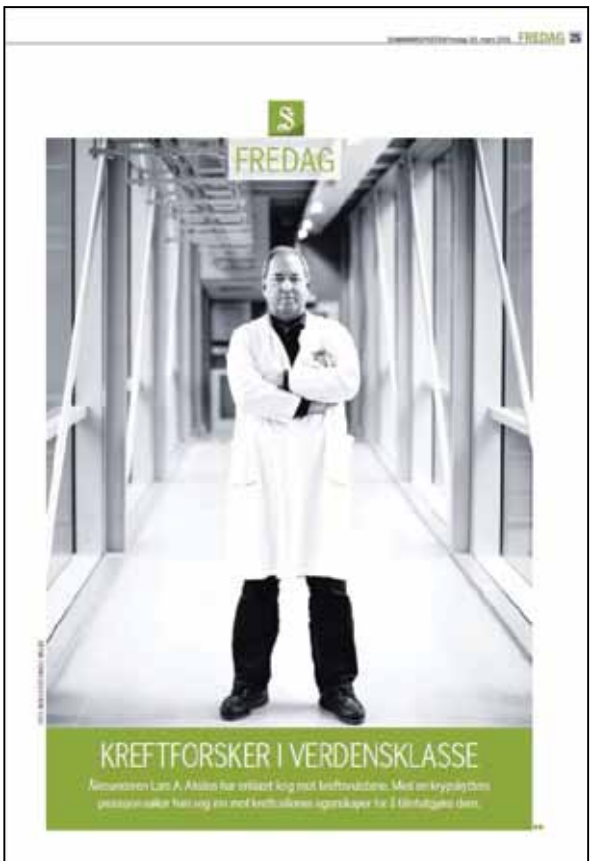
19.01.15 - PÅ HØYDEN
"Samfunnsansvar inn i virksomheten" - Roger Strand

01.02.15 – BERGENS TIDENDE
"Bergensforskere fant ny kreftmedisin"
Jim Lorens (http://www.bt.no/nyheter/lokalt/Bergensforskere-fant-ny-kreftmedisin-2978744.html)

06.02.15 - BERGENS TIDENDE
"Jan Helge Johanessen er pionérpasient"
- Bjørn Tore Gjertsen - James Lorens
(http://www.bt.no/nyheter/lokalt/gjesteredaktor/Jan-Helge-Johanessen-er-pionrpasient-3297460.html)

20.03.15 - SUNNMØRSPOSTEN
"Hver kreftsvulst skal få sin egen behandling - kreftforsker i verdensklasse" - Lars A. Akslen

21.03.15 - NRK LØRDAGSREVYEN
"Det verste var å vite at barna kanskje ikke ville huske meg"
- Lars A. Akslen - Oddbjørn Straume
(http://www.nrk.no/hordaland/_-det-verste-var-a-vite-at-barna-kanskje-ikke-ville-huske-meg-1.12272600)



20.03.15 - SUNNMØRSPOSTEN

26.03.15 - DAGENS MEDISIN -
"Kan stå overfor paradigmeskifte" - Bjørn Tore Gjertsen

26.03.15 - DAGENS MEDISIN
"3,4 millioner for én måneds behandling" - Bjørn Tore Gjertsen

01.04.15 - SCIENCE NORDIC
"Attacking cancer's command center" - Xisong Ke - Karl-Henning Kalland


21.03.15 - NRK LØRDAGSREVYEN

02.04.15 - NORDIC LIFE SCIENCE NEWS
"Chemo Hits Cancer Stem Cells" - Xisong Ke - Karl-Henning Kalland

23.04.15, HELSE VEST
"Vekas innovasjon: Biomarkør finn kreft" - Helga Salvesen - Lars A. Akslen

05.05.15 - AFTENPOSTEN
"Kreft: Det evige såret" - Ida W. Sørensen - Donald Gullberg
(http://www.aftenposten.no/viten/Kreft-Det-evige-saret-8006121.html)

18.05.15 – BERGENS TIDENDE
"Her blir kreftsvulsten fryst" – Karl Henning Kalland - Bjørn Tore Gjertsen
(http://www.bt.no/nyheter/lokalt/Her-blir-kreftsvulsten-fryst-3361607.html)

04.06.15 - TV2
"Revolusjonerende kreftmedisin - for dyr for Norge?"
- Oddbjørn Straume

CCBIO and communication

05.05.15 - AFTENPOSTEN

05.06.15 - HELSE VEST
"Vekas innovasjon: Frys ned kreften" - Karl-Henning Kalland

09.06.15 - TV2
"Seks kreftsyke nordmenn har fått den nye «superbehandlingen»" - Oddbjørn Straume (http://www.tv2.no/a/7023672)

15.06.15 - DAGENS MEDISIN
"Fryser ned prostatakreften"- Karl-Henning Kalland (http://www.dagensmedisin.no/artikler/2015/06/15/fryser-ned-prostatakreften/)

25.07.15 - BERGENSAVISEN
"Ingrids siste håp" - Oddbjørn Straume

04.08.15 - DAGENS MEDISIN
"Røyking kan bidra til å aktivere universelt "kreftprogram" - Helga Salvesen (http://www.dagensmedisin.no/artikler/2015/08/04/-royking-kan-bidra-til-a-aktivere-universelt-kreftprogram/)

05.08.15 - VG
"Urinprøver kan avsløre bukspyttkjertelkreft" - Lars A. Akslen (http://www.vg.no/forbruker/helse/vitenskap-og-forskning/urinprover-kan-avsloere-bukspyttkjertelkreft/a/23499456/)

05.08.15 - ABC NYHETER
"Forskere har funnet flere gener som øker risikoen for føflekkreft" - Lars A. Akslen

05.08.15 - FORSKNING.NO
"Oppdaget nye gener for føflekkreft" - Lars Akslen

07.08.15 - EKSTRA
"Fant nye gener for føflekkreft" - Lars A. Akslen

11.08.15 - VG
"Ny studie: Oppdaget nye gener for føflekkreft" - Lars A. Akslen

11.08.15 - AFTENPOSTEN
"Bør hver kreftpasient bli et eget forskningsprosjekt?" - Bjørn Tore Gjertsen (http://www.aftenposten.no/meninger/kronikker/Kronikk-Bor-hver-kreftpasient-bli-et-eget-forskningsprosjekt-8121171.html)

13.08.15 - SCIENCENORDIC
"New skin cancer genes located" - Lars A. Akslen

03.09.15 – PÅ HØYDEN
"UiB-selskap planlegger for børs" – Jim Lorens

05.08.15 - FORSKNING.NO

23.09.15 - THE NORWEGIAN CANCER SOCIETY
"Forsker på celleprøver for å forebygge gynekologisk kreft"
- Helga Salvesen

01.10.15 - UIB NEWS
"Internasjonale kreftspesialister underviser ferske forskere" and in English - "Educating a new generation of cancer researchers" - Lars A. Akslen
(http://www.uib.no/en/news/92006/educating-new-generation-cancer-researchers)

07.10.15 - INTRAFISH.NO
"Nye muligheter for behandling av blodkreft"
- Bjørn Tore Gjertsen

19.10.15 - VG
"Lette etter malariavaksine - kan ha funnet nytt kreftvåpen"
- Oddbjørn Straume

19.10.15 - PÅ HØYDEN
"Vil senda 28 SFF-søknader" - Lars A. Akslen
(http://pahoyden.no/2015/10/vil-senda-28-sff-soknader)

19.10.15 - HEGNAR ONLINE
"Fant mulig kreftvåpen ved en tilfeldighet" - Oddbjørn Straume
(http://www.hegnar.no/Nyheter/Politikk/2015/10/Fant-mulig-kreft-vaapen-ved-en-tilfeldighet)

22.10.15 - DAGENS MEDISIN
"Planlegger økt samarbeid innen akutt leukemi"
- Bjørn Tore Gjertsen

22.10.15 - DAGENS MEDISIN
"Skaper grunnlag for å søke EU-midler", Lars A. Akslen - Arne Östman

22.10.15 - DAGENS MEDISIN
"Knytter elastose til bedre prognose" - Lars A. Akslen
(http://www.dagensmedisin.no/artikler/2015/11/03/knytter-elastose--til-bedre-prognose/)

26.10.15 - BERGENS TIDENDE
"Vil ha kjøpemedisin på sykehusene" - Lars A. Akslen
(http://www.bt.no/nyheter/lokalt/Vil-ha-kjopemedisin-pa-sykehusene-3467717.html)


Vil ha kjøpemedisin på sykehusene

26.10.15 - FORSKNING.NO

27.10.15 - UIB NEWS
"35 nye millioner til kreftforskning" - Lars A. Akslen - Helga Salvesen - Bjørn Tore Gjertsen

28.10.15 - HELSE BERGEN
"Prisar til kreftforskning og innovasjon" - Helga Salvesen - James Lorens

30.10.15 – BERGENS TIDENDE
"En pris til alle kvinnene" – Helga Salvesen – Jim Lorens
(http://www.bt.no/nyheter/lokalt/--En-pris-til-alle-kvinnene-3469903.html)

26.11.15 - SCIENCENORDIC
"Your walk and odour betray you" - Roger Strand
(http://sciencenordic.com/your-walk-and-odour-betray-you)

01.12.15 - TIDSKRIFT FOR DEN NORSKE LEGEFORENING
"Jeg kunne blitt astronom" - Ying Chen
(http://tidsskriftet.no/article/3421899/)

29.12.15 - SUNNMØRSPOSTEN
Ålesunder vil forstå kreftcellene - Lars A. Akslen

The CCBIO Administration

In the 2014 report, we presented the younger researchers involved in CCBIO. This year we move on to presenting CCBIO's administrative core staff, i.e. staff being directly involved in CCBIO under the leader team's aegis. At the same time, we wish to acknowledge the administrative services provided by other admin-staff from UiB and Helse Bergen, ranging from secretaries to admin- and section leaders.

LØKEN, GEIR OLAV:

Born 1978, holds a Cand. Polit. degree from the UiB, also published as a book in Germany, as well as subjects from the Norwegian School of Economics (NHH). He is currently CCBIO's administrative leader and as part of the CCBIO management team, he has the overall responsibility for the administrative aspects of CCBIO's activities across its six UiB departments and CCBIO's interaction with collaborators nationally and abroad. Geir Olav has previously been research coordinator at the Department of Biomedicine's core facilities, project leader at the Faculty of Medicine and Dentistry and advisor at the Faculty of Medicine at NTNU, and also works part time as a sailing instructor.

HØGÅS, MILDRID BØNES:

Born 1962, holds a degree in business administration from the UiO, and education in teaching. She is currently employed as a financial officer at the Department of Clinical Medicine (K1) and is CCBIO's financial coordinator. Mildrid coordinates and follows up on CCBIO's overall economy across all involved departments and, together with Håvard Hoel Aass, she is responsible for CCBIO's further project portfolio at K1. Mildrid has been a UiB employee since 1997 as financial officer at department and faculty levels. Before that she worked as a financial officer at UiO as well as office manager, financial manager and teacher in economics at upper secondary schools.

AASS, HÅVARD HOEL:

Born 1983, holds a Master degree in finance, business analysis and performance management from the NHH. He is currently financial coordinator at the Department of Clinical Medicine (K1) and as part of CCBIO's financial team he handles CCBIO's project portfolio at K1 together with Mildrid Bønes Høgås. Håvard started at UiB in 2012 as financial officer at the Gade Institute.

GOTAAS, JANNE:

Born 1967, holds a Cand. Mag. in economy and law from UiB and NHH. She is currently controller at the Department of Biomedicine and within a CCBIO context she is part of the financial team as well as responsible for following up some of the economy of CCBIO's project portfolio at the department. Janne has been a UiB employee at the Department of Biomedicine since 2008. She has previously long experience from NAV as a controller and with calculation of pensions, and from Bergen municipality where she was leader of a unit within the field of health and social services.

HOVE, ELISABETH:

Born 1956, holds a degree in business administration from NHH. She is currently a higher executive officer at the Department of Biomedicine, and within the CCBIO context she is part of the financial team and responsible for following up the economy of CCBIO's project portfolio at the Department of Biomedicine. She has been employed at UiB since 2002 and has previously worked as a financial coordinator in a small entrepreneur company in Bergen and as a financial officer for Kongsberg Våpenfabrikk.

DYRKOLBOTN, KJETIL:

Born 1978, has a Master of Commerce/Business Studies from UiA from 2003. He has been financial officer at the Department of Clinical Science (K2) since 2011 and within the CCBIO context he is part of the financial team and handles the financial coordination of CCBIO's project portfolio at K2. Kjetil has previous experience as a bank corporate adviser and within auditing.

WITSØ, SOLVEIG LUND:

Born 1980, did her PhD at UiB in 2014 on cell– and molecular biology. She is currently a PhD coordinator at the Department of Clinical Medicine (K1) and is the administrative coordinator for the CCBIO Research School for Cancer Studies. Previously she has been working with PhD admission at the faculty level.

SOLHEIM, MARION:

Born 1978, holds a double Bachelor in journalism and communication and international studies from Iowa State University, USA. She is currently a media advisor at the Faculty of Medicine and Dentistry, UiB, and is CCBIO's communications advisor, being responsible for targeted outreach and dissemination, which includes media coaching, finding and elaborating news stories, dealing with journalists and other outwardly directed communication- and media related issues. Previously, Marion was a news and investigative tv- and radio journalist in NRK for more than a decade, working mostly with health care systems and crime journalism.

VIDHAMMER, ELI SYNNØVE:

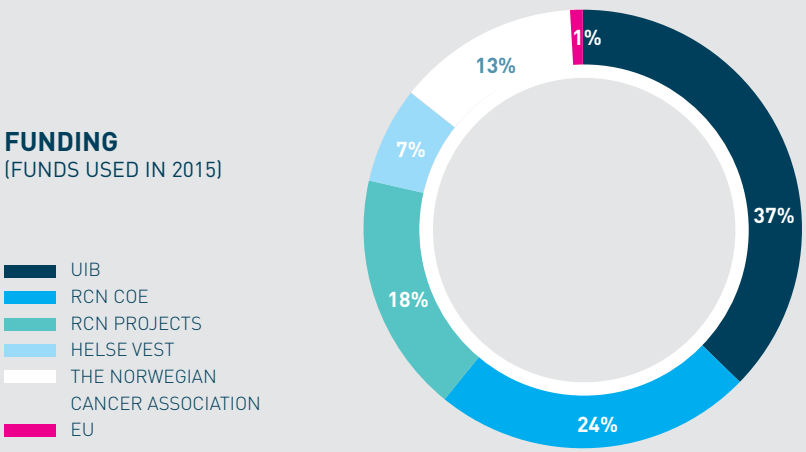
Born 1971, holds a Bachelor in languages and literature science from the UiB. She is currently CCBIO's web page- and newsletter editor, and also assists in other information related tasks (posters, news stories). Her expertise is particularly in design, photo and text editing. Eli has been a UiB employee since 2006, first in the Lab Animal Facility's administration, then at the Department of Clinical Medicine (K1), establishing the web pages and the K1-nytt newsletter. She has previously long experience from Fjord Line's marketing department as product manager.

FACTS AND FIGURES 2015

32

The 32 mass media stories in 2015 shows that CCBIO emphasizes public dissemination of its research results.

FUNDING
(FUNDS USED IN 2015)



TOTAL: 57,4 MILL NOK

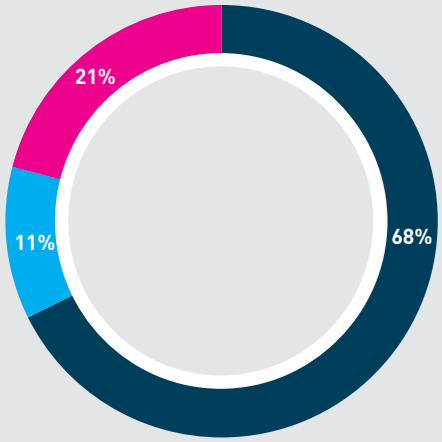
Total funds used in 2015 were 57.4 MNOK, of which 60% is the RCN CoE funding and own funding from the UiB. The total of 22.5 MNOK in external funding is over twice the budgeted amount and illustrates a high success rate with public and private funding agencies. CCBIO's research effort is resource intensive and more funding is needed. We expect to see a gradual 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.

PERFORMANCE INDICATORS

CCBIO's scientific production is high and set to rise as more PhDs and postdocs conclude their projects. The influx of external funding is good and increasing. Numbers on external funding are funds consumed during the respective years.

	2013	2014	2015	TOTAL
PUBLICATIONS	76	71	77	224
COMPLETED PHDS	5	6	3	14
EXTERNAL FUNDING MNOK	7.2	21.9	22.5	51.6
MEDIA APPEARENCES	39	11	32	82

INTERNATIONALIZATION
(STAFF COUNTRY OF ORIGIN)



TOTAL: 57,4 MILL NOK

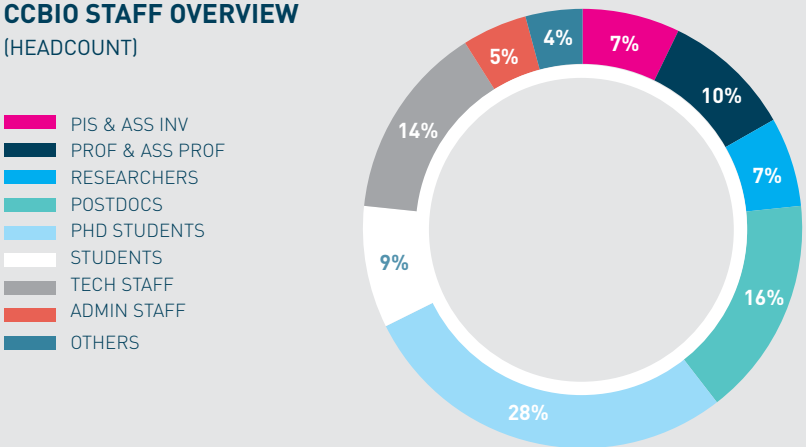
CCBIO's inherently international nature is illustrated through the distribution of its staff. Presently, 32% of CCBIO's staff is of non-Norwegian origin, while 45 % of CCBIO's PhDs and 56 % of its postdocs originate from outside of Norway and the same holds true for about 20% of CCBIOs PIs. CCBIO aims to continue recruiting among the best candidates worldwide and expects the amount of non-Norwegians to increase, also among senior scientific staff.

GENDER DISTRIBUTION
(HEADCOUNT)

TOTAL: 167 PERSONS

Of the 167 persons involved in CCBIO, 70 % 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 almost exactly balanced with 48% women and 52% men. For the period 2013-2015, the CCBIO's scientific management team consisted of one male and one female whereas the PI group was male dominated with a bit less than 80% males. In CCBIO's effort towards excellent research, it is crucial that all available talent is used to the fullest. Hence, one of CCBIO's strategic recruitment efforts is to attain a more balanced gender distribution in its top tire over time, e.g. by means of targeted recruitment of female associate investigators.

CCBIO STAFF OVERVIEW
(HEADCOUNT)



TOTAL: 167 PERSONS

The breakdown of CCBIO's headcount shows a balance between senior and younger researchers as well as "researchers to be" in the form of PhD students and master students. The researchers are supported by technical and administrative staff. CCBIO is in the process of augmenting its group of principal investigators (PIs) by recruiting further associate investigators, especially female junior investigators, so as to cater for CCBIO's continuation after 2023 as well as an improved gender balance in the CCBIO PI group.


CCBIO
Norwegian Centre of Excellence
The Research Council of Norway
5th ANNUAL CCBIO SYMPOSIUM
2015
APRIL 19-20
Solstrand (Bergen - Norway)

CCBIO 2015
LIST OF PUBLICATIONS

CCBIO - List of Publications

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

Jim HS, Lin HY, Tyrer JP; ... Pharoah PD, Sellers TA, Phelan CM. Common Genetic Variation in Circadian Rhythm Genes and Risk of Epithelial Ovarian Cancer (EOC). *J Genet Genome Res.* 2015;2(2) (Salvesen group).

Arteaga-Marrero N, Brekke Rygh C, Mainou-Gomez JF, Adamsen TC, Lutay N, Reed RK, Olsen DR. Radiation treatment monitoring using multimodal functional imaging: PET/CT ((18)F-Fluoromisonidazole & (18)F-Fluorocholine) and DCE-US. *J Transl Med*. 2015 Dec 18;13:383.

Tveitarås MK, Skogstrand T, Leh S, Helle F, Iversen BM, Chatziantoniou C, Reed RK, Hultström M. Matrix Metalloproteinase-2 Knockout and Heterozygote Mice Are Protected from Hydronephrosis and Kidney Fibrosis after Unilateral Ureteral Obstruction. *PLoS One*. 2015 Dec 16;10(12).

Bartlett TE, Jones A, Goode EL, Fridley BL, Cunningham JM, Berns EM, Wik E, Salvesen HB, Davidson B, Trope CG, Lambrechts S, Vergote I, Widschwendter M. Intra-Gene DNA Methylation Variability Is a Clinically Independent Prognostic Marker in Women's Cancers. *PLoS One*. 2015 Dec 2;10(12)

Cheng TH, Thompson D, Painter J; ... Houlston R, Spurdle A, Tomlinson I. Meta-analysis of genome-wide association studies identifies common susceptibility polymorphisms for colorectal and endometrial cancer near SH2B3 and TSHZ1. *Sci Rep.* 2015 Dec 1;5:17369 (Salvesen group).

Hodneland Nilsson LI, Nitschke Pettersen IK, Nikolaisen J, Micklem D, Avsnes Dale H, Vatne Røsland G, Lorens J, Tronstad KJ. A new live-cell reporter strategy to simultaneously monitor mitochondrial biogenesis and morphology. *Sci Rep*. 2015 Nov 24;5:17217.

Meeks HD, Song H, Michailidou K; ... Couch FJ, Spurdle AB, Goldgar DE. BRCA2 Polymorphic Stop Codon K3326X and the Risk of Breast, Prostate, and Ovarian Cancers.. *J Natl Cancer Inst*. 2015 Nov 19;108(2) (Salvesen group).

Bivol LM, Iversen BM, Hultström M, Wallace PW, Reed RK, Wiig H, Tenstad O. Unilateral renal ischemia in rats induces a rapid secretion of inflammatory markers to renal lymph and increased peritubular capillary permeability. *J Physiol.* 2015 Nov 20. (Epub ahead of print)

Hofvind S, Holen Å, Román M, Sebuødegård S, Puig-Vives M, Akslen L. Mode of detection: an independent prognostic factor for women with breast cancer. *J Med Screen*. 2015 Nov 17. (Epub ahead of print)

Thompson DJ, O'Mara TA, Glubb DM; ... Dowsett M, Easton DF, Spurdle AB. CYP19A1 fine-mapping and Mendelian randomization: estradiol is causal for endometrial cancer. *Endocr Relat Cancer*. 2016 Feb;23(2):77-91 (Salvesen group).

Multhaupt HA, Leitinger B, Gullberg D, Couchman JR. Extracellular matrix component signaling in cancer. *Adv Drug Deliv Rev*. 2016 Feb 1;97:28-40.

Teschendorff AE, Lee SH, Jones A, Fiegl H, Kalwa M, Wagner W, Chindera K, Evans I, Dubeau L, Orjalo A, Horlings HM, Niederreiter L, Kaser A, Yang W, Goode EL, Fridley BL, Jenner RG, Berns EM, Wik E, Salvesen HB, Wisman GB, van der Zee AG, Davidson B, Trope CG, Lambrechts S, Vergote I, Calvert H, Jacobs IJ, Widschwendter M. HOTAIR and its surrogate DNA methylation signature indicate carboplatin resistance in ovarian cancer. *Genome Med*. 2015 Oct 24;7(1):108.

Bredholt G, Mannelqvist M, Stefansson IM, Birkeland E, Bø TH, Øyan AM, Trovik J, Kalland KH, Jonassen I, Salvesen HB, Wik E, Akslen LA. Tumor necrosis is an important hallmark of aggressive endometrial cancer and associates with hypoxia, angiogenesis and inflammation responses. *Oncotarget.* 2015 Nov 24;6(37):39676-91.

Moshina N, Ursin G, Hoff SR, Akslen LA, Roman M, Sebuødegård S, Hofvind S. Mammographic density and histopathologic characteristics of screen-detected tumors in the Norwegian Breast Cancer Screening Program. *Acta Radiol Open*. 2015 Sep 17;4(9).

Ocal O, Pashkov V, Kollipara RK, Zolghadri Y, Cruz VH, Hale MA, Heath BR, Artyukhin AB, Christie AL, Tsoulfas P, Lorens JB, Swift GH, Brekken RA, Wilkie TM. A rapid in vivo screen for pancreatic ductal adenocarcinoma therapeutics. *Dis Model Mech*. 2015 Oct 1;8(10):1201-11.

Lawrenson K, Iversen ES, Tyrer J; ... Pharoah PD, Gayther SA, Schildkraut JM. Common variants at the CHEK2 gene locus and risk of epithelial ovarian cancer. *Carcinogenesis*. 2015 Nov;36(11):1341-53 (Salvesen group).

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Principal Investigators and Invited Speakers at the 3rd CCBIO Annual Symposium May 19-20 2015.

From left to right: Roger Strand, James B. Lorens, David Tuveson, Nils Halberg, Bjørn Tore Gjertsen, Bruce R. Zetter, Helga B. Salvesen, Arne Östman, Randolph Watnick, Donald Gullberg, Inge Jonassen, Ravi Bhatia, Lars A. Akslen, Karl-Henning Kalland, Thorarinn Gudjonsson, Rolf K. Reed, John Cairns, Per Øyvind Enger, Jean Paul Thiery, Klaus Pantel, Anne Christine Johannessen and Thomas Brabletz.

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