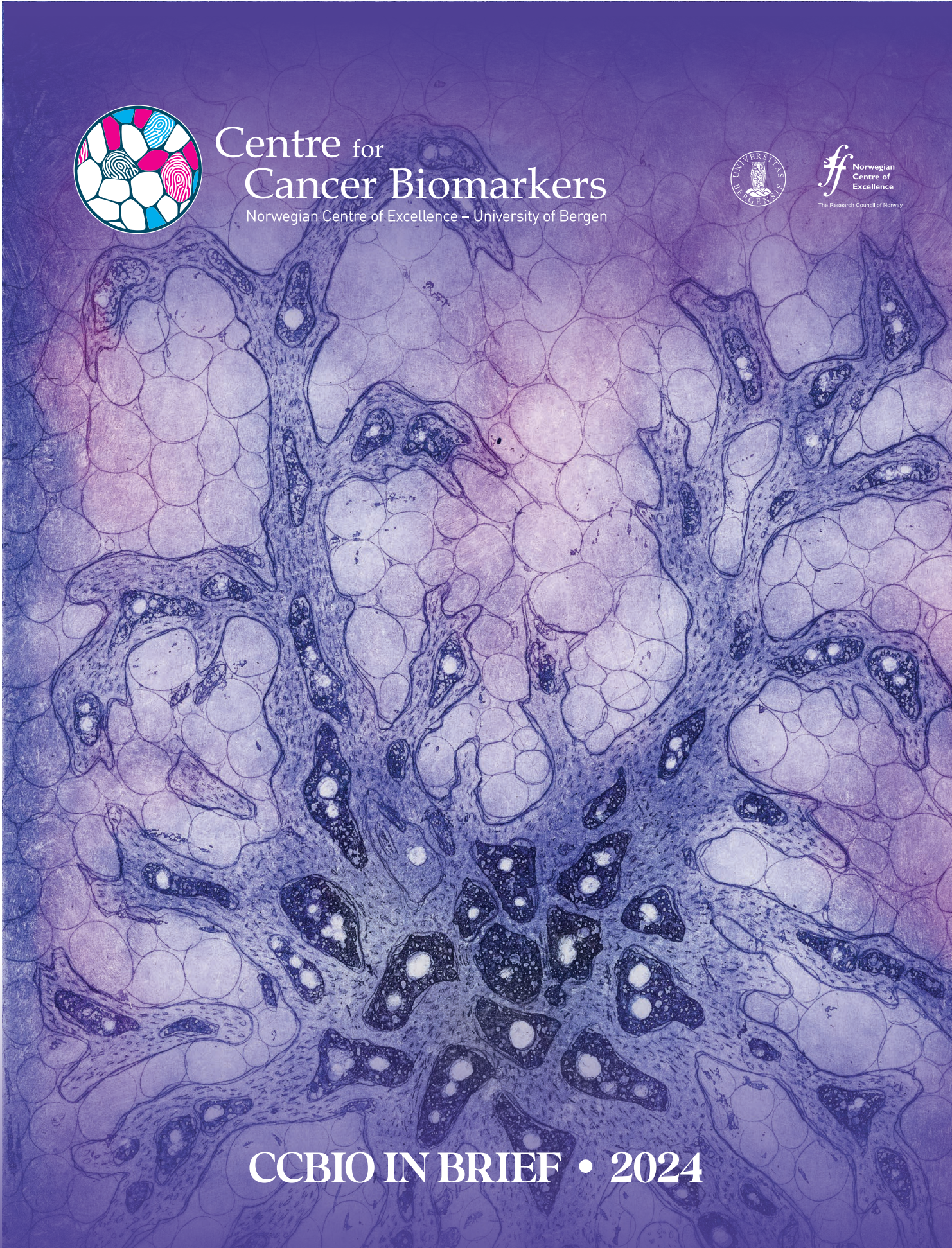
Centre for Cancer Biomarkers

Norwegian Centre of Excellence – University of Bergen

Norwegian Centre of Excellence

The Research Council of Norway



CCBIO IN BRIEF • 2024

Lars A. Akslen, Geir Olav Løken and Eli Synnøve Vīdhammer (editors)

Graphical design: Gaute Hatlem

CCBIO in brief 2024

A brief history of Centre for Cancer Biomarkers CCBIO 2013–2024 including activites 2023–2024

This final report has a main focus on activities during the 2013–2024 period, reflected in several texts, comments, pictures and graphics

The activities during 2023 and 2024 (first half) are included since these are not covered in previous annual reports

Centre for Cancer Biomarkers CCBIO
Norwegian Centre of Excellence
University of Bergen

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highlights



2013
2024

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overall review and activities during 2023–2024

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EXCLUSIVE COVER ART: The picture is a copper etching, 'This crab is about to lose its grip', made by Harald Kryvi. Kryvi is professor emeritus in zoological anatomy at UiB, and also works as an artist (see kryvi.no).




PART I
introduction
and highlights




director's
final cut
– a condensed portrait
of CCBIO



Tempus fugit – time has certainly been running throughout the years since CCBIO was established in 2013. At that point, we had already for a couple of years been carving out the basic concept and designing the structure of our proposal for a Centre of Excellence and its program. Some retrospective and prospective reflections are in place, and the contents of this report represent some of our history.

Biomedical research presents so many challenges at different levels, and the cancer landscape is remarkably complex. Basic studies are going deeper and deeper to figure out how it all works. It is tempting to quote the investigative journalist Carl Bernstein — it is all about "*the search for the best obtainable version of the truth*". The knowledge is increasing, like an "*expanding universe*", and a key challenge is to see the important patterns emerging. Then comes the application of knowledge — how to use the most significant pieces of evidence, for the patients and for the society. All our skill sets are needed, analytical capacity as well as inspirational creativity, and continuous hard work. *The future is shaped by participation*.

The *concept of excellence* is also challenging and constantly changing. It is important to think outside of the box and be willing to go sideways, and to use *elastic thinking*. Excellence is about strong focus as well as continuous reinvention. Sometimes my students are disappointed when their data are the opposite of what they expected, and I have to tell them that such findings are probably the most important, and fun. It is relevant to cite the famous Danish physicist Niels Bohr: "*Your theory is crazy, but it's not crazy enough to be true*". Thus, we should continue to ask stupid questions.

The *application* for a Centre of Excellence was based on many discussions and reiterations when working on drafts. The concept of novel biomarkers to help directing cancer therapy was on the rise and represented a theme that could carry essential subtopics, from basic research to clinical applications and societal perspectives — and the initiative was pathology-based. First, since many of the investigators had a deep interest in the tumor microenvironment and this was clearly an understudied area, it became a key topic. Second, we wanted to take a complementary approach to mainstream genomic studies at the time and focus more on proteomics, enabling projects on functional biomarkers, and extending into the fascinating microcosmos revealed by mass cytometry and single-cell spatial analytics of cancer landscapes. Third, the setup could not have been complete without including studies of societal perspectives (ethics, economics, philosophy) and the overarching importance of *self-reflection*. Lastly, the significance of education, communication, and career promotion was perceived as essential already from the beginning.

When the "*eagle landed*" and the grant was approved, the idea was to continue our studies of excellent translational cancer research with improved coherence and collaboration. At the same time, we aimed to establish frameworks for science-promoting and career-stimulating activities, like monthly seminars, junior scientist symposia, annual symposia, the Research School for Cancer Studies, and the Masterclass program, to mention some. We have focused on individual projects and on career promotion for the NGS group – *the Next Generation of Students and faculty*.

In 1889, the British surgeon Stephen Paget reported that metastases from breast cancer occurred in non-random patterns, and he coined the famous concept of "*seed and soil*".



Later, this has been applied in studies of how tumor cells interact with the complex tumor microenvironment (TME), locally and in distant tissues. As a metaphor, the "seed and soil" principle might be applied to our understanding of scientific communities and communication. Seeds would be parallel to ideas and intellectual input, and the soil would indicate the importance of permissive conditions within and among research groups. Also, this is about creating a fertile soil for young students. If successful, ideas and output would "metastasize" to distant places and lead to expanding knowledge at new sites. Sometimes, the spread of knowledge is followed by a phase of dormancy. The dormant knowledge might then be reactivated and reinforced later on, due to quite unpredictable influences.

What is then the *legacy of CCBIO*? Which lessons have we learned? Around 1000 papers have been reported, 105 PhD theses, and so many other outputs, like meetings and courses. In our own opinion, we have continued to practice and learn about excellence in science, organization, education, communication and collaboration, as key parts of the CCBIO signature. We have strived to represent a cutting-edge and sustainable research environment, and we have constantly been trying to exceed or own standards and renew our activities. I hope that the legacy of CCBIO will continue to unfold.

At this point, CCBIO has transitioned to the CCBIO2.0 phase and continues its efforts. Our research portfolio will be even more focused, with the aim to translate some of our findings to active clinical use. This goal also includes a stronger focus on innovation.

Some of the *key elements* in research are curiosity, passion, critical thinking, hard work — and *endurance*. Organization of knowledge is a challenge, and the role of artificial intelligence in some of these processes is emerging. Still, the value of creativity is a crucial part of science and cannot be replaced by computer algorithms. For scientists, seeking inspiration from completely different fields should be valued — as should mutual motivation in research teams, and centers.

So many people have contributed to the CCBIO journey. The administrative leader, our economy coordinator and communications officer: CCBIO would not have been the same without you! Our international faculty, and the scientific advisory board, have been tremendously important. For me and CCBIO, my friends and network at the Folkman lab and Vascular Biology Program at Boston Children's Hospital and Harvard Medical School have supported us all the way through.

To all of you in the CCBIO family — thank you!

And most important — *sempre avanti!*



Lars A. Akslen, MD, PhD
Director of CCBIO

Professor of Tumor Pathology
Senior Consultant, Surgical Pathology

CCBIO — capturing cancer complexities and clinical challenges

vision and research areas

CCBIO aims to discover, validate and translate cancer biomarkers to improve our understanding of tumor mechanisms, promote accurate diagnosis and stratification of cancer patients, and inform precise, cost-effective and responsible treatment of cancer.

CCBIO is especially focusing on the tumor microenvironment (TME) in primary and metastatic cancers, and how tissue context can instruct aggressive tumor traits and predict cancer behavior and prognosis.

The center is studying how crosstalk between tumor cells and TME niches reflects functional cancer complexity and heterogeneity at various levels.

CCBIO concentrates on the following integrated and overlapping programs:

1. **Mechanisms of Tumor-Microenvironment Interactions (*Basic Studies*)**
2. **Discovery and Validation of Cancer Biomarkers (*Biomarker Mapping*)**
3. **Clinical Applications and Early Trials (*Clinical Studies*)**
4. **Ethics, Economics and Priorities (*Societal Studies*)**

Biomedical projects are integrated with ethics and economics research, focusing on how to fund and prioritize expensive cancer diagnostics and treatment in the era of expanding and costly personalized medicine. Our International Faculty, as well as international and national collaboration partners, have been recruited to expand these programs and support CCBIO's policy development. ••



organization of the center

CCBIO is organized across seven departments and four faculties at the University of Bergen. Its main activities, with PIs, AIs and most of the other staff and equipment, are located at the Faculty of Medicine's Department of Clinical Medicine (CCBIO's host department), Department of Clinical Science, and Department of Biomedicine. CCBIO also has activity and staff at the Centre for the Study of the Sciences and the Humanities, the Departments of Global Public Health and Primary Care, Economics, and Informatics, as well as at the London School of Hygiene and Tropical Medicine. Haukeland University Hospital is an important collaborator with contributions towards CCBIO both in terms of staff, facilities, such as the Clinical Trials Unit, advanced equipment, and available biobanks.

Research management
In terms of science management, CCBIO is organized in four integrated research programs with associated teams (basic studies, biomarker studies, clinical studies, and societal studies), all supported by bioinformatics resources. Lab space and advanced core facilities are available for CCBIO, as is the Clinical Trials Unit at Haukeland University Hospital. The investigators meet monthly to discuss scientific and administrative issues and update each other on development and progress, and they also gather for a lunch-to-lunch strategy seminar bi-annually. The monthly meetings and the bi-annual strategy seminars are important platforms for communication and for the increasing collaboration and consolidation within CCBIO.

Management group
In 2023–24, CCBIO was managed by the director, Lars A. Akslen, the co-director Line Bjørge, and the administrative leader, Geir Olav Løken. The management was advised and assisted by the web- and newsletter editor (Eli S. Vidhammer), an economy coordinator (Mildrid B. Høgås), a PhD coordinator (Kjetil Harkestad), finance officers, the faculty communications officers and other administrative staff allocated to CCBIO in parts of their positions. CCBIO's head office (the "CCBIO-HQ") is located on the second floor of Haukeland University Hospital's main building.

Integration with the host institution and administrative support
In terms of administrative support, CCBIO aims to use its funds as efficiently as possible towards its research aims, while also ensuring excellent administrative services for its researchers and a good climate for collaboration with its departmental and institutional partners. Consequently, CCBIO is organized as a matrix structure to retain full control over resources while the day-to-day administration is delegated to the involved departments and administrative support units.

As a main principle, funds and positions are located at the respective department where the research and teaching activities take place. This enables researchers to interact with their familiar support staff, thereby minimizing resources used on day-to-day administration. In addition, it reduces CCBIO's vulnerability and creates common interests between CCBIO and its departments. This model has proven successful due to its efficiency and robustness and has ensured excellent collaborative relations. During its continuation phase, CCBIO aims to remain organized in much the same manner. ••



PRECLINICAL MODELS
Animals and cell models
MIC - PROBE - FLOW
Animal imaging

BIOMARKERS
Biobanks - Registries
Immunohistochemistry
Imaging mass cytometry
Proteomics - Bioinformatics

CLINICAL STUDIES
Infrastructure and logistics
Clinical Trials Unit HUH
Multicenter studies

comments on scientific activities

In the following, some reflections on how we perceive our scientific activities over the years are presented, in the context of contemporary cancer research. Science is in many ways a moving target, since the landscape of knowledge and know-how is constantly changing, and the pace is increasing. Thus, it is clearly expected that there will be some differences between the plans outlined in our CCBIO application, and what actually happened. Still, most of our plans have been carried out.

1. Initial considerations

When we started to draft the CoE application in 2011, it was clear to us that we wanted to go "sideways" and not only follow the "mainstream" programs. First, in biological terms, the *tumor microenvironment (TME)* had already for years been a field of interest for several of the PIs and was readily perceived as "common ground". Other PIs had significant interest in genomic studies in various tumors, but this was not considered to be contradictory but rather complementary, as is often the case in complex integrated studies with several types of "omics data" being combined. In terms of application strategy, we felt a need to distance our position from contemporary "massive sequencing" and genomic studies. We phrased this clearly in the application, and this was well aligned with our research interests and ongoing activities.

First, we used the term *contextual cancer codes* to highlight our view that the tumor microenvironment, or the *cancer cell context*, contained vitally important information to understand the complex dynamic interactions in solid and possibly also liquid cancers. Thus, the TME is not a passive bystander but rather an active and sometimes independent "driver" of malignancy development and progression. Co-dependency between epithelial and stromal compartments does not always implicate parallel co-evolution.

We considered TME research as significantly under-represented at the time and promoted this as a main area for our studies, and necessary to develop a deeper understanding of malignant tumors as *complex ecosystems*. This concept has been followed by several PIs and has resulted in novel information on TME biology, complexity, and stratification potential.

As for the more translational and clinical parts of the CCBIO concept, we stated that *biomarker studies* represented a main goal for the center. In other words, *biomarkers of the tumor microenvironment* was regarded as a suitable although not exclusive delineation of our interests. In contemporary medical oncology, biomarkers were considered to be significantly under-studied, in contrast to the "gold standard" of *companion biomarkers*, stating that "every drug or treatment should have their own biomarker". Subsequently, two books were also produced by CCBIO on this timely subject, both published by Springer.

Second, we stated that a primary focus was to be on the *protein (proteomics) level*, rather than on genes and genomic information, including epigenetics, as the singular solution. However, it should be stated, as mentioned above, that we strongly believe in "integrated science" and even systems biology perspectives in the studies of cancers as *complex organisms*. Further, we used the term *functional biomarkers* and their potentially increased predictive value with respect to prognostication and "early forecasting of response", the latter opening up for early adaptive treatment.

Third, we already from the beginning considered societal perspectives to be important in a center focusing on cancer biomarkers — from basic projects to clinical studies and further on to patients and the society. Therefore, activities on ethics, economics, priorities and philosophy were included and in part integrated in our projects and programs. We aimed to perform studies in the field of economic evaluation and cost-effectiveness analyses, and also look at models for prioritization and reimbursement policies.

On this background, we felt confident that many exciting studies — basic, translational and clinical — would be performed in the years to come. When the "eagle landed" and the grant was announced, we felt a strong motivation and excitement for the future.

2. What actually happened

Based on the initial ideas included in our application from 2012, we first organized our research in three different programs or teams: basic studies, translational studies of biomarker discovery and validation, and clinical studies including trials. Later on, a fourth team of societal studies





was included, although this topic was established from the beginning but later on strengthened and made more visible in the CCBIO organization. The aim of the latter studies was to focus on the societal implications of cancer biomarkers, including ethics and economics profiling. This program inspired increased self-reflection and awareness in the RRI context, as well as a more "holistic" view of cancer complexity.

Efforts were made to broaden our understanding of cancer biomarkers, by moving from simple (or individual) biomarkers, for example determined by immunohistochemistry on tissue slides, or determination of single molecules in blood tests, to more complex (or multiplex) markers by proteomic or transcriptional signatures determined by more advanced methods.

As promised, multiple studies have explored basic mechanistic aspects of the tumor microenvironment, ranging from global stromal proteomic patterns at baseline or hypoxia-induced, to immune markers and matrix biology. Innovative mapping of immune responses has been performed and discussed in multiple studies including some of our trials, although this topic was barely mentioned in the CoE application. Generally, the second wave of tumor immunology rapidly moved center stage and reached a peak with landmark discoveries of immunotherapy.

During the first half of the CCBIO period, several projects using *liquid biopsies* were performed and supported by strategic funding. During the second half of the period, methodology for *imaging mass cytometry and single-cell tissue analytics* was implemented and increasingly used by several groups. These initiatives and projects have shown that increased biomarker sensitivity towards clinical correlates and end-points can be obtained by using novel technology and more complex and information-rich composite biomarkers.

Regarding *clinical studies*, these are considered crucial in the translational pipeline, i.e. that results from basic studies should as soon as possible end up with the patients, in clinical studies or trials. At the same time, this has been a significant concern already from the beginning: it takes a lot of time for this to happen. The challenge became to find an appropriate mix of biomarker studies in already closed or ongoing clinical studies, with prospectively performed studies for which mature results might even fall outside of the CoE period. Importantly, it was clearly our aim to establish our own academic clinical trials with attached biomarker programs. We have realized that this might be very challenging in the context and timeframe of a Centre of Excellence.

Biomarker-intense clinical trials have been organized and conducted. In advanced prostate cancer, receptor sequencing of T-lymphocytes has demonstrated marked diversity of the immune response following cryo-immunotherapy. In leukemia, functional assays by single-cell profiling have been developed as a basis for early-phase dynamic monitoring and adaptive treatment. Anti-Axl therapy has been shown to restore PD-1 blockade sensitivity in lung cancer by increasing CD8 T-cells. More data will appear from ongoing studies and trials initiated by CCBIO.

Within CCBIO, several groups swiftly included immune interactions and metrics in their projects, both related to

basic mechanisms, through biomarker discoveries in the TME, and to the establishment and completion of novel academic trials (cryoimmunotherapy in prostate cancer, CryoIT; immunotherapy in metastatic melanoma), with multiple biomarker studies included and ongoing. *The story of immune biology and immunotherapy is just an example of the rapidly changing cancer landscape and our ability of adaptation and "rapid reprogramming" of our research projects.*

Further, important discoveries on regulation of immune suppression in the TME have been reported, as has the finding of a regulatory mechanism that could make distant stromal tissues resistant to metastatic cells. A related topic has been the many studies of relations between how tumor cells interact with the tumor microenvironment, through plasticity and epithelial mesenchymal transition (EMT), and how EMT appears to be coordinated with immune evasion.

The field of *cancer neuroscience* is rapidly emerging, and presence of nerves might represent an important TME program that was not apparent or mentioned in the CCBIO application. During the second half of the center period, we have established projects and reported data on how nerve cells interact with breast cancer cells to increase aggressiveness.

Swift implementation of novel methods has been essential for CCBIO, often with refinement and further development as a result. As a breakthrough technology, *imaging mass cytometry* with single-cell mapping and spatial analysis was rapidly established at CCBIO (as the first lab in Northern Europe) to improve resolution and advance deeper studies of cancer tissues, with a potential to identify *functional tumor niches* and novel biomarkers. Strategically, CCBIO has put focus on *deep tissue profiling* during the last years. Also, flow-based mass cytometry has been applied in multiple studies.

CCBIO has strong and increasing internal and international collaboration, and the recruitment of 17 international top scientists to adjunct positions played a very important part in achieving this. The center has organized 11 international symposia and multiple large meetings and workshops for exchange of ideas and results, and to promote research at large. As an example, in 2016 CCBIO initiated the annual Scandinavian network symposium for tissue-based tumor studies (SCANPATH), as an international initiative, and with a strong biomarker focus.

3. Some concluding remarks

CCBIO has reported multiple novel findings in the field of cancer biomarkers, with particular focus on the tumor microenvironment (TME). We have complied very well with the CCBIO application submitted in 2012, with a couple of notable exceptions. First, the field of tumor immune responses and immunotherapy has become essential in today's cancer research landscape. Second, the cancer neuroscience field is younger and less mature, but rapidly increasing in terms of activity and visibility. Both research areas have been successfully integrated into CCBIO's research effort. The ability to adapt and reprogram is essential for a Centre of Excellence.

The translation process is challenging and often time-consuming. CCBIO has performed and participated in multiple clinical trials on novel therapy for cancer patients, with attached studies on predictive biomarkers. These represent a combination of smaller academic trials organized by our own researchers, and participation in larger multi-center studies. New protocols and procedures for biomarker studies in trials have been presented. Biomarker-based trials are essential in the field of precision oncology.

Guidelines are crucial for good practice and change-of-practice. From CCBIO, novel pathology-based breast cancer markers have been included in national guidelines, and we have reported guidance for cost-effectiveness studies in relation to biomarkers in precision medicine. Evaluation of translational methods for personalized medicine, as well as recommendations for robust and reproducible preclinical research in this field, have been presented. Finally, research data from CCBIO have been made available to the research community at large.

Methods development is essential in today's cancer research. CCBIO has rapidly implemented and refined multiple techniques, with strategic focus on liquid biopsies and imaging mass cytometry for single-cell and spatial analytics of functional tumor properties.

Activities in communication and education have been considered essential in our center, as a prerequisite for excellent research. This aligns well with our fundamental focus on mentoring and career development, including self-empowering collaboration and networking strategies.

CCBIO is a cancer research center with a mission to perform fundamental studies along the translational chain. In terms of long-term gains, we believe that our results significantly improve the precision of diagnostic and therapeutic procedures in cancer medicine, leading to better outcomes for patients. Subsequently, this enables a better cost-effectiveness profile and more responsible cancer management. Thus, we contribute to improved public health in Norway and elsewhere.

Looking into the crystal ball, our main goal for the coming years is two-fold: to continue our deep profiling of malignant tumors, and to accelerate the translation of our results into practical and patient-oriented measures, by way of innovation projects and guideline processes. Our motivation is still *to capture cancer complexities and clinical challenges.* ••

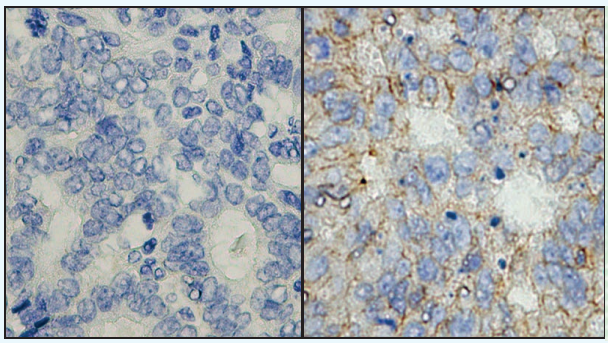
highlights – CCBIO at a glance

In the following, selected CCBIO highlights during 2013–2024 are listed, covering research output and other center activities. In a way, "*everything is connected*", and we here point to highlights and peak activities that we currently perceive as important and noteworthy. Over the years to come, the real impact of our results will emerge more clearly.

CCBIO has published more than 1000 papers in peer reviewed journals, many of them in high-impact channels, and 105 PhD theses have been defended. Below we have indicated some highlighted publications (the most recent listed first), followed by other types of highlights.

CCBIO has been very active in public dissemination with more than 500 media appearances, e.g. commentaries and interviews in newspapers and television, as well as more than 250 popularized presentations and events.

scientific papers

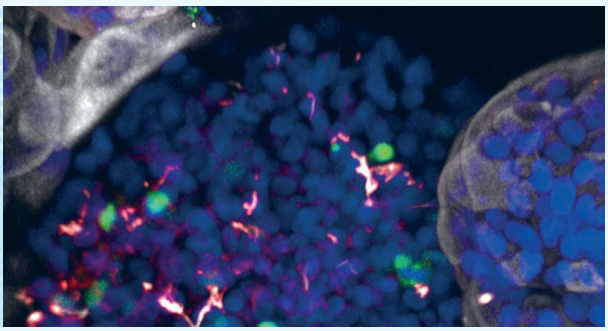


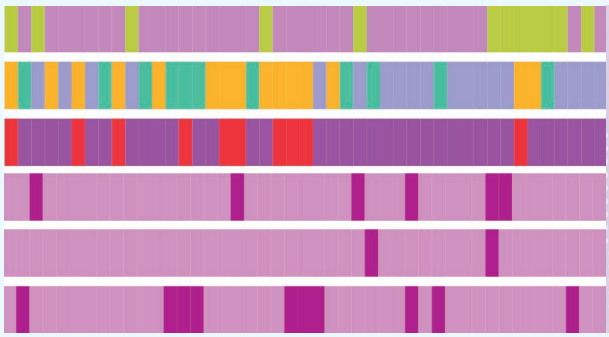
Krakstad C, Berg HF, Lindemann K, Halle MK. Frequency of ERBB2-Low Expression in Endometrial Cancer. *JAMA Oncol.* 2024; PMID: 39235791.

This paper reports on the prevalence of HER2-low and associations with molecular type and other tumor features in endometrial cancer.

Bjørnstad OV, Carrasco M, Finne K, Ardawatia V, Winge I, Askeland C, Arnes JB, Knutsvik G, Kleftogiannis D, Paulo JA, Akslen LA, Vethe H. Global and single-cell proteomics view of the co-evolution between neural progenitors and breast cancer cells in a co-culture model. *eBioMedicine* 2024. PMID: 39232464.

This translational and experimental study indicates that tumor-nerve interactions might lead to more aggressive tumor features in breast cancer cells, also shown for human tumors.



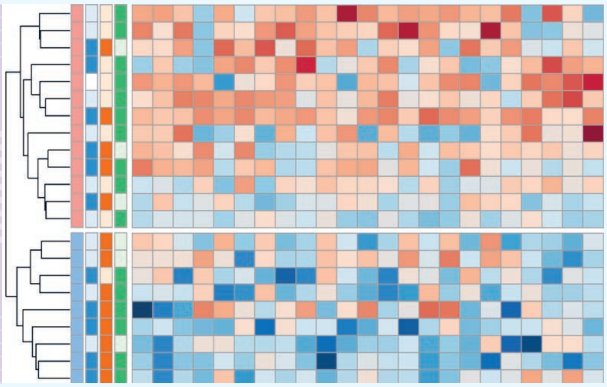


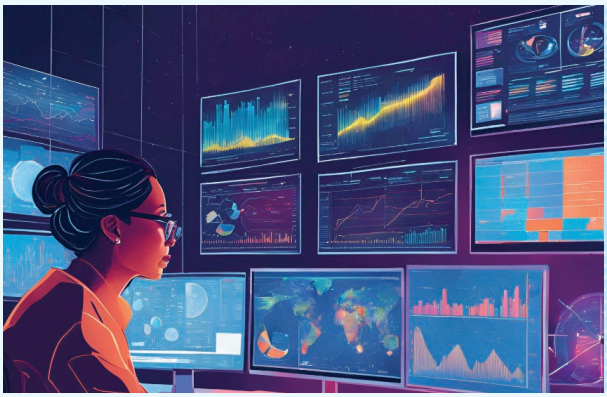
Ingebriktsen LM, Svanøe AA, Myrmel Sæle AK, Humlevik ROC, Toska K, Kalvenes MB, Aas T, Heie A, Askeland C, Knutsvik G, Stefansson IM, Akslen LA, Høivik EA, Wik E. Age-Related Clusters and Favorable Immune Phenotypes in Young Breast Cancer Patients. *Mod Pathol.* 2024. PMID: 38810731.

The paper reports new data on differences in immune phenotypes across age in breast cancer patients.

Torkildsen CF, Austdal M, Jarmund AH, Kleinmanns K, Lamark EK, Nilsen EB, Stefansson I, Sande RK, Iversen AC, Thomsen LCV, Bjørge L. New immune phenotypes for treatment response in high-grade serous ovarian carcinoma patients. *Front Immunol.* 2024. PMID: 38947323.

In this study, the team reports two different serum cytokine signatures (immune-high, immune-low) that could inform the treatment response and prognosis of high-grade ovarian cancer.



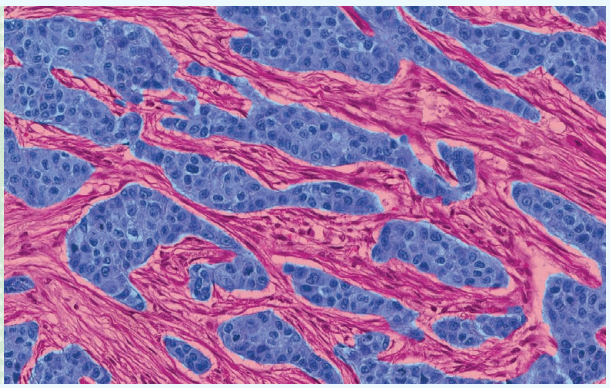


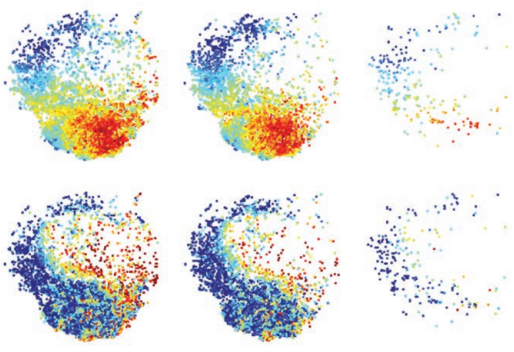
Kang J, Cairns J. Cross-sectional analysis of use of real-world data in single technology appraisals of oncological medicine by the National Institute for Health and Care Excellence in 2011-2021. *BMJ Open*. 2024. PMID: 38485485.

In this paper, the authors report on the diversity in the use of RWD (real world data) in processes of drug appraisals.

Kjølle S, Finne K, Birkeland E, Ardawatia V, Winge I, Aziz S, Knutsvik G, Wik E, Paulo JA, Vethe H, Kleftogiannis D, Akslen LA. Hypoxia induced responses are reflected in the stromal proteome of breast cancer. *Nat Commun* 2023. PMID: 37349288.

The paper reports novel significance of hypoxia-related stromal proteomic patterns, pointing to a strong and independent influence of the tumor microenvironment in tumor progress.



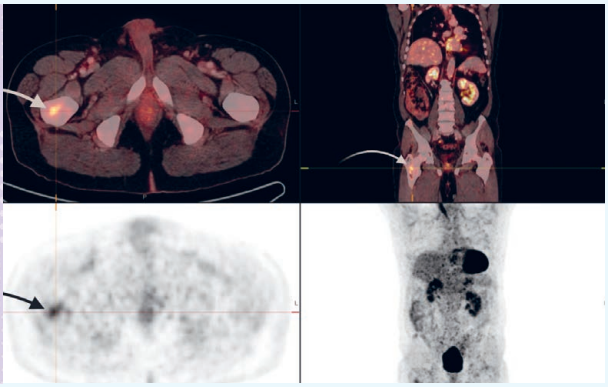


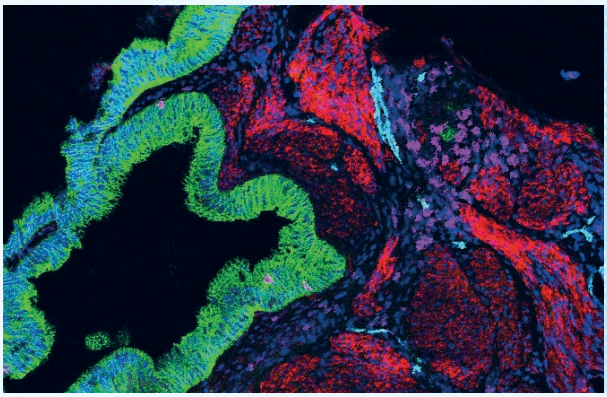
Tislevoll BS, Hellesøy M, Fagerholt OHE, Gullaksen SE, Srivastava A, Birkeland E, Kleftogiannis D, Ayuda-Durán P, Piechaczyk L, Tadele DS, Skavland J, Baliakas P, Hovland R, Andresen V, Seternes OM, Tvedt THA, Aghaeepour N, Gavasso S, Porkka K, Jonassen I, Fløisand Y, Enserink J, Blaser N, Gjertsen BT. Early response evaluation by single cell signaling profiling in acute myeloid leukemia. *Nat Commun* 2023. PMID: 36611026.

The paper presents studies by flow-based mass cytometry of single-cell signaling patterns as functional biomarkers and early predictors of response and basis for adaptive treatment in leukemia.

Thomsen LCV, Honoré A, Reisæter LAR, Almås B, Børretzen A, Helle SI, Førde K, Kristoffersen EK, Kaada SH, Melve GK, Haslerud TM, Biermann M, Bigalke I, Kvalheim G, Azeem W, Olsen JR, Gabriel B, Knappskog S, Halvorsen OJ, Akslen LA, Bahn D, Pantel K, Riethdorf S, Ragde H, Gjertsen BT, Øyan AM, Kalland KH, Beisland C. A phase I prospective, non-randomized trial of autologous dendritic cell-based cryoimmunotherapy in patients with metastatic castration-resistant prostate cancer. *Cancer Immunol Immunother* 2023. PMID: 36939854.

The paper presents a CCBIO-based trial using novel cryo-immunotherapy for advanced prostate cancer, showing promising responses and several candidate biomarkers.





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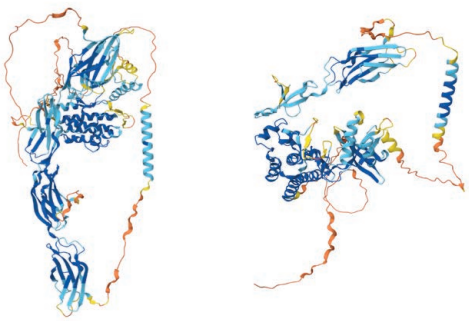



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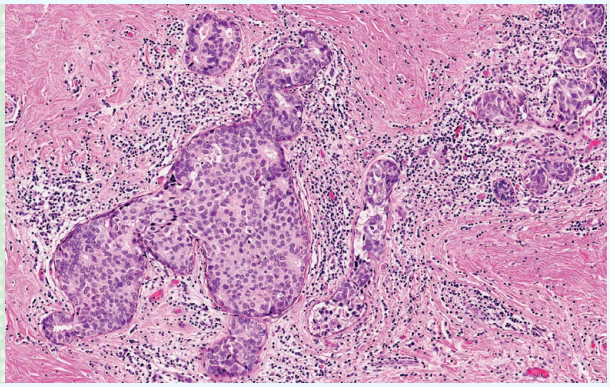

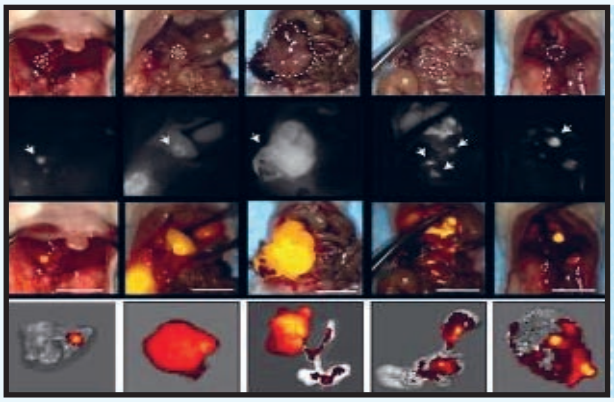

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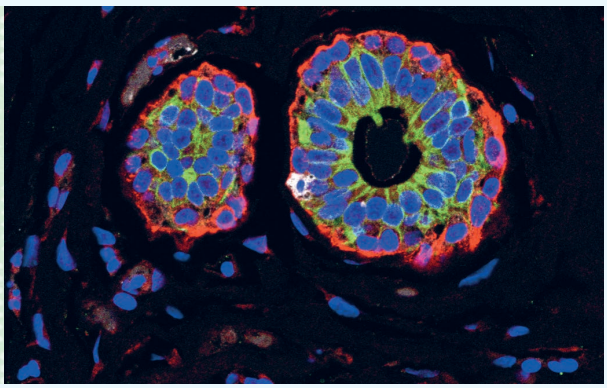

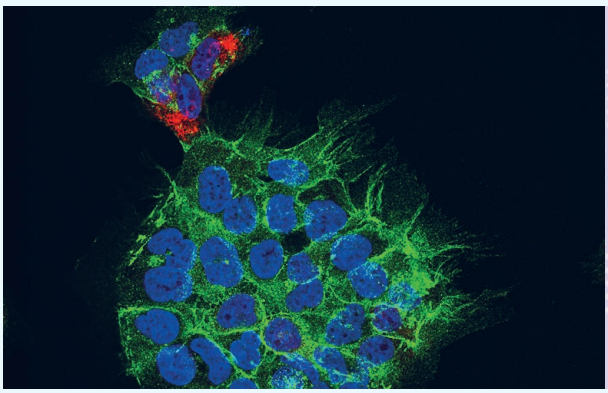

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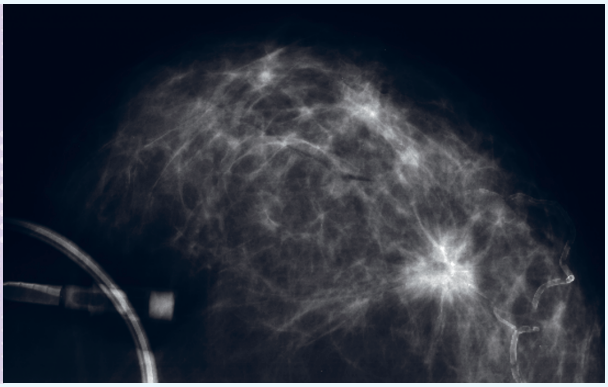
This paper indicates that digital breast tomosynthesis was not significantly different from standard digital mammography as a screening tool for the detection of breast cancer in a population-based screening program.





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This paper, the first of its kind, reports on the actual contribution of tumor metastasis to cancer mortality.

Qu Y, Olsen JR, Yuan X, Cheng PF, Levesque MP, Brokstad KA, Hoffman PS, Oyan AM, Zhang W, Kalland KH, Ke X. Small molecule promotes β-catenin citrullination and inhibits Wnt signaling in cancer. *Nat Chem Biol.* 2018. PMID: 29083417.

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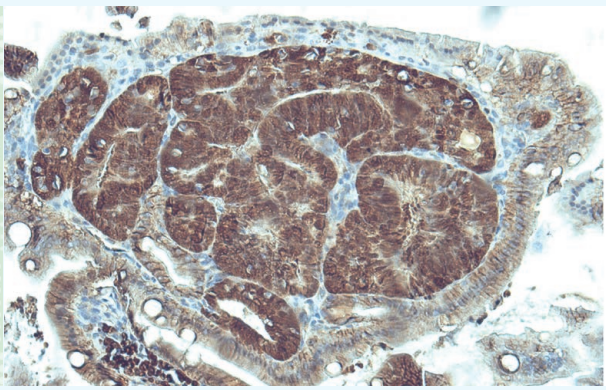

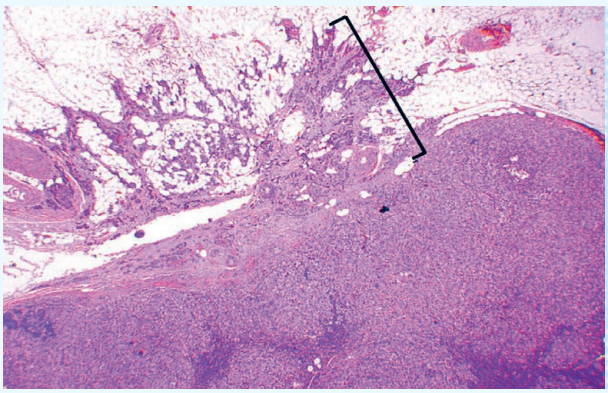

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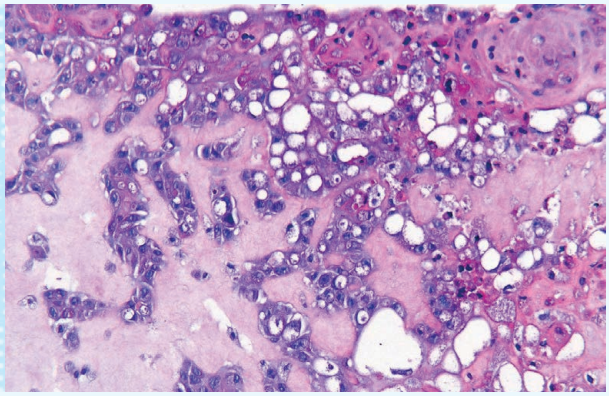
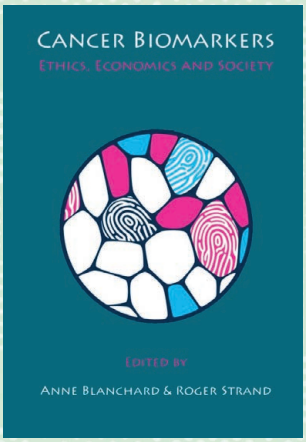
In this early study, the team reported two subtypes of tumor associated fibroblasts with different influence on oral cancer cells.

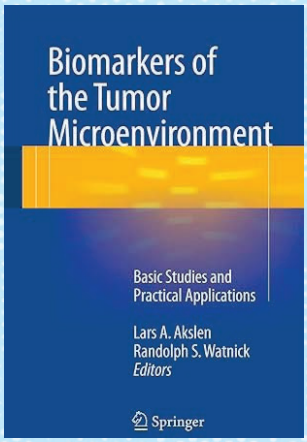


CCBIO books



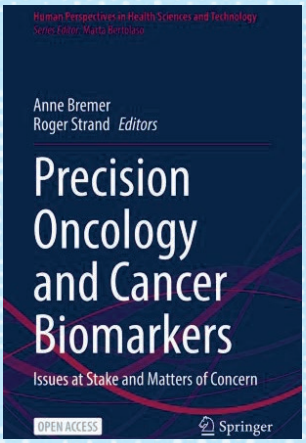
Cancer Biomarkers: Ethics, Economics and Society

Roger Strand and Anne Blanchard (eds): *Megaloceros Press*, 2017.



Biomarkers of the Tumor Microenvironment - Basic Studies and Practical Applications

Lars A. Akslen, Randolph S. Watnick (eds): *Springer*, 2017.



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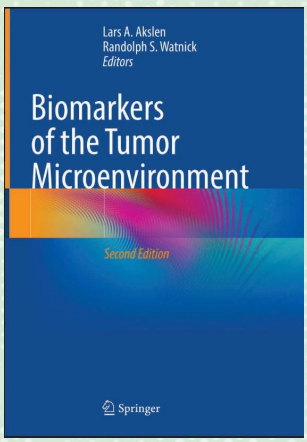

Biomarkers of the Tumor Microenvironment

Lars A. Akslen and Randolph S. Watnick (eds): *Springer*, 2022. (textbook; 2nd ed)

awards and accolades



CCBIO researchers have received multiple awards. A few distinct examples are highlighted below (the most recent listed first).



2024: Bjørn Tore Gjertsen is awarded a five-year KG Jebsen Centre for Myeloid Blood Cancer (C-MYC).



2023: Ole Frithjof Norheim is awarded a 10-year Centre of Excellence from the Research Council of Norway: the Bergen Centre for Ethics and Priority Setting in Health (BCEPS).



2023: Lars A. Akslen receives the Helse Vest Research Award (second time).

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ACADEMIA EUROPAEA
The Academy of Europe

2023: Lars A. Akslen is elected as member of Academia Europaea.



2023: Emmet McCormack receives the Inven2 Innovation Award together with Pascal Gélébart, Vibeke Fosse and Sébastien Wälchli.



2021: Bjørn Tore Gjertsen is awarded the King Olav V Cancer Research Prize.



2021: Ole Frithjof Norheim is elected as member of the Norwegian Academy of Science and Letters.



2021: Inge Jonassen is elected as member of the Norwegian Academy of Science and Letters.



2021: Daniela Costea receives the Pindborg Prize in Oral Pathology.



2020: James B. Lorens is elected as member of the Norwegian Academy of Science and Letters.



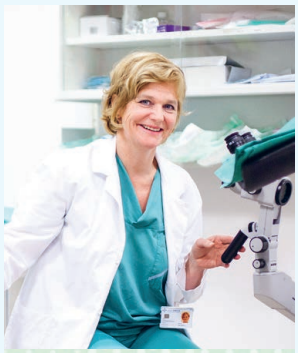
2019: Elisabeth Wik receives the Medical Faculty Internationalization Award.



2018: Lars A. Akslen is elected as Honorary Member of the Norwegian Society of Pathology.



2017: Lars A. Akslen and Elisabeth Wik receive the Olav Thon Foundation National Award for Excellence in Education.



2015: Helga B. Salvesen† is elected as member of the Norwegian Academy of Science and Letters.



2015: Helga B. Salvesen† and the Gynaecologic Research Group receive the Helse Vest Research Award.



2015: James B. Lorens receives the Helse Vest Innovation Award.



2015: James B. Lorens' group wins the faculty award Best Research Group.



2014: Emmet McCormack receives the Young Researcher Prize from the Norwegian Oncology Forum.



2014: Camilla Krakstad is awarded the Falch Junior Prize for young researchers.



2013: Lars A. Akslen is elected as member of the Norwegian Academy of Science and Letters.

other highlights

Over the years, CCBIO has established and been engaged in diverse activities to support excellent cancer research along with targeted recruitment and career development.

CCBIO Annual Symposium
As the top event during the year, this international meeting and vibrant gathering has been instrumental in creating a good atmosphere for learning and networking.





CCBIO Research School for Cancer Studies
This is the first (and only) cancer-based research school in Norway, with a core curriculum including 12 courses focusing on basic topics, translational knowledge and skills like scientific writing and communication.

The CCBIO Research Seminars
The monthly seminar series have provided continuous scientific updates in our field, has been an important meeting place and an arena for informal crosstalk and networking.





CCBIO Masterclass Program
The program is aimed to support young and excellent candidates on the road to independency, with tailored teaching on how to organize scientific projects and research groups.



The Doctoral Defenses
Every doctoral defense is a culmination of years of work, and a completed PhD is a celebration both for the individual student and for the research group, and for CCBIO as a whole.

The CCBIO-VBP Research Collaboration
The Bergen-Boston axis has been persisting through 20 years as a strong and developing relationship, with projects, lab visits and high-level education supported by the Vascular Biology Program.





The SAB Meetings
The annual meetings and discussions with the Scientific Advisory Board have been highly rewarding. The comments and recommendations from the SAB have been extremely important and of great inspiration and utility to CCBIO.

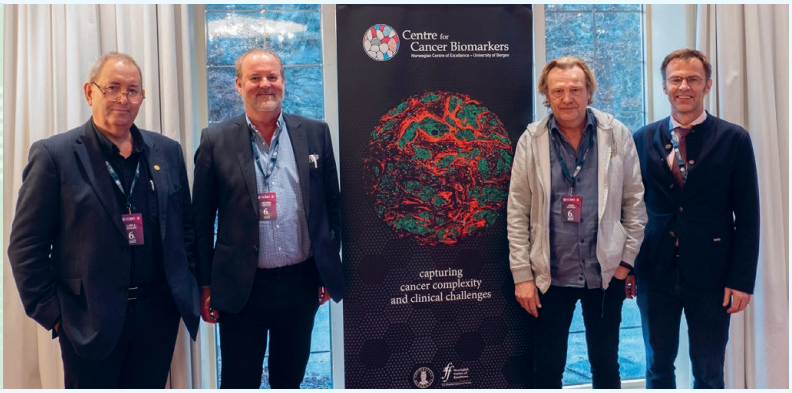
Societal Perspectives
It is essential for CCBIO to include perspectives on ethics, economics, priority studies and science philosophy, with the omnipresence of these topics strongly promoting self-reflection and responsibility.





Science Communication
Henriette Christie Ertsås, a CCBIO PhD graduate and a trained actor, is performing interactive theatre plays, based on our cancer-related textbook, with so far more than 100 performances for children aged 10–14 years, in schools and at Forskningsdagene (the Annual Science Fair).

ScanPath: Scandinavian Seminar on Translational Pathology
In 2016, CCBIO established this Nordic annual meeting, aiming to promote basic and translational tissue studies, and collaborations, using well annotated human cancer cohorts and cutting-edge technology.





Advanced Methodology
In 2019, CCBIO established, as the first lab in Northern Europe, the technology of imaging mass cytometry, thereby enabling spatial high-dimensional single-cell studies of tumor landscapes.

The CCBIO Annual Report
The CCBIO Annual Report has from the start been an important annual review and a tool for consolidation of the center and its people and collaborators.

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scientific advisory board

Presentation and Final Report

The CCBIO Scientific Advisory Board (SAB) consisted of Professors **Carl-Henrik Heldin** (chair), **Bruce Zetter** and **Ate van der Zee**, all three being internationally leading researchers in CCBIO-relevant fields. The SAB's mandate was to give the center director and center staff advice on science and scientific matters. Usually, the SAB convened once a year for a full day meeting with CCBIO's investigators, mostly in connection with the CCBIO Annual Symposium. The comments and recommendations from the SAB have been extremely important and of great inspiration and utility to CCBIO. Preceding every SAB meeting, CCBIO provided the SAB with a report on its response to their previous recommendations, as well as a written summary covering last year's activities. This was combined with presentations during the meeting as background for discussions.

The CCBIO SAB convened in-person in Bergen for the last time on May 13, 2024, to acquire the basis for a report covering CCBIO's full CoE period 2013–2024. Rather than commenting on the final SAB report, we this time reproduce it in its entirety, unedited, although with the conclusion being highlighted (by the editors).••

Carl-Henrik Heldin *is the chairman of CCBIO's SAB and is professor of molecular cell biology at Uppsala University, and former chairman of the Nobel Foundation.*

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

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



Report from the meeting with the Scientific Advisory Board of CCBIO in Bergen May 13, 2024

Introduction
The Scientific Advisory Board (SAB) of the Norwegian Centre for Cancer Biomarkers (CCBIO), consisting of Carl-Henrik Heldin (chair), Ate van der Zee and Bruce Zetter, met at Solstrand outside Bergen on May 13, 2024. Before the meeting, the SAB had received detailed documents including responses to the recommendations from the 2023 SAB meeting, descriptions of research activities and clinical trials from the last year, as well as descriptions of CCBIO Research School and other educational efforts. Since this SAB meeting marks the end of the 11 years of funding from the Norwegian Research Council, a CCBIO Self Evaluation, as well as performance indicators, various metrics and a complete list of publications from the 11-year period, were also provided.

During the meeting, the SAB listened to presentations on the over-all activities of CCBIO, as well as scientific presentations by each of the PIs. As before, the SAB was very much impressed by the progress of CCBIO; the research output continues to be of high quality with several publications in high impact journals, the level of external funding was higher in 2023 than in any of the previous years, the very successful educational program with a Research School offering 12 PhD student courses and the CCBIO Masterclass program for promising young scientists has continued, and the communication activities with a CCBIO Newsletter and many media appearances continues to be at a very high level. Moreover, CCBIO researchers have been successful in receiving prestigious research grants, including a Center of Excellence in Ethics and Priority Settings (opened in January 2024; O.F. Norheim) and a K.G. Jebsen Center on Myeloid Leukemia (to be opened in September 2024; B.T. Gjertsen).

An important reason for the successful development of CCBIO is that it benefits from a very strong and visionary scientific leadership by its Director Lars A. Akslen and an efficient administrative leadership by Geir Olav Løken.



Since the CCBIO funding from the Research Council ends on June 30, 2024, we will in this report give an overall evaluation of the accomplishments, rather than commenting specifically on the last year´s activities.

Research activities

The scientific endeavors of the CCBIO center have made marked progress in several regards over the course of the grant period. A PubMed search reveals multiple papers in highly prestigious journals including *Cancer Discovery, Cell Reports, Cell Reports Medicine, iScience, Journal of Clinical Oncology, Lancet Oncology, Nature Biotechnology, Nature Communications, Nature Genetics, Nature Medicine*, and *Science Translational Medicine.* Publication in these highly competitive journals demonstrates that the research is both rigorous and impactful. There is little doubt that the work of CCBIO investigators over the past 11 years has contributed significantly to the development of new cancer biomarkers and the implementation of these biomarkers into clinical trials. CCBIO researchers have also made inroads into fundamental aspects of cancer biology, leading to new targets for novel therapeutics and their companion biomarkers. They have expanded the quantity and impact of biomarker research both in Norway and internationally. The publication record also is indicative of increased collaboration, both within the CCBIO center and to collaborators abroad.

Whereas an exhaustive review of their scientific contributions is beyond the scope of this review, a few recent highlights, discussed at the SAB meeting include: 1. a novel biomarker proteomic signature for breast cancer prediction; 2. a comprehensive study of biomarkers of progression in ovarian cancer; 3. a novel set of biomarkers for outcome prediction in endometrial cancer; 4. a new biomarker signature that is an independent predictor of survival in younger women with breast cancer; 5. an experimental study of the promise of CAR-T cell therapy in the treatment of ovarian and endometrial cancers; and 6. a first of its kind examination of the actual contribution of tumor metastasis to tumor mortality which has galvanized the field of tumor metastasis.

In addition to work in basic science and biomarker discovery, CCBIO investigators have made prominent contributions to science policy, to the field of science ethics, to health economics and to the development of new model assays for cancer research. Their contributions have also resulted in the publication of books and monographs on the topics of Biomedical Ethics and on Cancer Biomarkers. The expansion of topics on policy, ethics and medical economics has been a great strength of CCBIO and has influenced new investigators to enter these fields. CCBIO also supports entrepreneurship with BerGenBio, representative of science that can move between the academic and company setting to accelerate the development of new cancer therapies.

Clinical activities

At the last SAB meeting, again an extensive summary and list of completed and planned clinical trials within CCBIO was made available. This table provides a nice overview of how efforts are made to indeed develop clinically relevant biomarkers within the context of either investigator-driven or pharma-sponsored local, national and/or international trials. Clinical trials have continued and, in particular, studies on leukemias, gynecologic cancers, prostate cancer and melanoma, have been or are being performed. The table illustrates that clinical CCBIO PIs all are members of

international consortia (HOVON/ENGOT/MOMATEC, etc), that allow them to generate enough power (e.g. number of patient samples) to combine these trials with in-depth biomarker profiling. Cutting edge projects using liquid biopsies, flow-based mass cytometry on single cells, and deep tissue profiling using imaging mass cytometry, have been performed and are ongoing. Translation of biomarkers from the lab to the clinic and vice versa, resulting in clinically applied biomarkers, remains a huge challenge. However, it is reassuring to see that within a 10-year timeframe CCBIO as a consortium has been able to build an infrastructure in which all the necessary ingredients are available to work on this ambitious goal, also during the follow-up of the CCBIO grant period. Moreover, it appears that especially Dr. B.T. Gjertsen and Dr. L. Bjorge have established themselves as clinical PIs in such an excellent way internationally, that they now participate in scientific committees that are pivotal in deciding which sets of biomarkers are going to be further evaluated within the context of multicenter international trials by highly rated international collaborative groups. It is without doubt that 10 years of CCBIO funding has given multiple Bergen based PIs the opportunity and chance to reach out internationally, and it is reassuring to see how many of them have indeed stepped up to this challenge which now presents Bergen/CCBIO as an international stronghold in the whole spectrum of biomarker research.

Educational activities

The fostering of the next generation of scientists has been an important goal for CCBIO. No less than 95 PhD theses have been completed between 2013 and 2023. In addition to regular interactions with supervisors, the PhD students have had access to additional educational programs. Thus, the development of a CCBIO Research School for PhD students and postdoctoral fellows has been a notable success. Twelve courses covering various skills and knowledge needed in cancer research have been established. The topics include experimental models and methods, translational research approaches and clinical studies, as well as courses on scientific writing, responsible research and innovation, and patient and public involvement in cancer research. The Research School is unique in its coverage and quality and provides an excellent opportunity for young scientists entering the cancer research field. Moreover, the Research School provides inspiration for young scientists in basic research to develop their project towards translation and the clinics. Through this initiative, CCBIO has provided the University of Bergen with an extremely valuable asset; it is very much in the interest of the University to continue and further develop the Research School.

In addition to the courses within the Research School, CCBIO has also established a Masterclass for particularly talented researchers. The first class of 8 students had 8 half-day interactive seminars during 2020 and 2022. Since the experience of this program was very positive and the initiative was much appreciated by the participants, a second class was started in 2022, and a third one is planned for 2024.



Media and communication

CCBIO has made commendable efforts to spread information within as well as outside the CCBIO community. A website has been established which is regularly updated

by information about upcoming events, as well as news about the research accomplishments in the Center, and a Newsletter has been published every 2–3 months during the whole period. In addition, CCBIO researchers have very often appeared in the media, no less than 488 times during the last 11 years. Through all these efforts, the CCBIO staff has been kept updated about each other´s activities, which has fostered



collaborations and interactions, and information about the scientific progress at CCBIO has been made available to the outside world.

Meetings and seminars

CCBIO has continuously maintained a seminar series of monthly seminars, as well as Junior Scientist Symposia about 4 times each year. In addition, except 2020, CCBIO Annual Symposia have been organized with internationally renowned scientists as speakers. In addition, several other types of meetings and seminars have been held, including the CCBIO Advanced Research Colloquium, consisting of monthly, internal discussions among the PIs of recent key publications in the field.

International faculty and global outreach

In order to strengthen the international visibility of CCBIO, and to promote interactions with excellent scientists in the biomarker field in different countries, an international faculty has been recruited. More than a dozen prominent scientists have been engaged on a 10% basis; through regular visits in Bergen and participation in the CCBIO Annual Symposia and by receiving CCBIO researchers in their laboratories, these scientists have contributed significantly to the CCBIO program, resulting in collaborations with CCBIO researchers and several co-authored publications. In addition, the International Faculty program has significantly promoted the internationalization of the CCBIO research activities.

Diversity and gender balance

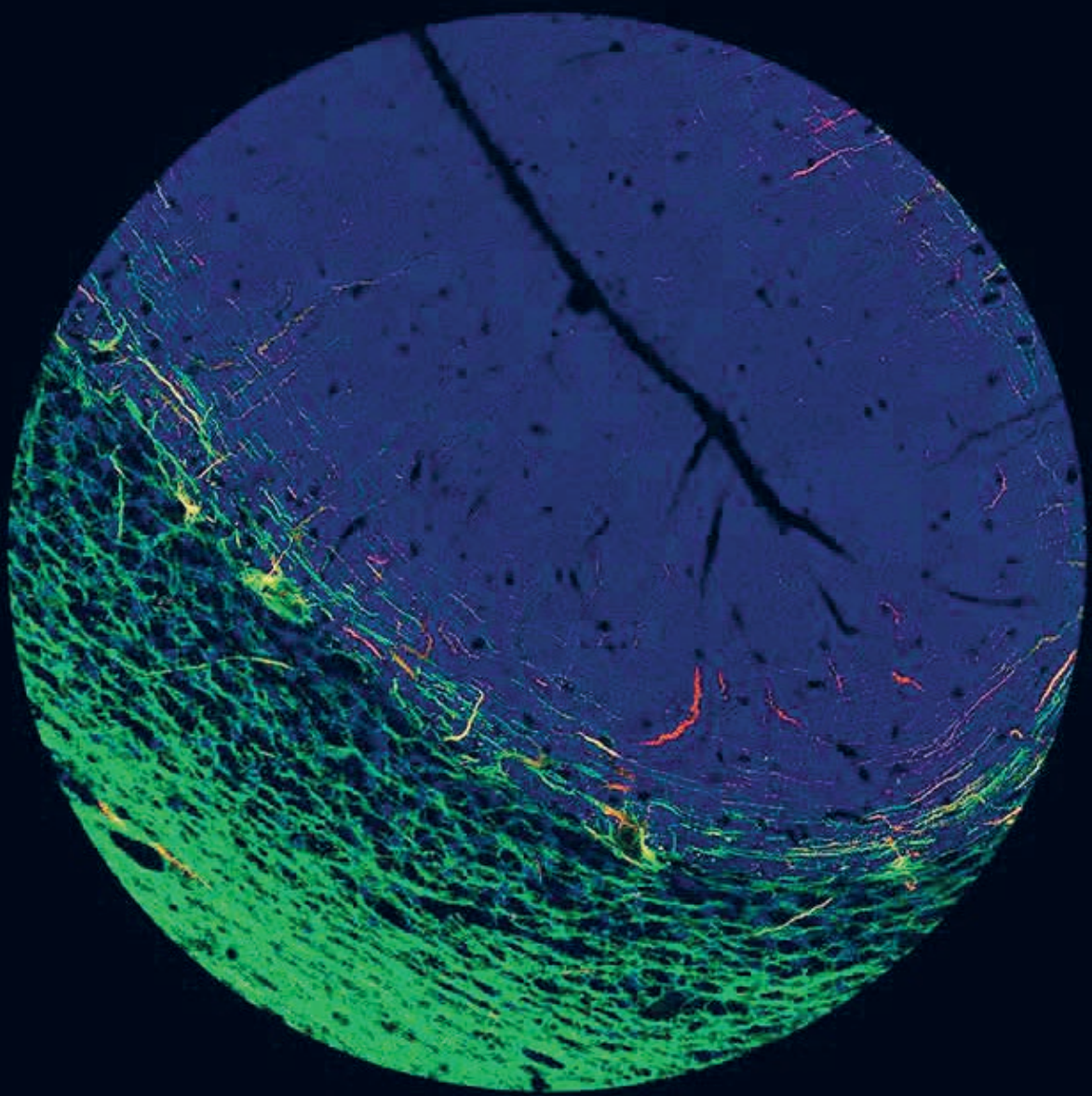
At the start of CCBIO, a vast majority of the PIs were men. Through a commendable effort, the CCBIO leadership has systematically worked to obtain a gender balance among the PIs. This effort has been very successful, and now 46% of the medical PIs are women.

Conclusion

The CCBIO Center of Excellence has been extremely successful, very much due to a strong and visionary leadership. A very strong consortium of scientists with complementing skills has been established. The research program spans from basic to translational and clinical research. A series of meetings, seminars and symposia has been organized, which has promoted interactions between researchers within as well as outside CCBIO, and which has strengthened the translational aspects of the research. An international faculty of excellent scientists has been recruited, which has promoted international visibility and interactions. The quality of the output of publications has been very high and has increased during the period of the program. In addition to the impressive research efforts, a high-quality educational program, including a unique Research School, has been established, and commendable efforts have been made with regard to internal as well as external communications.

The topic of the CCBIO program, i.e. biomarkers, was timely when the application was made 11–12 years ago, since improved biomarkers are crucial for diagnosis, prognosis, and monitoring of treatment of cancer patients, and this topic is of no less importance today.

Given the remarkable progress that has been achieved, the SAB strongly recommends the University of Bergen and its Medical Faculty to support a continuation of CCBIO, so at least the core research and educational activities can be maintained.••



Science Horizon - the Dawn of the Future

Tissue from cerebellum stained with a 38-plex antibody panel using imaging mass cytometry.
(Photo: Kenneth Finne/Lars A. Akslen, CCBIO)

CCBIO Opinion

Text: Ian Mills, CCBIO International Faculty



reflections on mentorship

In academia, everyone has or has had a supervisor, line manager or adviser. Mentorship by contrast is something that should also sit outside those formal working relationships to provide advice and support without interference from day-to-day working pressures and metrics. Publishing and funding metrics and the drive for those can on occasion bias advice or priority setting towards goals that do not align with the needs or interests of individual researchers and particularly those at early career stages. Having mentors who are removed from the daily pressures on the mentee but fully understand and appreciate them, provides a support structure that can make the day-to-day easier whilst helping to shape future direction. Ordinarily, mentoring is something that is acquired informally by those who are naturally adept at networking and therefore perhaps not the people who might benefit from it most.

I have become a mentor over the years for academics in Canada, Norway, Finland and the UK and this has mainly been informal although in the last five years, I have noted a step change. In the UK, now a number of major funders such as the Wellcome Trust and Cancer Research UK require trainees/fellowship applicants to include mentors when they apply for funding. In Canada, the University of British Columbia has a formal mentoring scheme in which mentors sign a contract to provide support to named mentees through regular meetings. In my own Department in Oxford, we have a mentoring scheme (RECOGNISE) which is voluntary, but for those signing up as mentors or mentees there is formal training in providing and receiving support and advice (Mentoring schemes — Nuffield Department of Surgical Sciences (ox.ac.uk)). This suggests increased recognition that mentoring can have a positive effect on the lives and careers of mentees and mentors by developing support structures that last beyond the funding of a grant or the terms of a contract. That in turn benefits the institution because the more supported employees feel they are, the more productive and motivated they will be. Mentoring is however not for everyone and many of us are better mentors than we are mentees and vice versa.



It might be interesting to conclude this short opinion piece with some reflections on mentorship. Firstly, I feel that mentoring is one of the joys of academic life in a research community because you have the opportunity to follow the career progress of your mentees whilst helping to shape them. Over time as they take on new roles and change the fields they work in, you have a sense of pride in those achievements. Many of the people I have supervised have become my mentees having left my groups and, for example, are leading academic research groups, working in pharma to establish clinical trials and are project managing multi-national European consortia in Norway. To help your mentees it is often important that you share your network and make connections for them. The key as a mentor in doing that is that you then fully step back having set the ball rolling but stand ready to re-engage if needed.

Providing feedback to your mentees and receiving feedback from them is of course essential. The way you do that needs to be tailored to the individual — in particularly stressful circumstances it is even more important to be calm, measured and to provide advice in an environment that's removed from the source of an issue. Listening is vital, as is interpreting behaviours and showing empathy. It is important to meet regularly and review past advice — how it is been used and what the effects have been. As a result, dialogue has to be open and there has to be a high level of trust between mentor and mentee.

Finally, it is absolutely possible to be both a supervisor and a mentor, but to do so, you will have to establish projects that allow your mentee to develop their interests and take full ownership of the results. By doing so you will enrich them, your environment and your institution. ••

CCBIO Opinion

Text: Yves Aubert, Senior Advisor and Innovation Lead, UiB



the road ahead for young talents

For the past several years, I had the pleasure of following the development of CCBIO and that of its researchers and students; at times closely, and at other times with an arm's length distance. There were many insights to be gained, and lots of learning to be done for my part — from new findings in cancer biology to the latest prevention and treatment approaches of various forms of cancer.

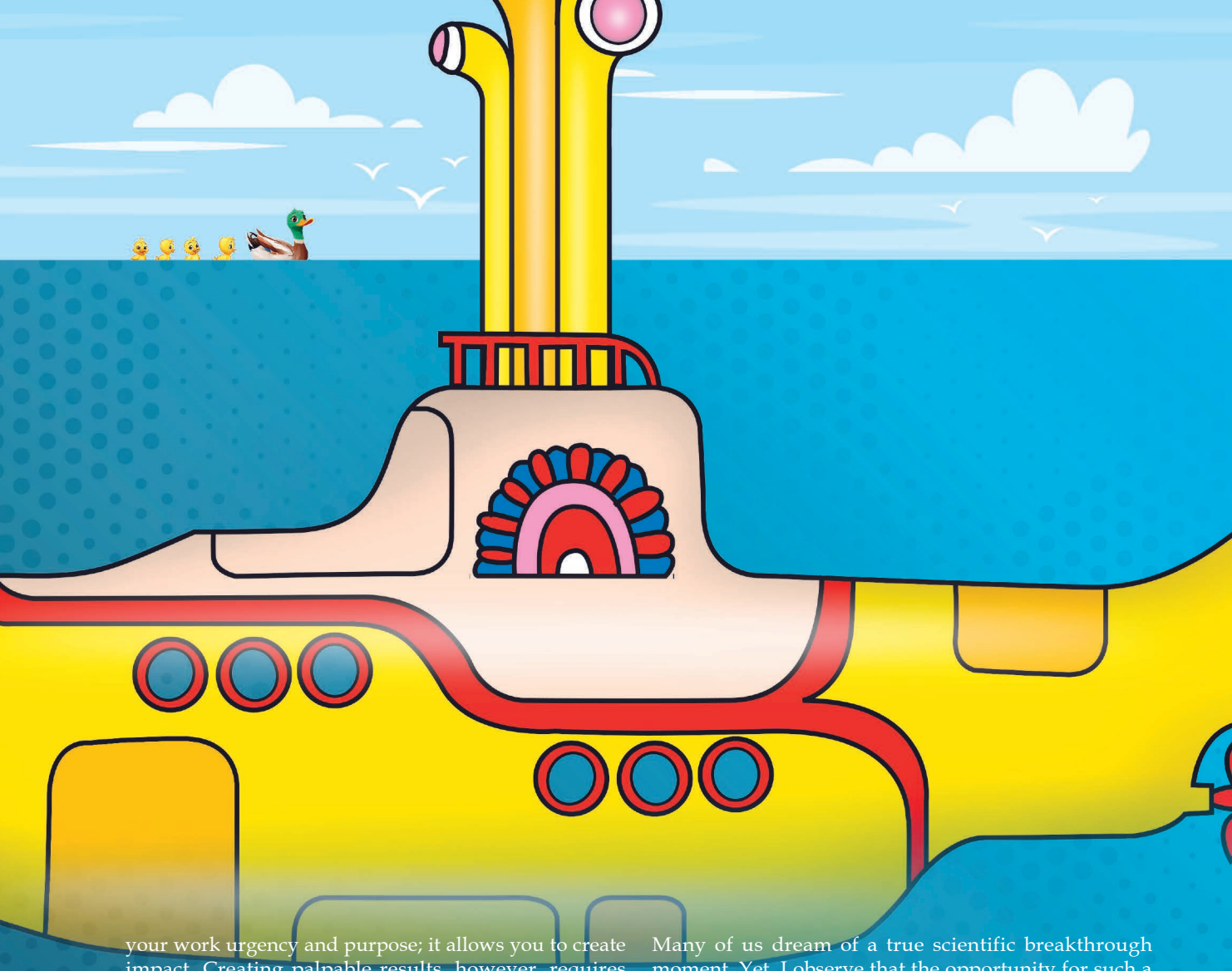
My perspective has been that of a semi-outsider: firstly, that of an innovation advisor, and secondly, that of a neuroscientist. This constellation has admittedly been a challenge at times, as it made it difficult for me to engage in in-depth scientific discussions. It has, however, allowed me to appreciate CCBIO's work from a broader perspective. This enables me to share some observations and advice for the travel ahead.

1. You are working in an environment of scientific excellence. All of CCBIO's research teams come with a strong academic track record, and most of you are nurturing strategic partnerships with internationally leading institutions in relevant fields.

Operating at the frontier of an academic discipline is not a given, nor does it come for free, but it ensures that your research findings push the boundaries of what is known, thus making them truly relevant to the scientific community. It usually takes strong focus and a systematic body of work to establish yourself within your field. Persistence will be a character trait that will carry you to achieve this aim. The frontier, however, is never static, it's a moving target. Staying relevant requires you to "re-invent" yourself throughout your career. When I visited Bruce Zetter at his lab in Boston back in 2018, I received a key piece of advice in the form of a reference to Bruce's own mentor Judah Folkman. The reference was: *Persistence does not equal obstinance*. To know when to persist and when to pivot is not always easy. I recommend that you use CCBIO's network of international peers and involve them in continued discussions. Use the opportunity to ask "an outsider" for perspective. The saying that "you can't see the forest for the trees" very much applies to scientific research. Make sure that you always keep sight of the bigger picture.

2. CCBIO combines the work of basic research with the clinical perspective. Translational science is a hallmark of the center.

The ability to translate your work to (clinical) applications is a privilege that should not be taken for granted. It gives



your work urgency and purpose; it allows you to create impact. Creating palpable results, however, requires several ingredients. You need to start with a significant question, you need to have literacy about your path to innovation, and you need the right partnerships to bring your solution to the beneficiaries. Speaking with research talents across our university's campus and beyond, I observe that some of the greatest ideas come from those who truly think transdisciplinary. It's the particle physicist that reads medical journals and sees a novel solution to a problem. It's the clinician that reads reports from NGOs and envisions a pathway to a fairer society. Next you need to pair this initial insight with translational expertise and networks. This may entail skills in science policy, entrepreneurship, IPR protection, clinical trials, or industry relations. CCBIO as a center has the potential to house much of this expertise under one roof. Emphasizing CCBIO's continued development in these areas will strengthen the center's future impact.

3. A EUREKA moment cannot be planned. You can, however, put yourself into a more likely position to experience one. Many of us dream of a true scientific breakthrough moment. Yet, I observe that the opportunity for such a moment is often hampered by a habit of locking oneself into rigid scientific thinking. As a budding young scientist, you may inherit a certain scientific hypothesis from your mentor. While the hypothesis may be a great starting point, I too often see that researchers stick with it for the remainder of their careers, without questioning its validity and at times abandoning common sense. As explored above, it is up to you to keep yourself updated with the frontier of your field. Even better, you probe beyond — into neighboring and eventually entirely unrelated fields. I don't think that a EUREKA moment is possible without probing, without openness to other ways of thinking, without scientific curiosity. Thus, my last message to you is: Never stop asking questions.

I will finish this opinion essay with a quote by Bob Langer, who has inspired much of my thinking that I have shared with CCBIO over the years: "*In school you are judged by the questions you answer; in real life, you are judged by the questions you ask.*" ••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PART II

activities

2023–2024

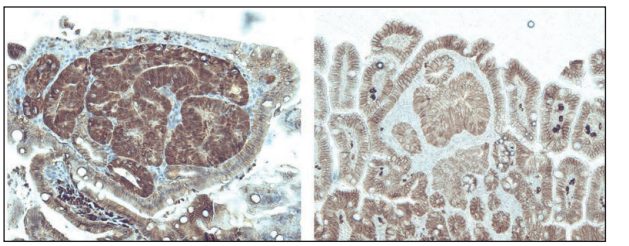
research activities and progress

Our research activities progressed steadily with significant output and emerging ideas for new studies during 2023–2024. Several high-impact publications were presented, and significant new funding was secured, including two new centers awarded to CCBIO PIs (Norheim and Gjertsen). The CCBIO Research School for Cancer Studies has a stable core curriculum with 12 credit giving courses and a range of other activities. The 1st CCBIO Masterclass for career development was an important program for 8 selected candidates (2021–2022), and the second group of 8 candidates has now completed their training (2022–2023). A third class is planned for the fall of 2024. It is rewarding that the Medical Faculty as well as the University of Bergen (central level) have been inspired by our masterclass concept to establish related programs. The INTPART II grant from the RCN enhances our international networking and the relationship with our long-term strong partner — the Vascular Biology Program at Boston Children's Hospital and Harvard Medical School.

In **Team 1,** projects are focusing on how tumor cells interact with and instruct their surrounding tumor microenvironment (TME), and how the "two compartments" co-evolve in progressing tumors. Key TME drivers such as immune responses, angiogenesis, neurogenesis, cancer associated fibroblasts, and matrix involvement are studied, favoring tumor growth and metastatic spread, and explaining development of treatment resistance.

The **Gullberg group** has been working on fibroblast biology and the importance of integrin α11 in the tumor microenvironment, by the characterization of novel integrin α11 function blocking antibodies and development of a mouse model to explore this molecule in tumor stroma. Establishing the ITGA11-Cre mouse strain was a major milestone in the group's work after 10 years of focused efforts. The detailed epitope mapping of mAb 210F4 and mAb 203E1 to a few amino acids is ongoing. One of the translational projects relates to the role of integrin α11 absence in the stroma of squamous cell carcinoma in collaboration with Dr. Heljasvaara (University of Oulu, Finland).

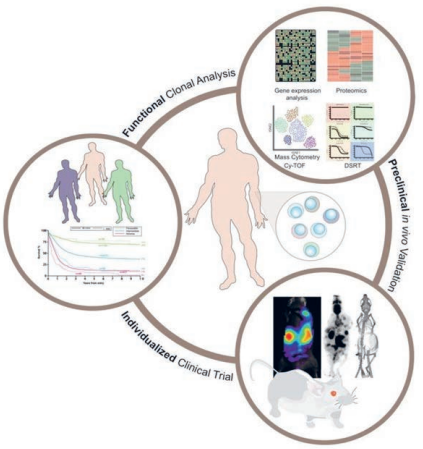
In the **Kalland group**, the focus has been on two strategies: drug discovery by repurposing, and the concept of cryoimmuno-based dendritic cell (DC) therapy. In a phase I clinical trial for cryoimmuno-therapy (CryoIT) for patients with advanced prostate cancer, immature DCs are placed in the inflammatory cryoablated prostate cancer tissue to detect and process the entire panel of tumor-associated neo-antigens, accounting for tumor heterogeneity. Treatment effects were suggested according to radiology, circulating tumor cells, serum auto-antibody profiling, and ultradeep T-cell receptor sequencing (Thomsen et al., *Cancer Immunol Immunother* 2023). The group continues to explore biomarkers in order to uncover positive results from clinical trials, and a second CryoIT clinical trial is being prepared for start-up. A paper on dendritic cell biology was recently presented by the group (Lellahi et al., *Front Immunol* 2023). The European Patent Office has approved the patent application of CryoIT combined with intratumoral injection of an immune checkpoint inhibitor. The national implementation phase is ongoing.



The **McCormack group** has had a focus on appropriate preclinical models (organoids, PDX, imaging) before clinical trials are performed. The group now has several biomarkers under development as novel targets for CAR-T, which will be developed in their novel immunocompetent PDX models. During 2023–2024, two important findings were presented. In the first study (Gelebart el al., *Blood* 2023), the presence and expression of a new isoform of the tyrosine kinase receptor Axl (Axl3) was reported in lymphoma cells. Functional characterization of Axl3, using CRISPR technology, revealed that only the knockdown of this isoform leads to apoptosis of lymphoma cells. Pharmacological inhibition of Axl activity resulted in a significant decrease in proliferation, and a xenograft

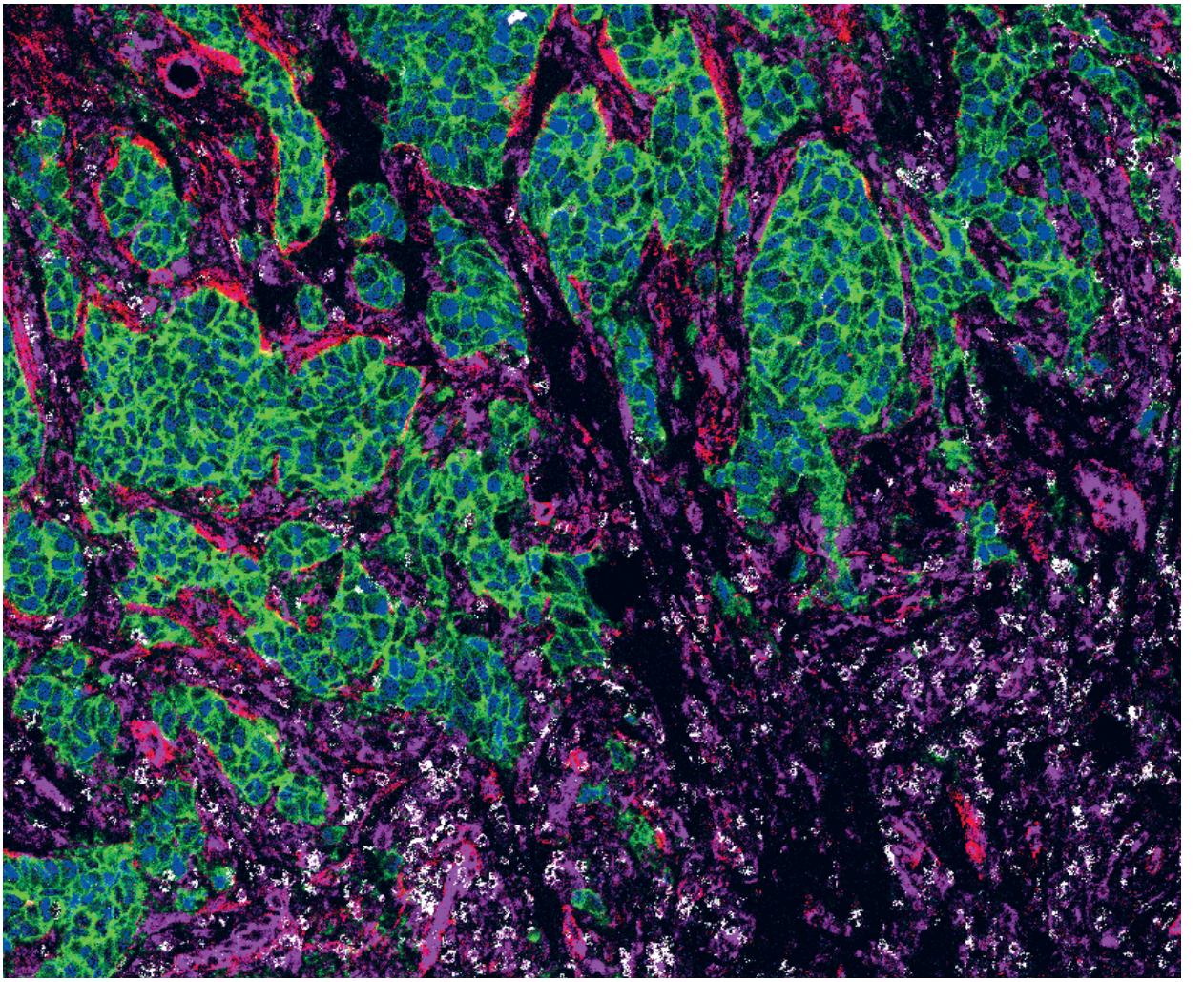


mouse model indicated that bemcentinib (anti-Axl) is more effective than Ibrutinib in reducing the tumor burden and to increase overall survival. In the second study, showing *in vitro* and *in vivo* data including PDX models, it was reported that the CA125 domain represents an excellent target for treating MUC16-positive malignancies using CAR-T targeting, relevant for ovarian cancer (Casey et al., *J. Immunother. Cancer* 2024).

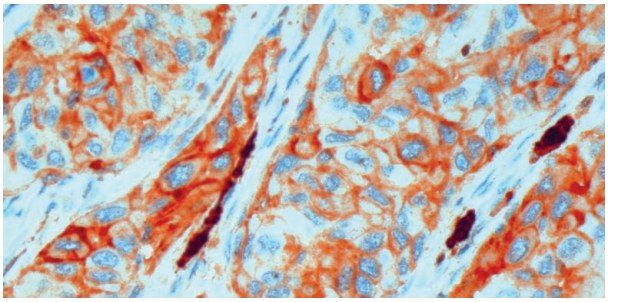


In **Team 2**, studies are being performed on biomarker discovery and validation in several human tumors, with additional work on how markers are related to mechanisms for tumor progress, especially within the TME. In particular, the novel technique of Imaging Mass Cytometry (IMC) has been applied for advanced multiplex tissue profiling at the single-cell level. Candidate biomarkers are used to map tumor diversity including associations with clinico-pathologic phenotypes and patient outcome.

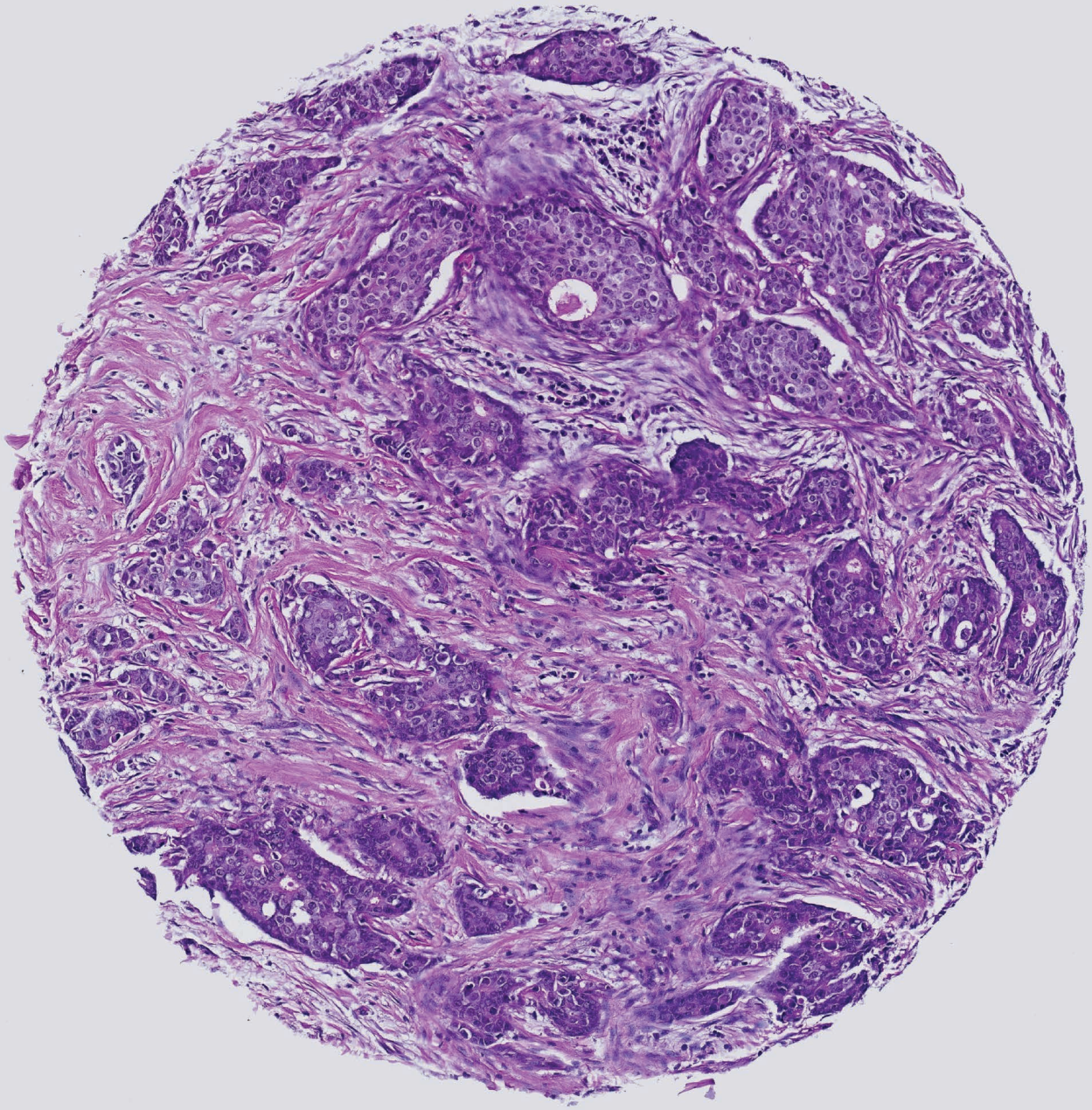
The **Akslen group** is concentrating on spatial single-cell and proteomics studies of breast cancer (BC), focusing on the biomarker value of these findings, as well as the emerging area of cancer neuroscience. The overall aim is to improve tumor stratification and treatment response prediction, and the focus is currently on profiling of luminal-like and basal-like breast tumors, using mass spectrometry proteomics (MSP) and imaging mass cytometry (IMC). By integrating BC cell line secretome data after hypoxia with stromal proteome information, unique TME-derived prognostic information and potential treatment predictive ability was found, indicating that stromal information is necessary to stratify these patients (Kjølle et al., *Nat Commun 2023*). Further, the group identified another stromal proteomic signature which could improve BC stratification, in particular among luminal tumors, and this finding has been validated in several independent cohorts (Finne et al., submitted). In clinical and experimental studies of cancer neuroscience, the group found that axonogenesis and angiogenesis are linked processes in aggressive breast cancer (Wik et al., in revision) and that co-cultivation of BC cells and neural progenitor cells leads to proteomic changes in both cell populations (Bjørnstad et al., *eBioMedicine*, in revision). In a study of breast and prostate cancer, the group recently also reported, in collaboration with Drs. Watnick and Brekken, that novel PRSS2 and TSP1 interactions could influence programming of the immune TME (Sui et al., *Nat Commun* 2022).



The **Lorens group** has been studying various aspects of how the Axl receptor tyrosine kinase is involved as a key regulator of normal adult epithelial progenitor cells and a determinant of carcinoma cell plasticity and interactions at the tumor-immune interface relevant for resistance to immunotherapy. Results have indicated an important role of Axl in epithelial-mesenchymal transition (EMT) and immune evasion (Engelsen et al., *Front Immunol* 2022), and studies have demonstrated how anti-Axl treatment (by bemcentinib) can reverse these processes. In a study of STK11/LKB1 mutant lung cancer (NSCLC), the team reported that Axl targeting can restore PD-1 blockade sensitivity (Li et al., *Cell Rep Med* 2022). Recently, the team reported that nuclear Axl and WRNIP1 interact and mediate replication stress response, promote therapy resistance, and support metastatic progression. This indicates that targeting the Axl/WRNIP1 axis is a potentially viable therapeutic strategy for breast cancer (Marquez-Palencia et al., *Cancer Res* 2024).

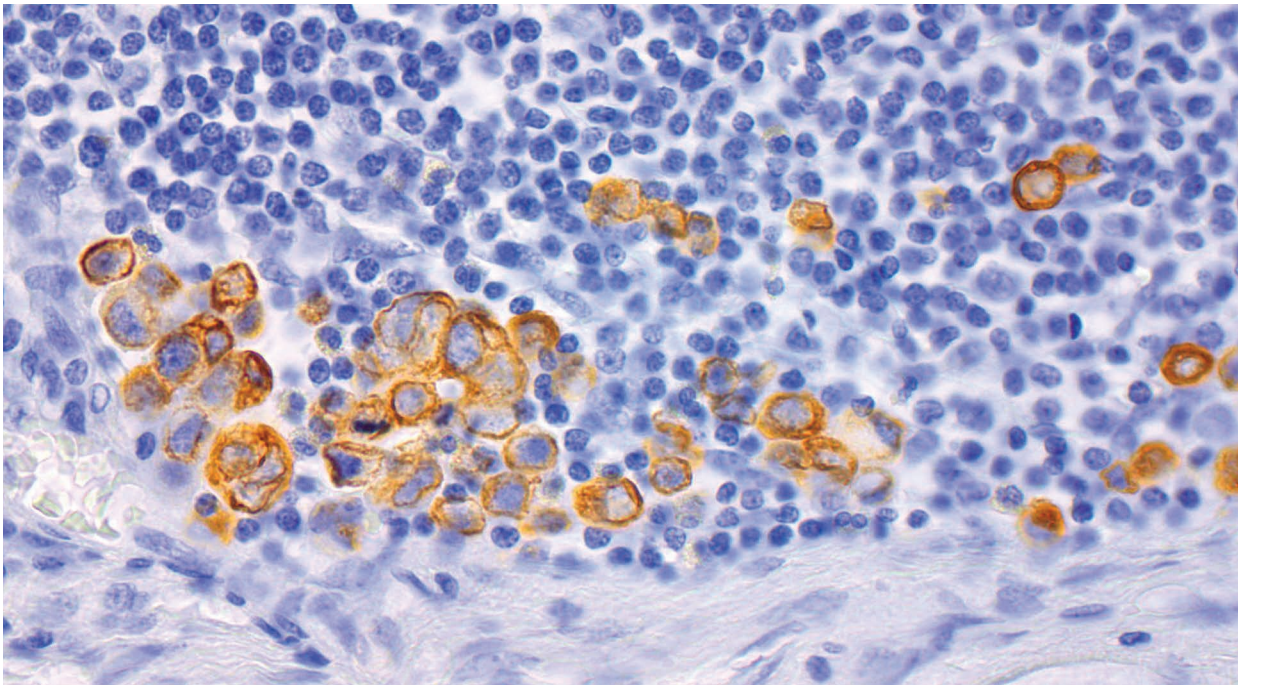


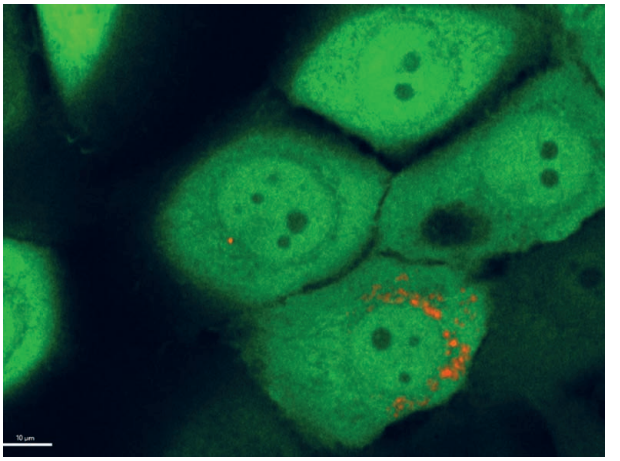
The **Costea group** studies mechanisms of tumor-stroma interactions in oral and vulvar squamous carcinoma, with focus on metabolic changes in carcinoma associated fibroblasts (CAFs), and the association with genetic alterations including HPV subtypes and their role for tumor progression. The group has presented data on miRNA profiling in head and neck cancer and found 12 differentially expressed miRs. Two of the significantly



The Cancer Globe

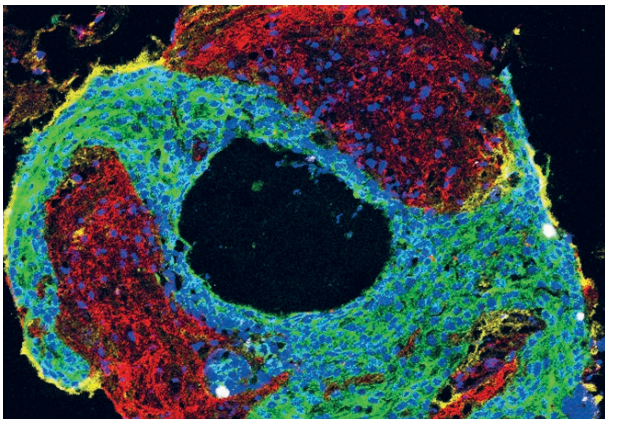
Tissue microarray core (diameter 1.0 mm) from a case of invasive breast cancer. Irregular 'geographical' areas of infiltrating tumor cells (darkest color) are surrounded by the supporting tumor microenvironment, with collagen fibers, inflammation, and scattered blood vessels.
(Photo: Kenneth Finne/Lars A. Akslen, CCBIO)





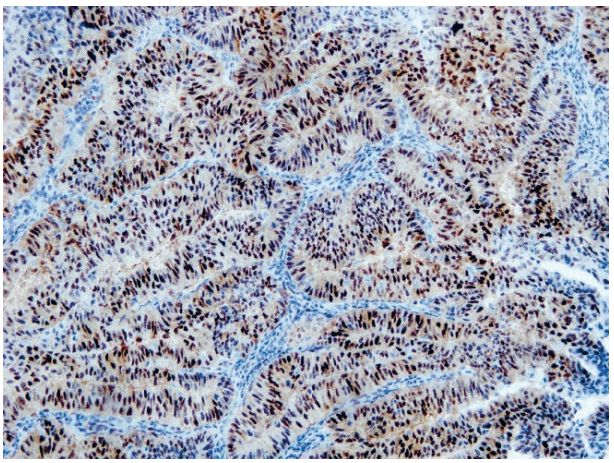
downregulated miRNAs in CAF, miR-204 and miR-138, have tumor-suppressive function through inhibition of fibroblast migration by modulating the expression of several different motility-related molecules (Rajthala et al., *Int J Mol Sci* 2021; Rajthala et al., *Front Oncol* 2022). The team recently reported that embryonic stem cells (ESC) can generate oral epithelia under matrix instruction (Das et al., *Int J Mol Sci* 2023). Also, a study of vulva squamous cell carcinoma demonstrated better survival for HPV positive cases (Dongre et al., *Acta Obstet Gynecol Scand* 2024).

The **Engelsen group** has focused on how phenotypic plasticity interferes with therapeutic efficacy and immune cell-mediated killing. The group has established lung cancer (NSCLC) patient-derived organoid and explant models recapitulating the complex tumor-immune microenvironment (TIME), and the current projects aim to elucidate the effect of phenotypic plasticity on the spatial organization of the TIME. This might illuminate how therapeutic targeting of phenotypic plasticity synergizes with immune checkpoint inhibition (ICI) therapy. Recently, the team reported how organoid and immune-competent explant models can be applied to explore how hypoxia and therapeutic interventions alter the cancer cell metabolism and the TIME structure (Zaarour et al., *Cancers* 2021; Engelsen et al., *Front Immunol* 2022). Also, tumor-stroma interactions in lung cancer were reported by spatial mapping using heterotypic spheroid models (Lotsberg et al., *Front Oncol* 2022).

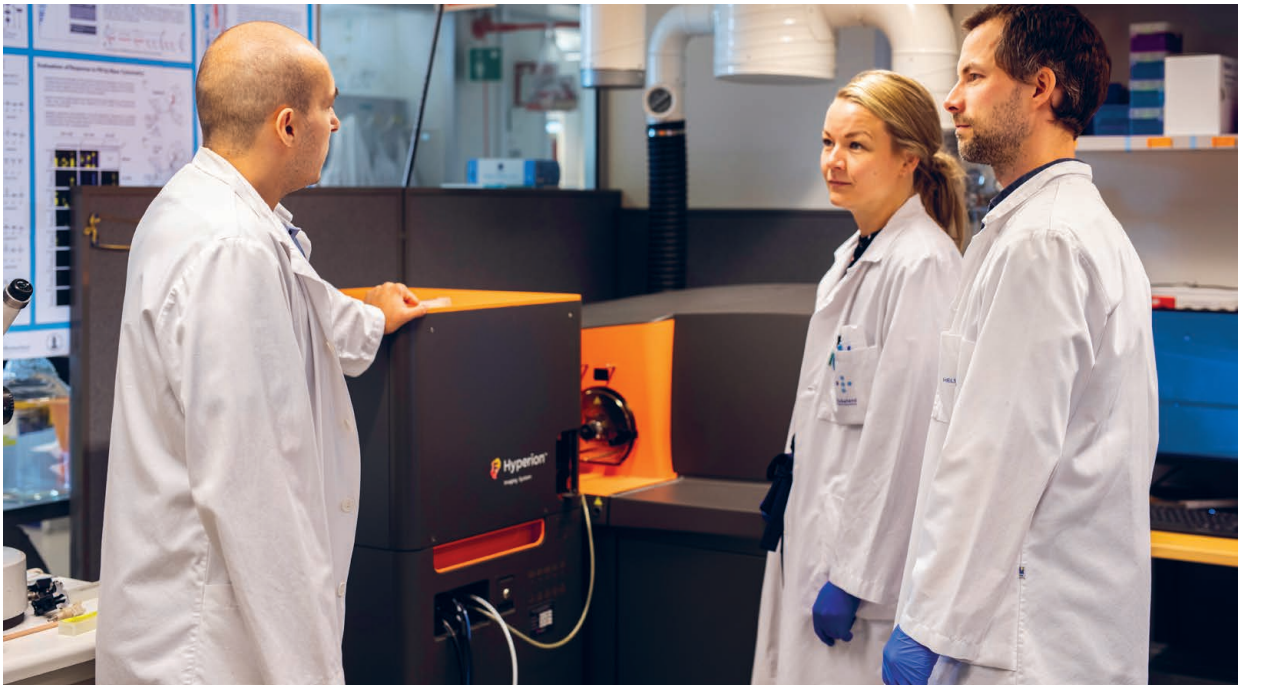




In studies of gynecologic cancers by the **Krakstad group**, tissue and serum-based biomarkers as well as genetic alterations are being explored. The inter-national MOMATEC2 study (NCT02543710), a phase 4 implementation trial for validation of ER/PR status to stratify for lymphadenectomy in endometrial cancer, is coordinated by the group. Models for endometrial cancer are being established and characterized, and integration of molecular and radiologic data with clinical phenotypes is ongoing. In a study investigating MMR status in paired preoperative and operative endometrial cancer biopsies, the group demonstrated a substantial agreement in MMR status between paired lesions (Berg et al., *Br J Cancer* 2023). In addition to determining MMR status, protein expression levels for MMR, particularly MSH6, may add prognostic information in endometrial cancer. Patients with endometrial cancer undergoing lymph node staging (LNS) without receiving chemotherapy are comparable with those not undergoing LNS (Forsse et al., *Am J Obstet Gynecol* 2022). The team found similar diagnostic performance in the low- and high-risk histology groups for central staging parameters by preoperative MRI and FDG-PET/CT (Fasmer et al., *Eur Radiol* 2022). The group recently reported that spatial single-cell analysis by imaging mass cytometry can improve stratification of low-risk endometrial cancer (Lien et al., *eBioMedicine* 2023).



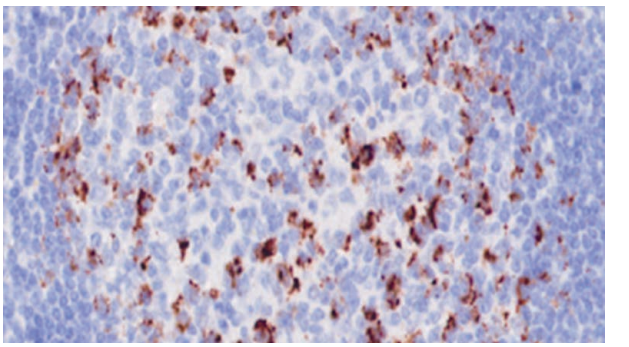
The **Strell group** studies regulatory mechanisms of early breast cancer evolution with a focus on genetic alterations and changes in the TME. The group aims to identify novel prognostic and predictive biomarkers which can support clinical decisions. Strell joined CCBIO during 2022 after receiving a Starting Grant from the Trond Mohn Research Foundation for the project *EvoMaps – understanding early breast cancer evolution in space and time*. Strell has been working on spatial tissue profiling techniques in Stockholm and Uppsala (Micke, Strell et al., *eBioMedicine* 2021). Previous work in the Mats Nilsson group (Science for Life Laboratory, Stockholm University) in collaboration with Lucy Yates (Wellcome Sanger Institute) has demonstrated a base specific *in situ* sequencing (BaSISS) approach to



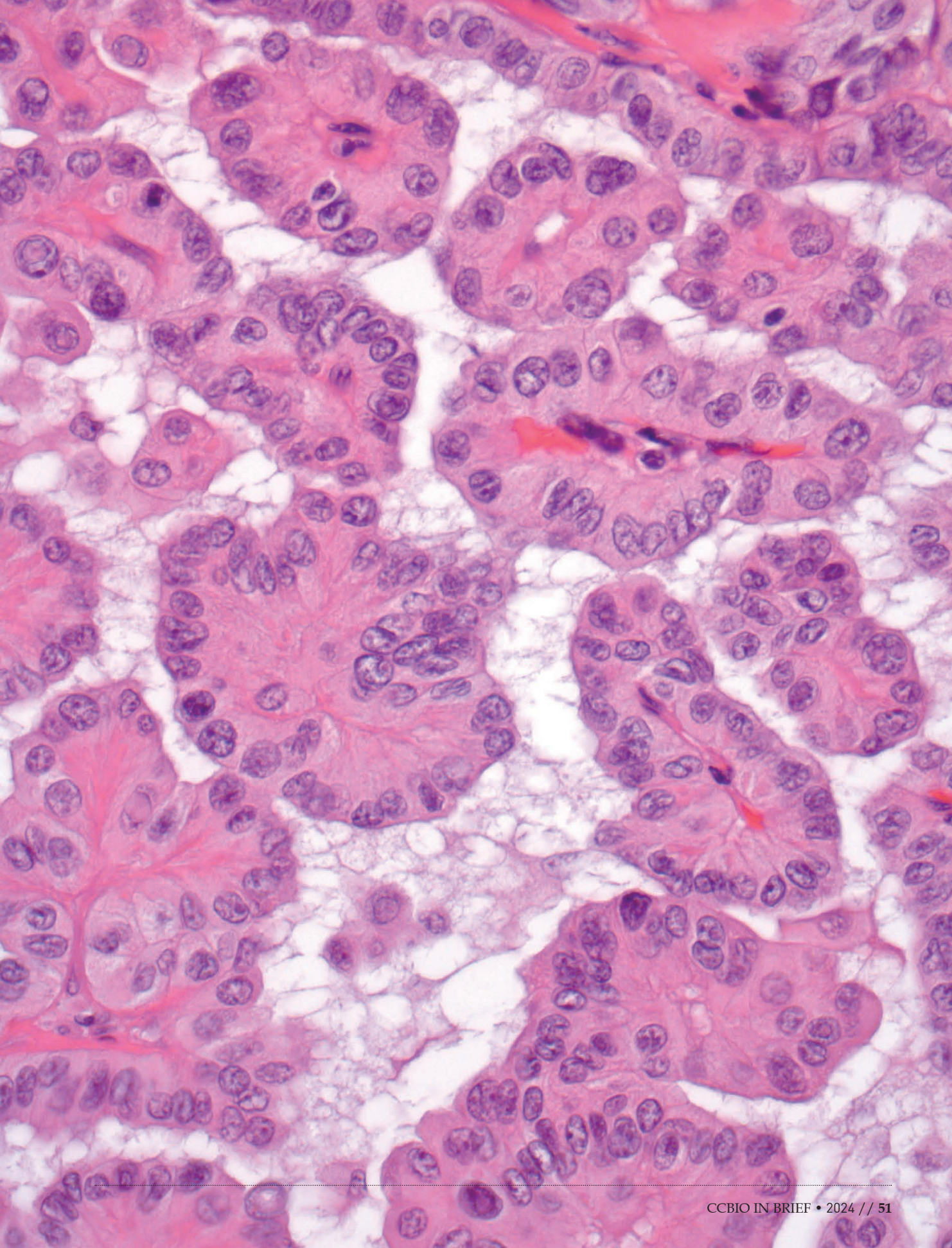
map mutations in breast cancer tissue sections in a highly multiplexed manner, allowing, for the first time, spatial lineage tracing of cancer cell clones in the histological context, with Strell being a key member of this team (Lomakin et al., *Nature* 2022). The affiliation with CCBIO will enable Strell to adapt the *in situ* sequencing approach to the Hyperion Imaging System for simultaneous mapping of genetic alterations and protein based cell typing. Strell is also working to decipher the immune architecture in DCIS; data on tumor infiltrating lymphocytes might define low risk DCIS (Schiza et al., *Eur J Cancer* 2022; Strell et al., *Clin Cancer Res* 2021).

The **Wik group** has a focus on breast cancer of the young and why these patients often experience a more aggressive disease behavior. A patient cohort has been established with multiple molecular and clinico-pathologic annotations, including primary tumors and metastases. Further genetic and imaging mass cytometric (IMC) profiling is ongoing. So far, studies on estrogen related signaling networks and transcriptomic profiles have revealed an age-related gene expression signature tightly linked to proliferation and prognosis (Ingebriktsen et al., *Br J Cancer* 2022). The team recently reported that young breast cancer patients (≤40 years of age) present more aggressive tumor features, including distribution of molecular markers, subtypes, metastases and poorer survival (Svanøe et al., *Int J Cancer* 2024; Ingebriktsen et al., *Mod Pathol* 2024; Ingebriktsen et al., *Breast Cancer Res* 2024).

In **Team 3**, the main focus is to perform clinical studies and trials with associated biomarker projects, and to promote novel findings on markers and treatments for clinical implementation and change of practice.



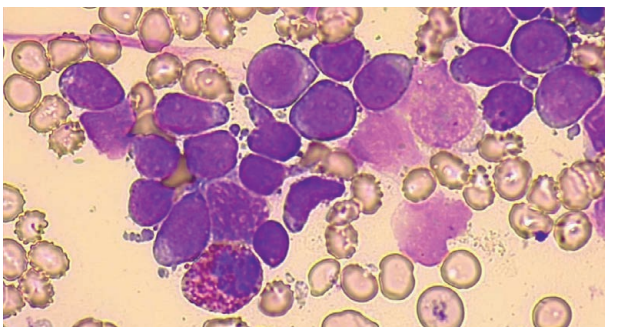
The **Bjørge group** is engaged in multicenter trials with translational research programs related to high-grade ovarian cancer, aiming to improve patient stratification and treatment efficacy. The group also has a focus on improved imaging guided cytoreduction surgery in this disease. In addition to clinical studies, PDX models and organoid cultures are being established. High-dimensional tissue profiling of ovarian cancer samples have been initiated with special attention to immune responses. Bjørge and colleagues reported on spatial profiling and phenotypic characteristics of the TME in ovarian cancers (Anandan et al., *Cancers* 2021). Data on immune profiling in ovarian cancer xenograft models after anti-PD-1 therapy have been presented (Kleinmanns et al., *Cancers* 2022). The team reported on metabolites during treatment of high-grade ovarian cancer (Torkildsen et al., *Metabolites* 2023) and on



CAR-T cell targeting of the CA125 domain (Casey et al., *J. Immunother Cancer* 2024).

Bjørge is currently president for NSGO (Nordic Society of Gynaecological Society), and she is a faculty member for gynecologic oncology at ESMO. From November 2022, Bjørge is the Co-Director of CCBIO.

The **Gjertsen group** concentrates on how intracellular signal transduction can be decoded to tell responders from non-responders early during cancer therapy. The experimental framework is based on tumor cells collected in clinical trials, dissecting how signaling in tumor cells is related to therapy response. In a recent key paper, the team reported on early response evaluation by single cell signaling profiling in acute myeloid leukemia (Tislevoll et al., *Nat Commun* 2023). In this study, it was reported that mass cytometry can be a valuable tool for early response evaluation and elucidate the potential of functional signaling profiling in precision oncology diagnostics. Further, Gjertsen is involved in multiple network projects. Huuhtanen et al. is the first to demonstrate a biological rationale for combining a small molecule inhibitor of ABL1 with immune therapy interferon alpha in a clinical trial (*J Clin Invest* 2022). Malani et al. follows up on a 2013 publication on *ex vivo* drug sensitivity screening in therapy guidance of the aggressive blood cancer AML. Notably, it is reported that as much as 60% of relapsed refractory patients can obtain therapy response if guided by drug sensitivity screen and gene expression analysis (*Cancer Disc* 2022). Also, Othman et al. indicate the complexity of AML genetics and how mutational panels are needed to optimize prognostication in AML (*Blood* 2022).



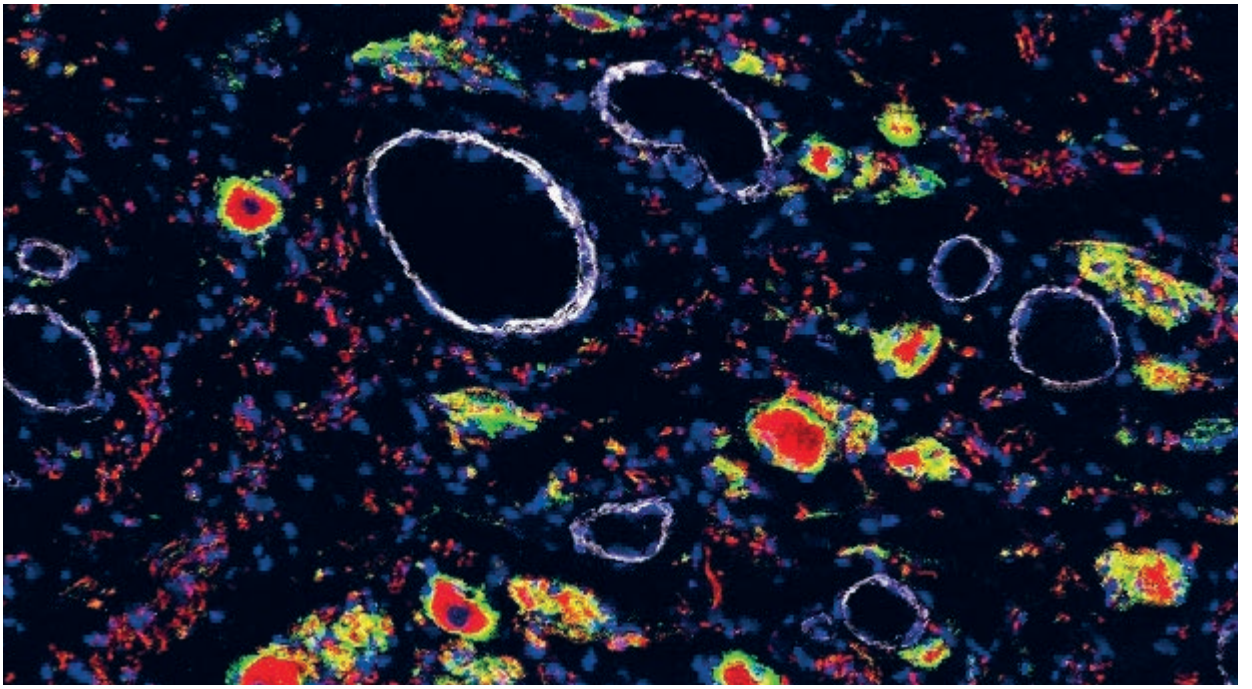
The **Straume group** is focusing on tissue biomarker studies in clinical trials. The group has reported an association between surgical tissue trauma and recurrence dynamics in high-risk breast cancer patients. A national academic trial combining anti-Axl treatment with immunotherapy is now closed (n=80) and is currently being explored for treatment predictive markers of anti-Axl therapy in advanced melanoma cases (Straume et al., *Ann Oncol* 2023; abstract). A national interventional study of patients with aggressive melanoma (IPI4; ipilimumab) is being analyzed, and some results have been presented. In 2021, data on ipilimumab treatment in metastatic melanoma from a phase IV trial was presented (Aamdal et al., *Int J* Cancer 2022; Aamdal et al., *ESMO Open* 2022).

In **Team 4**, the projects on ethics and economics of biomarker-based therapy are expanding and integrated in clinical trials. As CCBIO performs research on cancer biomarkers along the entire chain from studies of biological mechanisms to clinical practice, the main societal impact resides in this sense in the improvement of cancer diagnostics and therapies and in medical innovation. The main measure of this impact is ultimately its effect on the quality and cost-effectiveness of cancer management, whereas it cannot be precisely measured in the short-term. Better knowledge of cancer biomarkers is likely to affect the prioritization dilemmas, although the nature of that effect depends on the nature of the knowledge to be discovered.

CCBIO integrates work on societal perspectives and has established a team structure led by **Strand** to improve interdisciplinary humanities and social science programs to study the opportunities and challenges of precision cancer medicine. The team will continue their collaborations on the more conceptual research into RRI and the coproduction of science, technology, and society.

A key insight in Team 4 is that the quality of a biomarker is a complex issue with scientific and technical but also clinical, economic, ethical and political dimensions. Collaboration has increased between the **Strand group** and CCBIO economists (**Cairns group**) and ethicists (**Norheim group**). The team is responsible for the basic course *CCBIO903 – Cancer Research: Ethical, Economic and Social Aspects*.

The **Strand group** performs research on the ethical, legal, and societal aspects (ELSA) of CCBIO's research, distinguishing between three interrelated goals; 1: A better understanding of the developments, expectations and imaginaries of personalized and precision cancer medicine, including its political economy and ethical and social issues; 2: A better integration of this understanding into practices of "responsible cancer research" in the sense of RRI (Responsible Research and Innovation); 3: A better understanding of the complexity in cancer as illness, disease and sickness. The ELSA group of CCBIO interacts with and is tightly linked to similar ongoing RRI projects (NFR Res Publica and AFINO, and Horizon 2020 SuperMoRRI and TRANSFORM). In 2020, the group enjoyed a major strengthening with the inclusion of Professor Marta Bertolaso as adjunct professor, and a formalization of the collaboration with Bjørge's group. In 2022, the group reached an important milestone by the publication of the interdisciplinary research anthology *Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern*, edited by Anne Bremer and Roger Strand (Springer 2022). It constitutes a state-of-the-art



volume on interdisciplinary research on goal 1 above and represents if not the final word from CCBIO on these issues, at least the major milestone. While research with a strong philosophical dimension rarely can be summarized in terms of "findings", we may say that the volume offers a range of suggestions for how to *reframe cancer* and how to resolve the various ethical and social dilemmas around cancer biomarkers and personalized/precision cancer medicine, including those of equity and social justice as well as challenges of excessive medicalization. The aspect of media debates has been further pursued in 2022, also suggesting reframing as the solution (Nilsen et al., *Norsk Medietidsskrift* 2022; Stenmarck et al., *BMC Med Ethics* 2022). In the first results from the collaboration with Bjørge's group (Gissum et al., *Cancer Care Research* 2022), the team shows how aspects of ovarian cancer as illness, are poorly represented in treatment of the corresponding disease. The results have direct clinical relevance.

The main idea for the following years is to deepen existing collaborations, including with Bjørge's group, and with Akslen and Bertolaso on the understanding of complexity in cancer, also along the lines of Strand and Chu 2022, as well as to develop a stronger interdisciplinary collaboration with Cairns and Jiyeon Kang on the economic aspects of cancer biomarkers.

In the **Cairns group**, health economics research within CCBIO has focused on the economic evaluation of oncology drugs. Particular attention has been paid to the evaluation methods used and the contribution of different types of data (such as health outcomes recorded in clinical trials and real-world data). The most important project in recent years has been on *improving economic evaluation and decision-making for oncology drugs using real-world data*. This has involved a detailed analysis of two hundred and twenty-nine appraisals undertaken 2011–2021 in the UK. Another project has focused on how molecular targeted therapies and immune checkpoint inhibitors for the treatment of non-small cell lung cancer have been assessed.



Managed Access Agreements are being used increasingly in the UK as a means of improving access to treatments where the evidence of clinical effectiveness is too uncertain for the National Institute of Health and Care Excellence (NICE) to recommend routine commissioning. The Cancer Drugs Fund [CDF] was introduced in England in 2016 to give patients access to these potentially valuable treatments. The CDF provides the drugs for several years



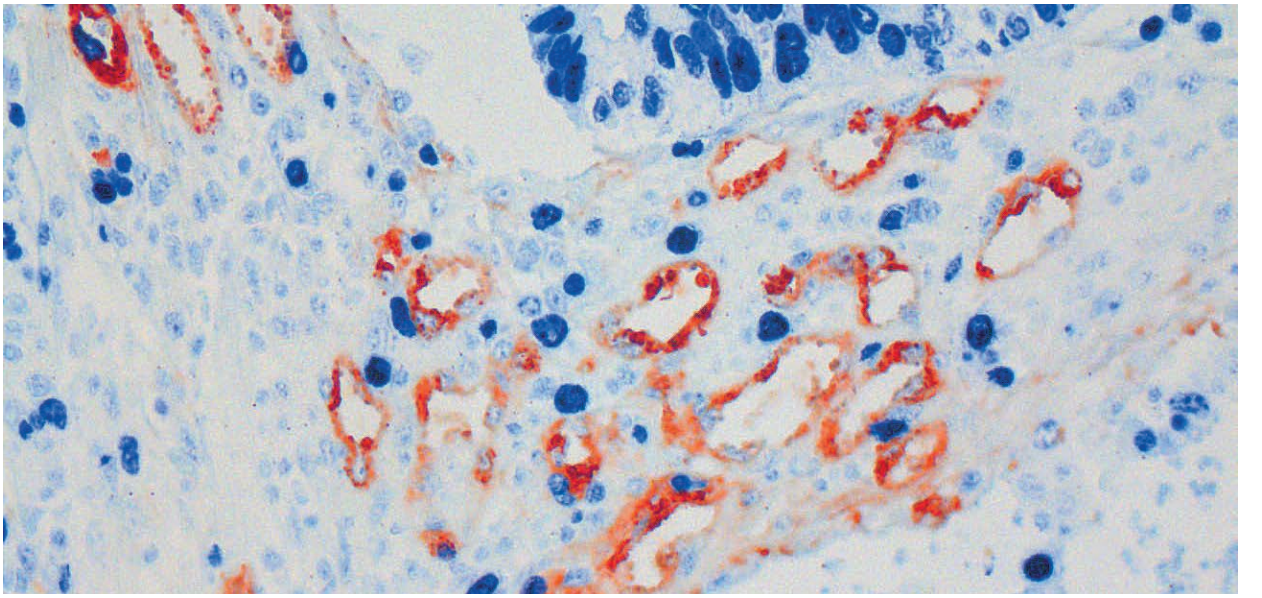
while additional data are collected before a final review of the drug takes place. An analysis by the Cairns group of the first twenty-four drugs to exit the CDF highlighted the important role played by longer follow-up of patients in the original clinical trials used to support the introduction of these drugs and the very limited role played by the data collected from patients receiving the drugs provided through the CDF. This is an important finding given the widespread enthusiasm for using real-world data to inform drug reimbursement decisions. Clear differences were observed between the appraisal of checkpoint inhibitors and that of molecular targeted therapies, at least in the context of non-small cell cancers. These differences derive from the more limited clinical data and the more restricted application of targeted medicines. In 2022, results were reported on the use of real-world data in access agreements appraisals of targeted cancer therapy (UK) (Kang et al., *Pharmacoeconomics Open* 2022; Kang et al., *BMC Cancer* 2022; Kang, Cairns, *BMJ Open* 2024). Notably, Jiyeon Kang successfully completed her CCBIO funded PhD thesis in 2023 at LSHTM.

In the **Norheim group**, the main aim has been to explore how biomarkers inform and potentially improve fairness in health care priority setting. Eirik Joakim Tranvåg's PhD thesis *Precision and Uncertainty* (2021) has been an important delivery. Findings in a conjoint analysis based on a survey of Norwegian medical oncologists suggest that biomarkers may be seen as relevant in clinical priority setting decisions for new and expensive cancer drugs. Results from an analysis of Norwegian drug appraisals also suggest that biomarkers are actively used and help facilitate drug coverage decisions at a national level. Despite this, Tranvåg argues in his thesis that priority setting actors still need to acknowledge that the increasing uncertainty in personalized medicine may lead to more difficult priority setting decisions. This cannot be dealt with only by developing better and more valid biomarkers, but also requires interaction between science and society, co-production of knowledge and a fair priority setting process.

Key publications from Norheim's group were Tranvåg's PhD thesis *Precision and Uncertainty: Cancer biomarkers and new perspectives on fairness in priority setting*, and the third and final paper in the thesis, *Appraising Drugs Based on Cost-effectiveness and Severity of Disease in Norwegian Drug Coverage Decisions* (published in *JAMA Network Open*, June 2022). The findings from this paper must be seen as a major result from the group, as it was highly relevant for the public debate about drug reimbursement in Norway. The group contributed to both of CCBIO's anthologies on the ethical, legal and societal aspects of cancer biomarkers, the last issue being *Precision Oncology and Cancer Biomarkers, Issues at Stake and Matters of Concern* (editors Anne Bremer and Roger Strand, Springer 2022).

During 2019–2022, the Global Health Priorities Research Group directed by Ole Frithjof Norheim has grown and developed into a center — the *Bergen Centre for Ethics and Priority Setting (BCEPS)*, with funding from the *Bill &*





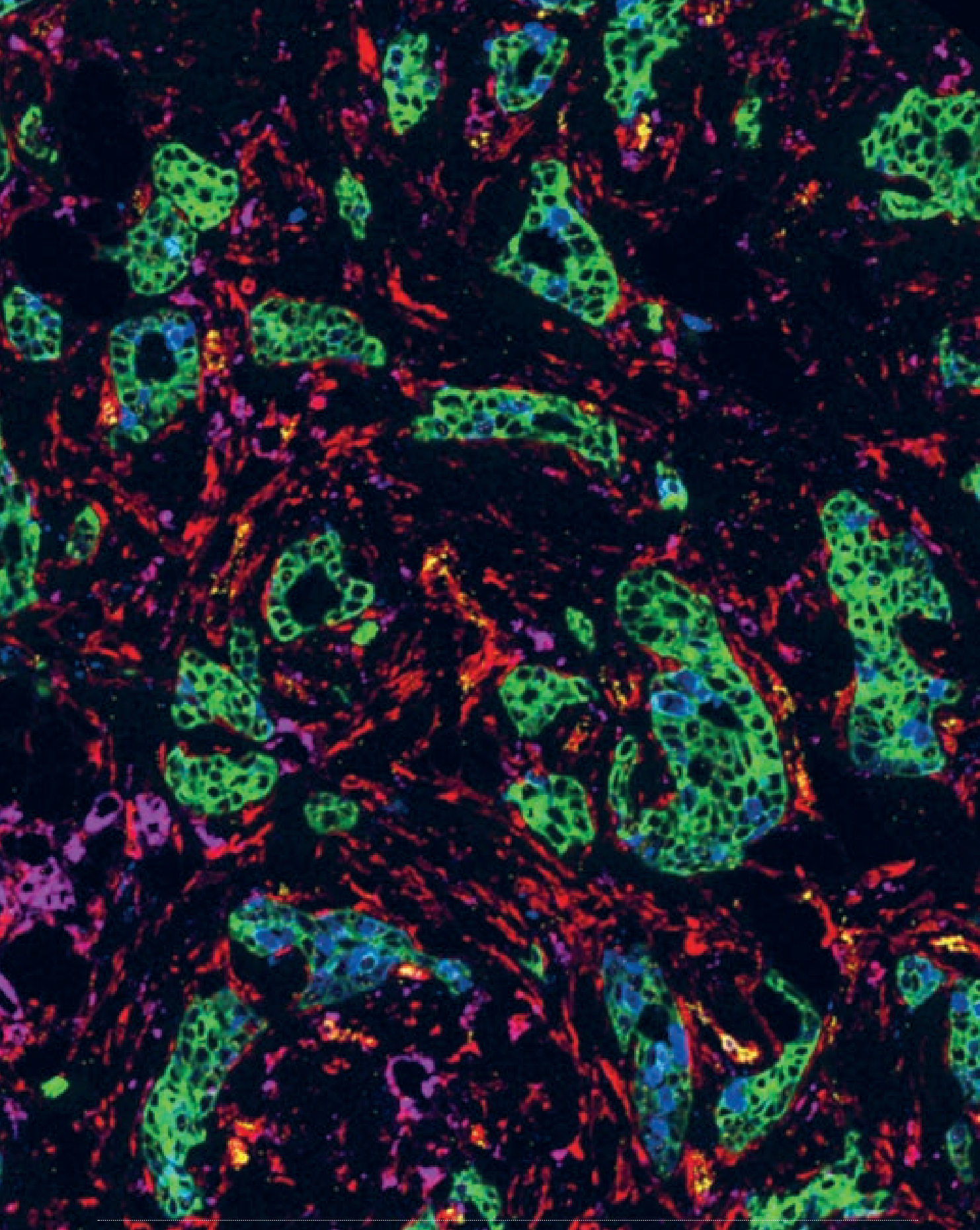
Melinda Gates Foundation among others. Notably, in 2022, Norheim was awarded a *Centre of Excellence (SFF-V)* from the Research Council of Norway, opened in January 2024.

The **Jonassen group**, working across the various teams and groups, performs research in developing computational methods for analyzing and discovering patterns in molecular biology data. Since the 1990s, the group has worked with a variety of different data types; new technologies have become available and new application areas have developed. In the context of CCBIO, the work has naturally focused on development of methods relevant for cancer studies and in particular to understand the TME and focusing on the use of RNA-seq gene expression data and later single-cell CYTOF and imaging mass cytometry (Hyperion) data. Within the frame of CCBIO, the group has had access to groups with leading expertise in different cancer types and the possibility to take part in experimental design of new studies coupled with planning the computational analysis of the resulting data and possible follow-up experiments.

An important sub-project has been the AML_PM project which has been funded by ERA_PerMed including Gjertsen from CCBIO and a consortium including groups from Germany, the Netherlands and Canada. In this project, the team has combined systems biology modeling of targeted signaling systems with machine learning approaches aiming to help select treatment options for individual patients based on the status of signaling pathways. Another important subproject has been the application of the Hyperion Imaging System to explore spatial aspects of the TME of breast cancer. The team has studied alternative workflows for image data processing and graph representations of the extracted data. This will indicate interactions between different cell types and their states and link this with patient prognosis and treatment response — and develop new biomarkers and information guiding design of new therapies. The team recently reported a novel spatial analysis approach called LOCATOR (Ehsani et al., *Bioinformatics Advances* 2023).

In conclusion, a range of research projects along with science education and communication have been conducted and reported on continuously since 2013. In addition, multiple new research initiatives have been conceived, in part based on increasing intramural collaboration and international networking. In addition to an increasing number of high-impact publications and four books presented by CCBIO (two of them published in 2022), multiple activities are being performed by the CCBIO Research School for Cancer Studies, with 12 core courses. Notably, the CCBIO Masterclass program has now completed two cycles (2021–2023), the third being planned for the fall 2024, with teaching and training of young investigators aiming for independence and future positions as group leaders. The CCBIO-ARC (advanced research colloquium) has been initiated. Notably, in 2022, Norheim was awarded a Centre of Excellence (SFF) from the Research Council of Norway, and Gjertsen was awarded a KGJ Center for leukemia studies. Akslen received the Helse Vest Research Award for 2023.

When CCBIO now approaches the transition phase to CCBIO2.0 and post-RCN continuation of the center, we plan ahead as we optimistically reflect on the "core concepts" and integrated activities of the center and the strive for responsible real-life impact. ••



research school activities

The CCBIO Research School for Cancer Studies (RSCS) has a focus on high-level educational activities related to basic, translational and clinical cancer research, health innovation, and ethical, legal and societal aspects of cancer research and treatment. The RSCS also supports flexible forms of international exchange, mobility and mentoring. The research school provides 12 ECTS-giving PhD-level courses and a broad range of other activities. The RSCS is well established as a scientifically stimulating and inclusive arena for students and researchers from various research fields, and the PhD candidates and postdocs get opportunities to meet and discuss their projects in an interdisciplinary and international research environment. CCBIO has successfully integrated its strategic activities, like the CCBIO Annual Symposium, CCBIO Junior Scientist Symposium series and CCBIO Seminar Series, into the RSCS.

All courses and most activities are open to researchers on all levels — from the youngest students to senior researchers and faculty, regardless of affiliation. CCBIO regards its open policy as an important measure to achieve a high degree of knowledge transfer and cross-field communication. As part of this open policy strategy, the RSCS offers participants to choose between receiving ECTS credits or attending for the transfer of knowledge only. It is our perception that open participation, also without taking ECTS credits, contributes towards the overall quality of our courses and strengthens the research environment, benefiting CCBIO and its PhD students. Events are announced also outside of CCBIO, through the Nordic Doctoral Education in Health Sciences (NorDoc) network and through CCBIO's international faculty and networks.

When inviting speakers for lectures and seminars, CCBIO normally uses the opportunity for students and researchers alike on all levels of seniority to meet the speakers, to allow mapping out of potential points of common research interests for future collaborations. In combination with the recruitment of a network of international affiliated researchers, this ensures that the center's researchers have access to renowned international and national scientists from other research communities irrespective of their career stage.

Agnete Engelsen and Erling A. Høivik in 2023 replaced Elisabeth Wik as Heads of the Research School for Cancer Studies (RSCS). The RSCS has an established collaboration with the Neuro-SysMed Research School, a center for clinical treatment research on neurological diseases. This collaboration has resulted in the development of three popular research courses: CCBIONEUR910 Patient and Public Involvement in Medical and Health Research, CCBIONEUR911 Clinical Trials course, and CCBIONEUR912 Health Innovation course.

In 2023 and the spring term of 2024, CCBIO held the courses that run continuously (CCBIO901 and CCBIO902), as well as CCBIO907 in March 2023, CCBIO908 in May 2023 and May 2024, CCBIO906 in October 2023, CCBIONEUR911 in January 2024, CCBIONEUR910 in April 2024, and CCBIO904 in May 2024. You can read more about these activities in separate paragraphs below. For 2025 and the fall of 2024, the RSCS plans to run CCBIO901 and CCBIO902 continuously as well as CCBIO905 in the fall term 2024, and CCBIONEUR911 and CCBIONEUR912 in the spring term of 2025. We seek to facilitate learning by the most suitable pedagogic methods and engage the students in various forms of active learning experiences. As examples of adapted methods, we would like to mention mixed onsite and online participation, case-based collaborative learning (CBCL), blended learning programs (CCBIONEURO912), as well as integrating patient user groups directly in the teaching (CCBIONEUR910). We aim to support the students' inner motivation by providing inspirational lectures, interdisciplinary collaboration and group presentations, as well as formative assessment.

CCBIO901 and CCBIO902
- Courses integrated into CCBIO's strategic activities
CCBIO's Junior Scientist Symposium, where PhDs and postdocs organize their own seminars and present their results four times annually, forms the PhD Course CCBIO901. CCBIO's monthly seminar series and the CCBIO Annual Symposium form the PhD course CCBIO902. These activities are described in detail in separate chapters.



CCBIO903
- Cancer Research: Ethical, Economic and Social Aspects
CCBIO903 is a two-week, 5 ECTS PhD course designed as a unique opportunity for PhD candidates to question the assumptions underlying their work, reflect on and discuss the robustness, opportunities, and limitations of their research, and anchor it in broader ethical, legal, societal, economic, and political contexts. The core of the course is structured around the two CCBIO books edited by Anne Blanchard and Roger Strand: "Cancer Biomarkers: Ethics, Economics and Society" (2017, Megaloceros Press), and "Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern" (2022, Springer).

CCBIO903 aims to address several key questions:
•What are the promises, limitations, and consequences of the "imaginaries" of precision oncology?

•What are the opportunities and limits of biomarkers, and what is a "good enough" cancer biomarker in that context?

•How do we take medical decisions when faced with risks, uncertainties and even ignorance?

•In a highly medicalized culture, what does a "good life" look like for (future) cancer patients? What does it mean, to be in "good health"?

•How is precision oncology addressed and framed in the media? What consequences does this have on society, economy, politics, and science?

• What is fair priority-setting for distributing the newest precision cancer therapies?

• How can economic models help guide health care resource allocation? Is it at all possible to assess the cost-effectiveness of cancer biomarkers?

The course is highly interactive, and the lectures invite the participants to take part in extended reflexive discussions with the teaching team and among themselves. At the end of the course, all candidates are asked to present their research in relation to broader social, ethical and economic aspects.

The teaching has from the outset been highly interdisciplinary with Roger Strand from philosophy of science, Anne Blanchard from science and technology studies, John Cairns from health economics and Marta Bertolaso who co-designed new elements in the course and introduced the participants to the philosophy of cancer and to emerging epistemological issues in cancer research as well as the complexity of cancer. In addition, several guest lecturers have been invited to share their perspectives across disciplines ranging from oncology, philosophy of medicine, economics, media studies and ethics of prioritization in health care.

The course has been held six times since 2015 and was last run in the fall term of 2021. The participants then came from a great variety of backgrounds, ranging from medical and clinical science to health economics and tissue engineering.

CCBIO903 is organized and executed by Roger Strand, Anne Blanchard, Marta Bertolaso and John Cairns.



CCBIO904
- Biomarkers and Tumor Biology in Clinical Practice
CCBIO904 is a 4 ECTS course covering broad tumor biological topics that are important for understanding how cancer occurs, and the mechanisms that control tumor growth and morbidity. The course has a particular focus on biomarkers that have or may have significance for personalized cancer treatment and clinical trials studies

of new diagnostics and treatment. The course includes lectures, demonstrations, group work, curriculum, and a written exam, aiming to give PhD candidates in cancer research a broad understanding of various aspects of tumor biology based on updated knowledge. The PhD candidates will also gain deeper insight into how knowledge about tumor biological changes affects our strategies to customize assessment and treatment for this group of patients.

Upon completing this course, the candidate should have the skills to:

- Formulate problems and suggest research on molecular biological aspects in cancer and cancer development in order to map tumor biological mechanisms.
- Critically assess the expediency and challenges of using different approaches for researching molecular and biological aspects of cancer.
- Select relevant literature that deals with molecular aspects important in cancer.
- Evaluate how knowledge about molecular changes in cancer may provide a better and more precise diagnosis.
- Propose new strategies for development of more targeted therapies and testing of cancer drugs.
- Understand challenges and possibilities for introducing more targeted therapies and better follow up of cancer patients.

To pass, the candidates need to participate in 90% of the lectures, prepare for and participate actively in the group assignments, and prepare an oral presentation together with the group. The course is completed by a one-hour written exam. CCBIO904 was most recently organized May 29-31, 2024.

Oddbjørn Straume has the academic responsibility for this course.

BMED904 - Matrix Biology

BMED904 is a 3 ECTS course from the Bergen Biomedical Research School (BBRS) that has been included into CCBIO's course portfolio as a joint effort with the CCBIO RSCS since 2015. The course focuses on basic molecular mechanisms pertaining to the biological role of the extracellular matrix and runs over five days every second year or on demand, including lectures from local researchers and several internationally well-known scientists within the field of matrix biology.

Upon completion of the course, the candidate should have knowledge of the different cell-matrix interacting components, and the underlying principles governing cell-matrix interactions. They will get an understanding of experimental procedures used to study interactions of cells with the extracellular matrix and of the role of the extracellular matrix for normal hemostasis and for selected clinical problems. At the end of the course, they should be able to demonstrate analytical thinking by critically evaluating a scientific article and proposing possible research questions and designing suitable research strategies for answering the questions.

The last course was held in June 2021, where it was combined with a DIKU summer school in fibrosis that is part of the MOTIF-network. BMED904 is normally a very hands-on course with personal attendance, but due to the pandemic, the course was adapted to digital teaching with online presentations of all lectures and video demonstrations of practical lab work. Three lecture highlights included speakers Ritva Heljasvaara (Oulu, Finland), Cathy Merry (Manchester, UK) and Joanna Philips (UCSF, San Francisco). In addition to attending lectures, the students read relevant articles, worked on articles group-wise and presented their articles online for the rest of the participants. Microscopy of integrin-tagged cells, cell cultures in 3D collagen matrices, spheroid formation and traction force microscopy were demonstrated. The participating students evaluated BMED904 as excellent and well organized, with inspiring and interesting lectures giving a good overview of the ECM and its importance in health and disease. Apart from the students, the lectures were open to all interested.

BMED904 is organized and executed by Marion Kusche-Gullberg and Donald Gullberg.

CCBIO905 - Methods in Cancer Biomarker Research

CCBIO905 is a 5 ECTS PhD-level course covering a wide range of topics from basic techniques on nucleotides and proteins to more advanced approaches, as well as bioinformatics and biobanking. The course focuses on methods to study biomarkers in tissue samples, blood samples, circulating tumor cells and DNA, and other biological materials. Methodologies like PCR techniques, microarray, next-generation sequencing, tissue microdissection and proteomics, bioinformatics and artificial intelligence, immunohistochemistry, *in situ* hybridization, imaging mass cytometry, protein ligation assays, Western blot and ELISA, flow cytometry including mass cytometry, and biobanking are presented. Changes in nucleic acids and proteins in different settings are discussed, as are the clinical applications of the various methods. As an integral part of the course, the students are required to prepare group presentations on important scientific papers describing results from clinical trials that have led to approval of new cancer treatments. The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presentations are given to the other course participants and a panel of experts that participate in discussions with the students. Based on the reflections and feedback from the students, this has proved a valuable learning experience for all. The course is concluded by a three-hour multiple-choice exam.

The course was last arranged September 27-29, 2022, and is scheduled again in the fall of 2024. Lars A. Akslen and Agnete Engelsen hold the academic responsibility for this course.



CCBIO906 - Cancer Genomics
CCBIO906 is a 3 ECTS course providing a broad understanding of the main aspects of cancer genome research by next generation sequencing (NGS) technologies and associated analytical tools, and how NGS can be applied both to identify new cancer biomarkers and for diagnostics as well as in treatment selection. To pass the course and earn credits, the candidate must be present in at least 90% of the course, participate actively in the group work, and pass a group assignment, to promote active learning, collaboration and networking.

CCBIO906 was first held November 2017. When the course was last held, October 23-26, 2023, an overview of NGS methods, data sharing and data management, as well as open sources for genomic data were covered. The topics also included single cell sequencing, data analysis of whole genome data, copy number variants, RNA, and structural variants. Furthermore, as there is increasing focus on liquid biopsies in current cancer research, this topic was timely and highly relevant for demonstrating how NGS can be implemented into the clinical work with cancer patients via clinical studies and clinical trials. The possibilities and challenges of drug repurposing and working with patients with heritable diseases and their families were also presented.





Group work is an important part of the course, and the participants did an excellent job in planning, discussing and presenting relevant topics within the field of cancer genomics, covering some of the main focus areas of the use of NGS in research settings and potential clinical applications, as well as the ethical aspects of applying new findings clinically. The participants also had the opportunity to pose questions prior to the course, and most questions were debated during the course.

In 2023, Erling A. Høivik was academically responsible for the course.



CCBIO907 - Cancer-Related Vascular Biology
CCBIO907 is a two-week intensive course (6 ECTS) that is part of the CCBIO-VBP/Harvard INTPART-II project "Bergen-Harvard Cancer Studies phase 2: Continued Partnership for Responsible Education, Research and Innovation Excellence." Participants benefit from experienced lecturers from the **Vascular Biology Program (VBP) at Boston Children's Hospital and Harvard Medical School** who have been in the frontline of vascular biology research for decades. Upon completing this course, the candidate should have:

- Knowledge about basic vascular biology, principles and challenges related to personalized medicine, cancer-related vascular biology and how this knowledge is applied within cancer treatment today as well as the status of frontline research of vascular biology, ways of exploiting knowledge of vascular biology in search for new treatment strategies, and cancer-related biomarkers in cancer diagnostics and treatment.

- The skills to formulate hypotheses to plan and conduct studies on cancer-related vascular biology, consider utility and limitations in use of cancer related biomarkers and be able to communicate relevant literature and methods concerning cancer related vascular biology, with critical reflection.

- The ability to evaluate how knowledge about vascular biology can assist in understanding tumor biological processes and mechanisms, and use it as a guide to


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improved diagnosis, targeted treatment, and follow-up of cancer patients.

Topics range from discovery to clinical application, lymph-angiogenesis and vascular biology in noncancerous diseases. The course presents knowledge about relationships between vascular biology, cancer progression, and diagnostic and treatment options directed towards the vasculature. Applied methods for studying vascular biology and biomarkers reflecting cancer-related vascular biology are also covered. In order to pass, the candidates need to participate in 80% of the lectures, prepare for and participate actively in the group assignments, and prepare an oral presentation together with the group.

CCBIO907 was arranged for the first time in 2018. The course was last held March 20-31, 2023, with VBP faculty Bruce Zetter, Diane R. Bielenberg, Michael S. Rogers, Steven Swendeman, Randolph Watnick, Ed Smith, and Dipak Panigrahy, in addition to CCBIO's local expert Oddbjørn Straume. During each course, the Harvard faculty also introduces a set of essential soft skills to the participants. In 2023 these were "Pitch preparing", "Proposal writing" and "Mentorship".

Agnete Engelsen and Lars A. Akslen held the academic responsibility in 2023, with facilitation on the US side by Michael S. Rogers from the VBP.

CCBIO908
- Scientific Writing and Communication Seminar
CCBIO908 is a 2 ECTS course that is part of the CCBIO/VBP-Harvard INTPART collaboration since 2017. It covers topics of scientific writing and communication, such as organizing ideas, improving manuscripts, clear writing, scientific storytelling, titles and abstracts, cover letters, common mistakes, and making a manuscript memorable. The lecturers draw from their vast experience both as writers of scientific texts and reviewers of publications. The main lecturer, Christine Møller, is a recognized lecturer in medical and scientific writing with many years of experience as assistant editor of APMIS (*Acta Pathologica Microbiologica et Immunologica Scandinavica*). Established additional lecturers are Randy Watnick (since 2017) and Diane Bielenberg (since 2024), both from the Vascular Biology Program and Harvard Medical School. In addition, CCBIO's media advisor Marion Solheim contributes with a session on science presentation, showing how to make a presentation stick — in a good way, also covering the use of



language, layout and how to avoid information overload, as well as body language and tone of voice.

CCBIO908 was first run in December 2017 and from 2019 onwards it has been an annual event due to its popularity. The course was last held May 21-22, 2024.

Elisabeth Wik was academically responsible until 2023, relieved by Erling A. Høivik as of 2024.

CCBIONEUR910 — Patient and Public Involvement in Medical and Health Research

CCBIONEUR910 is a 2 ECTS course that aims to create a platform for competence development and networking across professional- and user roles, facilitating communication and sharing of experience from multiple perspectives. Furthermore, an overarching ambition of the course is to stimulate increased user participation in clinical trials and research projects by presenting inspirational examples and tools for successfully implementing user participation in practice. The main objective is to develop the participants' capacity to assess and convey the value of patient and public involvement in general, as well as promoting productive user involvement in participants' research projects by educating both researchers and users in a colloquial setting.

The course was first run in 2021, then again in 2022, and most recently April 17–19, 2024. The course encompasses a broad spectrum of national and international lectures from researcher and user organizations, the Norwegian Research Council, professional users, and health care employees assigned to specific user representation tasks. Challenges are addressed from both researcher- and user representative perspectives, and specific advice as well as professional and personal opinions are shared. The atmosphere during the course reflects open-mindedness and an overall pragmatic attitude to find common denominators and move forward in the heterogeneous meadow of user representation in medical research.

Group sessions include pre-arranged case discussions as well as each participant bringing forward their own projects for scrutiny, discussion, and advice from user representatives. Finally — the researchers present the highlights from the group sessions in plenary sessions, also revealing custom-made take-home messages from the user representatives.

The course is a collaboration between CCBIO, Neuro-SysMed, REMEDY, NorHEAD, NorCRIN and FORMI and is in 2024 and 2025 supported by a grant from the DAM Foundation through Nasjonalforeningen for Folkehelsen. Participating user organizations also contribute towards the running costs of the course and cover the reimbursement of travel and housing costs of their participating representatives.

Nina Jebsen (CCBIO) and Kjell Morten Myhr (Neuro-SysMed) and Tone Skår (Neuro-SysMed/VIS) hold the academic responsibility for this course.



CCBIONEUR911 — Clinical Trials in Cancer Research
CCBIONEUR911 is a 2 ECTS course qualifying for a Good Clinical Practice (GCP) certificate, first held in 2019 and at that time organized by Line Bjørge, and Hani Gabra from our International Faculty. It has since been expanded as a collaborative effort with Neuro-SysMed and is held as an ECTS giving course in addition to qualifying for the GCP certificate.

Clinical trials are studies performed in humans, aimed at evaluating one or more medical, surgical or behavioral interventions. Such trials are the primary method to determine whether a new treatment is safe and effective, and whether companion biomarkers can be applied to stratify patients for novel therapy. Usually, a clinical cancer trial compares the most effective known treatment for a specific type or stage of cancer with a new approach, although other designs are increasingly used. Today, there are clinical trials for almost every type of cancer, and the numbers are increasing. While many trials focus on late-stage disease, there are also trials for cancer prevention and early diagnosis and survival and prevention of recurrence.

The course modules are based on the ICH_GCP R2, and cover topics from design planning to execution, such as general principles of clinical trials, ethics and the patient perspectives, GCP overview, operations and practicalities, formalities and regulations, translational research protocols, making clinical trials part of normal clinical operations, success factors and clinical trials in the future. Examples from cancer research and neurological research are embedded in the sessions. In addition to lectures, the participants are engaged in group work with presentations, where they discuss interesting ethical issues in clinical studies within the fields of cancer research and neurology, emphasizing autonomy, beneficence, and justice.



The course was most recently organized January 17–19, 2024, with Line Bjørge (CCBIO) and Øivind Grytten Torkildsen (Neuro-SysMed) as academically responsible.

CCBIONEUR912 — Health Innovation Course
CCBIONEUR912 was established as the first PhD course at the UiB with a focus on health innovation and was arranged for the first time in 2021. This course provides an invaluable opportunity, especially for early career medical researchers, to gain insights on how to bring research to society and offer perspectives on alternative entrepreneurial career paths. The overall aim of this course is to encourage and enable PhD students and young researchers to identify and evaluate their own research projects' innovation

potential. The course consists of two modules over a total of four seminar days of synchronous work in addition to three modules of asynchronous online work. Team-based discussions and assignments are part of the asynchronous online program. CCBIONEUR912 is a collaboration between CCBIO and Neuro-SysMed and benefits greatly from affiliates of both centers with innovation experience. The course provides inspiring lectures by people who have walked this path before them, and thus various routes to exploitation of research-driven innovations.

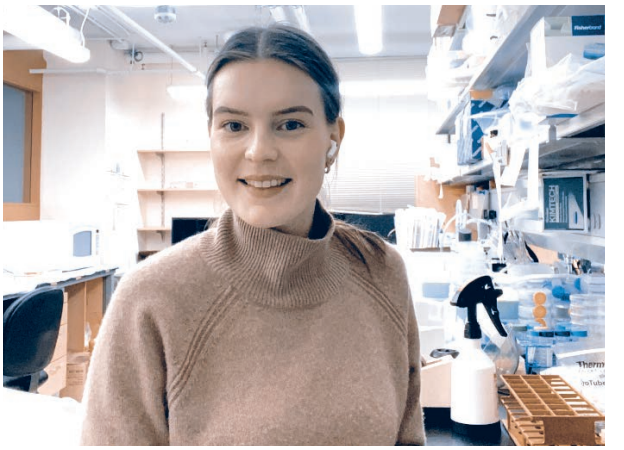


The course was last run November 8-9 and December 2-3, 2021. Jim Lorens focused on how the rich innovation culture at Stanford University was an essential inspiration for his own career path and encouraged him to think outside the box. Emmet McCormack shared his insight into what it takes to make a successful company like Kinn Therapeutics in addition to running a research lab, and Karl-Henning Kalland presented his research and the exciting work of the company he founded, Alden Cancer Therapy II. An absolute highlight was the inspirational keynote lecture by Professor Robert S. Langer, researcher and co-founder of the biotech-company Moderna, with a talk on his successful career path. He encouraged the participants to look for good role models, endure criticism and think big. Further sessions with Ingunn Johanne Ness and Ole Dahlberg were made available to a wider audience as a Special Seminar on Creativity and Innovation Leadership. The Design Thinking workshop, tailored especially to the PhD students, also scored very highly on the students' evaluations. This engaging and intense 5-hour workshop was created and arranged by Federico Lozano, Susan Johnsen and Yves Aubert, and focused on how to achieve human-centered innovation and an open mindset that facilitates the generation, testing and exploitation of creative ideas and solutions. The students were also encouraged to develop a "solution" to a selected problem and deliver their investor pitches to an expert panel consisting of Yves Aubert, Maija Slaidina and Andreas Vestermoen.

Agnete Engelsen (CCBIO) and Magnus Alvestad (Neuro-SysMed) had the academic responsibility for CCBIONEUR912 in 2021/2022. The course is scheduled to run again in the spring term of 2025.

CCBIO-VBP Lab Visit Program

CCBIO and the Vascular Biology Program (VBP) at Boston Children's Hospital and Harvard Medical School established a Lab Visit Program in 2018, as part of the CCBIO-VBP/Harvard INTPART collaboration. Selected PhD candidates as well as master-level students from the Medical Student Research Program (UiB) have since been offered internships at VBP labs. In 2018 and 2019, three students attended this program each year for 8–12 weeks. The students were warmly welcomed by PIs and staff in the labs of Randy Watnick, Marsha A. Moses, Diane Bielenberg, and Michael Rogers, learning a range of different lab techniques and improving their presentation skills and critical paper reading.



Due to the pandemic, the program was on hold throughout 2020–2022. In 2023, three CCBIO students participated in a 12-week lab exchange in the spring term (the Rogers, Watnick and Hla labs), and one student in the spring term of 2024 (the Rogers lab). Joining the Lab Visit Program has proven educational, inspiring, and challenging, and all CCBIO students attending have reported great educational and scientific benefits from their Boston visits. Networking with students and faculty at the VBP is rewarding for the students, and of great value for their research careers.

Since the fall of 2022, the CCBIO–VBP Lab Visit Program has been organized by Agnete Engelsen.

International Collaboration and Further Development of Courses

As part of its strategic emphasis on internationalization, CCBIO has recruited an international network of adjunct



researchers. These international collaborators take an active part in projects and in CCBIO RSCS courses, seminars and larger meetings as well as tutoring and mentoring younger researchers. Other external international and national faculty are also invited as lecturers to courses and seminars. In sum, this provides ample opportunities for CCBIO RSCS affiliated students and researchers and other interested staff to meet and interact with influential experts in the cancer research field.

As part of its extended internationalization effort, CCBIO was granted a total of 7.5 mill NOK from the *International Partnerships for Excellent Education and Research (INTPART)* program, run jointly by the Research Council of Norway (RCN) and the Norwegian Directorate for Higher Education and Skills (HK-dir). This funding was granted in two batches, first in 2016 (INTPART-I), and then a continuation grant in 2020 following excellent reviews (INTPART-II).

The INTPART project is a reinforcement of existing collaborations between CCBIO and Boston Children's Hospital and Harvard Medical School, following Lars A. Akslen's collaboration with the Folkman lab since 2004 and later with strong support from the subsequent director of VBP Marsha A. Moses as well as from Bruce Zetter, member of the CCBIO SAB since 2013. Also, Roger Strand's connection with Harvard Kennedy School was included in INTPART-I. Activities are set up to foster stronger integration between excellent teaching and research environments in collaboration with international partners. In addition to including master level students into all CCBIO RSCS courses, CCBIO established the INTPART courses *CCBIO907 Cancer-Related Vascular Biology*, *CCBIO908 Scientific Writing & Communication*, *CCBIONEUR912 Health Innovation*, and a workshop on design principles with EMBO. These courses are rather resource intensive and of very high quality. Further INTPART activities include the Boston Lab Visit Program and the 1st CCBIO VBP Research Meeting held in Iceland 2019, and the 2nd CCBIO VBP Research Meeting held in Bergen in August 2024, as well as several seminars and other meetings. Integrating INTPART with CCBIO's existing activities and developing a new curriculum to be used in the years to come is a priority.

Lars A. Akslen and Marsha A. Moses (Director, VBP) are the INTPART project leaders. Elisabeth Wik was in 2017–2022 the main coordinator in Bergen and Randy Watnick the coordinator in Boston. Since the fall of 2022, Agnete Engelsen has been the main coordinator in Bergen, with Michael Rogers and Randy Watnick as coordinators in Boston. For CCBIO907 and the CCBIO-VBP Research Meetings, Michael Rogers is the Boston coordinator.

The CCBIO RSCS aims to continue and further develop the established courses CCBIO901–908 and CCBIONEUR910–912 and its other activities together with the many excellent partners. Further courses will be established when needed. ••

CCBIO
RESEARCH SCHOOL
FOR CANCER STUDIES

junior scientist symposium

The **CCBIO Junior Scientist Symposium (JUSS)** takes place four times a year and is part of the CCBIO Research School as the course CCBIO901. Junior scientists are invited to present their research in an academic environment, thus providing the opportunity for feedback across disciplines. Notably, the symposium acts as a training arena for younger colleagues to organize the meetings and chair the sessions. Students, PhD candidates, postdoctoral fellows, researchers, CCBIO affiliates, staff and visitors are all welcome to attend the Junior Scientist Symposia.



Throughout the seminar series, young researchers are encouraged to practice relevant skills for a future academic career, including oral presentations in front of an audience, as well as scientific writing. The participants are encouraged to reflect on their projects and critically evaluate different aspects of their daily work. CCBIO901 provides 3 ECTS for students who are required to give one oral presentation based on their own work, to actively participate in at least four symposia, and to write four reports summarizing four different presentations. Fruitful discussions and informal interaction and networking are important parts of the JUSS concept. Each JUSS includes presentations from students, PhD candidates and postdoctoral fellows or other researchers at an early career stage. In addition, the symposia feature keynote presentations from experienced researchers.



The first keynote speaker in 2023 was Harsh Dongre who gave an enlightening talk about how to make the jump of academic independence and establish your own research group. The next keynote was held by Dimitrios Kleftogiannis who gave an educational talk about bioinformatics. In December, Daniela Costea gave an inspirational talk about how life as a scientist can be, elaborating on the 'driving forces'. She used a phone quiz to challenge the audience to reflect on their own motivation and future career plans. Most answered that they hoped to still be in science five years from that point. In February 2024, Hege Berg gave a keynote talk about the important topic of how to succeed with clinical implementation of multi-omics methodology in cancer diagnostics. Finally, CCBIO's Administrative Leader Geir Olav Løken gave a thought-provoking talk titled "Navigating the system". By utilizing his decades' long experience in mediating between researchers and the administration, he elaborated on how to best interact with "the other side" and point out pitfalls, coping strategies and possibilities.

Vladan Milosevic and Mari Kyllesø Halle organized these symposia. ••







Centre for Cancer Biomarkers

SCIENTIFIC PROGRAM
February 2, 2023
B301 Sentralblokka, Haukeland University Hospital

Symposium chairs:
Mari Kyllesø Halle and Vladan Milosevic

09.00-09.15: Introduction

09.15-10.00: Keynote lecture by Harsh Dongre: "My insights on making the jump: transitioning to academic independence?"

10.00-10.20: Coffee

10.20-10.45: Yaping Hua: "Drug discovery of small molecules against prostate cancer"

10.45-11.10: Angela Sofia Geros Mesquita: "Patient-derived xenograft (PDX) models as preclinical tool for investigation of myelodysplastic syndromes (MDS)"

11.10-12:00 Lunch

12:00-12:25: Shannon Moreino: "Mitochondria transfer from the microenvironment promotes oxidative metabolism and invasion of glioblastoma"

12.25-12:50: Ranveig Seim Brekke: "The role of CEL in pancreatic disease"

12:50-13:00: Concluding remarks

Centre for Cancer Biomarkers

SCIENTIFIC PROGRAM
June 8, 2023
B302 Sentralblokka, Haukeland University Hospital

Symposium chairs:
Mari Kyllesø Halle and Vladan Milosevic

09.00-09.15: Introduction

09.15-10.00: Keynote lecture by Dimitrios Kleftogiannis: "Let's talk about bioinformatics…."

10.00-10.20: Coffee

10.20-10.45: Titas Gladkauskas: "Corneal vascularization associated with a novel PDGFRB gene variant"

10.45-11.10: Mireia Mayoral Safont: "Visualization and establishment of acute myeloid leukaemia (AML) patient-derived xenografts (PDX)"

11.10-12:00 Lunch

12:00-12:25: Rose Meng Gold: "Detecting Imperfect Homology at Structural Variant Breakpoints in Cancer"

12:25-12:30: Concluding remarks

Centre for Cancer Biomarkers

SCIENTIFIC PROGRAM
December 6, 2023
B302 Sentralblokka, Haukeland University Hospital

Symposium chairs:
Mari Kyllesø Halle and Vladan Milosevic

09.00-09.15: Introduction

09.15-10.00: Keynote lecture by Daniela Costea: "My Path in the World of Cancer Research"

10.00-10.20: Coffee

10.20-10.45: May Eriksen Gjerstad: "Preclinical development of novel therapeutics in Mantle Cell Lymphoma"

10.45-11.10: Hanne Borge: "Sjögren's syndrome – Assessment of salivary gland manifestations and their association with renal disease"

11.10-12:00 Lunch

12:00-12:25: Shamundeeswari Anandhan: "Brain-derivedblood exosomes – a potential for new biomarkers inmultiple sclerosis: Pilot study results from relapsing MS patients under anti-CD20 therapy"

12:25-12:50: Rezvan Ehsani: "Spatial analysis of the cancer tissue microenvironment using mass cytometry imaging technologies"

12:50-13:00: Concluding remarks

Centre for Cancer Biomarkers

SCIENTIFIC PROGRAM
February 1, 2024
The Conference room, BB-building

Symposium chairs:
Mari Kyllesø Halle and Vladan Milosevic

09.00-09.15: Introduction

09.15-10.00: Keynote lecture by Hege Berg: "Clinical implementation of multi-omics methodology in cancer diagnostics"

10.00-10.20: Coffee

10.20-10.45: Oleksii Nikolaienko: "The role and inheritance of BRCA1 epimutations"

10.45-11.10: Ryan Dunkel: "Pre-Clinical and Phenotypic Characterization of a Novel CAR T Therapy for B-cell Lymphoma Malignancies"

11.10-12:00 Lunch

12:00-12:25: Katrin Kleinmanns: "Advanced Preclinical Models to Investigate Promising Drugs targeting Resistant Subpopulations in Ovarian Cancer"

12:25-12:50: Sturla Magnus Grøndal: "Mapping Disease Landscapes: CyTOF Applications in Oncology and Fibrosis"

12:50-13:00: Concluding remarks

Centre for Cancer Biomarkers

SCIENTIFIC PROGRAM
June 6, 2024
U364 Glasblokkene, Haukeland University Hospital

Symposium chairs:
Mari Kyllesø Halle and Vladan Milosevic

09.00-09.15: Introduction

09.15-10.00: Keynote lecture by Geir Olav Løken: "Navigating the system"

10.00-10.20: Coffee

10.20-10.45: Anna Gorbunova: "Prognostic signature based on mitochondria quality control proteins for the prediction of lung adenocarcinoma patients survival"

10.45-11.10: Synnøve Yndestad: "Targeting Homology Repair Deficiency in Breast Cancer"

11.10-12:00 Lunch

12:00-12:25: Masoumeh Jahani Kadousaraei: "Casting vs 3D-Bioprinting of Human Bone Marrow Mesenchymal Stem Cells for Bone Tissue Engineering Applications"

12:25-12:50: Constance de Montlaur: "Precision medicine in children's cancers"

12:50-13:00: Concluding remarks

CCBIO masterclass program

The CCBIO Masterclass program aims to prepare up-and-coming post-PhD researchers for a successful transition from being part of a research group, to establishing an independent research profile, funding portfolio and staff. Masterclass groups consist of 8–10 junior researchers, typically postdocs or researchers already having completed their postdoc period, who receive individual mentoring as well as several plenary workshops over a full academic year.

The mentorship program provides each candidate with an experienced CCBIO mentor from outside of their own group. Together, they focus on guiding the mentee's career development, both in a broad sense and in setting up short- and long-term goals. Regular meetings allow for both planning and follow-up. The plenary workshops focus on a range of topics related to the following:

- Mentoring and career development
- Conceptualizing research projects
- Research project management
- Recruitment and establishing a team
- Being a good group leader
- Research collaborations and networks
- Science communication
- Application writing
- Presentations by the candidates

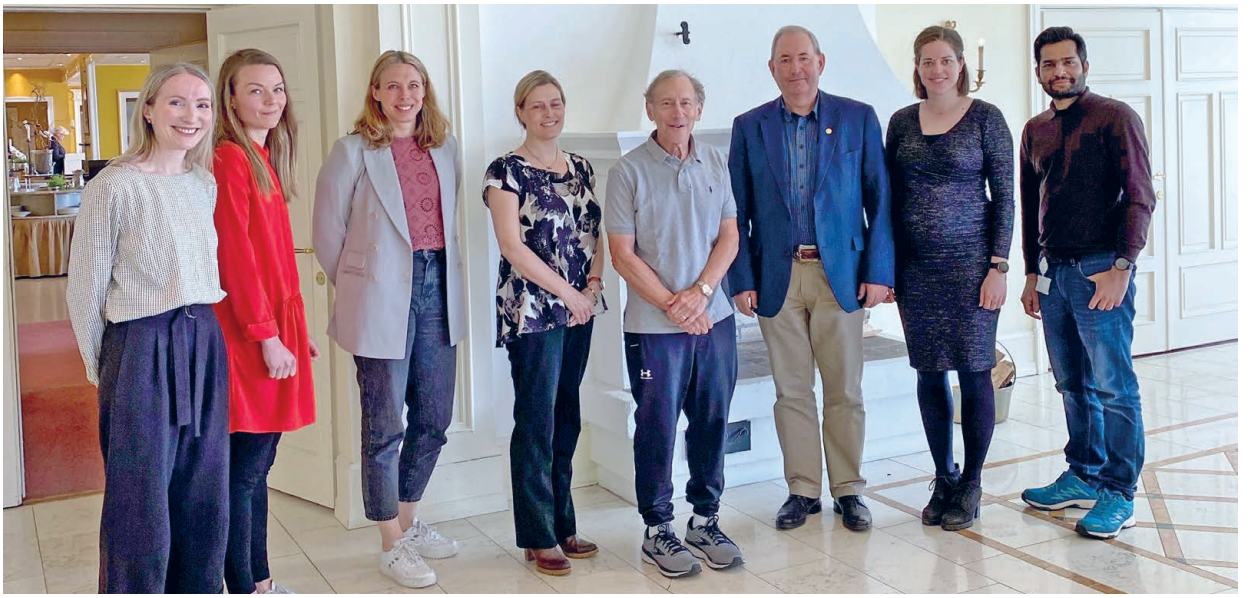
Throughout the workshops, the candidates receive targeted input from CCBIO's PIs, network, and administration, as well as from staff from the Faculty of Medicine, The University of Bergen's HR department, and the university library. Each Masterclass period is concluded with a gathering mapping out and deliberating upon each candidate's career plan. The Masterclass program was conceived and coordinated by CCBIO's Director Lars A. Akslen, together with CCBIO's Research Advisor Yamila Torres Cleuren in 2022 and CCBIO's Administrative Leader Geir Olav Løken in 2023. Below we account for the 2022–2023 Masterclass group.

The second CCBIO Masterclass group was launched in September 2022 in a session held by Yamila T. Cleuren, presenting the Masterclass concept and introducing the candidates to each other, presenting themselves and their future ambitions, as well as providing an overview of expectations at each career stage, drafting CVs and the benefits of mentoring.



In October 2022, the candidates' attention was focused on how to establish and run a research group. In addition to the introduction by Cleuren, Lars A. Akslen and Daniela Costea coached the group on how to form the right team and find the right team members, and the tasks of a group leader.

Based on the experiences from the first Masterclass group, the session on grant applications and opportunities was this time held later, in November 2022, rather than at the beginning. As well as Cleuren, a research advisor focused on grants sharing her accumulated experience in grant writing, the Masterclass alumni Harsh Dongre and



Heidrun Vethe shared their own experiences. This very important session covered topics like: Identifying relevant opportunities, main funding agencies, the individual parts of an application, collaborators and partners, grant writing logistics and focus on cutting-edge research and innovation.

The December 2022 session focused in detail on how to conceptualize a research project. CCBIO's Line Bjørge and Professor Charalampos (Haris) Tzoulis from Neuro-SysMed held an interactive workshop focused on the process from idea to execution and the translation from basic research to clinical studies including trials.

In April 2023, Line Bjørge introduced our Masterclass candidates to how the ability to conduct research is influenced by project management and understanding the system. Ingve Bergheim and Ole Christian Laukli from the UiB's central HR department provided a very engaging introduction to the HR perspective on leadership and leading a research group. This was followed by two sessions held by CCBIO's administrative leader Geir Olav Løken, on the lessons learned at CCBIO with regards to general project management, followed by an interactive session on how to navigate the system at the UiB in the broad sense and especially with regards to the administration.

In May 2023, CCBIO's director Lars A. Akslen hosted a session on science communication, jointly with Paul André Sommerfelt from the Faculty of Medicine elucidating how to succeed in getting the best out of interaction with journalists and the media, both from the researcher and journalist perspective, and how to promote yourself online. Caroline Armitage from the University Library provided very useful input on profiles, publishing statistics and monitoring outreach.

The final session of the 2022–2023 Masterclass group took place as a full day seminar with CCBIO's director and administrative leader in June 2023, befittingly for a Centre of Excellence in Fossestova at Litteraturhuset — named after Jon Fosse (Norwegian Nobel Laureate in literature in 2023). Each candidate held a ten-minute presentation answering the question "Why do you want to work in science and how do you plan your career?", followed by five minutes for immediate response and discussion. Before an informal dinner, the whole group discussed in plenary for a full hour.

The CCBIO Masterclass program has received very positive feedback from the participants and their mentors, from CCBIO's research groups as well as from the CCBIO SAB. From both the 2021–2022 and 2022–2023 Masterclass groups, the overarching feedback is that this kind of introductory program to the most important aspects of group leadership is extremely useful, to the extent that the universities should have similar coaching arrangements tailored for each career stage, starting at the early PhD-level. Also, small, close-knit groups of peers forward the establishment of lasting relations and potential future scientific collaborations. Several mentor-mentee pairs have continued their meetings after their formal mentoring periods expired, illustrating the mutual benefit of interacting in defined roles across groups and levels of seniority. CCBIO aims to launch its third Masterclass group in late 2024, following the influx of a new generation of junior researchers. This is contingent upon CCBIO's funding situation during its continuation phase. ••

the 2022-2023 masterclass candidates



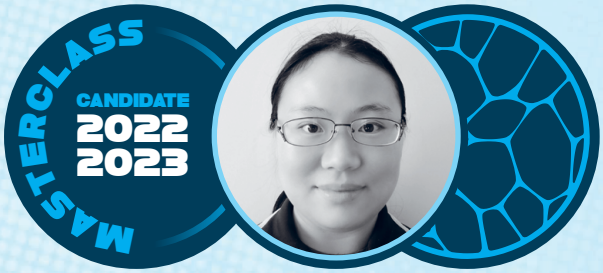
Hege Fredriksen Berg holds a PhD from the University of Bergen focused on organoid models and novel biomarkers for endometrial cancer. She is currently a postdoctoral fellow in the Krakstad group where she is working on preclinical modeling and drug resistance. Currently, Berg is studying chemo-resistance in endometrial cancer. The project combines patient data and functional genomic screening of organoid models to identify the molecular drivers of resistance to carboplatin. As part of this project, Berg recently completed the first part of a research stay at Dana-Farber Cancer Institute and Broad Institute of MIT and Harvard. She hopes to identify targetable alterations that can improve the efficacy of platinum-based drugs and ultimately improve outcomes for advanced and metastatic cancer. After her postdoc, she aims to secure funding for her research to establish independence with the long-term goal of leading her own research team.



Manuel Carrasco, PhD, earned his doctorate in developmental biology from the Andalusian Molecular Biology and Regenerative Medicine Centre (CABIMER) in Spain. After completing postdoctoral training with Dr. Helge Ræder at the University of Bergen, where he studied the role of stem cells in diabetes, Carrasco joined the Akslen lab as a researcher focused on understanding the role of the nervous system in breast cancer progression. His research employs spheroid and organoid models to investigate the interactions between breast cancer cells and the tumor microenvironment, with a particular emphasis on nerves and autonomic signaling. Currently, his work aims to unravel the complexities of sympathetic signaling within the breast cancer microenvironment. Drawing on his expertise in pharmacology and developmental biology, he is committed to advancing research in this area, seeking to secure funding and foster collaborations with other research groups to broaden the understanding of nerve-tumor interactions in breast cancer.



Christiane Helgestad Gjerde has an MD from the University of Bergen, where she also completed the Medical Student Research Program. She completed her PhD in June 2024 in the McCormack and Bjørge groups, where the focus of her PhD research was development of *in vitro* 3D models for ovarian cancer. The goal was to establish patient-derived organoids on decellularized peritoneal scaffolds to create a model that better represents the tumor microenvironment of ovarian carcinoma, with the hope that the model can be used to study tumor biology and evaluate new therapies. Gjerde was in 2022 awarded NOK 200 000 from the Kolbjørn Brambani Cancer Research Fund to support her PhD project. She is currently working as an intern at Haukeland University Hospital. Her long-term professional goal is to establish her own group with a focus on translational cancer research.



Yaping Hua received her PhD at the University of Bergen in 2020. Currently, she is a researcher in Karl-Henning Kalland's group. The theme of her project is the discovery of novel potential anti-cancer compounds and the identification of corresponding molecular targets in human prostate cancer cells. This innovative project strategy combines cancer cell cryoimmunotherapy with exclusively available panels of biologically active compounds that are isolated from medicinal herbs and plants (phytochemicals). Yaping Hua will continue the collaboration with the Harvard/Shanghai/Bergen/KTH groups to develop novel small molecular compounds and identify effects on signal transduction pathways as well as target and mechanism validation in immune cells and cancer cells. This collaborative project will benefit her as an independent group leader in the future.



Stein-Erik Gullaksen has a master's degree in nanotechnology and microfluidics, followed by a PhD from the University of Bergen on high dimensional single cell analysis of blood samples using mass cytometry. This work is continued in his current position as a postdoctoral scholar where he is analyzing samples from patients with leukemia enrolled in international clinical trials. His aim is to generate profiles of the therapy-induced changes in both leukemic and host immune cells after only hours and days since starting therapy. The goal is then to leverage these changes against clinical data to identify biomarkers that identify poor responders and possibly predict side effects. The focus is on early time points after starting therapy: hours to days after start of therapy. Gullaksen aims to achieve scientific independence as a young investigator by combining multidisciplinary skillsets with a focus on a growing repertoire of cutting-edge single cell technologies in the field of hemato-oncology.



Erling A. Høivik has a PhD in molecular biology from the University of Bergen at the Department of Biomedicine. He has an extensive background as a researcher within female cancers under the CCBIO umbrella. First, through previous work in the Bergen Gynecological Cancer Research Group, and now in his current position in the Breast Cancer Research Group of Elisabeth Wik. His research interest is particularly centered around younger breast cancer patients, where he uses multiangled "omics"-approaches, including epigenetics, genomics and transcriptomics characterizations. By these explorative approaches, he aims to identify and characterize new biomarkers to improve cancer treatment for this patient group and make an impact in the research field.



Vladan Milosevic, MD, holds a PhD in molecular medicine from the University of Turin, Italy, where he investigated the potential role of malignant pleural mesothelioma stem cells in the development of chemo-resistant and immune-resistant phenotypes of these aggressive tumors. He is currently a researcher in the Östman and Akslen groups, aiming to identify novel biomarkers and therapeutic targets of aggressive breast cancer through high-multiplexed profiling of the tumor microenvironment using the Hyperion imaging mass cytometry platform. His long-term goals are to establish his own research group in the field of molecular medicine and cancer research and to pursue a clinical career in pathology.



Cornelia Schuster has a PhD from the University of Bergen on predictive markers in melanoma treatment and recently finished her postdoc in Straume`s group at CCBIO. Her research focuses on identifying predictive markers for side effects and response to immunotherapy in melanoma. Her work includes both a retrospective series and two national clinical trials in collaboration with the national PIs at Haukeland University Hospital and Oslo University Hospital. Her special interest is on the impact of adrenergic signaling in cancer progression and resistance to therapy. As a medical oncologist, she has broad experience in treating melanoma patients and clearly sees the urgent need of validated predictive markers for response and the risk of developing severe side-effects in the era of immune checkpoint blockade. Her aim is to combine clinical work and translational research to contribute to optimized personalized medicine. She is currently establishing her own research group.



Cédric Zeltz has a PhD in molecular and cellular biology from the University of Reims Champagne-Ardenne, France, focusing on melanoma inhibition. He is currently a researcher in the Gullberg group. For over a decade, his research was essentially based on the interactions between cells and the extracellular matrix, and on the determination of biomarkers and potential therapeutic targets in tissue and tumor fibrosis. During his postdoc in the Princess Margaret Cancer Centre in Toronto, Cédric investigated the heterogeneity of cancer-associated fibroblasts in non-small cell lung carcinoma, and he established 3D co-culture models of tumor and stromal cells. His current project focuses on new integrin alpha11 mouse models for stroma targeting. His long-term professional goal is to establish his own research group in the field of tissue and tumor fibrosis. ••



research seminars

CCBIO's monthly research seminars gather a wide range of researchers and others with a common interest in cancer biomarkers for updates on cutting edge research. The speakers are of a high international standard. Being open to all, the seminars are well visited, also by staff outside of CCBIO. The CCBIO Seminars continue to be an arena for informal crosstalk that both strengthens cohesion within CCBIO and often leads to fruitful scientific collaborations.

The seminar series' main aim is to convey relevant biomarker research to CCBIO staff and the local scientific community, also preparing the ground for future contacts and recruitment. In most cases, targeted meetings with the speakers are arranged before or after the lectures so that CCBIO researchers, in particular the younger ones, get the opportunity to discuss projects and collaboration with high level scientists.



Donald Gullberg had the academic responsibility for the seminars until Carina Strell took over in the spring of 2024. The CCBIO seminars form part of the PhD-level course CCBIO902 and the master-level course BMED380. Since the start in 2013, the collaboration with the BMED380 group has been a success, benefiting both CCBIO and the Department of Biomedicine.

Information on upcoming speakers and abstracts is posted on CCBIO's web pages and circulated by means of round-mails, posters, and various newsletters, reaching researchers well beyond CCBIO. This ensures that the CCBIO Seminars are well visited by participants on all levels from a wide range of UiB and hospital departments. ••

research seminars in 2023 and spring term 2024

All seminars in 2023 and 2024 were held in-person to allow for research group meetings with the speakers. CCBIO faculty and other invited international speakers provided interesting scientific talks, occasionally widening our horizon with other but still related topics, such as neural regeneration in the human central nervous system.

JANUARY 26, 2023

Bjørn Tore Gjertsen, CCBIO PI, Professor of Hematology at the Department of Clinical Science, University of Bergen, and Consultant Hematologist at the Helse Bergen Health Trust, Bergen, Norway: *Early response evaluation by single cell signaling profiling in myeloid leukemia*. Chair: Erling Høivik.

MARCH 30, 2023

Martin Götte, Professor at the Department of Gynecology and Obstetrics, University of Münster, Germany: *The multifunctional nature of Syndecan-1 in breast cancer*. Chair: Donald Gullberg.

APRIL 27, 2023

Linda Lindström, Associate Professor in Cancer Epidemiology and Group Leader at the Department of Oncology and Pathology, Karolinska Institute, Sweden: *Breast cancer inter and intra-patient heterogeneity and long-term risk to develop distant metastatic disease*. Chair: Lars A. Akslen.

MAY 25, 2023
JianFeng Chen, Professor at the Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China: *Control of lymphocyte homing by two-way tuning of integrin activation*. Chair: Donald Gullberg.

JUNE 15, 2023
Tuula Salo, Professor at the Department of Oral and Maxillofacial Diseases, University of Helsinki, Finland: *Personalized oral cancer treatment assays*. Chair: Daniela E. Costea.

AUGUST 31, 2023
Juan Rodríguez Vita, Group Leader of the Tumor-Stroma Communication Research Group, Príncipe Felipe Research Center Foundation (CIPF), Valencia, Spain: *Hyaluronic acid is a master regulator of tumor stroma*. Chair: Line Bjørge.

SEPTEMBER 28, 2023
Oddbjørn Straume, CCBIO PI, Professor at the University of Bergen and Head of Department of Oncology, Haukeland University Hospital, Bergen, Norway: *Predictive markers of response to immune checkpoint blockade in melanoma - experience from a randomized clinical trial*. Chair: Donald Gullberg.

OCTOBER 26, 2023
Arne Östman, Adjunct Professor at CCBIO and Professor at the Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden: *Spatially enriched multi-marker human CAF-subsets linked to treatment response, prognosis, driver mutations, immune features and micro-niches*. Chair: Lars A. Akslen.

NOVEMBER 23, 2023
Christopher Elnan Kvistad, Postdoc at Neuro-SysMed, University of Bergen and Neurologist at Haukeland University Hospital, Bergen, Norway: *A brief history of the (failing) neural regeneration in the human CNS (central nervous system)*. Chair: Lars A. Akslen.

DECEMBER 14, 2023
Thomas H. Barker, Professor of Biomedical Engineering, Cell Biology and Pulmonary and Critical Care Medicine, Schools of Engineering and Medicine, University of Virginia, Charlottesville, USA: *Targeting the Matrix in a matrix-centric disease: The holy grail of Fibrosis therapeutics?* Chair: Donald Gullberg.

JANUARY 25, 2024
Vibeke Fosse, CCBIO, MS in veterinary companion animal oncology and veterinary surgeon, and PhD candidate in the McCormack and Bjørge groups: *Comparative oncology: a valuable model for cancer immunotherapy research*. Chair: Emmet McCormack.

FEBRUARY 22, 2024
Diane Bielenberg, Assistant Professor, Harvard Medical School, Boston Children's Hospital, Boston, Massachusetts, USA: *Neuropilin-2 is Immune Suppressive During Early Stages of Carcinogenesis.* Chair: Daniela E. Costea.

MARCH 21, 2024
Mika Kontro, MD, PhD, Adjunct Professor and Consultant in clinical hematology at the Helsinki University Hospital Comprehensive Cancer Center: *Functional Screening for Precision Medicine Approaches in Acute Myeloid Leukemia*. Chair: Bjørn Tore Gjertsen.

APRIL 25, 2024
Ingvild Sandøy, Professor at the Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, and Deputy Director for BCEPS & CISMAC: *Presentation of BCEPS, the Bergen Centre for Ethics and Priority Setting in Health.* Chair: Roger Strand.

JUNE 20, 2024
Synnøve Yndestad, Researcher at the Department of Clinical Science, University of Bergen: *Homology Repair Deficiency in Breast Cancer; Lessons from the PETREMAC trial.* Chair: Carina Strell.

AUGUST 29, 2024
Mari Kyllesø Halle, Molecular Biologist with the Bergen Gynecological Cancer Research Group, University of Bergen: *Decoding the Landscape of Cancer Vulnerabilities in high-risk Cervical Cancer*. Chair: Stein-Erik Gullaksen.

special seminars and meetings



When CCBIO members have something particularly interesting to convey or they have senior researchers or international collaborators visiting or taking part in courses outside of the monthly seminars or larger meetings, or the opportunity arises to invite especially interesting scientists, CCBIO encourages them to arrange talks under the umbrella of the *CCBIO Special Seminars and Mini-Symposia*. Special Seminars are extra-curricular talks more or less of the same format as ordinary CCBIO Seminars, whereas the CCBIO Mini-Symposia are longer meetings of 2–3 hours with several speakers elucidating different aspects of a given topic. Both formats are integrated into CCBIO's seminar series with its support apparatus and wide announcement. In this way, CCBIO gives its members and the wider audience the chance to get input from and interact with high-level researchers and to attend meetings going deep into especially interesting and new topics.

CCBIO Mini Symposium on AML January 18, 2023: Development of novel therapy for acute myeloid leukemia (AML): from novel drug formulations, preclinical models to leukemic stem cells.

AML was the origin of the stem cell concept in cancer more than 20 years ago. Diagnostics and risk stratification of AML has been dominated by genetics for decades, and the recent five years, several new drugs have been introduced. At the same time, AML is hard to treat and only incremental increases in survival are experienced. This mini symposium elucidated new aspects and optimizing models in therapy development, and strategies to overcome therapy resistance. The mini symposium also provided an update on the leukemic stem cell concept and how that may influence future treatment. Chair was CCBIO PI **Bjørn Tore Gjertsen**, and the speakers included **Lars Herfindal**, Professor in Pharmacology at the Centre for Pharmacy and Group Leader of the Pharmacology and Pharmaceutics Research Group, University of Bergen (UiB); **Emmet McCormack**, CCBIO PI and Professor of Pharmaceutics, Department of Clinical Science, UiB; **Kim Theilgard-Mönch**, Senior Consultant in Hematology at Rigshospitalet and Research Group Leader at Rigshospitalet and the University of Copenhagen (UCPH) in Denmark; and **Mhairi Copland**, Professor of Translational Haematology and Honorary Consultant in Haematology at the University



of Glasgow, Scotland, UK. A panel debate and discussions followed the scientific talks.

CCBIO Special Seminar March 23, 2023, with Michael Rogers, Harvard Medical School and the Vascular Biology Program, Boston Children's Hospital: Neuro-immune communication in endometriosis, a novel therapeutic target?
Dr. Rogers gave a talk on intriguing discoveries recently made in his laboratory about interactions among lesions, nerves, and immune cells in endometriosis. Endometriosis is a painful and debilitating inflammatory disease that affects approximately 10% of reproductive-age women. Treatment options are currently limited to NSAIDs, hormones, and surgery. For ~30% of patients, none of these options are effective and for many, symptom relief is only temporary. Because neuroimmune communication plays a role in several inflammatory conditions, Rogers sought evidence for a role for neuroimmune communication in endometriosis-associated pain and lesion growth. To that end, the group leveraged their mouse model of endometriosis-associated pain, finding that neuroimmune communication mediates lesion growth and pain in their endometriosis model. This implies that blocking neuroimmune communication may be effective in treating endometriosis.

CCBIO Special Seminar March 30, 2023, with Edward R. Smith, Harvard Medical School and the Vascular Biology Program, Boston Children's Hospital: **Learning from tumor to treat stroke.**
Dr. Smith showed how the cross-pollination between benchtop scientists and full-time clinicians led to a unique insight that a shared biological mechanism might be pathologic in one disease process — and helpful in another, seemingly unrelated, disease. In his lecture, a review of the impact of axon guidance factors — proteins that influence the growth of the brain and associated vasculature in embryonic development — in the pathogenesis of brain tumors and stroke conditions in childhood is presented. Emphasis on the interconnected aspects of normal and pathologic growth programs in the central nervous system was highlighted, with discussion centered on the importance of multidisciplinary research teams. Dr. Smith discussed the role of axon guidance factors in the pathogenesis of these diseases and identified opportunities for future research relevant to innovating new therapies.

CCBIO Special Career Seminar April 5, 2024: From startup to pharmaceutical industry.
As many of our CCBIO students had expressed curiosity about a career in the pharmaceutical industry, CCBIO PI **Bjørn Tore Gjertsen** hosted a CCBIO Special Career Seminar. Speakers were **Gro Gausdal**, PhD, CEO, Bjørgvin Therapeutics Group AS; **Camille Claudius**, MD, HD, Head of Medical Affairs, Astellas Nordics; and **Ann Theres Poblenz**, PhD, Medical Affairs Therapy Area Lead, Oncology, Astellas Nordics. Together they introduced the audience to career opportunities in biotech, startups and in the pharmaceutical industry, sharing their career stories and broader experience. ••

the 11th CCBIO annual symposium 2023

The 11th CCBIO Annual Symposium was this time enlarged with a generous time frame and two overnight stays, May 8–10, 2023. Although there was an option for online attendance — only 14 participants chose to attend online, and the rest of the total of 235 decided to enjoy the company of colleagues and the informal and mutually fertilizing scientific crosstalk in the breaks and the evenings.



Day 1 started with a strong keynote presentation by Professor **Alexander Swarbrick** from the **Garvan Institute of Medical Research, University of New South Wales**, Sydney, Australia. He explained the work at his lab where they are parsing breast cancer ecosystems with cellular genomics, presenting interesting recent data using cellular genomics to discover new biomarkers and therapeutic strategies for breast cancer.

Ovarian cancer was covered by **Iain McNeish** who gave a talk on copy number alterations, as well as **Anniina Färkkilä**, explaining how HRD/BRCA-status influences these tumors. Other highlights included **Stephane Terry** on the role of hypoxia, EMT and AXL in cancer immune escape; **Ingrid Hedenfalk** who explored the normal-like subtype of breast cancer; **Catherine Alix-Panabières** who presented metastasis-initiating circulating tumor cells in colon and breast cancers; **Amy LeBlanc** who gave an overview of the US National Cancer Institute's Comparative Oncology Program and its contributions to cancer research and drug development; **Benno Schwikowski** who explained how to build computational approaches to discover causal paths in cancer; **Caroline Heckman** who gave a talk on functional precision medicine for treatment and biomarker discovery in high-risk hematological malignancies; and **Brunangelo Falini** who showed the impact of anti-NPM1 monoclonal antibodies in the characterization of NPM1-mutated AML.

The program also featured great talks from several members of the CCBIO International Faculty, including an energetic keynote by **Klaus Pantel**, explaining how liquid biopsy and single-cell analysis can become gamechangers in cancer treatment. A simple test can detect cancer cells and cancer DNA in the blood or another body fluid, contribute to earlier detection of cancer and provide valuable information about the tumor in a number of cancers. Inspiring talks were given by **Ian Mills, Frédéric Amant, Mark LaBarge, Rameen Beroukhim** and **Jean Paul Thiery**. Other international faculty were also enjoying the symposium as active audience, including **Arne Östman, Jean-Christophe Bourdon** and **Rolf Brekken**. The CCBIO International Faculty of internationally high-ranking scientists have successfully strengthened CCBIO's collaborative networks as well as its research and educational efforts, and we are always very happy to welcome them to our annual gathering.



CCBIO has for many years now had a strong link to the Vascular Biology Program at Boston Children's Hospital, through the INTPART project, and building on the director **Lars A. Akslen's** collaboration with Judah Folkman and his team. Also on this occasion, we had the pleasure of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having Harvard faculty members as speakers. The notable keynote lecture on day 2 by **Robert D'Amato**, Professor of Ophthalmology at **Boston Children's Hospital and Harvard Medical School**, reflected on some of this special background. D'Amato presented exciting new data on *Deciphering the mechanism of tumor acquired resistance to antiangiogenic therapies*. **Michael Rogers** from the same institutions provided the talk *What happens when an endothelial cell loses its compass? A role for CMG2 in chemotaxis*.

The chairs **Line Bjørge** and **Katrin Kleinmanns** ran a tight ship during the speed presentation session, where 17 young researchers had 3 minutes each to present their research using one single slide. The speed talk session has become a popular opportunity for younger researchers to train in presentation skills and simultaneously show their research to top notch scientists in their field. The audience voted for the two best speed presenters — this year **Hilde Lien** and **Luka Tandarić.**

The program included two poster sessions, this year featuring an all-time high poster number of 51, giving ample opportunity for mingling and fruitful scientific discussions. The audience voted for the two best posters each day, giving awards to **Sina Thorsen Takle, Christiane H. Gjerde**, **Martine Lode**, and **Tara Helen Dowling**.

Anne Blanchard chaired a panel debate session with the participants **Linn Getz**, NTNU; **Caroline Engen**, Neuro-SysMed/UiB; **Line Bjørge** and **Karen Rosnes Gissum**, CCBIO. The panelists critically discussed what responsible clinical trials entail, by zooming in on clinical trials and zooming out on personalized cancer medicine in general. They addressed the current challenges met in clinical trials as well as the vision, assumptions, hopes and practices around personalized cancer medicine, and rounded up the discussions by looking at the patients' role in clinical trials. The session was concluded by Linn Getz stating: "Clinicians and oncologists should only recommend treatments if they, themselves, would take them."

"This year's symposium was perhaps the most vibrant one ever — under the motto *come together*", CCBIO Director **Lars A. Akslen** said.

"The presentations were amazing and most stimulating, covering a wide range of topics and learning possibilities, as usual. The crosstalk and networking in between could easily be compared to a beehive. After 10 years, the activities and formats are still expanding. We sure look forward to the next phase," Akslen concluded. ••

Centre for Cancer Biomarkers

11th CCBIO Annual Symposium 2023

May 8-10, 2023 (Bergen — Norway)

DAY1 Monday May 8, 2023

13:00-13:15 **Welcome and Opening: Lars A. Akslen (Director of CCBIO)**

Chair: Arne Östman

13:15-14:00 CCBIO Keynote Lecture
Alexander Swarbrick: Parsing breast cancer ecosystems with cellular genomics

14:00-14:45 Ian Mills: Spatial lessons from prostate cancer research

14:45-15:30 **Coffee**

Chair: Line Bjørge

15:30-16:00 Iain McNeish: Ovarian cancer and copy number alterations

16:00-16:30 Anniina Färkkilä: How HRD/BRCA status influences the ovarian cancer TME

16:30-17:00 Frédéric Amant: How to organize translational cancer research, including the importance of preclinical models

19:30: **Dinner**

DAY2 Tuesday May 9, 2023

Chair: Carina Strell

09:00-09:45 CCBIO Keynote Lecture
Robert D'Amato: Deciphering the mechanism of tumor acquired resistance to antiangiogenic therapies

09:45-10:15 Michael Rogers: What happens when an endothelial cell loses its compass? A role for CMG2 in chemotaxis

10:15-11:15 **Coffee**

Chairs: Katrin Kleinmanns & Line Bjørge

11:15-12:30 Speed presentations by young investigators

12:30-14:30 **Lunch and poster session 1**

Chair: Anne Blanchard

14:30-15:45 Responsible clinical trials in the age of personalized medicine
Panel: Linn Getz, NTNU; Caroline Engen, Neuro-SysMed/UiB; Line Bjørge and Karen Rosnes Gissum, CCBIO.

15:45-16:15 **Coffee**

Chair: Agnete Engelsen

16:15-16:45 Stephane Terry: Role of hypoxia, EMT and AXL in cancer immune escape

16:45-17:15 Ingrid Hedenfalk: Exploring the normal-like subtype of breast cancer

19:30: **Dinner**

DAY3 Wednesday May 10, 2023

Chair: Karl-Henning Kalland

09:00-09:45 CCBIO Keynote Lecture
Klaus Pantel: Liquid biopsy: From discovery to clinical implementation

09:45-10:15 Catherine Alix-Panabières: Metastasis-initiator circulating tumor cells in colon and breast cancers

10:15-10:45 **Coffee**

Chair: Jim Lorens

10:45-11:15 Mark LaBarge: Integrating noise into a signal: loss of lineage specificity presages breast cancer susceptibility

11:15-11:45 Amy LeBlanc: The US National Cancer Institute's Comparative Oncology Program: Contributions to cancer research and drug development

11:45-12:15 Benno Schwikowski: How to build computational approaches to discover causal paths in cancer

12:15-12:45 Rameen Beroukhim: Detecting effects of SVs on cancer cellular fitness

12:45-14:45 **Lunch and poster session 2**

Chair: Bjørn Tore Gjertsen

14:45-15:15 Caroline Heckman: Functional precision medicine for treatment and biomarker discovery in high-risk hematological malignancies

15:15-15:45 Brunangelo Falini: Impact of anti-NPM1 monoclonal antibodies in the characterization of *NPM1*-mutated AML

15:45-16:30 Jean Paul Thiery: Development of differentiation and immunotherapy strategies interfering with bladder carcinoma progression

16:30-16:45 **Closing remarks: Line Bjørge (Co-Director of CCBIO)**

The 11th CCBIO Annual Symposium

May 8-10, 2023
at Solstrand Hotel & Bad












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the 12th CCBIO annual symposium 2024

The 12th CCBIO Annual Symposium took place May 14–15, 2024, at Solstrand outside of Bergen in excellent weather, providing a radiant frame for networking and meetings in the sunshine during the breaks. The program showcased current cancer biomarker research as well as taking a step back to consider global perspectives on cancer. This was the final symposium during CCBIO's 10-year period as a Norwegian Centre of Excellence (CoE), however not the last. The next 10 annual symposia are already plotted in the calendar.

As is CCBIO's tradition, the scientific program covered a broad range of current topics within cancer biomarkers, with many renowned international speakers. One of the current "hot topics", and a strategic field for CCBIO, relates to imaging mass cytometry — and was particularly covered in the exciting and stimulating keynote presentation by **Raza Ali** from **Cambridge University**.

Keynote speaker on day 2, **Göran Jönsson** from **Lund University Cancer Centre**, showed that although recent breakthroughs in the management of melanomas take advantage of the power of the immune system to achieve previously unattainable control of the disease, the current immunotherapies do have limitations, and more knowledge on how immunotherapy affects the tumor, the surrounding stroma and the anti-tumor immune response, is needed.

Treatment resistance was also discussed by **Anna Vähärautio** from **the University of Helsinki**. Her group addresses the challenge by developing ReSisTrace, a methodology that utilizes shared transcriptomic features of sister cells to predict the transcriptomic states priming treatment resistance in cancer.

One session, chaired by **Roger Strand**, was dedicated to global perspectives on cancer, comparing the Global North to the Global South. The session was initiated by **Kjell-Arne Johansson** from **the Bergen Center for Ethics and Priority Setting (BCEPS)**, and by CCBIO's **Dana Costea** who has several collaborations with the Global South and who reflected on cancer research in the different global regions. A panel conversation also including **John Cairns, London and CCBIO** and **Dr. Karpal Singh, Dar es Salaam** touched upon the huge differences between the regions.

Prior to the symposium, the CCBIO Scientific Advisory Board (SAB), **Professors Carl-Henrik Heldin**, **Ate van der Zee,** and **Bruce Zetter** had its closing meeting with the CCBIO management after its 10 years of service. **SAB chair Carl-Henrik Heldin**, professor in molecular cell biology at Uppsala University, and former chairman of the Nobel Foundation, stated in an interview during the symposium, that he finds the symposium to be a big success through CCBIO's 11 years as a Centre of Excellence. "I think it would be a very good idea to continue it," he said, and continued: "I think — from the university perspective — this should have high priority, because through the Centre of Excellence CCBIO, the university gained a lot."



As in previous years, CCBIO facilitated speedtalks and poster sessions for young cancer researchers to show their research and provide presentation experience. 13 speedtalks and 43 posters highlighted a wide range of the work of the young researchers. The audience had the opportunity to vote for the two best presenters of each session. **Lorena Larios Salazar** won both a speed talk and a poster award, whereas the other speed talk prize was awarded to **Eric Holt**. Other poster prizes were awarded to **Inês Ferreira**, **Gina Nyhus Stangeland**, and **Ariell Thale Toftesund Longva**.

The next CCBIO Annual Symposium takes place May 13–14, 2025, this time also at Solstrand. ••


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Centre for Cancer Biomarkers

12th CCBIO Annual Symposium 2024

May 14-15, 2024 (Bergen - Norway)

DAY1 Tuesday May 14, 2024

10:15-10:30	**Welcome and Opening: Lars A. Akslen (Director of CCBIO)**
	Chair: Carina Strell
10:30-11:15	CCBIO Keynote Lecture: Raza Ali: Charting the intact breast tumour microenvironment
11:15-11:45	Patrick Micke: Functional diagnostics for optimised lung cancer therapy
11:45-13:30	**Lunch and poster session 1**
	Chair: Jim Lorens
13:30-14:00	Ian Mills: Spatial approaches and imaging to improve prostate cancer stratification
14:00-14:30	Rolf Brekken: Phosphatidylserine — a marker of the tumor microenvironment and much more
14:30-15:15	**Coffee**
	Chair: Roger Strand Global perspectives on cancer
15:15-15:40	Kjell-Arne Johansson: Prioritizing Cancer Care in Low- and Middle-Income Countries (LMICs): Addressing the Humanitarian Crisis and Competing Health Priorities
15:40-16:00	Daniela Costea: Reflections on cancer research for the global north and the global south
16:00-16:35	Panel conversation: Karpal Singh, Kjell-Arne Johansson, Daniela Costea, and John Cairns
18:00	**Posters & Prosecco**
19:00	**Dinner**

DAY2 Wednesday May 15, 2024

	Chair: Oddbjørn Straume
09:00-09:45	CCBIO Keynote Lecture: Göran Jönsson: Understanding response to immune checkpoint blockade in melanoma
09:45-10:15	Randy S. Watnick: Discovery of a novel signalling pathway mediating immuno-suppression in solid tumors
10:15-11:30	**Coffee**
	Chairs: Katrin Kleinmanns & Line Bjørge
11:30-12:30	Speed presentations by young investigators
12:30-14:30	**Lunch and poster session 2**
	Chair: Line Bjørge
14:30-15:00	Linda Lindström: Insights into the heterogeneity of ER-positive breast cancer — long-term risk, endocrine treatment benefit and intra-tumor heterogeneity
15:00-15:30	Anna Vähärautio: Tracing back primed resistance in cancer
15:30-16:00	Fran Balkwill: Modelling and targeting the tumour microenvironment of high-grade serous ovarian cancer
16:00-16:15	**Closing remarks: Line Bjørge (Co-Director of CCBIO)**

The 12th CCBIO Annual Symposium

May 14-15, 2024
at Solstrand Hotel & Bad


















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other meetings



While CCBIO is very satisfied with the annual symposium and seminar structure, we and our research groups also organize and contribute to a range of other meetings and activities as shown by the below examples.

Mulighetsreisen, the Medical Faculty UiB, February 15, 2023.
Mulighetsreisen is a seminar series by the Medical Faculty at the University of Bergen, highlighting academic career stories to inspire its students. CCBIO Researcher **Heidrun Vethe** was their first speaker, having done her master as well as her PhD at the University of Bergen, and continued her career journey as a postdoc and researcher at CCBIO in Lars A. Akslen's group. She has also been one of CCBIO's Masterclass candidates and was a great source of inspiration to the young students attending the seminar.

Converging on the Person. Emerging Technologies for the Common Good, guest lecture at the Vatican City, Rome, February 20, 2023.
CCBIO PI **Roger Strand** held the opening lecture at the online international workshop *Converging on the Person, Emerging Technologies for the Common Good*, February 20–21, 2023, in the Vatican City, Rome. The assembly's focus on converging and emerging technologies was requested by Pope Francis in *Humana Communitas* in 2019. New technologies described as "emergent" and "convergent" include information and communication technologies, biotechnologies, nanotechnologies and robotics. The results obtained from these technologies may imply profound interventions on living organisms. The workshop promoted a need to understand these epochal changes and new frontiers in order to determine how to place them at the service of the human person, while respecting and promoting the intrinsic dignity of all. Strand gave the keynote lecture *Ethical issues of converging technologies*, where his main message was that converging technologies and the ethical issues that they raise are linked to structural features of contemporary modern societies and should be addressed as such. Neither science nor technology emerges in a vacuum but are co-produced with the society in which they take place.

Workshop on Modelling Immuno-Oncology, March 30, 2023, online event.
CCBIO PI **Emmet McCormack** in 2023 joined the new COST Action *IMMUNO-model*, where a network of scientists involved in the development and implementation of

preclinical models evaluating the response and toxicity induced by immunotherapies, is challenged to expand our knowledge in their mechanisms of action and improve the survival and quality of life of cancer patients. In that respect, he co-organized the first online workshop of this COST Action, with a focus on *in vivo, ex vivo* and *in vitro* models. Internationally renowned speakers presented their work on a rich selection of topics such as targeted therapies, the role of select pathways and translational patient models. The speaker list included CCBIO researcher **Katrin Kleinmanns** on the topic *Advanced ovarian cancer models for immunotherapy applications – key aspects, major drawbacks, and future perspectives.*

Seminar on Gynecological Oncology, November 28, 2023, in Oslo.
This was an event hosted and organized by Dagens Medisin, Norway's main newspaper for medical professionals, featuring CCBIO scientists **Line Bjørge**, **Mari K. Halle**, and **Karen Rosnes Gissum**. Line Bjørge chaired the event. Topics discussed were targeted therapy of cervical cancer, large-scale characterizing of treatment strategies for patients with high-risk cervical cancer, cell therapy for solid tumors, surgical trials in gynecologic oncology – from tumor debulking to precision medicine, update on the IMPRESS-Norway trial, and the patients' and healthcare providers' perspectives on understanding and managing cancer, including a panel debate on whether we are able to meet all perspectives and needs.

Webinar on Early Response Evaluation by Single-Cell Signaling Profiling in Acute Myeloid Leukemia, January 25, 2024.
This webinar was given by CCBIO PI **Bjørn Tore Gjertsen.** Acute myeloid leukemia (AML) is a hematopoietic stem cell-derived myeloid malignancy characterized by manifold genetic aberrations and poor overall survival. Gjertsen showed how his group, by using a state-of-the-art 36-marker mass cytometry panel and by focusing on functional signaling analysis, was able to shed light on one of the most critical aspects of cancer treatment – the initial response to chemotherapy in a cohort of 32 AML patients. Gjertsen also explained the significant predictors of patient 5-year overall survival in this cohort, specifically the reduction of extracellular-signal-regulated kinase (ERK) 1/2 and p38 mitogen-activated protein kinase (MAPK) phosphorylation. He also showed how RNA sequencing and proteomics confirm the mass cytometry data and that there is a potential for this assay to be used in the future of precision oncology.

Nordic AML Meeting 2023, August 24-25, in Bergen.
This event was supported by CCBIO and hosted by the Nordic AML group, of which CCBIO PI **Bjørn Tore Gjertsen** is chair. The Nordic AML meeting showcased the latest clinical and scientific developments in the field of AML (acute myeloid leukemia). The meeting featured renowned keynote speakers from the Nordic countries as well as worldwide, covering a broad range of topics, including novel therapies, clinical trials, genetics, and molecular biology, and a poster session. Speakers included Sören Lehmann, Jorrit Enserink, Krister Wennerberg, Caroline Heckman, Päivi Östling, Martin Jädersten, Kim Theilgaard-Mönch, Daniel A. Pollyea, Tom Erkers, Thoas Fioretos, Gunnar Kvalheim, Karl-Johan Malmberg, Sébastien Walchli, Gunnar Juliusson, Gerwin Huls, Hans Beier Ommen, Marianne Tang Severinsen, Oscar Brück, J.J. Schuringa, Mika Kontro, Jeffrey Tyner, James Lorens, Sonia Loges, Uwe Platzbecker, **Jean-Christophe Bourdon**, Eva Hellström-Lindberg, and Martin Höglund.

SCANPATH – the 7th Scandinavian Symposium on Translational Pathology, October 30-31, 2023, in Helsinki, Finland.
SCANPATH is a CCBIO-initiated annual network meeting for Scandinavian tumor pathologists and pre-clinical scientists with an interest in the prospects of next generation tissue profiling. The aim is to stimulate tissue-based studies of tumor mechanisms and biomarker mapping. SCANPATH was founded by CCBIO Director **Lars A. Akslen** and PI **Arne Östman** in 2016 and is now a well-established annual forum. Since the first meeting in Bergen, Norway (2016), further meetings were held in Sigtuna, Sweden (2017), Gustavelund, Tuusula, Finland (2018), Solstrand, Bergen, Norway (2019), and Tylösand, Sweden, (2021). The 2020 event was cancelled due to the pandemic. In 2022, SCANPATH returned to Solstrand, Bergen, hosted by CCBIO. At the Helsinki meeting in 2023, hosted by the Institute for Molecular Medicine Finland (FIMM), the University of Helsinki, and the SCANPATH society, several CCBIO researchers contributed, including talks by **Carina Strell** and **Arne Östman**, as well as many poster presentations.

2nd CCBIO-VBP Research Meeting, August 28–31, 2024, Solstrand, Norway.
This meeting was the second joint meeting in the INTPART collaboration between CCBIO and the Vascular Biology Program (VBP), Boston Children's Hospital and Harvard Medical School, gathering 57 participants at Solstrand. The INTPART effort is an RCN and HK-dir funded program aiming to better integrate excellent research and training. CCBIO's project is a reinforcement of existing relations between CCBIO and Boston Children's Hospital and Harvard Medical School, following CCBIO Director Lars A. Akslen's collaboration with the Folkman lab since 2004. The project has benefitted from strong support from the current director of VBP Marsha A. Moses as well as from Bruce Zetter, a member of the CCBIO SAB since 2013. Activities are set up to foster stronger integration between excellent teaching and research environments in collaboration with international partners. Lars A. Akslen and Marsha A. Moses (Director, VBP) are the INTPART project leaders. Agnete Engelsen was the main coordinator in Bergen for this meeting, with Michael Rogers as the Boston coordinator.

Following the opening remarks by Akslen, the meeting started with all participants presenting themselves in 3-minute speedtalks. The **Vascular Biology Program** at **Boston Children's Hospital** takes an interdisciplinary approach to the study of physiological and pathological processes that are dependent, in some way, on adaptations of the vascular system. They examine biological processes and search for solutions to the studied diseases, the same way CCBIO researchers study the microenvironment of cancers, including the vascular and neural systems, to find new approaches of cutting the tumor off from their supporting mechanisms.



Main speakers included renowned professors as well as junior scientists presenting their current research. Keynote speaker **Timothy Hla** shared his inspiring career journey. **Hong Chen** explained how recruiting neural stem cells to the endothelium could enhance endothelial resilience.



Endometriosis is one of the VBP research fields. **Daniëlle Peterse** gave a talk about fatty acid synthesis as a potential target to treatment of this disease. **Victor Fattori** explained how nociceptor neuron to macrophage communication via CGRP/RAMP1 signaling is a driver of endometriosis-associated pain and lesion growth. **Michael S. Rogers**' focused on the insulin PI3 kinase signaling pathway in endometriosis, and how reducing this signaling might reduce pain in endometriosis. **Aram Ghalali**'s research focused on drug development targeting childhood brain cancer. **Joseph Ogbede** explained his work with designing nanoparticle-based therapeutic strategies to overcome drug resistance in multiple myeloma. **Lufei Sui** showed how breast cancer stem cell function is driven by a cleavage-independent non-canonical Notch1 pathway via activation of the p53 superfamily, and **Joyce Bischoff** (standing in for **Annegret Holm**), explained how an endothelial SOX18-mevalonate pathway axis enables repurposing of statins for infantile hemangioma. **Edward Smith** discussed the possibility to supplement — or replace — current antiquated, anatomically-based disease classification systems with a molecular taxonomy, and how molecular genetic data is already informing clinical trials and catalyzing the development of targeted therapies.



From CCBIO, **Dana Costea** showed how her group used imaging mass cytometry to reveal distinct subpopulations of cancer associated fibroblasts (CAFs) in oral squamous cell carcinoma. **Katrin Kleinmanns** explained how her team developed and characterized humanized patient-derived xenograft (PDX) models with a functional human immune system and an orthotopically implanted primary ovarian cancer tumor and evaluated encouraging immunological targets. **Lorena Larios Salazar** presented work on the development of double-functionalized nanodiamonds (NDs) for targeted treatment to prevent oral cancer recurrence. **Agnete Engelsen** showed how they apply preclinical models and recently established clinical cohorts to explore how phenotypic plasticity interferes with therapeutic efficacy and immune cell-mediated killing in non-small cell lung cancer. **Erling A. Høivik** gave an overview of breast cancer among the young, mapping somatic mutations in this group. **Rasmus O.C. Humlevik** presented results indicating that young breast cancer patients showed significantly higher expression of immunosuppressive genes, including CTLA4 and PD1. **Heidrun Vethe** explained studies on how nerves emerge in breast cancer and potential mechanisms, using cell models and human tissue, and **Kenneth Finne** showed results from stromal-based breast cancer proteomics and spatial analytics by imaging mass cytometry (IMC). **Carina Strell** explained her group's work on *in situ* detection of PD1-PDL1 interaction as a functional predictor for response to immune checkpoint inhibition in non-small cell lung cancer. The program also included a CCBIO alumna, **Silje Kjølle**, now working in Erler's group at the



Biotech Research & Innovation Centre (BRIC), University of Copenhagen, and focusing on novel therapies for metastatic cancers. She presented work on hypoxia markers in breast cancer. Although very diverse backgrounds and research fields, the spectrum of methods and results were highly interesting for all participants.

One session was dedicated to a discussion on the topic *Futures of cancer research and cancer care*, with a panel consisting of **Marta Bertolaso** (Rome), **Caroline Engen** (Bergen), **Jiyeon Kang** (London) and **Roger Strand** (Bergen). This was a *looking beyond the slides*-kind of conversation between the panelists as much as with the rest of the room, offering philosophical, ethical, societal and economic perspectives. These kinds of discussions have become an important CCBIO tradition, lifting the view from the microscope and to ethical, economic and social aspects of our research.

As is also a tradition in the CCBIO–VBP meetings, the program included sessions on so-called "soft skills" of research. **Diane Bielenberg** from the VBP focused on the power of mentoring in a career development workshop, with tips for both mentor and mentee, and discussed the role that each play in a productive laboratory environment. Mentoring, not to be confused with supervision, has increasingly been focused in CCBIO since the CCBIO–VBP collaboration, notably in the Masterclass program.

Yves Aubert from UiB's Division of Research and Innovation explored how researchers can make their work more relevant, how clinicians can respond more effectively to medical needs, and how centers and institutions may establish infrastructure and support systems to promote their research staff and create impactful outputs.

The design theme from this meeting was maritime, inspired by the common US-Norwegian maritime heritage, by the fjords nearby and the imagery of the two research environments navigating together towards excellence in research, education and innovation. As a reflection, the very last session was held during a 5-hour trip with the 140-year-old and authentically restored wooden ship Mathilde from Hardanger Fartøyvernsenter. With a lot of heave and hoys, the enthusiastic CCBIO/VBP crew set full sails and steered towards the symbolic great unknown, together.

"Towards the end of the third day, scientists at sea used the opportunity to reflect on the importance and fun of teamwork — and the necessity of navigation — in science and in life. The meeting again proved the power of personal proximity — with a lot of science to discuss," Lars A. Akslen concluded. ••

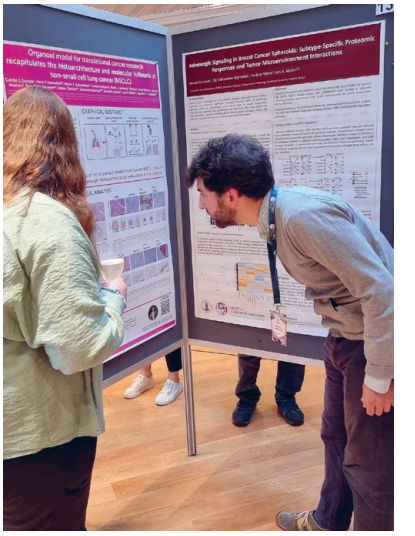
2nd CCBIO–VBP Research Meeting

August 28-31, 2024
Solstrand Hotel & Bad



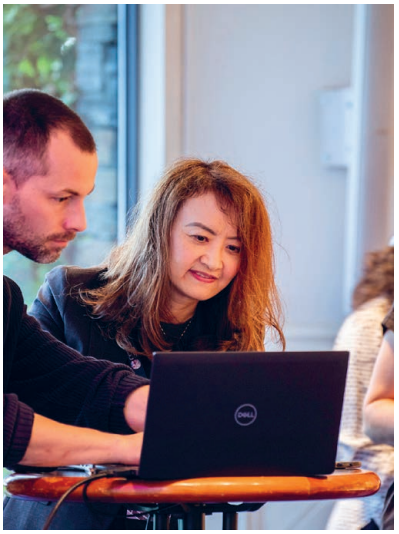


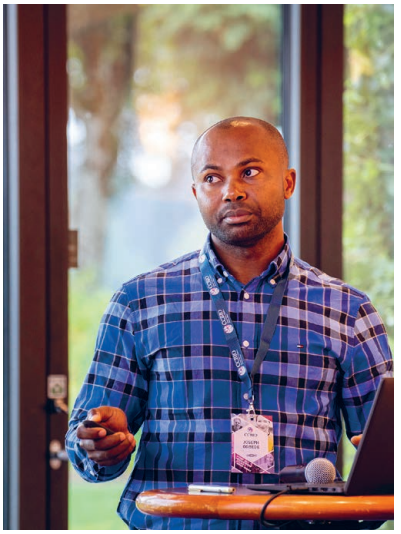






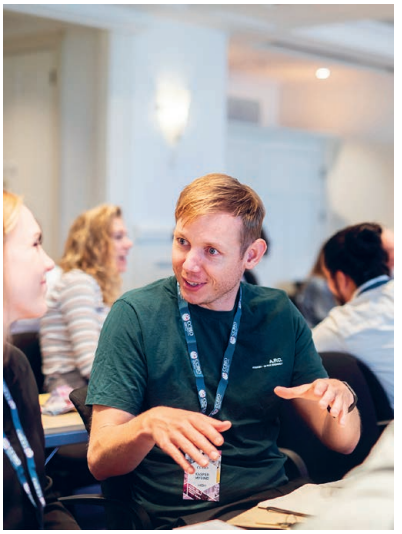






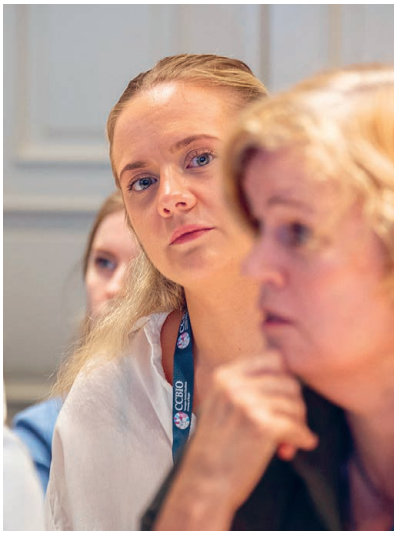


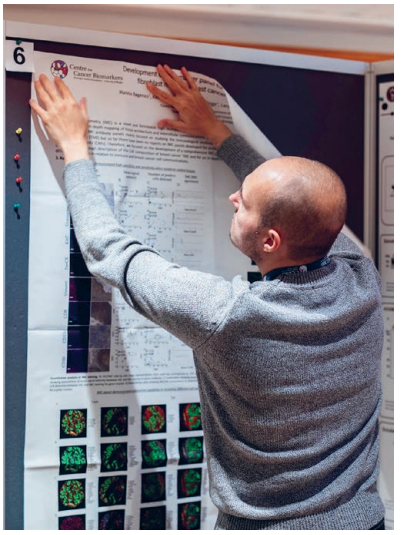















Centre for
Cancer Biomarkers
Norwegian Centre of Excellence – University of Bergen
CCBIO
ERLING
HOVIK

dissertations 2023–2024

Our PhD candidates' doctoral defenses are among the absolute highlights throughout each year. The award of a PhD is a celebration of the individual student's skills and development, as well as an expression of a long-term team effort, including supervisors, collaborators, and support staff. We are also confident that the CCBIO Research School for Cancer Studies (RSCS) provides added substance and quality to the training of a PhD candidate. The RSCS is a scientifically stimulating and inclusive educational environment and an important meeting place for junior scientists within cancer research with a common focus on translational studies of cancer biomarkers in the widest sense. It also serves as a bridge to CCBIO's ELSA efforts, providing future research leaders with important tools for research conduct and responsible decision making. During courses and other research school activities, PhD candidates and younger researchers meet and deliberate upon their research projects across the established groups. Through CCBIO's seminars, symposia and international faculty, our PhD candidates also get an unprecedented opportunity to interact with senior international researchers and establish new collaborations.

We congratulate the following PhD candidates who successfully completed their degrees in 2023 and the spring term of 2024:



BENEDICTE SJO TISLEVOLL

Single-cell protein profiling in early therapy response evaluation of acute myeloid leukemia by mass cytometry. Supervisors: Bjørn Tore Gjertsen and Vibeke Andresen. Defense date: January 19, 2023.



MARIA KATHRINE TVEITARÅS

Immunotherapy and HBOT – from bench to bedside. Supervisors: Linda Stuhr and Rolf Reed. Defense date: January 20, 2023.



KRISTINE ELDEVIK FASMER

MRI and 2- [18F] FDG PET/CT for staging, prognostication, and tailoring treatment in endometrial cancer. Supervisors: Ingfrid Haldorsen and Camilla Krakstad. Defense date: January 20, 2023.



NEHA RANA

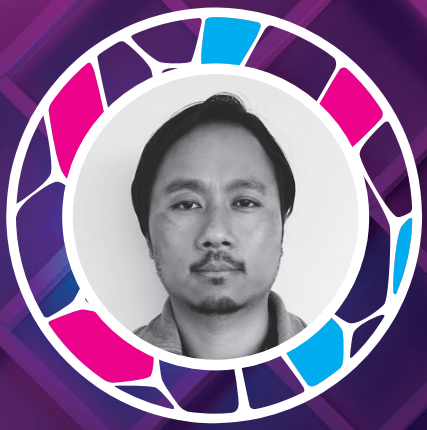
Immunomodulatory effects of mesenchymal stromal cells and calcium phosphate scaffolds in bone regeneration - Preclinical and clinical studies. Supervisors: Kamal Mustafa, Bjørn Tore Gjertsen, Sonia Gavasso and Salwa Suliman. Defense date: February 24, 2023.

dissertations 2023–2024



LOUISE BERGSJØ SAND

Synthetic studies toward [18F]-fluorination of solid-supported silyl ethers. Supervisors: Bengt Erik Haug, Ole Heine Kvernenes and Emmet Mc Cormack. Defense date: May 25, 2023.



SAROJ RAJTHALA

Functional and Prognostic Role of MicroRNAs in Cancer Associated Fibroblasts and Stroma in Oral Squamous Cell Carcinoma. Supervisors: Anne Christine Johannessen, Daniela-Elena Costea and Dipak Sapkota. Defense date: November 23, 2023.



CECILIE FREDVIK TORKILDSEN

Rethinking High-Grade Serous Ovarian Carcinoma: Comprehensive Bioprofiling for Enhanced Identification of Surgical Phenotypes and Treatment Outcomes. Supervisors: Liv Cecilie Vestrheim Thomsen, Line Bjørge and Ragnar Kvie Sande. Defense date: September 29, 2023.



LISE MARTINE INGEBRIKTSEN

Breast cancer of the young: Exploring age-related breast cancer biology. Supervisors: Elisabeth Wik, Lars A. Akslen and Erling Høivik. Defense date: November 30, 2023.



VICTORIA XENAKI

Nanosafety aspects: Dental health care workers' perception of nanomaterials and in vitro nanotoxicity assessment using new approach methodologies. Supervisors: Anne Nordrehaug Åstrøm, Mihaela Roxana Cimpan, Daniela Elena Costea and Ileana-Mihaela Cuida Marthinussen. Defense date: May 23, 2024.



OLE VIDHAMMER BJØRNSTAD

Neural Interactions in the Breast Cancer Microenvironment. Supervisors: Heidrun Vethe, Manuel Carrasco, Dimitrios Kleftogiannis and Lars A. Akslen. Defense date: May 31, 2024.



HASSAN ALI

Stemness and osteogenic differentiation of induced pluripotent stem cells generated in xeno-free conditions. Supervisors: Kamal Mustafa, Daniela Costea, Helge Ræder and Salwa Suliman. Defense date: May 24, 2024.



CHRISTIANE HELGESTAD GJERDE

Development of Advanced 3D Ovarian Carcinoma Models. Supervisors: Line Bjørge, Emmet Mc Cormack and Katrin Kleinmanns. Defense date: June 24, 2024.

dissertations 2023–2024



KAREN ROSNES GISSUM
Unveiling the Complexities: Patients' and Healthcare Providers' Perspectives on Understanding and Managing Ovarian Cancer. Supervisors: Line Bjørge, Roger Strand, Ingvild Vistad, Sigrunn Drageset and Liv Cecilie V. Thomsen. Defense date: June 28, 2024.



AUSTIN RAYFORD
Studies on the effect of AXL inhibition in non-small cell lung cancer. Supervisors: James B. Lorens, Agnete S. T. Engelsen and David Micklem. Defense date: October 11, 2024.



HILDE EIDE LIEN
Single cell expression patterns in endometrial cancer and novel biomarkers for improved treatment. Supervisors: Camilla Krakstad, Lars A. Akslen and Ingfrid Salvesen Haldorsen. Defense date: September 13, 2024.



STURLA GRØNDAL
Mechanisms of Immune Dysregulation through AXL Receptor Tyrosine Kinase Signaling in Cancer and Fibrotic Diseases. Supervisors: James Lorens and Silke Appel. Defense date: October 14, 2024.





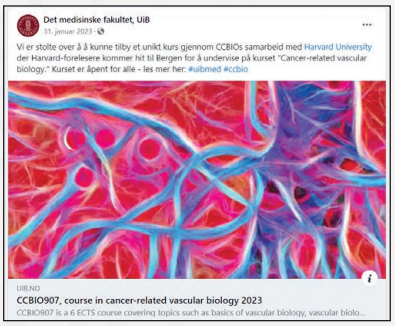

science
communication
2023-2024

dissemination and communication 2023–2024

CCBIO aims to communicate and disseminate its findings to the public and continues to do this in a timely and informative way. In addition to publications and events for the scientific community, our research can be viewed, read, and listened to in national mainstream media and at public popular scientific meetings and debates. CCBIO issues a newsletter at regular intervals (6 issues per year) and keeps its webpages updated, presenting news stories from our research community, and ensuring that our numerous open events are well advertised.

Also, social media has grown to be a tool and connector for governmental organizations, businesses, and individual users. We promote our researchers, scientific findings, happenings, media appearances and behind-the-scenes glimpses via the Faculty of Medicine's Facebook and X accounts and encourage our researchers and students to promote their research and activities through the social media as well. As of summer 2024, CCBIO has established its own social media (X, LinkedIn) to signal that we are continuing our research and educational efforts beyond June 30, 2024.

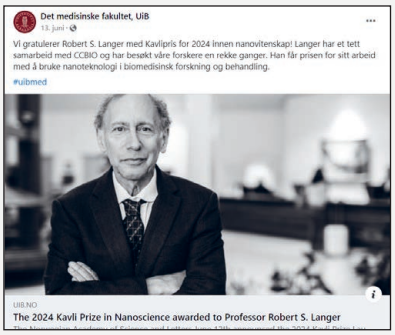
Examples of dissemination and communication efforts through social media in 2023 and the spring term of 2024:



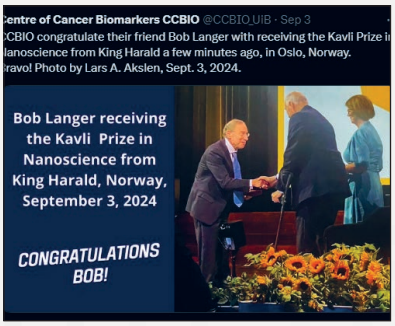
Facebook post from the Medical Faculty advertising the unique CCBIO907 course, a collaboration with the Vascular Biology Program (VBP) at Boston Children's Hospital and Harvard Medical School.



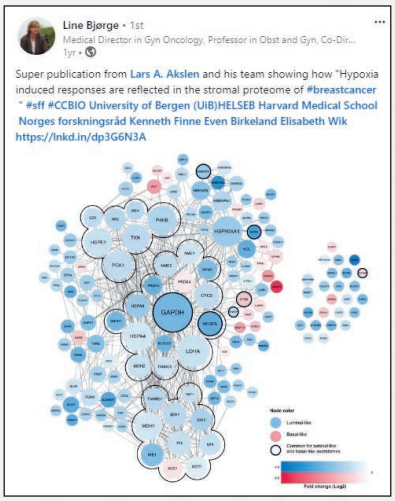
X entry reposted by the Medical Faculty from original post by CCBIO Co-Director Line Bjørge, highlighting important work of Bjørn Tore Gjertsen's group and their publication in Nature Communications as well as interviews on national TV.



Facebook post from the Medical Faculty conveying the CCBIO news article congratulating Robert S. Langer with the Kavli Award 2024.



Follow-up on CCBIO's **X** profile congratulating Robert S. Langer, from the Kavli Award ceremony with King Harald September 3, 2024.



LinkedIn-post by the CCBIO Co-Director Line Bjørge, highlighting a publication from the Akslen group in Nature Communications.



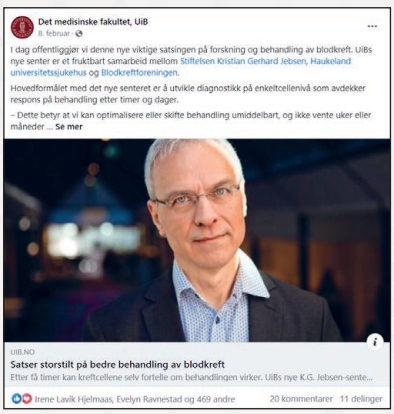
Facebook post from the Medical Faculty fronting CCBIO PhD Candidate Christiane Helgestad Gjerde as one of the finalists in the national Researcher Grand Prix event.



X entry reposted by the Medical Faculty from original post by Professor Haldorsen, congratulating CCBIO PhD Candidate Kari Wagner-Larsen with best research paper 2022, awarded by the Norwegian Radiology Association.



X entry reposted by the Medical Faculty from original post by CCBIO Co-Director Line Bjørge, conveying that the regional health authority Helse Vest's Research Award 2023 goes to Professor Lars A. Akslen and CCBIO for ground-breaking research on cancer biomarkers.



Facebook post from the Medical Faculty celebrating the new KG Jebsen Center for Myeloid Blood Cancer, to be headed by CCBIO PI Bjørn Tore Gjertsen.



Facebook post from the Medical Faculty advertising a new seminar series "Mulighetsreisen", where they showcase exemplary research careers for inspiration to all students at the Medical Faculty. First up was CCBIO Postdoc Heidrun Vethe.



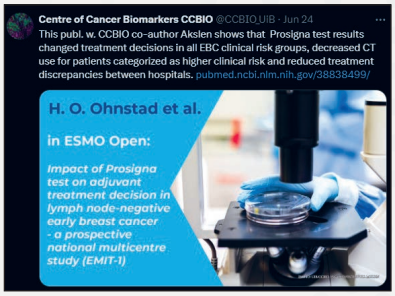
LinkedIn example from CCBIO's own newly established account from June 2024, showing how we announce our new doctorates.



X example from CCBIO's own newly established account from June 2024, showing how we announce our new doctorates.



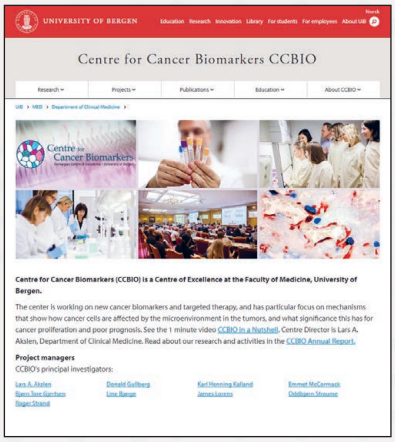
LinkedIn example from CCBIO's own newly established account from June 2024, showing how we announce new CCBIO publications.



Example in **X** from CCBIO's own newly established account from June 2024, showing how we announce new CCBIO publications.



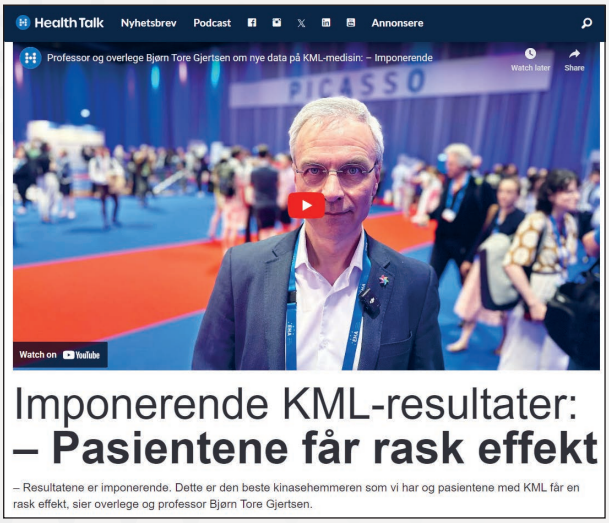
CCBIO also has a unique dissemination effort in collaboration with the actor and molecular biologist Henriette Christie Ertsås, a CCBIO alumna. She offers interactive performances and lectures on cancer and biomarkers to schools on CCBIO's behalf. Henriette stages stories that take place inside the body, more specifically within the individual cell, and introduce that teeny-tiny biology not visible even in the microscope. A perceived total lack of common decency among cancer cells invites relatable stories that can explain cancer to a child. Henriette is a molecular biologist with experience in age-dependent cancer. Having also studied acting, she tells the story of the wondrous biology of cells with great skill. In 2023/24, 477 students in Bergen schools were confronted with the nagging dilemma of a cell growing up in a hostile microenvironment through 5 interactive performances of "Stine Stem Cell finds herself" and 8 performances of "Kristine Cancer Cell — a sociopath in the body".



CCBIO's web pages.

media appearances 2023-2024

Media stories in 2023 and the spring term of 2024, with date, news medium, title and CCBIO person mentioned or interviewed:

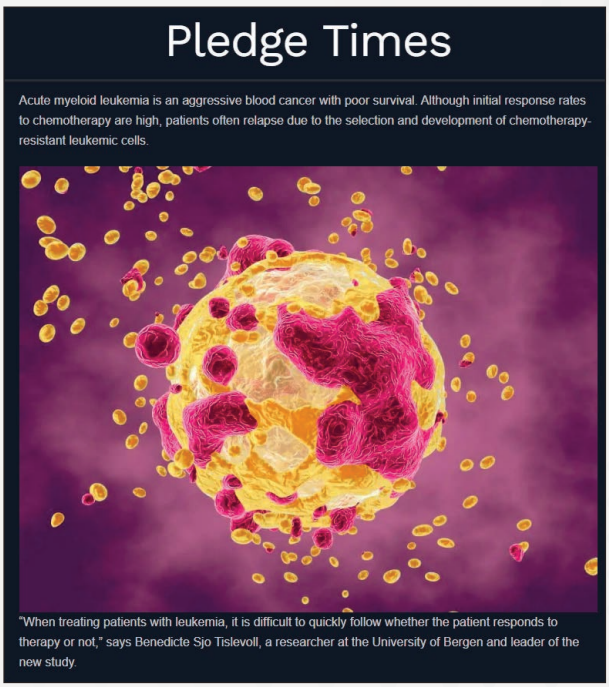


JUNE 16, 2024 - HEALTHTALK
"Imponerende KML-resultater: – Pasientene får rask effekt" - Bjørn Tore Gjertsen

JUNE 14, 2024 - UIB/DRIV
"Dette forsker vi på" - Camilla Krakstad

JUNE 13, 2024 - HEALTHTALK
"Hematologi: Flere norske leger reiser til blod-kongressen EHA i Madrid" - Bjørn Tore Gjertsen

MAY 20, 2024 - HELSE FØRDE
"Brukarmedverknad gir betre forsking" - mention of CCBIO's course in patient and public involvement in medical research



MAY 17, 2024 - PLEDGE TIMES
"New path to tumor cell death due to chemotherapy discovered" - Benedicte Sjo Tislevoll

MAY 10, 2024 - TV2
"Håper å revolusjonere kreftbehandlingen"
- Bjørn Tore Gjertsen



MAY 07, 2024 - NRK
"Nye krefttall forbauser – særlig ett grep får æren"
- Oddbjørn Straume

MARCH 21, 2024 - SHIFTER.NO
"Sliter med å skape business av helseforskning:
– Triste og tragiske tall" - mention of CCBIO



MARCH 20, 2024 - HEALTHTALK
"Livmorkreft: Dette bør du vite om symptomer
– diagnose og behandling" - Line Bjørge

MARCH 19, 2024 - DAGBLADET
"Ny kreftbehandling hylles: – Stor glede!"
- Line Bjørge



MARCH 09, 2024 - HEALTHTALK
"Prisvinneren: – Helga var en inspirator for mange – og en pioner innen gynekologisk kreftforskning" - about the late Helga B. Salvesen

FEBRUARY 19, 2024 - VG
"Brystkreftmedisin under lupen: – Ser ut til å ha dårligere overlevelse" - Oddbjørn Straume

FEBRUARY 15, 2024 - FIRDAPOSTEN
"Florømann leier storsatsing på blodkreft-behandling"
- Bjørn Tore Gjertsen



media appearances

FEBRUARY 08, 2024 - NRK
"Helge vart kreftfrisk gjennom forskingsprosjekt:
– Har betydd alt" - Bjørn Tore Gjertsen, Benedicte Sjo Tislevoll

FEBRUARY 08, 2024 - BERGENS TIDENDE
"43 millioner til nytt blodkreft-senter"
- Bjørn Tore Gjertsen

FEBRUARY 08, 2024 - NTB/UiB
"Satser storstilt på bedre behandling av blodkreft"
- Bjørn Tore Gjertsen

JANUARY 29, 2024 - FORSKERFORUM
"Mot normalt" - Anne Blanchard



JANUARY 19, 2024 - UIB NEWS
"Mottar 400 000 for kurs i brukermedvirkning i forskning"
- CCBIO

JANUARY 17, 2024 - NRK
"Vil bruke fingeravtrykk til å avsløre brystkreft"
- Oddbjørn Straume

JANUARY 04, 2024 - HEALTHTALK
"Livmorkreft: GSKs kreftkombinasjon når hovedmålet i senfase-studie" - Line Bjørge

DECEMBER 20, 2023 - HELSE BERGEN NEWS
"Oddbjørn Straume ny direktør for Kreftavdelinga"
- Oddbjørn Straume

DECEMBER 20, 2023 - MEDWATCH
"Avexxin Oncology har gjennomført tidlig studie på potensiell blodkreft-behandling" - Bjørn Tore Gjertsen



DECEMBER 19, 2023 - DEN NORSKE PATOLOGIFORENING
"Intervju med Elisabeth Wik," - Elisabeth Wik

DECEMBER 15, 2023 - HEALTHTALK
"Livmorkreft: Frykter sen innføring av medisin:
– 2025 er helt uakseptabelt" - Line Bjørge

DECEMBER 14, 2023 - DAGENS MEDISIN
"Mener norsk legemiddel må tas ned fra hyllen"
- Bjørn Tore Gjertsen

DECEMBER 12, 2023 - DAGENS MEDISIN
"Vaksinestudier på AML presentert på ASH: – Oppsiktsvekkende gode resultater"
- Bjørn Tore Gjertsen



NOVEMBER 24, 2023 - HELSE VEST NEWS
"Tildeling av Helse Vest sine forskingsmidlar 2024"
- CCBIO & Lars A. Akslen

NOVEMBER 23, 2023 - DAGENS MEDISIN
"Helsefolk" - Lars A. Akslen



NOVEMBER 20, 2023 - ONCLIVE
"Bemcentinib Plus SOC Is Well Tolerated - But Does Not Improve Efficacy in Metastatic Melanoma"
- Oddbjørn Straume

NOVEMBER 19, 2023 - ONKOLOGISK TIDSSKRIFT
"Kreftregisterets tall: Null tilfeller av livmorhalskreft blant 25-åringene i 2022" - Line Bjørge

NOVEMBER 17, 2023 - HELSE VEST NEWS
"Detektiven som ville løyse kreftgåta" - Lars A. Akslen



NOVEMBER 16, 2023 - HELSE VEST NEWS
"Gjeve prisar til kreft- og stamcelleforsking"
- Lars A. Akslen

OCTOBER 25, 2023 - HEALTHTALK
"Norsk kreftlege presenterte norsk medisin på Europas største kreftkongress" - Oddbjørn Straume

media appearances



OCTOBER 24, 2023 - ONKOLOGISK TIDSSKRIFT
"Induksjonskjemoterapi til lokalt avansert livmorhalskreft kan bli ny standard" - Line Bjørge

OCTOBER 21, 2023 - HEALTHTALK
"Livmorkreft: Nye data fra studie som imponerte,"
- Line Bjørge

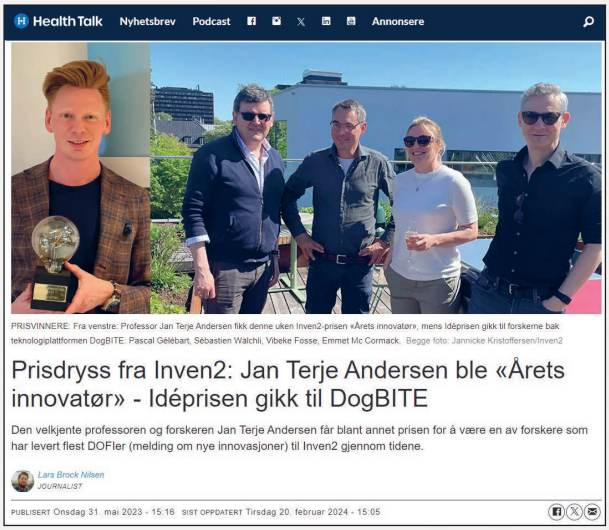
OCTOBER 21, 2023 - DAGENS MEDISIN
"Presenterte norsk forskning på pasienter med metastatisk melanom" - Oddbjørn Straume

OCTOBER 18, 2023 - STAVANGER AFTENBLAD
"Kan kirurgisk behandling av eggstokkreft skreddersys?"
- Cecilie Fredvik Torkildsen

OCTOBER 02, 2023 - NKS FREDRIKKE
"Hvordan gi bedre livskvalitet til kvinner med eggstokkreft" - Line Bjørge, Karen Rosnes Gissum

JULY 23, 2023 - ONKOLOGISK TIDSSKRIFT
"Overlege: Ruby-studien gir håp for pasienter med spesiell type livmorkreft" - Line Bjørge

JUNE 11, 2023 - BERGENSAVISEN
"Hadde kreft i tre føflekker" - Emilia Hugdahl



MAY 31, 2023 - HEALTHTALK
"Prisdryss fra Inven2: Jan Terje Andersen ble «Årets innovatør» – Idéprisen gikk til DogBITE" - Pascal Gélébart, Vibeke Fosse, Emmet Mc Cormack

MAY 26, 2023 - HELSE VEST
"Ny forskningsrapport klar: Dette forsket sykehusene på i 2022" - Nina Louise Jebsen





HELSE VEST

Injisering direkte i kreftsvulst er testet på mennesker

25.5.2023 14:56:23 CEST | Helse Vest RHF

Del

30 prosent av de norske pasientene i denne kliniske studien opplevde betydelig reduksjon av svulsten. Det er resultatet forskerne kan vise til etter at første fase nå er avsluttet. Injisering av medikamentet LTX-315 kan gi forlenget levetid for pasientene.

Flere kreftleger, radiologer og studiesykepleiere deltok i studien. Her er prosessen illustrert med studiesykepleier Torill Våge (ved sengen), overlege Nina Louise Jebsen, foran radiolog Dag Jøssang og studiesykepleier Mari Helgesen Holsen. Foto: Jan Inge Haga

MAY 25, 2023 - HELSE VEST
"Injisering direkte i kreftsvulst er testet på mennesker" - Nina Louise Jebsen

MAY 24, 2023 - ROMSDALS BUDSTIKKE
"Beslutningsforum utsatte vedtak om blodkreft-medisin" - Bjørn Tore Gjertsen



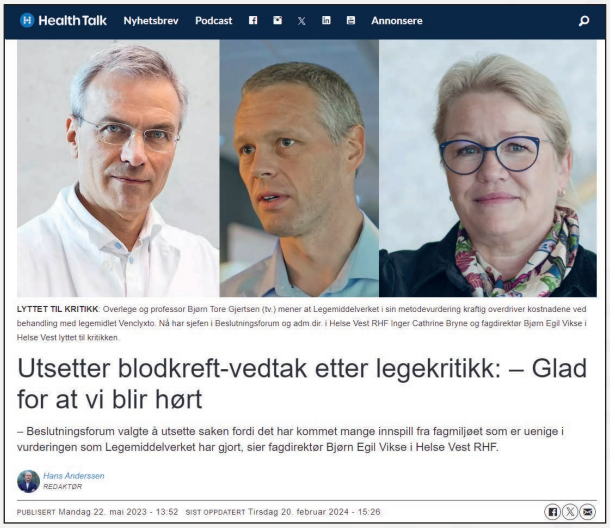
forskning.no Kultur Helse Miljø Samfunn Teknologi Naturviten Podcast Nyhetsbrev

Finnes løsningen på kreftgåten? – Det grunnleggende problemet er hvordan kroppen vår er konstruert, sier professor

Jo bedre behandlingen blir, jo mer kreft blir det i befolkningen.

Elise Kjørstad
JOURNALIST

PUBLISERT 27.04.2023 - 04:31



Health Talk Nyhetsbrev Podcast Annonsere

LYTTET TIL KRITIKK: Overlege og professor Bjørn Tore Gjertsen (tv.) mener at Legemiddelverket i sin metodevurdering kraftig overdriver kostnadene ved behandling med legemidlet Venclyxto. Nå har sjefen i Beslutningsforum og adm.dir. i Helse Vest RHF Inger Cathrine Bryne og fagdirektør Bjørn Egil Vikse i Helse Vest lyttet til kritikken.

Utsetter blodkreft-vedtak etter legekritikk: – Glad for at vi blir hørt

– Beslutningsforum valgte å utsette saken fordi det har kommet mange innspill fra fagmiljøet som er uenige i vurderingen som Legemiddelverket har gjort, sier fagdirektør Bjørn Egil Vikse i Helse Vest RHF.

Hans Anderssen
REDAKTØR

PUBLISERT Mandag 22. mai 2023 - 13:52 SIST OPPDATERT Tirsdag 20. februar 2024 - 15:26

MAY 22, 2023 - HEALTHTALK
"Utsetter blodkreft-vedtak etter legekritikk: – Glad for at vi blir hørt" - Bjørn Tore Gjertsen

MAY 22, 2023 - HEALTHTALK
"Beslutningsforum sa ja til 15 legemidler – to saker med Venclyxto utsettes" - Bjørn Tore Gjertsen

MAY 19, 2023 - ROMSDALS BUDSTIKKE
"Jeg har fått forlenget levetiden med mange år" - Bjørn Tore Gjertsen

MAY 19, 2023 - TANNLEGETIDENDE
"Immunmodulering ved stamcellebehandling for beinregenerering" - Neha Rana

MAY 18, 2023 - HEALTHTALK
"Ny podcast: Frykter det blir nei i Beslutningsforum; Arctic Bioscience med stor studie og lovende kreftvaksine" - Bjørn Tore Gjertsen

APRIL 29, 2023 - ABC NYHETER
"Finnes løsningen på kreftgåten?" - Lars A. Akslen

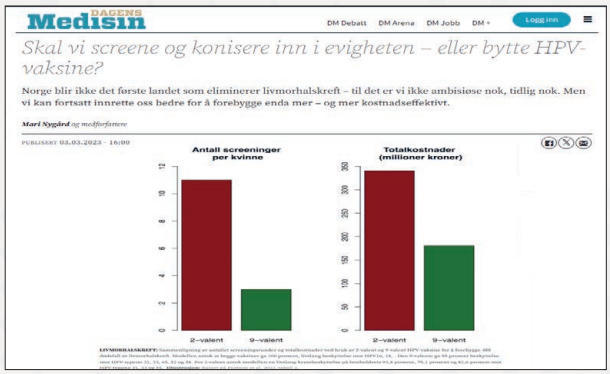
APRIL 27, 2023 - FORSKNING.NO
"Finnes løsningen på kreftgåten? – Det grunnleggende problemet er hvordan kroppen vår er konstruert – sier professor" - Lars A. Akslen

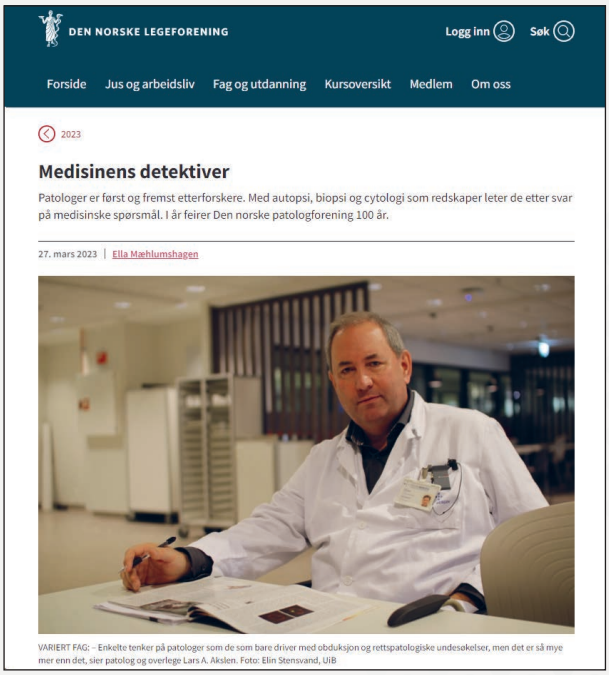


APRIL 11, 2023 - TV2 NYHETER
"Snart kan Julie slippe «drittjobbene»"
- Julie Dybvik, Ingfrid Haldorsen

APRIL 05, 2023 - BØMLO-NYTT
"Han held fast i livet mot alle odds" - Oddbjørn Straume

MARCH 29, 2023 - BERGENS TIDENDE
"Kvinner i kø for livmorhalsprøve. Nå tar det tre måneder å få svar" - Elisabeth Wik





MARCH 27, 2023 - DEN NORSKE LEGEFORENING
"Medisinens detektiver" - Lars A. Akslen

MARCH 25, 2023 - HORDALAND
"Tredobla ventetid på svar på celleprøvar"
- Elisabeth Wik

MARCH 21, 2023 - ONKOLOGISK TIDSSKRIFT
"Behandlingen av livmorkreft i Norge er ikke optimal"
- Line Bjørge

MARCH 03, 2023 - DAGENS MEDISIN
"Skal vi screene og konisere inn i evigheten – eller bytte HPV-vaksine?" - Line Bjørge

FEBRUARY 24, 2023 - HEALTHTALK
"Professor: – Gentesting er avgjørende for å utvikle ny behandling – men ikke glem at livmorhalskreft kan forebygges" - Camilla Krakstad

JANUARY 27, 2023 - SUNNHORDLAND
"Kvinnhering sentral i kreftgjennombrot"
- Benedicte Sjo Tislevoll

JANUARY 21, 2023 - KVINNHERINGEN
"Benedicte (30) har leia forsking som gir blodkreftpasientar livsviktig tid: – Det er veldig stort" - Benedicte Sjo Tislevoll

JANUARY 19, 2023 - BERGENSAVISEN
"Venter at det vil ta lengre tid å få svar på celleprøver i Bergen" - Elisabeth Wik

JANUARY 18, 2023 - MEDSCAPE
"Blood Test 24 Hours After Starting Chemo Predicts AML Survival" - Benedicte Sjo Tislevoll

JANUARY 13, 2023 - BERGENS TIDENDE
"Avslører tidlig om kreftbehandlingen virker"
- Benedicte Sjo Tislevoll

JANUARY 13, 2023 - NTB
"Blodprøve tatt timer etter cellegift forutsier overlevelse"
- Benedicte Sjo Tislevoll



JANUARY 12, 2023 - NRK DAGSREVYEN
"Ny cellegift-forskning" - Benedicte Sjo Tislevoll

JANUARY 12, 2023 - NRK1 ROGALANDSNYTT
"Kreftforskning" - Benedicte Sjo Tislevoll

JANUARY 12, 2023 - NRK VESTLANDSREVYEN
"Kreftforskning" - Benedicte Sjo Tislevoll

JANUARY 12, 2023 - NRK VESTLAND
"Gjennombrot i kreftforsking: På eitt døgn kan legane finne ut om cellegifta fungerer" - Benedicte Sjo Tislevoll

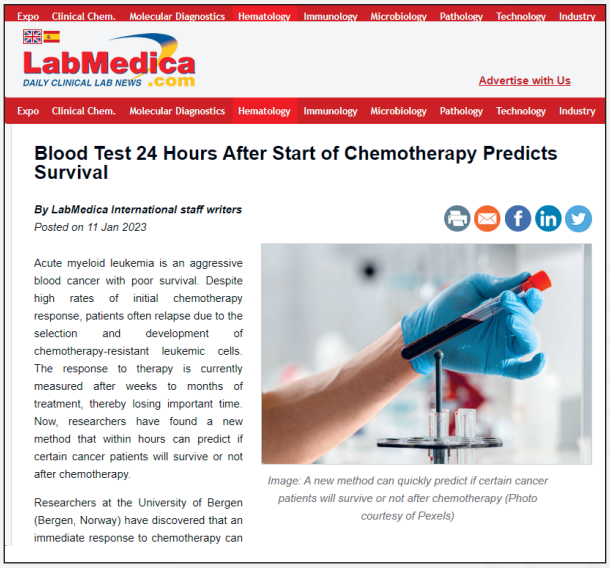


Image: A new method can quickly predict if certain cancer patients will survive or not after chemotherapy (Photo courtesy of Pexels)

JANUARY 11, 2023 - LAB MEDICA
"Blood Test 24 Hours After Start of Chemotherapy Predicts Survival" - Benedicte Sjo Tislevoll

JANUARY 10, 2023 - ALPHA GALILEO
"Cancer breakthrough - a blood sample 24 hours after start of chemotherapy predicts survival"
- Benedicte Sjo Tislevoll





PART III

Overall Activities

2013-2024



research programs and teams

From the opening in 2013, CCBIO was organized in three scientific programs – *preclinical models, biomarkers, and clinical studies*. CCBIO had nine founding PIs: Lars A. Akslen, Bjørn Tore Gjertsen, Donald Gullberg, Anne Christine Johannessen (until 2017), Karl-Henning Kalland, James Lorens, Rolf Reed (until 2018), Helga Salvesen† (until 2016), and Oddbjørn Straume. Roger Strand (ELSA studies), Inge Jonassen (bioinformatics) and Oddvar Kaarbøe (health economics, until 2017) were included as associate investigators from 2013. John Cairns (London and UiB) was also recruited as associate investigator (health economics, since 2014).

For the second part of CCBIO (2018–2024), the organization was slightly modified to better reflect the ongoing research activities. We now have four teams and corresponding project areas: *basic studies of tumor-microenvironment interactions* (**Team 1**), *discovery and validation of cancer biomarkers in human tissues* (**Team 2**), *clinical studies and early trials* (**Team 3**), and *societal studies with projects on ethics, economics, philosophy, and priorities* (**Team 4**). Additional investigators were recruited as PIs or associate PIs: Line Bjørge (since 2016), Daniela Costea (since 2016), Camilla Krakstad (since 2016), Emmet Mc Cormack (since 2016), Ole Frithjof Norheim (since 2016), Elisabeth Wik (since 2016), Carina Strell (since 2022) and Agnete Engelsen (since 2022).

Lars A. Akslen has been the director of CCBIO since the center was established. The following have been co-directors: Helga Salvesen† (2013–2016), Bjørn Tore Gjertsen (2016–2022), and Line Bjørge (since 2022).

The four research programs are cross-linked and strengthened with resources in bioinformatics and processing of big data, coordinated by Inge Jonassen. Increased connectivity and collaboration within CCBIO have taken place over the years. The center is supported by an International Faculty of 14 top scientists in different fields, promoting widespread international collaboration and networking.



Team 1

mechanisms of tumor microenvironment interactions

The aim of this program is to examine how tumor cells interact with the surrounding tumor microenvironment with different cell types such as immune cells, fibroblasts, vascular cells, nerve cells and stem cells embedded in the complex extracellular matrix. This team consists of the PIs Gullberg, Kalland, and Mc Cormack.





Donald Gullberg

the matrix biology group

Short bio
Professor Donald Gullberg, originally from Sweden, did his PhD in 1990 at the Department of Medical and Physiological Chemistry, Uppsala University, Sweden, where he also worked as a researcher till 2003, apart from his postdoc period at the Molecular Biology Institute, University of California, Los Angeles in 1990–1992. He was recruited to the University of Bergen in 2004 as professor at the Department of Biomedicine, working on collagen receptors and integrin biology, a role he currently holds as well as directing the Matrix Biology Group at the Department of Biomedicine and CCBIO. He has on different occasions had two years of research stays at the University of California, San Francisco at the labs of Professor Valerie Weaver, Department of Surgery, and Professor Dean Sheppard, the Lung Biology Center.

Professor Gullberg's research interests are characterizing the integrin α11β1, which is expressed on subsets of normal fibroblasts and on carcinoma-associated fibroblasts. Cells lacking α11β1 display disturbed cell-collagen interactions, altered metalloproteinase synthesis and reduced cell proliferation.

Brief group presentation and history
The Matrix Biology Group in its current form was created in 2004 when Donald and Marion Kusche Gullberg started working at the UiB.

Research focus
The research in the group is focused on work related to integrin α11. The CCBIO projects deal with understanding the role of integrin α11 at the molecular and cellular levels to ultimately reach a better understanding of its role in the tumor stroma.

Subprojects
1. One focus of the CCBIO-supported activities has been to develop a new fibroblast specific transgenic Cre driver mouse strain where Cre-recombinase is driven by a human integrin α11 promoter (ITGA11-Cre strain). Characterization of the functionality of Cre-recombinase in this mouse strain has been determined by crossing with the Rosa26R reporter strain. The first publication with this novel mouse strain was in Alam J. et al., *Matrix Biol. Plus*. 2020. The Cre mouse strain has now been bred with a tdTomato strain for direct visualization of ITGA11 expression.

2. A second project relates to epitope mapping of integrin α11 monoclonal antibodies (mAbs). The Gullberg group has finished epitope mapping of mAb 210F4 and is in the final stages of mapping the epitope of the function blocking antibody 203E1. This project was reinforced by an NCS supported researcher, Cédric Zeltz, who started in 2022.



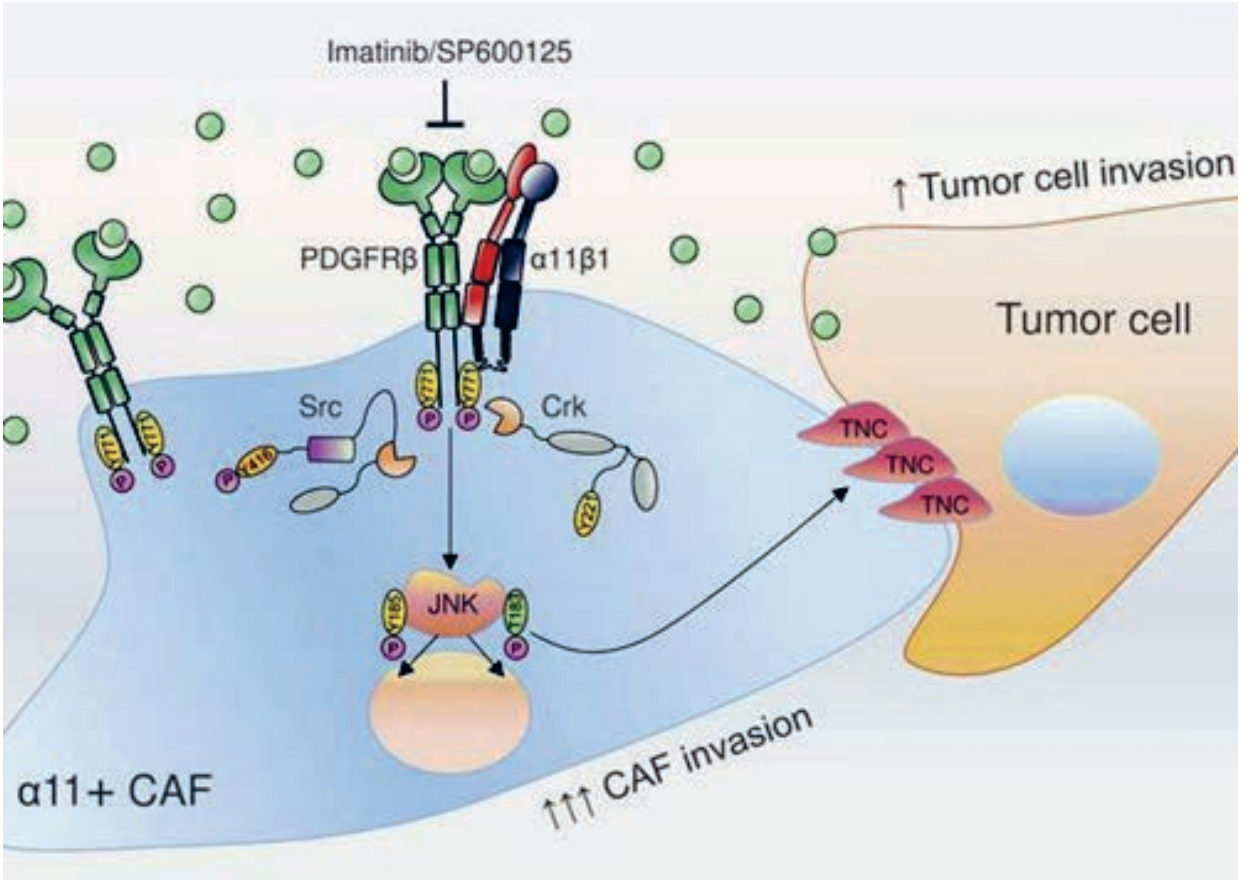
Most important results
The finalization of the ITGA11-Cre mouse strain was a major milestone in the Gullberg group after 10 years of efforts on this project. Further breeding into a fluorescent reporter strain will be another step forward. The detailed epitope mapping of mAb 210F4 and mAb 203E1 to a few amino acids also illustrates the importance of consistent systematic work spanning several years to reach long-lasting, well-cited results.

Most important papers
1. Romaine A. et al. Overexpression of integrin alpha11 induces cardiac fibrosis in mice. *Acta Physiol (Oxf)* 2018. PMID: 28771943.

2. Erusappan P et al. Integrin alpha11 cytoplasmic tail is required for FAK activation to initiate 3D cell invasion and ERK-mediated cell proliferation. *Sci Rep* 2019. PMID: 31653900.

3. Primac I. et al. Stromal integrin alpha11 regulates PDGFR-beta signaling and promotes breast cancer progression. *J Clin Invest* 2019. PMID: 31287804.

4. Zeltz C. et al. α11β1 Integrin is Induced in a Subset of Cancer-Associated Fibroblasts in Desmoplastic Tumor Stroma and Mediates In Vitro Cell Migration. *Cancers* 2019. PMID: 31159419.



5. Alam J. et al. Generation of a novel mouse strain with fibroblast-specific expression of Cre recombinase. *Matrix Biol Plus* 2020. PMID: 33543038.

6. Zeltz C. et al. Cancer-associated fibroblasts in desmoplastic tumors: emerging role of integrins. *Semin Cancer Biol* 2020. PMID: 31415910.

7. Sawant M. et al. Ablation of integrin-mediated cell-collagen communication alleviates fibrosis. *Ann Rheum Dis* 2023. PMID: 37479494.

Translational, clinical and societal importance

The Matrix Biology Group considers themselves as basic scientists, but during the past 10 years, as data have accumulated on the crucial role of integrins in remodeling the fibrotic microenvironment, they have started several collaborations using translational mouse tumor models and human clinical material with the aim to move their projects in a more clinical direction. In short term, the described project will add molecular detail to our understanding of how a subset of fibroblasts in the fibrotic stroma affects fibrosis development. In the long term, they believe the work will generate data that will significantly impact our overall knowledge on the role of integrins in fibrosis biology.

Other important outputs and achievements

The group has organized the PhD level course BMED904, Matrix Biology, which is part of the CCBIO research school. Gullberg coordinated the monthly CCBIO research seminars during 2013–2023.

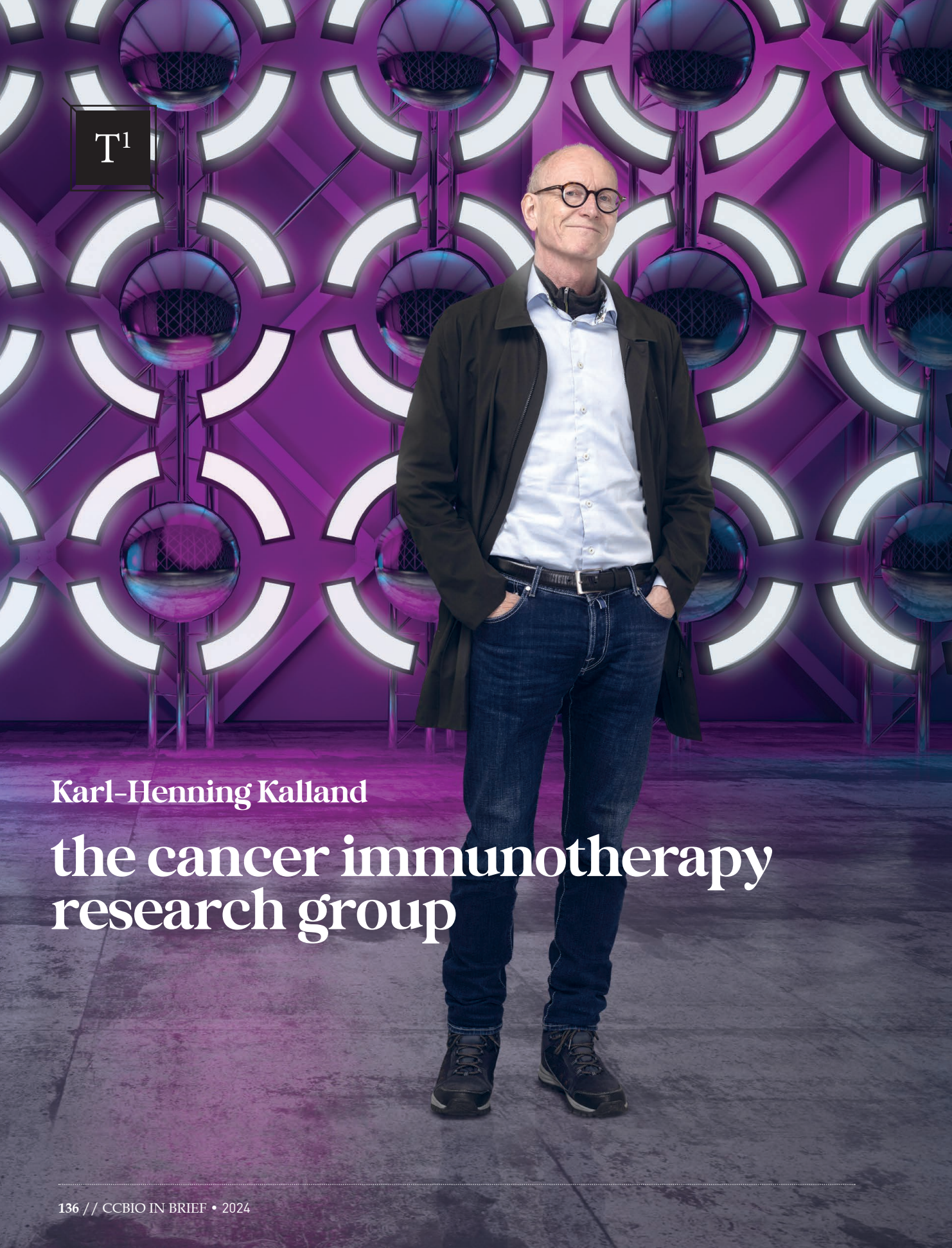
CCBIO significance

Gullberg finds it intellectually stimulating to have taken part in seminars and conferences arranged by CCBIO. Financial support in the form of one 3-year PhD position, grant support and salary for a part-time technician has also been valuable at a time when other grant support was scarce.

Future perspectives

Gullberg looks forward to taking part in seminars and conferences and contributing to common grant proposals whenever relevant and benefiting to the Matrix Biology Group's research. ••





Karl-Henning Kalland

the cancer immunotherapy research group

Short bio
Karl-Henning Kalland, MD, PhD, has been a professor at the University of Bergen (UiB) since 1993 and serves as a senior consultant at the Department of Microbiology, Haukeland University Hospital, Bergen. Since 2013, he has been the group leader of the Cancer Immunotherapy Research Group and a principal investigator at CCBIO. Kalland completed his PhD (dr.med.) at UiB in 1989, focusing on the cloning and sequencing of the measles virus and the development of nucleic acid probes. His postdoctoral work at Dana Farber Cancer Institute, Harvard Medical School, under the invitation of Professor William A. Haseltine, focused on HIV molecular research. He continued this research at the UiB through the 1990s. Between 2000 and 2003, Kalland undertook research stays at the University of Washington and the Institute for Systems Biology in Seattle, invited by Professor Leroy Hood, and again at the University of Washington from 2012 to 2013. Recently, he initiated a phase I clinical trial for dendritic cell (DC)-based cryoimmunotherapy (CryoIT) to treat patients with advanced metastatic prostate cancer.

Brief group presentation and history
The Kalland research group was established in the 1980s, initially focusing on the molecular mechanisms of gene regulation using virus-infected cells as models. Significant early contributions include the cDNA cloning and sequencing of the measles virus, RNA editing, and nucleocytoplasmic transport. Major discoveries include RNA editing in the measles virus (PMID: 2789811) and the identification of a nuclear export peptide sequence in HIV-Rev (PMID: 7935458; PMID: 7745679), which revealed novel gene expression mechanisms and provided the first evidence of an active nuclear export signal of proteins.

Around 2000, the group developed a cDNA array platform, as proposed already in 1988 for large-scale transcription monitoring (PMID: 3348914), and later established the Agilent microarray platform, to compare gene expression in malignant and benign tissue samples from cancer patients. This work led to collaborations with the Institute for Systems Biology in Seattle and researchers in Bergen, including Professors Lars A. Akslen, Helga Salvesen, Øystein Bruserud, Bjørn Tore Gjertsen and Emmet Mc Cormack, and the bioinformatics group of Professor Inge Jonassen. Through these collaborations, the group identified overexpression of several transcription factors, including ERG and other ETS-family factors (ETV4, ETV5), in prostate cancer tissue compared to benign tissue (PMID: 15645116; PMID: 17143509; PMID: 17289882). Similar approaches were applied to endometrial cancer biopsies and acute myeloid leukemia samples, identifying malignant gene expression patterns.

Research Focus
- Prostate cell differentiation and carcinogenesis
- Transcriptional regulation and molecular mechanisms in cancer and immune cells
- Developing new drugs and DC-based immunotherapy

Subprojects
1. Experimental Models of Prostate Cell Differentiation and Carcinogenesis:
The aims are to establish experimental models to study prostate cancer differentiation and investigate the molecular mechanisms underlying normal prostate cell differentiation. Methods include cell cultures of primary prostate cells and cancer cell lines, gene overexpression and knock-down, genome-wide gene expression analyses, and multiple functional assays. The group discovered molecular mechanisms of benign prostate basal to luminal cell differentiation, particularly related to the expression of the androgen receptor (AR) and its target genes. A stepwise prostate tumorigenesis model was developed without carcinogen use, starting from hTERT-immortalized prostate epithelial cells, identifying tumorigenic cells characterized by an IL-6/STAT3 regulatory loop (PMID: 24101153). This model has been used in drug discovery, identifying small molecular compounds that inhibit transcription factors AR, β-catenin, and STAT3.

2. Dendritic Cell (DC)-based Cancer Immunotherapy:
Cancer cell heterogeneity contributes to the failure of drug monotherapy. CryoIT, involving the injection of naïve immature DCs into cryoablated cancer tissue, was hypothesized to address this heterogeneity. The aim with this project is to conduct a phase I clinical trial of CryoIT, with safety as the primary endpoint and evidence of efficacy as secondary endpoint. Methods include cryoablation of cancer tissue, differentiation of monocyte-derived DCs (moDCs), and analysis of patient samples using clinical biochemistry, pathology, radiology, liquid biopsies, T-cell receptor sequencing (TCR-seq), and CyTOF mass spectrometry. The phase I trial (NCT02423928) showed favorable safety and good patient tolerability. Evidence of therapeutic effects was suggested by circulating tumor cell enumeration and TCR-seq of peripheral blood. As of 2024, 8 of the 18 patients remain alive, with survival times ranging from 4.5 to 9 years.

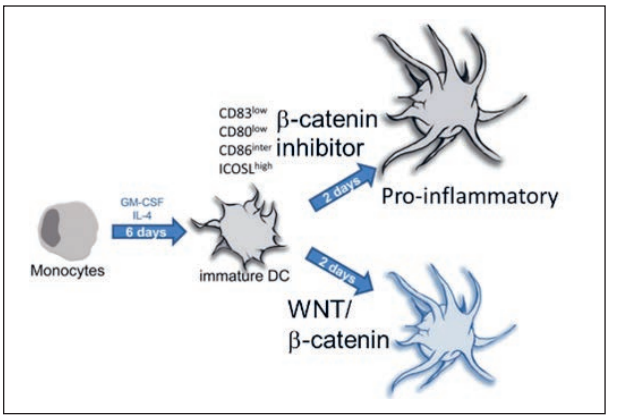
3. Robust Production of More Potent Therapeutic DCs:
The full potential of DC-based therapy has yet to be realized, and the aim of this project is to investigate mechanisms to enhance pro-inflammatory DCs. Methods include isolation of leukocyte subpopulations, differentiation and maturation of DCs, characterization using RNA-seq, flow cytometry, cytokine and kynurenine secretion, functional assays, and the effects of small molecular compounds on signal transduction pathways. The group discovered that

moDCs exhibit both pro-inflammatory and tolerogenic features. They then identified critical gene expression patterns affected by WNT/β-catenin and STAT3 modulators and evaluated conventional DCs as possible replacements for moDCs in future CryoIT.

Most important results

• Identification of small molecular compounds with activity against β-catenin signaling with simultaneous identification of their cellular target proteins and the molecular mechanisms of β-catenin inhibition represent significant achievements (PMID: 27482107; PMID: 29083417).

• Completion of the CryoIT clinical trial with implementation of advanced biomarkers to document effects is a translational milestone (PMID: 36939854).



Most important papers

1. Vestrheim Thomsen LC et al. A phase I prospective, non-randomized trial of autologous dendritic cell-based cryoimmunotherapy in patients with metastatic castration-resistant prostate cancer. *Cancer Immunol Immunother* 2023. PMID: 36939854.

2. Lellahi SM et al. GM-CSF, Flt3-L and IL-4 affect viability and function of conventional dendritic cell types 1 and 2. *Front Immunol* 2023. PMID: 36713392.

3. Azeem W et al. Dual Pro- and Anti-Inflammatory Features of moDCs. *Front Immunol* 2020. PMID: 32292402.

4. Qu Y et al. Nitazoxanide and β-catenin inhibition. *Nature Chem Biol* 2018. PMID: 29083417.

5. Qu Y et al. Axitinib and β-catenin inhibition. *Proc Natl Acad Sci U S A* 2016. PMID: 27482107.

6. Olsen JR et al. Context dependent regulatory patterns. *BMC Cancer* 2016. PMID: 27378372.

7. Qu Y et al. Generation of Prostate Tumor-initiating Cells and IL6/STAT3 Signaling. *Cancer Res* 2013. PMID: 24101153.

Translational, clinical, and societal impact

The group's research has had significant translational and clinical impacts, particularly in cancer treatment:

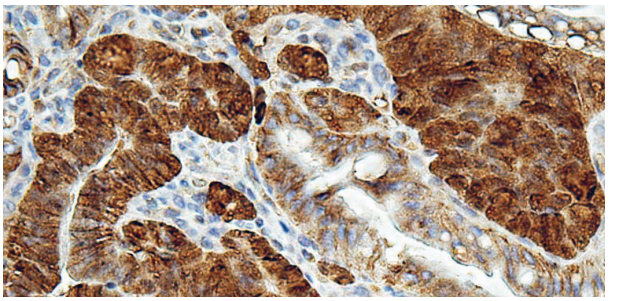
Clinical impact: The development of CryoIT, a DC-based immunotherapy, has shown promising results in a phase I clinical trial for metastatic castration-resistant prostate cancer, demonstrating prolonged survival and few adverse events.

Research protocols: Insights from transcription factor studies and prostate cancer models have influenced research protocols and therapeutic strategies.

Societal importance: Advances in cancer immunotherapy have the potential to improve patient outcomes and provide new treatment options. Biomarkers identified in the research are being evaluated for inclusion in clinical trials and practice.

CCBIO significance

CCBIO has promoted scientific interactions and development. Both national and international interactions have been enhanced, *e.g.* the current ongoing collaboration with Professor Klaus Pantel, Hamburg, and the INJURMET-ERC project.



Future perspectives

Enhance CryoIT: Further to refine and improve DC production and functionality and expand clinical trials to include more cancer types.

Advance biomarker research: Utilize high-resolution sequencing and spatial tissue characterization to better understand and treat cancer.

Innovate cancer therapy: Develop new therapeutic strategies based on the group's extensive research on transcription factors and molecular mechanisms in cancer.

Expand collaborations: Continue collaborating with international partners to leverage diverse expertise and resources in cancer research and treatment. ••





Emmet Mc Cormack

the PreCOS and INOvA groups

Short bio
Emmet Mc Cormack (Ireland) received a double honors degree in mathematics and chemistry from DIT and TCD, Ireland (1994-98), before pursuing a PhD in Pharmacognosy at the School of Pharmacy, TCD, where he designed, synthesized, and characterized the biological efficacy of novel dual antimitotic/aminopeptidase N molecules. Subsequently, Mc Cormack took a researcher position at the lab of Professor Bjørn Tore Gjertsen (2002), shifting fields to preclinical modeling and molecular imaging. In 2008, Mc Cormack and Gjertsen founded KinN Therapeutics AS. Mc Cormack was awarded TMF funding to start his own research group, founding PreCOS in 2011. In 2013, Mc Cormack was made Professor of Pharmaceutics. More recently, he has a 20% researcher position at Haukeland University Hospital, is associated PI at NCMM, CanCELL SFF and has served as head of innovation (2017–2021), and periodically, vice-head of department (2018–2020) at the Department of Clinical Science, UiB, head of the preclinical facilities at UiB (2020–2022) and is working group 2 leader of the COST action "Immunomodel".

Brief group presentation and history
PreCOS was founded in 2011, and together with Professor Line Bjørge, Mc Cormack founded INOvA in 2016. The current dogma of rushing novel pharmaceuticals through inappropriate preclinical models is one of the major reasons for the limited clinical penetration of novel drugs. Despite this, the preclinical step in drug development is generally overlooked and models are chosen to fit the desired result, rather than using them as valuable tools to drive clinical development.

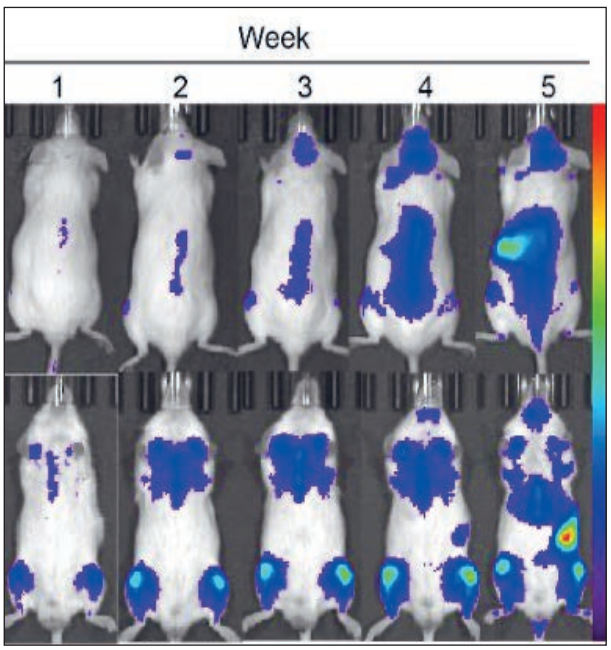
Research focus
The group's core activities focus on development, characterization and application of clinically relevant models (patient derived xenografts (PDX), Hu-PDX, *in vitro* decellularized scaffold platforms) and multimodal molecular imaging strategies and how they believe judicious application of these technologies can expedite clinical development of novel therapeutics. More recently, the group has focused on the development of novel immunotherapies (CAR-T and BiTes).

Subprojects
SonoCURE: This project explored the application of sonoporation in the treatment of PDAC. The application aimed to preclinically elucidate, evaluate, and potentiate a new era of sonoporation theranostics for PDAC through application of innovative biomarker mining, organoid models and preclinical modeling. This work provided the preclinical platform (Kotopoulis et al., *Mol. Imaging Biol.* 2014) for the world's first clinical trial in sonoporation (Dimcevski et al., *J. Controlled Release* 2016). Furthermore, a novel decellularized porcine tissue platform was developed for PDAC and ovarian cancer (Helgestad Gjerde et al., manuscript 2024.)

Novel Models and Therapeutic options for Haematological Malignancies: This work elucidated a novel Axl isoform, Axl3, and demonstrated the application of Axl inhibition as a novel therapeutic strategy in mantle cell lymphoma (Gelebart et al., *Blood* 2023). Additionally, Li et al., *Cell Stem Cell* 2014 elucidated a novel therapeutic strategy targeting leukemic stem cells' expression of the biomarker FLT3 ITD. Lee et al., *PNAS* 2012 and subsequently, Shafiee, et al., *Br. J Haematol.* 2021 described novel scaffold derived hematopoiesis and MDS models, respectively.

ISPIC: PreCOS and INOvA received 3 ESRs as part of this consortium, with UiB's mandate to develop novel immunocompetent models of cancer, develop FGS to aim surgical resection in addition to high dimensional analysis of HGSOC. Kleinmanns et al., *ebiomedicine* 2020 are two works based on the use of the biomarker CD24 to non-invasively image HGSOC and application in fluorescence image-guided surgery (FGS) to increase tumor debulkment. Furthermore, Kleinmanns et al., *Cancers* 2022 describes the development of an innovative model of orthotopic HGSOC complete with human immune system, characterized by high-dimensional CyTOF analysis and used to evaluate the use of immunotherapeutics.

IDDEA: In collaboration with OUS (Sébastien Wälchli), the project aims to generate and evaluate novel CAR-T. To date, the project has resulted in two high impact publications. Casey et al., *J. Immunother. Cancer* 2024 details the development and implantation of MUC16 targeted CAR-T, while Caulier et al., *Cell Rep Med* 2024 describes the identification of CD37 as a novel therapeutic target in AML and successful targeting a preclinical development of a novel CD37 CAR-T.



Most important results
The role of Axl has been associated with promoting cell proliferation (through the PI3K/Akt and MAPK/ERK pathway), inhibition of apoptosis, metastasis, invadopodium formation, angiogenesis, immune evasion, resistance to therapy, and influencing the tumor environment. Axl has also been described as a potential prognostic marker in multiple cancers including ovarian-, pancreatic-, breast- and lung cancer. Importantly, Axl has been implicated as a key factor in tyrosine kinase drug resistance (ALK, EGFR, VEGFR), and resistance to chemotherapy and radiation treatments. Given the extensive involvement of the Axl receptor across cancer types and functions, the description of a novel Axl3 isoform is a potential game changer in the function, localization, and regulation of Axl in cancer.

In the group's work with CD37 targeted CAR-T, they demonstrate the preclinical efficacy and superiority in AML versus other CAR concepts currently in clinical development. Results from this work have formed the foundation for clinical trial funding (KLINBEFORSK) of CD37 by Professor Bjørn Tore Gjertsen at Haukeland University Hospital. Should the preclinical results translate into clinical efficacy, this work could have a major impact in a disease with very poor outcomes.



The SonoCURE team have demonstrated preclinical development and participated in the clinical application of sonoporation in a world's first clinical trial in pancreatic ductal adenocarcinoma. In this study, patients survived on average 17.6 months, compared with 8.9 months through the simple addition of sonoporation to a standard of care treatment protocol.

Most important papers

1. Li L et al. SIRT1 activation by a c-MYC oncogenic network promotes the maintenance and drug resistance of human FLT3-ITD acute myeloid leukemia stem cells. *Cell Stem Cell* 2014. PMID: 25280219.

2. Dimcevski G et al. A human clinical trial using ultrasound and microbubbles to enhance gemcitabine treatment of inoperable pancreatic cancer. *J. Controlled Release* 2016. PMID: 27744037.

3. Gelebart P et al. Inhibition of a new AXL isoform, AXL3, induces apoptosis of mantle cell lymphoma cells. *Blood* 2023. PMID: 37339584.

4. Kleinmanns et al. CD24-targeted intraoperative fluorescence image-guided surgery leads to improved cytoreduction of ovarian cancer in a preclinical orthotopic surgical model. *ebiomedicine* 2020. PMID: 32454402.

5. Caulier B et al. CD37 is a safe chimeric antigen receptor target to treat acute myeloid leukemia. *Cell Rep Med* 2024. PMID: 38754420.

6. McCormack E et al. Bi-specific TCR-anti CD3 redirected T-cell targeting of NY-ESO-1- and LAGE-1-positive tumors. *Cancer Immunology Immunotherapy* 2013. PMID: 23263452.

7. Kleinmanns K et al. Humanized Ovarian Cancer Patient-Derived Xenografts for Improved Preclinical Evaluation of Immunotherapies. *Cancers* 2022. PMID: 35804867.

Translational, clinical and societal importance
The finding that sonoporation impacted the growth of PDAC in preclinical models was successfully translated to the clinic, resulting in a major improvement of clinical outcome (17.6 vs. 8.8 months). KinN Therapeutics AS' preclinical collaboration with Celegene (now BMS) on the compound CC90009 resulted in a clinical trial and one cure (to date) for a patient with AML. Preclinical development of vididencel by scientists at PreCOS and KinN Therapeutics AS led to a clinical trial of this DC based vaccine by Mendus AB. Currently, vididencel has reached phase II. The Mc Cormack group was the first to demonstrate the preclinical activity of tebentafusp, a bi-specific gp100 targeted T cell receptor protein (KIMMTRAK™; Mc Cormack et al., *Cancer Immunol. Immunother.* 2012) in collaboration with Immunocore. KIMMTRAK is now approved for HLA-A*02:01–positive metastatic or unresectable uveal melanoma. Fosse et al., *BMC Med.* 2023 outlines recommendations for robust and reproducible preclinical research in personalized medicine and is anticipated to increase the impact of preclinical research.

Other important outputs and achievements
Based on the research output, Mc Cormack's team has been awarded with three innovation prizes for the commercial development of its research both locally (UiB Idé) and nationally (Invent2 innovation prize 2023).

CCBIO significance
In addition to the financial support received from CCBIO, undoubtedly the CCBIO annual symposium has been a stimulating meeting place with excellent speakers, a forum for establishing new collaborations and the possibility to hear/meet world class speakers.

Future perspectives
Ideally, the Mc Cormack group would welcome an SFI grant to continue the great work started at CCBIO. ••





Team 2

discovery and validation of cancer biomarkers

The aim of this program is to explore and validate different classes of biomarkers in tissues and blood samples from human patient cohorts and clinical trials. The investigators take advantage of the recently established technology of single-cell analytics by mass cytometry (flow and imaging based), using panels of multiple antibodies for high dimensional mapping of cell subpopulations and tissue niches in parallel with functional interrogation. The studies examine associations with clinico-pathologic phenotypes as well as prognostic and predictive signals. This team consists of the PIs Akslen (CCBIO director), Costea, Engelsen, Krakstad, Lorens, Strell, and Wik.





Lars A. Akslen

the cancer biomarker group

Short bio
Lars A. Akslen, MD, PhD, is a trained surgical pathologist. He became an associate professor at UiB and senior consultant at Haukeland University Hospital in 1988, and a full professor in medicine (tumor pathology) in 1993 (UiB). His PhD thesis (1993, on thyroid cancer) was performed in part at the Cancer Registry of Norway. Akslen has had several research visits abroad, e.g. at the University of Pennsylvania (1998–1999), invited by Virginia A. LiVolsi, and at Harvard Medical School and Boston Children's Hospital (2004–2005), invited by Judah Folkman. He has received multiple awards, such as King Olav V's Cancer Research Award (2009) and the Helse Vest Research Award (2023; second time). Akslen is an elected member of the Norwegian Academy of Science and Letters (2013) and of Academia Europaea (2023). He has been the Director of CCBIO since 2013.

Brief group presentation and history
At first, Akslen's research was pathology based and focused on markers and regulation of tumor proliferation (Ki67, p16, p53) in different tumor types. His research team, the *Tumor Biology Research Group,* was initiated in 1995 at The Gade Institute (UiB). At the same time, he became interested in the tumor microenvironment, and subsequently several papers were presented on tissue based vascular metrics and tumor biomarkers, especially in breast cancer (Salvesen et al., *J Clin Oncol* 1999; Foulkes et al., *JNCI* 2003; Stefansson et al., *J Clin Oncol* 2004; Bachmann et al., *J Clin Oncol* 2006; Stefansson et al., *Cancer Res* 2006; Gravdal et al., *Cancer Res* 2009; Salvesen et al., *PNAS* 2009; Straume et al., *PNAS* 2012). In a long-lasting collaboration with Randy Watnick from the Folkman lab and VBP, several papers have been presented on properties of the tumor microenvironment (Kang et al., *PNAS* 2009; Catena et al., *Cancer Discov* 2013; Wang et al., *Science Transl Med,* 2016; Sui et al., *Nat Commun* 2022).

CCBIO was established in 2013, and Akslen's team decided to focus on proteomics of breast cancer. Later, the "*in situ* proteomics" technique of imaging mass cytometry (IMC) was established, enabling single-cell spatial analytics of tumor tissue sections. Recently, the team has focused on the expanding field of *cancer neuroscience*.

Research Focus
The focus has been to discover and validate novel tissue-based cancer biomarkers for molecular grading, especially related to the tumor microenvironment — for improved biological understanding and better prediction of aggressive tumor behavior and treatment response.

Subprojects
1. Stromal proteomic patterns and stratification of breast cancer

2. Breast cancer hypoxia responses at the proteome level

3. Markers of cancer-neural interactions in primary and metastatic breast cancer

4. Roles of Nestin and Stathmin in *BRCA1*-related and basal-like breast cancer

Most important results
1. Proteomic profiling of laser captured micro-dissected breast cancer tissues has been performed, separating cancer cells and the microenvironment compartment. Stromal protein signatures are different between hormone receptor positive (luminal-like) and hormone receptor negative (basal-like) tumors, being prognostically independent of intrinsic molecular classification (PAM50 based), also after external validation. For the first time, the group demonstrated that a stromal proteome signature can split the most frequent luminal A breast cancers in low-grade and high-grade categories (Finne et al., in submission).

2. Stromal protein profiles have been integrated with breast cancer cell line secretome data from baseline and hypoxic conditions, demonstrating metabolic reprogramming and differences between subtypes. The novel 33P stromal signature was identified and found to provide better prognostic stratification than standard factors including molecular subtype (Kjølle et al., *Nat Commun* 2023).

3. The group has studied the presence of neurogenesis and angiogenesis in breast cancer across subtypes, at the level of single protein expression (IHC), single-cell based multimarker mapping by imaging mass cytometry (IMC), and by proteomics and transcriptomics at case-level. First, co-cultures of breast cancer cells and neural progenitor cells demonstrate significant mutual effects, and the tumor cell proteomic response could be validated in human cohorts (Bjørnstad et al., *eBioMedicine* 2024). Also, data on neurogenesis and angiogenesis indicate that these programs are associated features and linked to aggressive breast cancer, suggesting novel tools for improved stratification and better treatment possibilities (Wik et al., in revision).

4. Data from the group have indicated that Stathmin might be a regulator of angiogenic and immunogenic responses in the microenvironment of aggressive breast cancer (Askeland et al., *Sci Rep* 2020). The project is followed up by single-cell spatial mapping (IMC) of Stathmin in relation to immunogenic and angiogenic cell populations. Further, Nestin, which is associated with Stathmin in breast cancer, has been linked to aggressive phenotypes and stemness (Krüger et al., *Sci Rep* 2017). The role of Nestin in breast cancer is being explored by CRISPR-based knockdown and animal models (Ardawatia et al., in preparation).

Most important papers
1. Kjølle S et al. Hypoxia induced responses are reflected in the stromal proteome of breast cancer. *Nat Commun* 2023. PMID: 37349288.

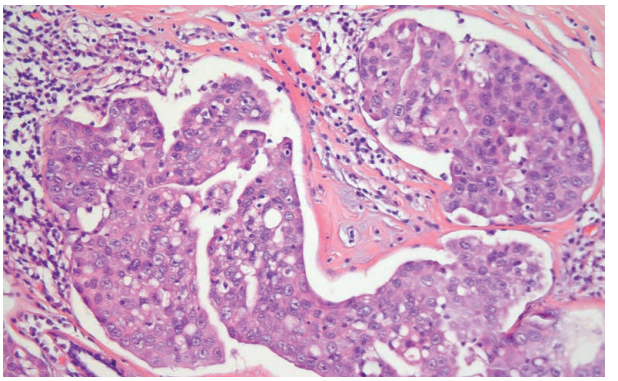
2. Bjørnstad OV et al. Global and single-cell proteomics view of the co-evolution between neural progenitors and breast cancer cells in a co-culture model. *eBioMedicine* 2024. PMID: 39232464.

3. Wik E et al. Axonogenesis and angiogenesis are associated features of aggressive breast cancer. 2025 (in revision).

4. Sui L et al. PRSS2 remodels the tumor microenvironment via repression of Tsp1 to stimulate tumor growth and progression. *Nat Commun* 2022. PMID: 36575174.

5. Krüger K et al. Predictive value of tissue-based angiogenesis markers in a randomized phase II clinical trial of neoadjuvant bevacizumab in locally advanced or large breast cancer. *Sci Rep* 2021. PMID: 28439082.

6. Askeland C et al. Stathmin expression associates with vascular and immune responses in aggressive breast cancer subgroups. *Sci Rep* 2020. PMID: 32076022.



Translational, clinical and societal importance

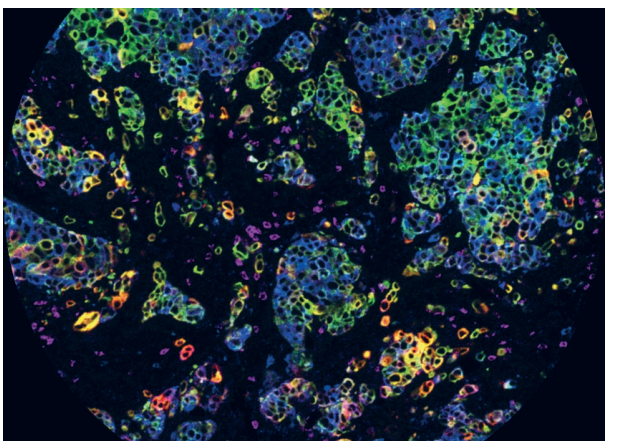
Several of the translational papers have provided biomarkers with improved ability to separate prognostic subgroups and provide a better basis for precise treatment. This is a prerequisite for better patient outcome. As a step further, some of the group's studies have been mapped in clinical trials where markers have shown independent prognostic- and treatment-predictive value (Krüger et al., *Sci Rep* 2021; Finne et al., in preparation). Further, the group reported a pathology-based improvement of nodal substaging of breast cancer which was implemented in national guidelines from the NBCG (Norwegian Breast Cancer Group) (Aziz et al., *Plos One* 2017). Ultimately, better tools for patient stratification will improve cost-effectiveness and societal responsibility of a given treatment. Importantly, some of the group's datasets have been made available and can be used by other researchers.

Other important outputs and achievements

Akslen has developed fruitful contact and collaboration with several members of the CCBIO International Faculty, in particular with Watnick and Östman. Two book volumes have been presented (Akslen & Watnick, eds.; Springer 2017 (1st ed) and 2022 (2nd ed; as a Springer textbook). Book chapters and multiple media appearances have been provided. In 2016, Akslen & Östman founded SCANPATH, a Scandinavian-based network for basic and translational tumor research, with annual meetings (80–120 participants) and increasing collaboration. Akslen is an elected member of the Norwegian Academy of Science and Letters (2013) and of Academia Europaea (2023). In 2023, Helse Vest awarded Lars A. Akslen and CCBIO with its research prize. Also in 2023, Akslen chaired the 100th Anniversary Symposium for The Norwegian Society of Pathology and edited the anniversary book (Akslen LA, Alfsen GC, Chen Y (eds): *Pathology and pathologists through 100 years: The Norwegian Society of Pathology 1923–2023;* 2023 (495 pages; in Norwegian).

CCBIO significance

As the CCBIO Director since 2013, Akslen feels that it has been extremely rewarding to observe the increasing enthusiasm and motivation among all members and staff, with continuous strengthening of joint projects and educational activities. There has been a strong focus on mentoring and career development, and the support from international collaborators and advisors has been essential. For the Akslen group, recruitment of young and energetic colleagues has been a key feature in later years, along with methods development and international contacts. CCBIO has introduced significant added value and strong synergism, and the center has become a prolific soil for future achievements.



Future perspectives

The Akslen group will continue to use single-cell mapping of cancer architecture to define multicellular niches with potential functional importance. The group will explore the phenotypic diversity and complexity of breast cancer subtypes. In particular, interactions between tumor cells and nerves, immune cells and vascular cells will be focused upon. Hopefully, this strategy will increase the precision of prognostic and treatment-predictive biomarkers. ••





James Lorens

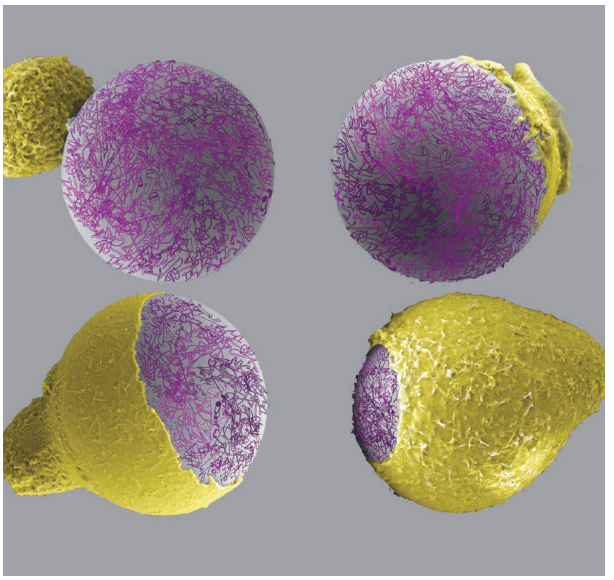
the tumor plasticity group

Short bio
Professor Lorens did his PhD in Molecular Biology at the University of Bergen in 1992 and completed his postdoc at Stanford University Medical Center in 1996, working with cancer biology and immunology. He founded the Tumor Plasticity Group at the University in Bergen in 2004, as well as the company BerGenBio ASA in 2007, and was Chief Scientific Officer at BerGenBio in Bergen, Norway and Oxford, UK, and previously Director of Oncology Research and Development, Rigel Pharmaceuticals Inc, South San Francisco, CA USA. Currently, he is professor at the Department of Biomedicine, University of Bergen, as well as PI at CCBIO.

For the last 25 years, Lorens has studied molecular mechanisms regulating tumor progression and developed novel targeting agents to facilitate clinical translation both in the academic and biotech setting. He applied functional genetic approaches to delineate new mechanisms that regulate tumor angiogenesis, apoptosis and epithelial-to-mesenchymal transition (EMT), metastasis and acquired drug resistance.

Brief group presentation and history
In 1999 Lorens cloned the *AXL* receptor tyrosine kinase as part of a functional genetic screening effort and oversaw the development of the first selective small molecule Axl kinase inhibitor (bemcentinib). The Tumor Plasticity Group was established in 2004, and using a novel retroviral RNA interference system, the group discovered a central role for Axl in tumor plasticity, metastasis and drug resistance, and subsequently showed that Axl regulates both tumor intrinsic and immune cell functions that affect cancer treatment outcomes. Lorens founded BerGenBio ASA in 2007 to facilitate clinical translation of these results. In 2013, bemcentinib was the first Axl kinase inhibitor to enter clinical trials and has subsequently been studied in 14 phase I/II studies spanning both myeloid leukemia and solid tumors, and COVID-19. His group has also contributed anti-Axl antibodies that formed the basis for clinical targeting agents in three more clinical trials. They have further studied the role of Axl in viral infection, fibrosis and neurodegenerative diseases where Axl expressing immune cells serve key roles in disease progression. Lorens has active research programs to study Axl in cancer immunotherapy resistance and multiomic analysis of tumor biopsy samples from a melanoma clinical trial (NCT02872259).

Research focus of the group
The Tumor Plasticity Group focuses on how the altered tumor microenvironment drives tumor plasticity, metastases and acquired resistance to cancer treatments. The confounding reality for cancer treatment is the astonishing heterogeneity of tumors. The breakdown of normal tissue architecture by a growing tumor exposes cancer cells to numerous biophysical and metabolic challenges such as oxygen and nutritional deprivation and an altered microenvironment. These conflate to drive tumor cell phenotypic plasticity related to EMT that increases metastases and confers resistance to cancer treatments including immunotherapy. The Axl receptor is a key determinant of tumor cell phenotypic plasticity and important clinical cancer target and biomarker.



Subprojects
Axl in acquired resistance to cancer therapy.

Most important results
• Association of AXL and PD-L1 expression with clinical outcomes in patients with advanced renal cell carcinoma (Terry et al., *Clin Can Res* 2021) and NSCLC (Rayford et al., submitted) treated with anti-PD-1.

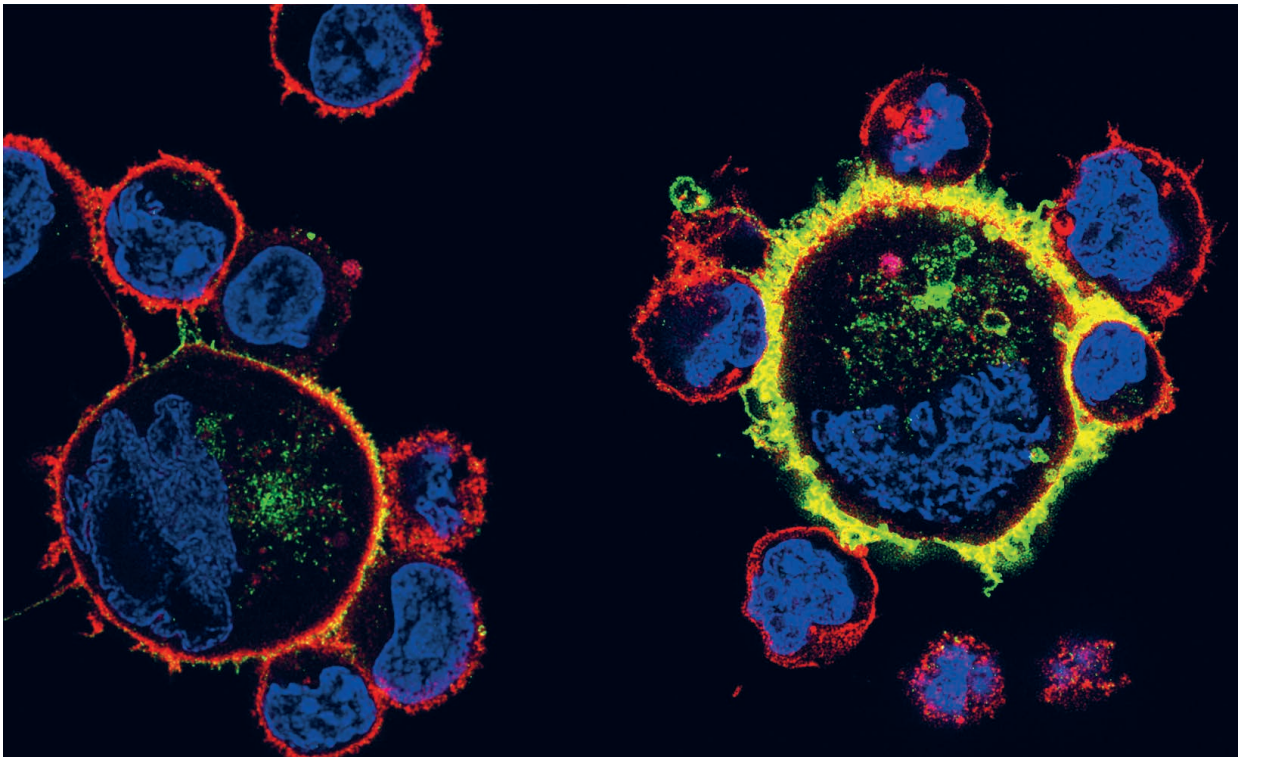
• AXL targeting abrogates autophagic flux and induces immunogenic cell death in drug resistant lung cancer cells (Lie et al., *J Thorac Onc* 2020).

• AXL targeting enhances lymphocyte-mediated cytotoxicity of lung cancer cells (Terry et al., *Can Immunol Res* 2019).

• AXL inhibition improves immunotherapy by targeting tumor infiltrating suppressive DC cells (Davidsen, Grøndal et al., in revision).

• AXL inhibition promotes cytosolic DNA sensor cGAS activity and sensitizes poorly immunogenic low TMB tumors to chemo-immunotherapy (Dhakal et al., submitted).

• AXL targeting restores PD-1 blockade sensitivity of STK11/LKB1 mutant NSCLC through expansion of TCF1+ CD8 T cells (Li et al., *Cell Rep Med* 2022).



Most important papers

1. Holland SJ et al. Multiple roles for the receptor tyrosine kinase Axl in tumor formation. *Cancer Res* 2005. PMID: 16230391.

2. Gjerdrum C et al. Axl is an essential epithelial-to-mesenchymal transition-induced regulator of breast cancer metastasis and patient survival. *Proc Natl Acad Sci U S A* 2010. PMID: 20080645.

3. Pelissier Vatter, FA et al. AXL is a driver of stemness in normal mammary gland and breast cancer. *iScience* 2020. PMID: 33103086.

4. Lotsberg ML et al. AXL Targeting Abrogates Autophagic Flux and Induces Immunogenic Cell Death in Drug-Resistant Cancer Cells. *J Thorac Oncol* 2020. PMID: 32018052.

5. Haaland GS et al. Association of Warfarin Use with Lower Overall Cancer Incidence Among Patients Older Than 50 Years. *JAMA Intern Med* 2017. PMID: 29114736.

6. Ludwig KF et al. Small-Molecule Inhibition of Axl Targets Tumor Immune Suppression and Enhances Chemotherapy in Pancreatic Cancer. *Cancer Res* 2018. PMID: 29180468.

7. Terry S et al. AXL targeting overcomes human lung cancer cell resistance to NK and CTL-mediated cytotoxicity. *Cancer Immunol Res* 2019. PMID: 31488404.

Translational, clinical and societal importance

The Lorens group has contributed to the clinical translation of Axl targeting agents that have been used in 17 clinical trials; Axl small molecule kinase inhibitor (bemcentinib, BerGenBio ASA); and Axl antibodies developed in the Lorens laboratory: anti-Axl monoclonal antibody (tilvestamab, BerGenBio ASA); anti-Axl ADC (ADCT-601, ADC Therapeutics).

CCBIO significance

Lorens commends CCBIO's ability to bring together a diversity of PIs and international faculty that enabled productive clinical translation of the research results of the involved groups. Further, he finds that the stellar CCBIO scientific environment promoted the training and career development of a new generation of cancer researchers, ensuring the continued impact of the center's scientific principles and results.

Future perspectives

The Tumor Plasticity Group is continuing to apply high dimensional multiomic analysis of patient samples to derive predictive biomarkers for immunotherapy response. In particular, they are following up with a deep biomarker profiling for patients that participated in their combination immunotherapy trial. ••





Daniela Elena Costea

the experimental pathology research group

Short bio
Daniela Elena Costea has an education in dentistry (1991–1997) and oral pathology (2006), with a PhD in oral sciences from 2005. She has been conducting research in epithelial-mesenchymal interactions in normal tissues and carcinoma since 2000. She has been a professor in tumor pathology at the Medical Faculty, University of Bergen (UiB) since 2013 and carries out surgical pathological diagnostic pathology in oral and ear-nose-throat areas since 2011. She served as a representative for the UiB in the Board of the Norwegian Cancer Association Norway and is Chair of the Scientific Advisory Board, National Institute for Cancer Research, Czech Republic. She has been PI or co-PI of several national and EU-funded grants.

Brief group presentation and history
Costea's group was established in 2011 with a grant awarded in 2010 to Costea from the Bergen Medical Research Foundation.

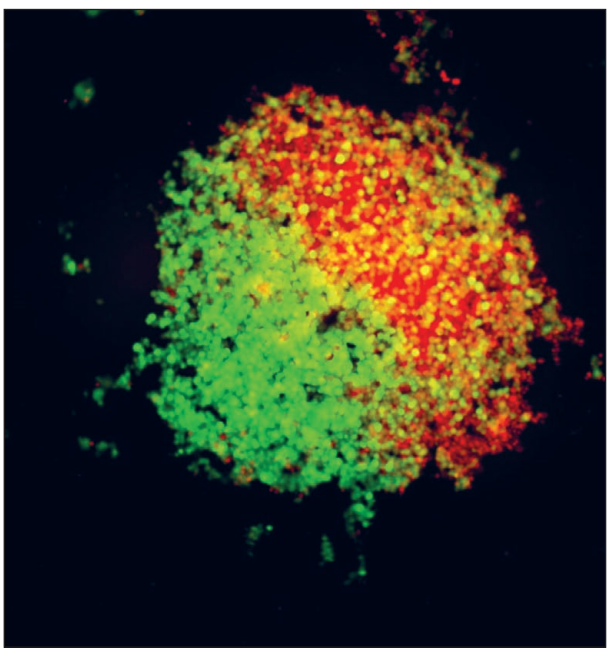
Research Focus
Research in Costea's group is focused on tumor-stroma interactions for identification of tumor microenvironment-related prognostic biomarkers in mucosal squamous cell carcinomas. The group is developing relevant experimental models that are sufficiently elaborated to mirror the complex *in vivo* tumor microenvironment, yet feasible enough for individual analysis and modulation of its different components. The aim is to reveal cancer associated fibroblasts' (CAFs) respective contribution to drug resistance and tumor progression.

Subprojects and **Most important results**
1. Mechanisms of tumor-stroma (fibroblasts) interactions
Costea's group has demonstrated that interactions between carcinoma cells and surrounding fibroblasts occur first at the metabolic level, before fibroblasts are induced into CAF activated phenotype and senescence by cancer cells. The major and novel finding was the observation that normal neighboring fibroblasts are induced to export mitochondria towards carcinoma cells through both direct contact and by indirect mechanisms (Zhang Z et al., *Cell Mol Life Sci.* 2020). Furthermore, the group's studies showed that while metformin (newly proposed as adjuvant for head and neck squamous cell carcinoma — HNSCC) could significantly inhibit cell growth and induce apoptosis of cancer cells, its effects on cancer cells are annihilated when CAFs are present through inhibiting AMPK and PARP activity, maintaining mitochondrial membrane potential, and increasing oxidative stress (Zhang Z et al., *Cell Cycle*, 2019).

2. Stroma as a source of prognostic biomarkers
The group's transcriptomic studies showed molecular evidence for the existence of at least three subgroups of CAF in HNSCC, and functional evidence for a pro-tumorigenic role of two of the three CAF subgroups. This was a major finding and one of the first papers pointing towards the heterogeneity of CAF in the tumor microenvironment (Costea et al., *Cancer Res* 2013). A subsequent global miRNA array study identified twelve differentially expressed miRNAs. One of these, miR-204, had a tumor-suppressive function through inhibition of fibroblast migration by modulating expression of several motility-related molecules (Rajthala S et al., *Int J Mol Sci.* 2021). It was shown, for the first time, that miR-204 targets integrin α11, a collagen I receptor that has been involved in cell motility and showed previously to be specifically upregulated in CAFs. For further phenotypical characterization of CAFs at the protein level and elucidation of CAF heterogeneity, imaging mass cytometry was applied (Tornaas S et al., *Heliyon.* 2024).

3. Establishing novel, more representative human-based models in carcinoma research
In collaboration with Line Bjørge's group, the Costea group established novel cell lines from mucosal carcinomas. Of note is a unique cell line developed from a vulva cancer patient with lichen atroficus et sklerosus, the first isolated cell line of this type (Dongre H et al., *Exp Cell Res,* 2020).

4. Development of point-of-care cancer diagnostic tools for use in resource poor settings
Oral cancer is increasing at an alarming rate, particularly in low-income countries. This urges for research into noninvasive, user-friendly diagnostic tools that can be used in limited-resource settings. The Costea group tested and validated the feasibility of e-nose technology for detecting oral cancer in the limited-resource settings of the Sudanese population, where it offers a valuable cost-effective strategy to tackle the burden posed by oral squamous cell carcinoma (OSCC) (Mohamed N et al., *Healthcare.* 2021).



Most important papers

1. Costea DE et al. Identification of two distinct carcinoma-associated fibroblast subtypes with differential tumor-promoting abilities in oral squamous cell carcinoma. *Cancer Res* 2013. PMID: 23598279.

2. Zhang Z et al. Fibroblasts rescue oral squamous cancer cell from metformin-induced apoptosis via alleviating metabolic disbalance and inhibiting AMPK pathway. *Cell Cycle* 2019. PMID: 31014173.

3. Zhang Z et al. Metabolic reprogramming of normal oral fibroblasts correlated with increased glycolytic metabolism of oral squamous cell carcinoma and precedes their activation into carcinoma associated fibroblasts. *Cell Mol Life Sci* 2020. PMID: 31270582.

4. Dongre H et al. Establishment of a novel cancer cell line derived from vulvar carcinoma associated with lichen sclerosus exhibiting a fibroblast-dependent tumorigenic potential. *Exp Cell Res* 2020. PMID: 31654625.

5. Rajthala S et al. Profiling and Functional Analysis of microRNA Deregulation in Cancer-Associated Fibroblasts in Oral Squamous Cell Carcinoma Depicts an Anti-Invasive Role of microRNA-204 via Regulation of Their Motility. *Int J Mol Sci* 2021. PMID: 34769388.

6. Tornaas S et al. Development of a high dimensional imaging mass cytometry panel to investigate spatial organization of tissue microenvironment in formalin-fixed archival clinical tissues. *Heliyon* 2024. PMID: 38803925.

7. Mohamed N et al. Feasibility of a Portable Electronic Nose for Detection of Oral Squamous Cell Carcinoma in Sudan. *Healthcare* (Basel) 2021. PMID: 34063592.

Translational, clinical and societal importance

• The Costea group identified a number of genes/miRNAs significantly dis-regulated in CAFs. Integrin α11 and mir204 are further investigated for their prognostic marker value.

• Costea's results indicate that metformin effects on cancer cells are modulated by the microenvironment and that this must be taken into consideration in the context of developing new combination of drugs including metformin for cancer treatment.

• The group is providing robust experimental tools to the research community. In collaboration with the Bergen Technology Transfer Centre (VIS), they made available some of their cell lines through the CRUK-related company Ximbio and are now in process of a establishing their own spin-off UiB-related company for commercialization of their own isolated and characterized cell lines and 3D models.

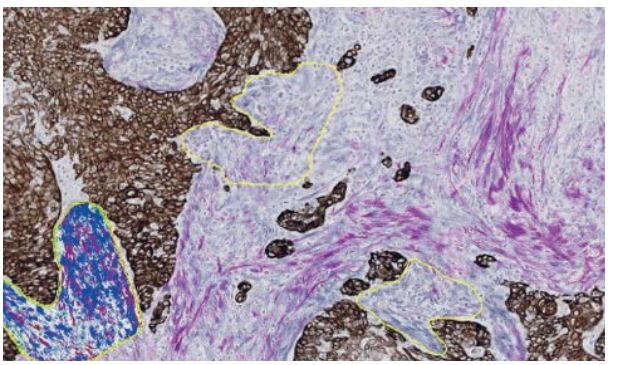
• The results of the e-nose study provide data to substantiate proposing this device as a feasible solution for oral cancer screening in resource-limited areas where OSCC poses a major burden of disease.

Other important outputs and achievements

In 2020, Costea got the Pindborg Prize, an award issued every second year by the Scandinavian Fellowship of Oral Pathology and Oral Medicine (SFOPOM), in memory of the late Professor Jens J. Pindborg, the founder of oral pathology. In June 2021, she held the Pindborg lecture for over 900 digital participants at the 20th International Congress on Oral Pathology & Oral Medicine.

CCBIO significance

Costea finds that CCBIO has boosted all aspects of research activity in her group, especially the biomarker discovery part through providing an excellent arena for scientific discussions among both junior and senior scientists. CCBIO has also supported the PhD and postdoc members of her group by providing an excellent environment at its research school, access to high quality courses and lectures through the courses of the research school and many symposia and scientific events.



Future perspectives

The Costea group will continue their biomarker discovery studies by deep tissue profiling of comprehensive signatures of distinct CAF niches, as well as the niches' relationship with each other and other components of the microenvironment in clinical cohorts of head and neck and vulva carcinoma. Costea also plans to translate the group's laboratory findings on the tumor-stroma interactions and recently identified key involved molecules towards clinical use, as both prognostic biomarkers in prospective trials for better stratification of patients and for development of more personalized therapies that target both cancer cells and their microenvironment.

They are also developing *in vitro* multicellular models as "avatars" for vulvar and oral cancers for testing the concept of "trial in a dish" for these cancers. ••


CCBIO



Camilla Krakstad

the bergen gynecologic cancer research group

Short bio

Professor Camilla Krakstad is PI for the Bergen Gynecologic Cancer Research Group. She did her PhD at the University of Bergen in 2005 and has a broad background in cell biology, with specific training in translational cancer research. In 2013 she received funding from the Trond Mohn Research Foundation and established her own research portfolio focusing on model systems for gynecological cancers. She was appointed associate professor at the Department of Biomedicine in 2015, and full professor at the Department of Clinical Science in 2017. Krakstad has been PI or co-investigator on several national and international grants and has built a solid international network. She has contributed to more than 140 publications over the last decade focusing mainly on endometrial cancer (EC).

Brief group presentation and history

The group has a long tradition of translational research in gynecologic cancers, with a primary focus on molecular characterization of various cancer stages, functional studies and model systems, identification of new diagnostic (bio)markers and preoperative imaging, the latter in collaboration with Professor Haldorsen's group. Headed by the late Professor Helga B. Salvesen until 2016, the group has been an integrated part of the Women's Clinic (KK) at Haukeland University Hospital and the Department of Clinical Science, UiB for more than two decades. The research group is deeply involved in biobanking from all gynecological malignancies, in close collaboration with clinicians. Professor Krakstad joined the research group as a researcher in 2010 and has led the group since 2016.

Research focus

The research group has a strong focus on better understanding of endometrial and cervical cancer development, molecular subtypes and mechanisms that can be exploited for future improved treatment. The group performs molecular profiling of cervical and endometrial cancers, including in recent years also a stronger focus on single-cell phenotypes and clonal evolution. To enable more relevant studies on mechanisms of cancer growth and metastasis, endometrial cancer organoid models have been established from all histological grades and subtypes.

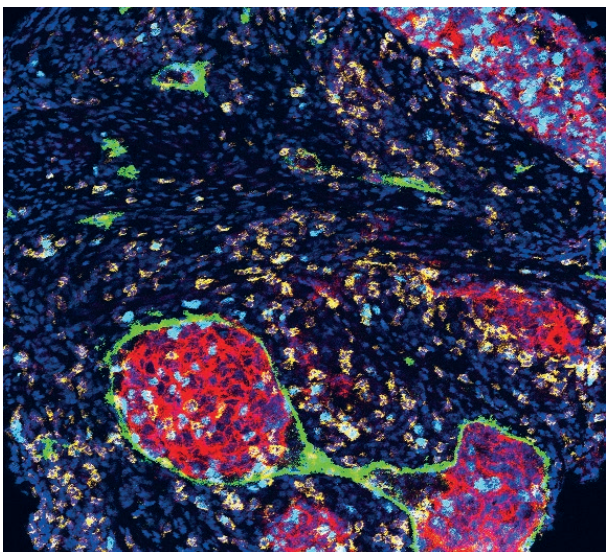
Subprojects

1. Identification and implementation of biomarkers for endometrial cancer

Improving current diagnostic protocols by integrating available data, performing genetic profiling and identifying new markers that can better stratify patients to correct risk-groups, preferentially pre-operatively. The MOMATEC2 study, a phase 4 implementation trial for validation of ER/PR status to stratify for lymphadenectomy in endometrial cancer, is ongoing and also includes collection of Quality-of-Life data from women treated for endometrial cancer.

2. Generation of relevant model systems for endometrial cancer

Organoid models of endometrial cancer have been developed by the research group and extensively characterized (histology, genetics and biomarker expression). Metastatic potential of models from aggressive subtypes is confirmed in orthotopic mice models (O-PDX). The group is prospectively building a model biobank. The models are used in projects exploiting different library screening and barcoding techniques in collaboration with groups at DFCI/Harvard and The Broad.



Most important results

1. Generation of relevant model systems for endometrial cancer

The group established EC organoid models from all histological grades and subtypes that mimic key features and heterogeneity of endometrial tumors. Together with O-PDX models, this comprises a platform with broad applications in experimental and preclinical research. The striking prognostic potential of the identified gene signature is interesting and supports the strong clinical relevance for future drug testing studies in EC organoid models.

2. Genetic and phenotypic profiling of endometrial cancer

The group has shown that paired primaries and metastases from several dozen ECs spread through a strong bottleneck, suggesting evolutionary selection. Tumors revealed cellular heterogeneity in low stage endometrioid tumors and identified low epithelial vimentin expression in low-stage endometrial cancer with high-risk of recurrence. Integrated genomic analyses of cervical squamous cell carcinomas identified two therapy-relevant subtypes.

3. Identification of biomarkers for endometrial cancer

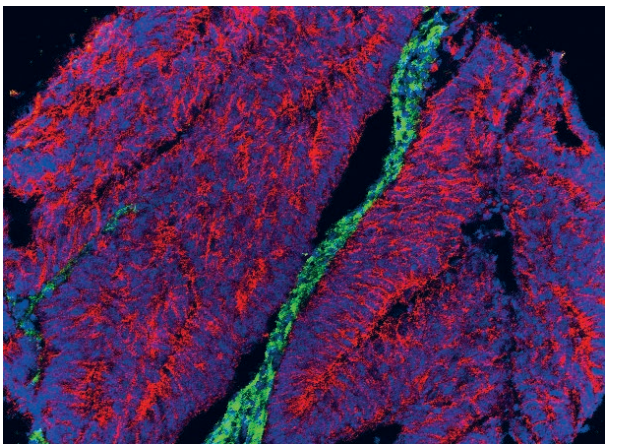
• MSH6 is an independent prognostic marker in an MMR-D classifier in endometrial cancer.

• PD-L1 and PD-1 are frequently expressed in endometrial cancer with similar expression patterns across MSS and MSI tumors, but in metastatic lesions, expression is intra-variable compared to primary tumors.

• High HER2 protein is significantly associated with features of aggressive disease and increased mRNA ERBB2 levels.

4. Implementation of biomarkers in clinical practice
• Self-reported QOL-data for patients with endometrial cancer show that patients receiving adjuvant chemotherapy have a higher risk of experiencing long-term neuropathy, lymphedema, and fatigue and inferior physical function compared to patients undergoing LNS alone or no LNS. Further striving to individualize adjuvant treatment is more pressing than adopting new surgical staging techniques.

• The interim analyses of MOMATEC2 data show that preoperative stratification by imaging and histological assessment permits a reduction in lymphadenectomy to around 50%, and this is achievable without an increase in recurrences at 3 years.



Most important papers

1. Krakstad C et al. Frequency of HER2 low in Endometrial Cancer. *Jama Oncol* 2024 (accepted).

2. Lien HE et al. Single-cell profiling of low-stage endometrial cancers identifies low epithelial vimentin expression as a marker of recurrent disease. *eBioMedicine* 2023. PMID: 37146405.

3. Berg HF et al. Mismatch repair markers in preoperative and operative endometrial cancer samples; expression concordance and prognostic value. *Br J Cancer* 2022. PMID: 36482191.

4. Forsse D et al. Longitudinal effects of adjuvant chemotherapy and lymph node staging on patient-reported outcomes in endometrial cancer survivors: a prospective cohort study. *Am J Obstet Gynecol* 2022. PMID: 34400137.

5. Berg HF et al. Patient-derived organoids reflect the genetic profile of endometrial tumors and predict patient prognosis. *Commun Med (Lond)* 2021. PMID: 35602206.

6. Halle MK et al. HER2 expression patterns in paired primary and metastatic endometrial cancer lesions. *Br J Cancer* 2018. PMID: 29169184.

7. Forsse D et al. Maintained survival outcome after reducing lymphadenectomy rates and optimizing adjuvant treatment in endometrial cancer. *Gynecol Oncol* 2021. PMID: 33317908.

Translational, clinical and societal importance
• MOMATEC2 trial on ER/PR for clinical implementation.

• Her2 paper for endometrial cancer *Br J Cancer* 2018, PMID: 29169184 has informed clinical trials for Her2 targeted therapy in EC and has gained recent attention due to the relevance and introduction of ADC-based therapies. A paper on this has been accepted by *Jama Oncol* (2024).

• For societal importance, see paper*:* Fonnes T, Telle IO, Forsse D, Falck R, Trovik J, Haldorsen IS, Krakstad C. Cancer awareness in the general population varies with sex, age and media coverage: A population-based survey with focus on gynecologic cancers. *Eur J Obstet Gynecol Reprod Biol* 2021, PMID: 33161211.

Other important outputs and achievements
Krakstad is head of the Bergen Biobank of Gyn Cancer since 2016, with samples from more than 7000 women with gynecological cancer collected prospectively since 2001, including 2000 women diagnosed with EC.

CCBIO significance
CCBIO provides a platform for collaborations, discussions and education between researchers with complementary interests and background. For the younger researchers, the research school has been instrumental in bridging groups as well as inspiring and educating new talents. Available infrastructure has enabled development of new research projects and added valuable new possibilities to explore biomarkers in cancer.

Future perspectives
The group will continue to focus on improving treatment for patients with gynecological cancers, with a special focus on endometrial cancer. They will continue their strong international collaborations and focus on identification of cellular and genetic mechanisms leading to metastatic spread. ••





Elisabeth Wik

breast cancer of the young – bergen (BCY-B)

Short bio
Elisabeth Wik completed her MD at the University of Bergen in 1998, and her PhD in 2013 (UiB). She did residency in gynecology, obstetrics and surgery in 2002–2007; and residency in pathology in 2013–2016. She was a postdoc at CCBIO in 2013–2018; consultant in pathology from 2017, and associate professor from 2018. From 2018–2023, she was Head of CCBIO's Research School for Cancer Studies. She has also served as coordinator for the CCBIO-VBP INTPART project. From 2022, she is Head of the Department of Pathology, Haukeland University Hospital, and she has been group leader of the Breast Cancer of the Young Group since 2019.

Brief group presentation and history
The research group Breast Cancer of the Young — Bergen (BCY-B) was established in 2019. Two PhD candidates and two Medical Student Research Program students (UiB) were part of the group from the beginning. Since then, the group has expanded and counts today two PhD candidates (MD Anna K.M. Sæle, MD Rasmus O.C. Humlevik), three Medical Student Research Program students (Amalie Bark Kvamme, Ulrikke Hugaas, Amalie Fagerli Tegnander), and one pre-PhD student (MD Astrid A. Syrtveit). Researcher Erling A. Høivik teamed up with the group in 2022. In 2023, Lise M. Ingebriktsen completed the first PhD from the group. Høivik is from 2023 co-leader of the CCBIO Research School for Cancer Studies together with Engelsen, and he is academically responsible for CCBIO908 (Scientific Writing and Communication Seminar) and CCBIO906 (Cancer Genomics).

Research focus
Young patients with breast cancer experience more aggressive tumors and poorer survival compared to what is expected based on traditional clinico-pathologic prognostic measures. Breast cancer (BC) in the young (age ≤ 40 at diagnosis) is one of the most frequent causes of death among women in this age group. The research group BCY-B studies age-related breast cancer biology, aiming for diagnostic biomarker development and improved prognostication for the group of young breast cancer patients — a project of high clinical relevance. There is a gap in the understanding of age-related tumor alterations in BC, how these contribute to the increased tumor aggressiveness seen in young patients, and whether this should affect the diagnostic and treatment strategies. This also applies to the comprehension of immune cell and tumor angiogenesis phenotypes among the young, and how these inter-relate towards cancer aggressiveness, prediction of therapy resistance, and outcome. The group's results show more frequent aggressive tumor features like high histologic grade, lymph node metastases, triple negative and HER2+ phenotypes, increased proliferation, and reduced survival in BC patients ≤40 years, clearly pointing out the need to consider age-related biological differences in clinical management.

Subprojects
1. Age-related biological tumor characteristics affecting clinical outcome

2. Estrogen receptor-related biology in breast cancer of the young

3. Age-dependent transcriptomic alterations in breast cancer of the young

4. Age-dependent differences in immuno-angiogenic responses in breast cancer

5. Targets for therapy in primary and metastatic lesions in breast cancer of the young

Most important results
• The identification of an age-related proliferation-based six-gene signature with strong prognostic value in breast cancer with potential clinical relevance is considered a major finding. Several follow-up studies on age-related breast cancer biology build on the results from this study.

• The proliferation marker Ki67 presents a poorer prognostic value in young patients with breast cancer.

• The estrogen receptor-related factors GATA3, TFF1, and AGR2 are identified as prognosticators with biological roles independent from estrogen receptors that may interfere with tumor progression and responses to anti-hormonal therapies.

Most important papers
1. Ingebriktsen LM et al. Age-related clusters and favorable immune phenotypes in breast cancer of the young. *Mod Pathol* 2024. PMID: 38810731.

2. Svanøe AA et al. Age-related phenotypes in breast cancer: A population-based study. *Int J Cancer* 2024. PMID: 38319154.

3. Ingebriktsen LM et al. A novel age-related gene expression signature associates with proliferation and disease progression in breast cancer. *Br J Cancer* 2022. PMID: 35995935.

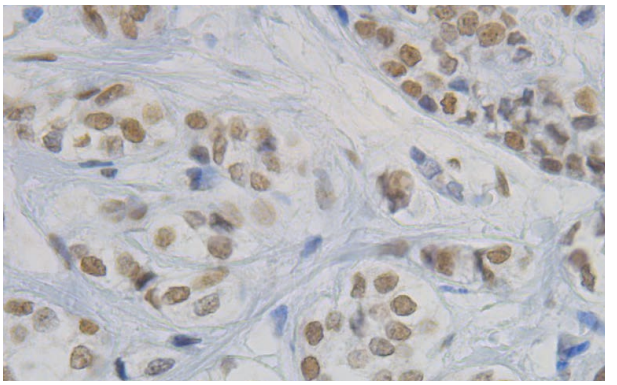
4. Sæle AKM et al. Loss of GATA3 expression associates with immune responses and metabolic alterations in aggressive breast cancer. (submitted 2024).

5. Syrtveit AA et al. Tumor Necrosis Associates with Aggressive Breast Cancer Features, Increased Hypoxia Signaling and Reduced Patient Survival. (submitted 2024).

6. Humlevik ROC et al. Young patients with breast cancer: more aggressive tumor features, reduced survival, and treatment differences. (submitted 2024).

Translational, clinical and societal impact
Breast cancer of the young is recognized to pose specific societal challenges (e.g. contribution to family life; work

life, etc.). Wik regards this project as having the potential to contribute to major scientific, clinical, and societal impact. Study results from the BCY-B group have provided attention to the group of young breast cancer patients, and the particular attention this group would need, based on age-related tumor characteristics — pointing to a need for age-based therapy guidance and follow-up. The clinical and societal impacts from BCY-B study results are emerging, as the group is asked to present data from their studies for the leading national diagnostic and clinical environment.



Other important output and achievements
Members of BCY-B have co-authored several book chapters in the CCBIO period (2013–2023):

• Genomic Landscapes and Tumor Evolution in Metastatic Gynecological Cancers. E.A. Høivik. Book chapter in "*Metastasis*". Editor Consolato M. Sergi. *Exon Publications*, 2022.

• HER2 revisited — Reflections on the future of cancer biomarker research. A. Bremer, E. Wik, L.A. Akslen. Book chapter in the anthology «*Precision Oncology: Issues at Stake and Matters of Concern*". Editors Anne Bremer & Roger Strand. *Springer*, 2022.

• Gene Expression Signatures of the Tumor Microenvironment: Relation to Tumor Phenotypes and Progress in Breast Cancer. E. Wik, L.M. Ingebriktsen, L.A. Akslen. Book chapter in "*Biomarkers of the Tumor Microenvironment (2. edition)*". Editors: L.A. Akslen & R. Watnick. *Springer*, 2022.

• What is a good (enough) biomarker? A. Blanchard & E. Wik. Book chapter in "*Social, ethical and economic aspects of cancer biomarkers.*" Editors: Anne Blanchard & Roger Strand. *Megaloceros Press*, 2017.

• Gene Expression Signatures of the Tumor Microenvironment: Relation to Tumor Progress in Breast Cancer. E. Wik & L.A. Akslen. Book Chapter in "*Biomarkers of the Tumor Microenvironment.*" Editors: LA Akslen R Watnick. *Springer*, 2017.

Awards:
• Ulrikke Hugaas (2022): Poster award winner, 6th SCANPATH 2022 ("Metastatic ER, PR and HER2 expression in young breast cancer patients").

• Amalie Fagerli Tegnander: Talent award, Sparebank1 Midt-Norge.

• Elisabeth Wik (2019): UiB Medical Faculty Award for Internationalization in the study programs (for running the CCBIO-INTPART program).

• Elisabeth Wik and Lars A. Akslen (2017): Thon Foundation Prize for National Educational Research Projects («Harvard Cancer Research: Partnership for excellent education and research").

• Amalie A. Svanøe (2016): Presentation award at the European Conference of Pathology.

• Elisabeth Wik (2016): Professor Kreyberg's Award for second best PhD thesis in experimental pathology (the prize is being awarded every 4th year).

• Elisabeth Wik (2009–2015): International awards for scientific presentations (European Congress of Pathology, Belgrade/2015; European Congress of Pathology, Prague/2012; Research School Clinical Medicine, Haukeland University Hospital, Annual Meeting on Research Presentations; 2010; Bi-annual Meeting of European Society of Gynecologic Oncology, Belgrade/2009.)

CCBIO significance
CCBIO has provided a motivating research (micro and macro) environment — stimulating us to establish our independent research group. It has been a vivid environment for our students and PhD candidates with vast possibilities for joining high-quality research courses, seminars, and workshops. Being part of CCBIO has also given us valuable networking possibilities both locally and with international faculty.

Future perspectives
The BCY-B studies will continue the tissue-based studies, integrating histopathologic, clinical, and molecular data, with support of large-scale (omics) data. Continued work includes projects focusing on age-dependent hormone receptor-related alterations, the breast cancer immune cell landscape across ages, and metastases in the young, and will include spatial biomarker information for improved understanding of cancer progress. The BCY-B leadership aims to establish international networks on cancer of the young — aiming for BCY-B to make a difference in research and clinical medicine, particular for the younger breast cancer patients. ••


Elisabeth
WIK



Carina Strell

the early breast cancer group

Short bio
Carina Strell holds a diploma in biochemistry (2004) and a PhD in tumor biology (2009) from the Witten/Herdecke University in Germany. She performed her postdoctoral studies in the group of Professor Arne Östman at the Karolinska Institute, where she started working on DCIS (2010–2016). Thereafter, Strell worked as senior researcher in Professor Mats Nilsson's lab at the Science for Life Laboratory in Stockholm, focusing on *in situ* sequencing to spatially study gene expression patterns in breast cancer. In 2019, she moved to Uppsala University, where she qualified as associate professor in experimental pathology in 2020 and was appointed independent PI in 2023 (continued affiliation). Supported by a Starting Grant from the Trond Mohn Research Foundation (TMF) in 2022, Strell became a CCBIO-affiliated principal investigator and now holds a researcher position at the University of Bergen (UiB).

Brief group presentation and history
The Early Breast Cancer Group was established in 2022, after Carina Strell received a TMF Starting Grant and became a CCBIO-associated principal investigator. The group comprises one researcher (Lars Muhl), one postdoc (Anna Gorbunova) and one PhD student (Ghazal Toussi) at the UiB site, and one researcher (Aglaia Schiza), two PhD students (Viktoria Thurfjell, Amanda Lindberg) and one lab manager (Neda Hekmati) at the Uppsala site.

Research focus
The research in Strell's group focuses on the biology of breast ductal carcinoma *in situ* (DCIS), with the overall ambition to comprehensively elucidate the underlying regulatory signaling mechanisms of early breast cancer evolution towards clinical disease progression and therapy response. Special emphasis is placed on understanding the interplay between genetic alterations and the tumor microenvironment by using state-of-the-art spatial mapping techniques for tissue analysis. Moreover, Strell's team extend their investigation beyond biological aspects, aiming to uncover new therapeutic possibilities and develop clinically relevant treatment stratification models tailored for women with early-stage breast cancer.

Subprojects
1.EvoMaps – understanding the interplay of genetic alterations and the tumor microenvironment in DCIS

2. Study the impact of the DCIS immune architecture on disease progression

3. ImSignal – mapping active immune cell signaling

Most important results
EvoMaps
a) Genetic alterations required for invasion were already detected at the *in situ* stage of breast cancer. This major discovery prompts the hypothesis that cancer cell invasion into surrounding tissues is largely influenced by characteristics of the tumor microenvironment.

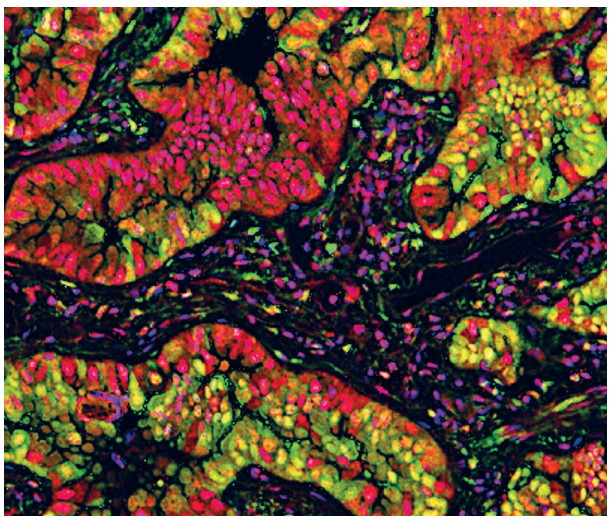
b) In DCIS cases, HER2 amplification represents 30%, correlating with heightened T-cell infiltration and a poor prognosis. In invasive breast cancer, only 15% of cases are HER2 positive.

DCIS immune architecture
a) In contrast to findings in invasive breast cancer, the group found that high TILs level in DCIS are associated with an increased recurrence risk. This study was addressed by a Commentary in *Eur J Cancer*, "The Art of Thinking Counterintuitive", highlighting that this study shows that some of the established dogmas within invasive cancers may not apply for early cancer stages. Moreover, the clinical significance of this study lies in the ability of TILs scoring to refine the definition of low-risk DCIS. Integration of TILs scoring into diagnostic routines, as conducted on H/E sections, offers a straightforward approach.

b) In DCIS, the presence of a softer extracellular matrix (myxoid matrix) along with TILs directly interacting with lesions is specifically linked to invasive recurrences.

ImSignal
a) In NSCLC, the interaction between PD1-PDL1, evaluated through second-generation proximity ligation assay, emerges as a new, superior predictive biomarker for immunotherapy benefit compared to the current standard of PDL1 protein assessment by IHC.

b) Furthermore, the group can map PDL2-PD1 interactions in tissue samples and investigate their role as a potential resistance mechanism. An adaptation of the PLA to the Hyperion Imaging System is ongoing.



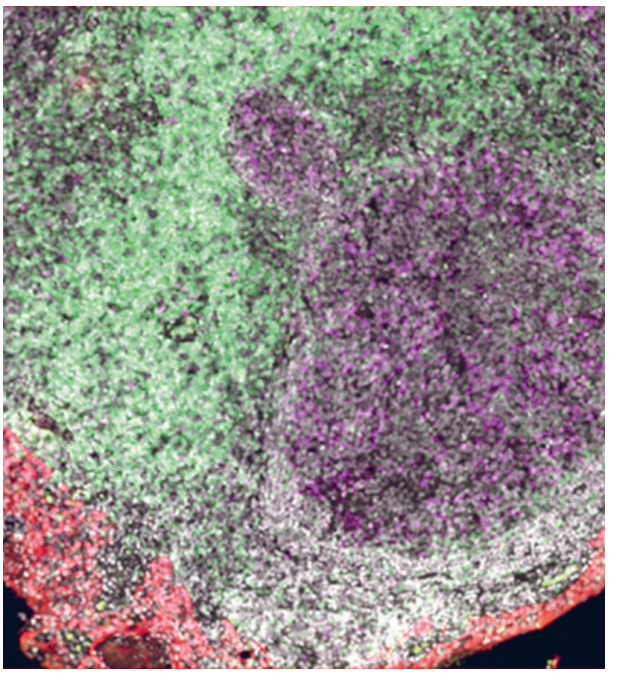
Most important papers

1. Strell C et al. Use of beta-blockers in patients with ductal carcinoma *in situ* and risk of invasive breast cancer recurrence: a Swedish retrospective cohort study. *Breast Cancer Res Treat* 2024. PMID: 38763971.

2. Lomakin A et al. Spatial genomics maps the structure, nature and evolution of cancer clones. *Nature* 2022. PMID: 36352222.

3. Schiza A et al. Tumour-infiltrating lymphocytes add prognostic information for patients with low-risk DCIS: findings from the SweDCIS randomised radiotherapy trial. *Eur J Cancer* 2022. PMID: 35236568.

4. Strell C et al. High PDGFRb Expression Predicts Resistance to Radiotherapy in DCIS within the SweDCIS Randomized Trial. *Clin Cancer Res* 2021. PMID: 33952629.



Translational, clinical and societal importance

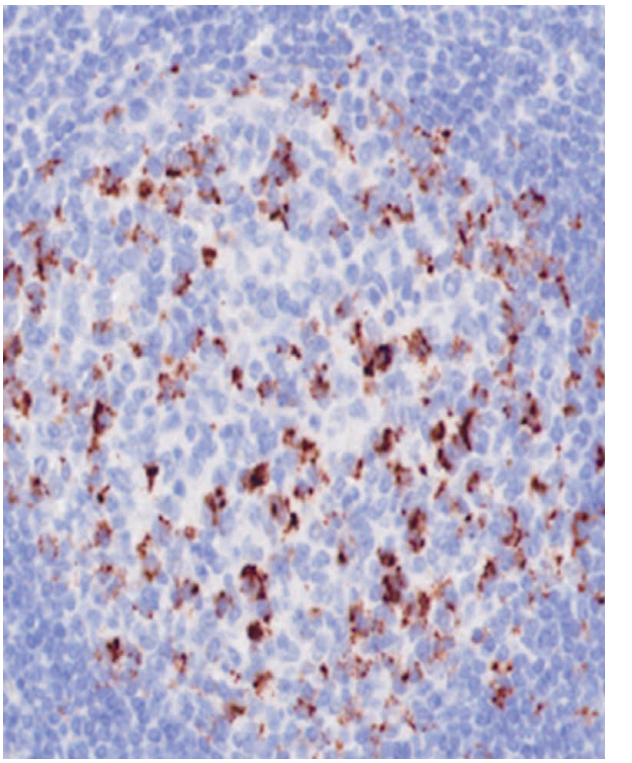
Stromal PDGFRb as a response predictive biomarker for radiotherapy benefit in DCIS and early breast cancer; currently undergoing independent validation studies in a collaboration with a US based breast cancer diagnostic company.

PD1-PDL1 interaction as a response predictive biomarker for efficacy of PD1/PDL1 targeting immune checkpoint inhibition in NSCLC; currently the group performs independent validation studies and test the predictive capacity in other solid cancers treated with immunotherapy.

Myxoid stroma matrix as a marker for high risk of invasive progression of DCIS; the group is looking into potential independent validation cohorts.

Other important outputs and achievements

Findings from the ImSignal project were presented at the Keystone Symposium on Cancer Immunotherapy and the AACR Annual Meeting 2024. Amanda Lindberg received a travel grant for the Keystone symposium; PhD student Viktoria Thurfjell received a clinical PhD fellowship from the Swedish Bröstcancerförbundet.



CCBIO significance

CCBIO offers the ideal framework for tissue-based studies with a focus on biomarker discovery and the identification of new cancer treatment targets. It inspires new collaborations and exchanges between researchers with complementary backgrounds and experiences.

Future perspectives

The research team will prioritize the adaptation of their established spatial tissue profiling techniques to the Hyperion Imaging System. This will complement the ongoing spatial proteomics efforts at CCBIO with approaches for spatial genomics and signaling pathway mapping. The group will also seek contacts with CCBIO bioinformaticians and big data specialists to facilitate the integration of multiple layers with different spatial omics data into current bioinformatical analysis pipelines for tissue profiling. ••





Agnete Engelsen

cancer cell plasticity and therapy resistance group

Short bio
Agnete Engelsen completed her Cand. Scient. in cell and developmental biology at the University of Bergen in 2003, and her PhD at the same university in 2013. Since 2013, Engelsen did her postdoctoral training in the Cellular Networks Laboratory, mentored by CCBIO PI Professor James B. Lorens. From 2017–2020 she continued as a Marie Skłodowska-Curie Actions (MSCA) fellow to pursue the research project *Impact of cellular epithelial plasticity programs on the anti-tumor response*, co-mentored by Professor James B. Lorens, Salem Chouaib and Jean Paul Thiery at the Gustave Roussy Cancer Center in Paris, France. Since 2023, Engelsen has been heading the CCBIO Research School for Cancer Studies (RSCS).

Brief group presentation and history
The research group was established in 2022, when Engelsen became an associate PI of CCBIO's Team 2: Discovery and validation of cancer biomarkers.

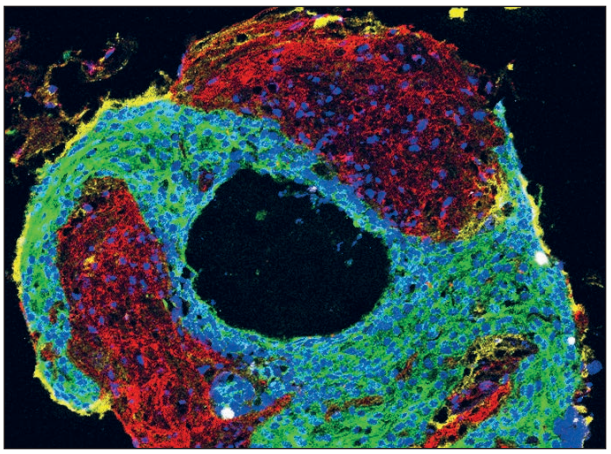
Research focus of the group
Recent research from CCBIO laboratories and others has shown that extracellular stressors, including exposure to anti-cancer therapies, low oxygen availability, immune editing, and extracellular matrix interactions, contribute to promoting phenotypic epithelial-to-mesenchymal plasticity, a well-recognized cancer hallmark. As a postdoc and later researcher with CCBIO, Engelsen has been dedicated to exploring how phenotypic plasticity interferes with therapeutic efficacy and immune cell-mediated killing. The existence of rare cancer cells that sporadically acquire drug-tolerance through epigenetic mechanisms is proposed as one mechanism that drives cancer therapy failure. The group has shown that hypoxia, targeted therapies and specific microenvironments impose non-sporadic expression of Axl, a driver of epithelial phenotypic plasticity and therapy resistance.

Subprojects
The group has been dedicated to establishing improved preclinical models of non-small cell lung cancer (NSCLC) to explore how phenotypic plasticity interferes with therapeutic efficacy and immune cell-mediated killing. The current projects aim to unravel the best molecular targets to prevent phenotypic plasticity-driven therapy resistance and immune escape in solid tumors, and to elucidate the effect of phenotypic plasticity on the spatial organization of the tumor immune microenvironment, to uncover predictive mechanisms of resistance in ICI-treated NSCLC patients.

In one of the group's subprojects, they explore a therapeutic intervention with hyperbaric oxygen therapy (HBOT) to improve the efficacy of immune checkpoint inhibition by modulating the metabolism of and crosstalk between malignant cells and cells of the tumor immune microenvironment. The goal of this project is to address the remaining clinical challenge, that most NSCLC patients do not experience long-term benefit from ICI therapy.

Most important results
The Engelsen group has shown that targeting Axl impacts the immune system in several ways: 1) via the release of damage-associated molecular patterns (DAMPs) to attract immune cells to the tumor bed, 2) via the modulation of MHC class 1 molecules that aid in the presentation of peptides on the cell surface for recognition by T cells, and 3) via modulation of adhesion molecules involved in the successful formation of an immune synapse.

In collaboration with peers at the Gustave Roussy Cancer Center, the group has shown that Axl targeting overcomes resistance of mesenchymal phenotype human lung cancer cells to Natural Killer (NK) cells and Cytotoxic T-lymphocytes (CTL) mediated cytotoxicity. This is an important finding because it indicates that Axl plays an important role in mediating the fatal encounter, and the formation of a successful immunological synapse between the killer and the cancer cell.



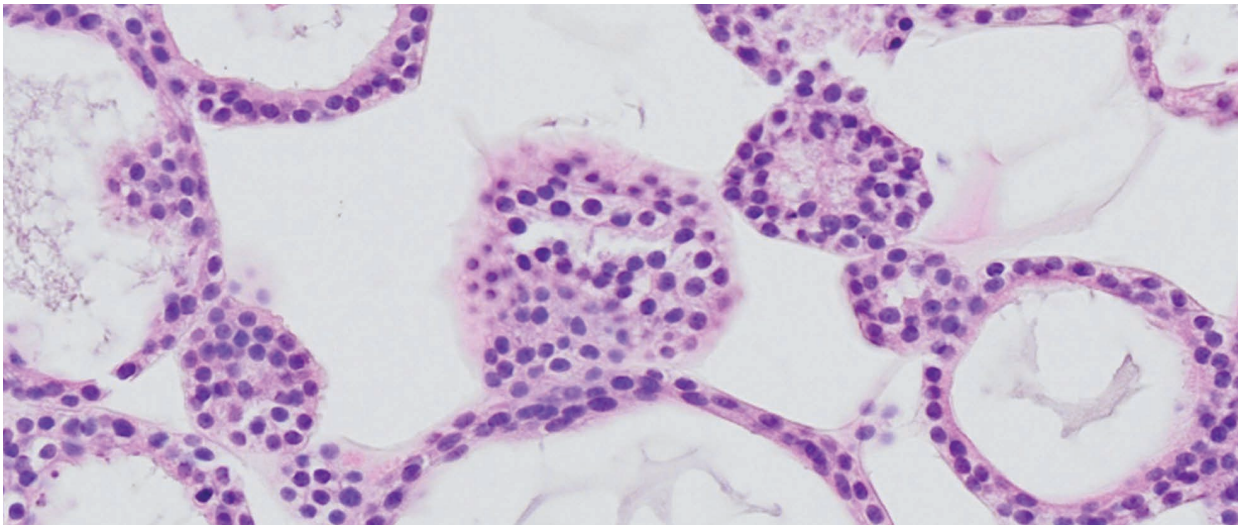
Most important papers:

1. Jokela TA et al. Microenvironment-Induced Non-sporadic Expression of the AXL and cKIT Receptors Are Related to Epithelial Plasticity and Drug Resistance. *Front Cell Dev Biol* 2018. PMID: 29719832.

2. Engelsen AST et al. AXL Is a Driver of Stemness in Normal Mammary Gland and Breast Cancer. *iScience* 2020. PMID: 33103086.

3. Lotsberg ML et al. AXL Targeting Abrogates Autophagic Flux and Induces Immunogenic Cell Death in Drug-Resistant Cancer Cells. *Journal of Thoracic Oncology (JTO)* 2020. PMID: 32018052.

4. Terry S et al. AXL Targeting Overcomes Human Lung Cancer Cell Resistance to NK- and CTL-Mediated Cytotoxicity. *Cancer Immunol Res* 2019. PMID: 31488404.



5. Lotsberg ML et al. Intrinsic Differences in Spatiotemporal Organization and Stromal Cell Interactions Between Isogenic Lung Cancer Cells of Epithelial and Mesenchymal Phenotypes Revealed by High-Dimensional Single-Cell Analysis of Heterotypic 3D Spheroid Models. *Front Oncol* 2022. PMID: 35530312.

6. Rayford A et al. AXL expression reflects tumor-immune cell dynamics impacting outcome in non-small cell lung cancer patients treated with immune checkpoint inhibitor monotherapy (in preparation, 2024).

Translational, clinical and societal importance

The group's results provide insight into the complex molecular alterations and immune cell dynamics serving as potential biomarker signatures of the tumor microenvironment that predict response to ICI treatment in NSCLC. Results from their studies support the role of Axl as a negative-feedback mechanism to anti-tumor immunity and warrant future combination therapy trials to overcome ICI-resistance in NSCLC patients.

Other important outputs and achievements

Books: Engelsen has contributed three book chapters as senior and corresponding author (*Biomarkers of the Tumor Microenvironment: Basic Studies and Practical Applications* (eds. Akslen and Watnick, 2017); *Biomarkers of the Tumor Microenvironment* (eds. Akslen and Watnick, 2022; and *Autophagy in Immune Response: Impact on Cancer Immunotherapy* (ed. Chouaib, 2020).

Awards: Best PhD of the Year at the Medical Faculty, UiB, 2014. Graduation certificate *with distinction,* and *Recognition of excellence* award on the Hallmarks of Cancer Team Project at HICR Postgraduate Medical Education, Harvard Medical School, 2019. Faculty of Medicine's elect for the UiB's career development program *Momentum* in 2019/20.

Memberships: Member of European Organization for Research and Treatment of Cancer Pharmacology and Molecular Mechanisms (EORTC PAMM) group, Marie Curie Alumni organization (MCAA), Harvard Alumni association (HAA).

Special grants: FRIPRO Mobility Grant, personal overseas mobility grant — Co-funded by RCN and the EU 7th FP Marie Curie Actions (MCA COFUND).

CCBIO significance

Engelsen is grateful for the continued support from CCBIO mentors Lars A. Akslen and James B. Lorens throughout the years and for fruitful collaborations within the extended CCBIO family, including international faculty. Furthermore, Engelsen is grateful for the opportunities to participate with increasing responsibilities in CCBIO's research school activities.

Future perspectives

From 2022, Engelsen coordinates the *INTPART project* "Bergen- Harvard Cancer Studies: A partnership for Excellent Education and Research". It is her ambition to continue this successful research collaboration in CCBIO's continuation phase. Together with peers from the Vascular Biology Program at Boston Children's Hospital and Harvard Medical School, she recently organized the 2nd CCBIO-VBP Research Meeting, a great opportunity for trainees to engage in the fruitful research and education partnership initiated by CCBIO's Director Lars A. Akslen together with the VBP Director Marsha A. Moses. As head of the Research School for Cancer Studies, Engelsen's ambition is to continue developing the research school activities and provide an inspirational learning environment for new generations of cancer researchers in Bergen. ••





Team 3

clinical applications and early trials

The aim of this program is to perform clinical trials with associated biomarker studies, and to promote novel findings on markers and treatment targets for clinical implementation and change of practice through updated guidelines. This team consists of the PIs Bjørge (CCBIO co-director from November 16, 2022), Gjertsen (CCBIO co-director until November 16, 2022), and Straume.





Line Bjørge

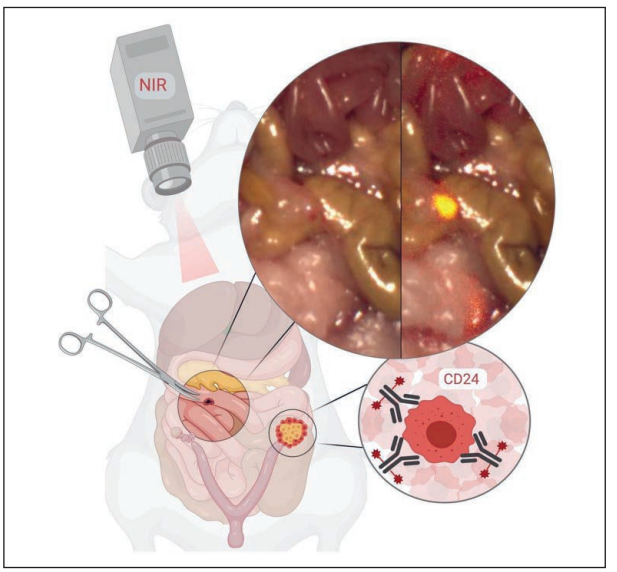
the INOvA group (innovative novel ovarian cancer treatment approaches)

Short bio

Line Bjørge, MD, PhD, is the Medical Director at Haukeland University Hospital, Bergen, Norway and a professor at the University of Bergen. She co-directs and is a principal investigator at CCBIO. Bjørge earned her medical degree (1992) and PhD (1996) from the University of Bergen and an MBA from ESSEC Paris and Mannheim Business School (2010). She trained in obstetrics and gynecology at Haukeland University Hospital and completed a post-doctoral fellowship in cancer immunology at the University of Helsinki and University of Innsbruck. Her research focuses on gynecological oncology, particularly ovarian and vulva cancer with profiling of preclinical models and clinical trials. She has received multiple national and international grants and is a seasoned supervisor and mentor with a comprehensive publication record.

Brief group presentation and history

Since 2009, Bjørge and Professor Emmet Mc Cormack have collaborated on research projects and co-supervised PhD candidates. In 2015, they received a significant grant from the Innovative Training Networks (ITN) under the H2020-MSCA-ITN-2015 program for their project, "Image-Guided Surgery (IGS) and Personalized Postoperative Immunotherapy to Improve Cancer Outcomes." This grant also funded positions for early-stage researchers. To manage this project, Bjørge and Mc Cormack established the INOvA Research Group, which quickly attracted talented young researchers and thrived in advancing cancer research.



Research focus

Over the past decade, the INOvA Research Group has developed a multidisciplinary project portfolio focused on high-grade serous ovarian carcinoma. The "Rethinking Ovarian Cancer" (RETHINK) initiative aims to transform tumor profiling data into strategies for personalized patient care. The RETHINK portfolio is divided into four key programs: tumor microenvironment profiling, preclinical modeling, antibody-based diagnostics, and clinical translation. Recently, a similar approach is being developed for vulva cancer in collaboration with Professor Daniela Costea.

Subprojects

1. Immunophenotyping of HGSOC

Mutational processes, tumor localization, and clonal heterogeneity affect immune recognition and contribute to TME heterogeneity. In HGSOC patients, the role of immuno-therapy is not clear. Spatial communication in the TME might influence its efficacy, but this research is still in the early stages. The aim of the project is to develop robust methods to understand spatial and functional interactions, crucial for identifying biomarkers and improving immunotherapy. Methods include multi-omics immunoprofiling using cytokine mapping, single-cell mass cytometry of tumor and peripheral blood cells, and imaging mass cytometry of tumor tissues. Established profiling panels and new algorithms for extended phenotyping have confirmed tumor heterogeneity, revealed new cell subsets, and identified biomarkers for prognosis and treatment selection.

2. Experimental preclinical models

Preclinical models are essential for basic research and therapeutic discovery, but current models fail to mimic real tumor complexity, leading to many therapeutics failing in clinical trials. The aim of the project is to develop advanced 3D systems using decellularized tissue as an extracellular matrix substitute and a mouse xenograft platform for HGSOC. A sophisticated 3D platform with a decellularized peritoneum as an organ-specific matrix, supported by custom 3D-printed molds for dynamic imaging, has been established. Models of primary tumors, functional drug response assays, and cell-based immunotherapies have been implemented. Additionally, a mouse xenograft platform with orthotopic PDX models, immunocompetent, and surgical models have been developed for HGSOC.

3. Clinical translation

Translating new biological knowledge into innovative therapies requires integrating predictive biomarkers with functional analysis. By using data from comprehensive tumor profiling and functional analysis in preclinical models, the goal is to develop tools to identify effective therapies and guide clinical decisions. Cytokine profiling in the IMPACT study revealed two distinct immunological subgroups for treatment selection. Targets for image-guided surgery with near-infrared probes were identified. The 3D HGSOC models accurately mimicked tumor responses to platinum-based treatments. Mass cytometry analysis of human peripheral blood cells identified cell subsets for monitoring combined CD73 and PD-L1 blockade immunotherapy in HGSOC patients.

Most important results

• Establishment of multi-omics platforms for profiling of blood and tissue samples for characterization of the tumor microenvironment in ovarian and vulva cancer.

• Establishment of advanced preclinical models for ovarian and vulva cancer.

• Discovery of a promising immunosignature for personalized treatment selection in ovarian cancer patients.

Most important papers

1. Kleinmanns K et al. CD24-targeted fluorescence imaging in patient-derived xenograft models of high-grade serous ovarian carcinoma. *eBioMedicine* 2020. PMID: 32454401.

2. Kleinmanns K et al. CD24-targeted intraoperative fluorescence image-guided surgery leads to improved cytoreduction of ovarian cancer in a preclinical surgical orthotopic model. *eBioMedicine* 2020. PMID: 32454402.

3. Anandan S et al. Phenotypic Characterization by Mass Cytometry of the Microenvironment in Ovarian Cancer and Impact of Tumor Dissociation Methods. *Cancers (Basel)* 2021. PMID: 33670410.

4. Kleinmanns K et al. Humanized Ovarian Cancer Patient-Derived Xenografts for Improved Preclinical Evaluation of Immunotherapies. *Cancers (Basel)*, 2022. PMID: 35804867.

5. Torkildsen CF et al. Primary Treatment Effects for High-Grade Serous Ovarian Carcinoma Evaluated by Changes in Serum Metabolites and Lipoproteins. *Metabolites* 2023. PMID: 36984856.

6. Casey NP et al. Efficient CAR T cell targeting of the CA125 extracellular repeat domain of MUC16. *J Immunother Cancer* 2024. PMID: 38604812.

7. Torkildsen CF et al. New immune phenotypes for treatment response in high-grade serous ovarian carcinoma patients. *Front Immunol* 2024. PMID: 38947323.

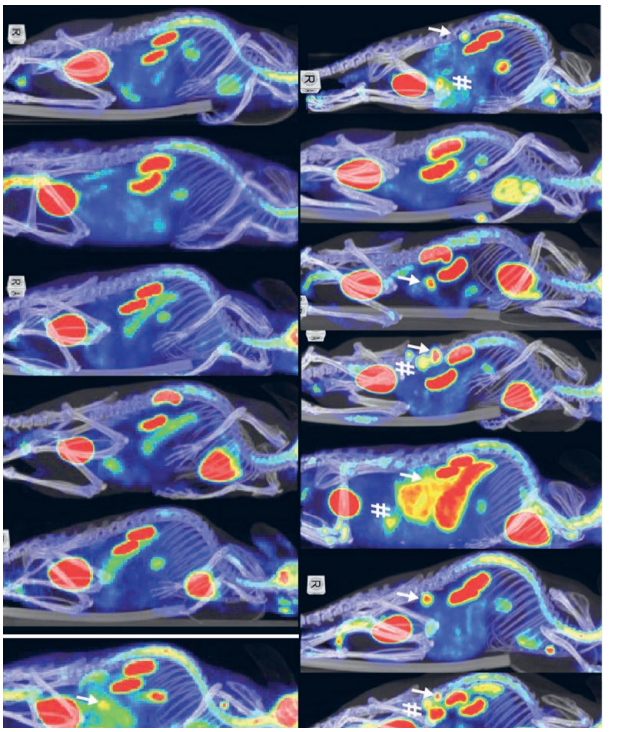
Other important outputs and achievements

Bjørge has been a board member and treasurer of NSGO since 2014 and its president since 2022. She is active in European and international networks for translational research in gynecological cancers and led the Norwegian "Onkologisk Forum" during 2018–2022. Additionally, she serves on boards for NSGO-CTU, Oslo Cancer Cluster and KinN Therapeutics and is involved in several steering and advisory committees for clinical trials and research centers. She is also an expert in gynecological oncology for the national second-opinion panel for incurable diseases and a faculty member of ESMO for the Gynaecological Cancers group. The other group members are also excellent presenters and have frequently been awarded at conferences and meetings. Other mentions:

• Kolbjørn Brambanis Cancer Research Grant 2022 to Christiane Helgestad Gjerde

• NSGO Research Grant 2024 to Katrin Kleinmanns

• UiB-Idé Grant 2022 to the INOvA team



CCBIO significance

Our projects align well with CCBIO's goals, incorporating elements from all four main programs. CCBIO's excellent research environment has provided invaluable support and resources, ensuring sustained funding and access to cutting-edge technologies. The center's focus on collaboration and education fosters a nurturing atmosphere for young researchers, encouraging innovation and excellence. Affiliation with CCBIO integrates us into a prestigious network of scientists dedicated to pioneering cancer research. This has elevated our group's capabilities and contributed significantly to developing innovative therapeutic strategies and improving clinical outcomes for cancer patients.

Future perspectives

In research, continued focus will be on development and application of preclinical models and biomarker discovery, validation and application with focus on anti-body-based therapeutics. In parallel, the group will focus on the development of future research leaders. ••





Bjørn Tore Gjertsen

signaling-targeted therapy group

Short bio
Bjørn Tore Gjertsen, MD (1992), PhD (1995), is professor of hematology (2007-) at the University of Bergen (UiB), and senior consultant hematologist (2007-) at Haukeland University Hospital. Gjertsen was a postdoc at the MD Anderson Cancer Center, Houston, from 1997–1999, part-time postdoc at the UiB from 2001–2005 and completed his specialist training in clinical hematology in 2007. From 2016–2022 he served as co-director for CCBIO. From 2010 to 2018, Gjertsen developed a phase I clinical trials unit at Haukeland University Hospital. His clinical practice in hematology is focused on clinical trials in chronic and acute myeloid leukemia (AML). His laboratory is working on intracellular signal transduction and regulation of the tumor suppressor protein p53. He has a special interest in single cell analysis and detection of circulating tumor cells for early response evaluation. Dr. Gjertsen is a founding member and chair of the Norwegian AML Group and the Nordic AML Group, and is member of EHA, ASH, ASCO, and the Nordic CML Study Group. He is co-founder of four small biotech companies.

Brief group presentation and history
The group was built on Gjertsen's experiences during his PhD-fellowship (kinases and phosphatases in regulation of cell death) and his two postdoc periods (MDACC, Houston, on p53 and Bcl-2). The second postdoc in Bergen was used to establish models of acute myeloid leukemia, *in vitro* and *in vivo*, and at this time, the power of primary cells from cancer patients was made clear. Three publications formed the way forward: Gausdal et al. on early proteome modulation after start of chemotherapy, including regulation of phosphorylation. Then the single cell phospho-flow paper describing that functional assays on living tumor cells could indicate prognosis. This was conceptually copied in CML patients dosed with a specific kinase inhibitor, indicating that response to therapy can be identified after hours and days, not weeks and months. By support from the Norwegian Cancer Society and a repatriation grant in functional genomics from the Research Council of Norway, a research laboratory was established.

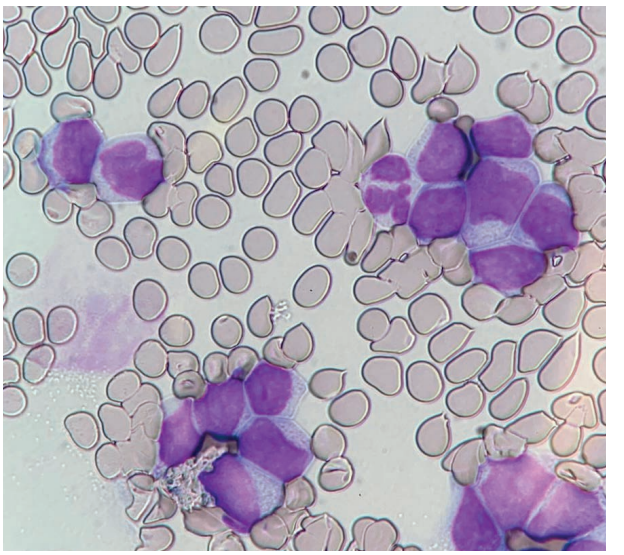
Research focus
The Gjertsen group focuses on single cell immune and signaling profiling in early response evaluation of AML and CML patients, as well as therapy development in AML using single cell analysis as companion diagnostics.

Subprojects
KG Jebsen Centre for Myeloid Blood Cancer: This opened in September 2024 and acts as an overarching structure to support establishment of new single cell technologies, validation of these technologies including mass cytometry, and outreach to secure larger biobank materials from clinical trials.

Repurposing drugs in cancer: Focusing on AML and with preliminary data indicating clinical benefit, the concept will be tested in advanced cancer with particularly low survival. Companion diagnostics through single cell profiling should improve precision of the therapy chosen. Results indicate that ERK1/2 pathway and p53 protein modulation, as well as the mutational status of TP53 and signaling, are candidate companion diagnostics.

Single cell immune and signaling profiling in cancer: This project aims to show the potential of single cell immune- and signaling profiling in cancer prognostication and response evaluation, based on biobanked peripheral blood in small clinical trials. Immune profiling with intracellular signaling demonstrates that AML patients in complete remission are very different from healthy individuals. Imaging mass cytometry can be used in skin biopsies to examine the mechanisms involved in cell vaccination with dendritic cells. Advanced cancer patients can be response evaluated by peripheral blood single cell profiling.

Tumor suppressor p53 protein profiling in cancer: Profiling of p53 isoforms and posttranslational modifications in single cells will be developed and connected to the signaling state and phenotype of the cell.



Most important results
In general, single cell profiling of peripheral blood leukocytes seems to include information about the prognosis and predict the therapeutic effect of cancer therapy. By monitoring intracellular signaling pathways, transcription factors and cell death regulators, response is possible to determine after hours and days. If the patient is a non-responder, therapy can be adapted or replaced weeks or months before the current standard of care.

Most important papers

1. Tislevoll BS et al. Early response evaluation by single cell signaling profiling in acute myeloid leukemia. *Nature Communications*, 2023. PMID: 36611026.

2. Gullaksen SE et al. Single cell immune profiling by mass cytometry of newly diagnosed chronic phase chronic myeloid leukaemia treated with nilotinib. *Haematologica* 2017. PMID: 28522574.

3. Hellesøy M et al. Sex disparity in acute myeloid leukaemia with FLT3 internal tandem duplication mutations: implications for prognosis. *Mol Oncol*. 2021. PMID: 34101344.

4. McCormack E et al. Multiplexed monoclonal antibodies: A new strategy in preclinical time domain imaging of acute myeloid leukemia. *Blood.* 2013. PMID: 23243270.

5. Omsland M et al. Tyrosine kinase inhibitors and interferon-α increase tunneling nanotube (TNT) formation and cell adhesion in chronic myeloid leukemia (CML) cell lines. *FASEB J.* 2020. PMID: 31945226.

6. Sulen A et al. Elevated monocyte phosphorylated p38 in nearby employees after a chemical explosion. *Sci Rep*. 2016. PMID: 27380711.

7. Andresen V et al. Anti-proliferative activity of the NPM1 interacting natural product avrainvillamide in acute myeloid leukemia. *Cell Death Dis*. 2016. PMID: 27906185.

Translational, clinical and societal importance

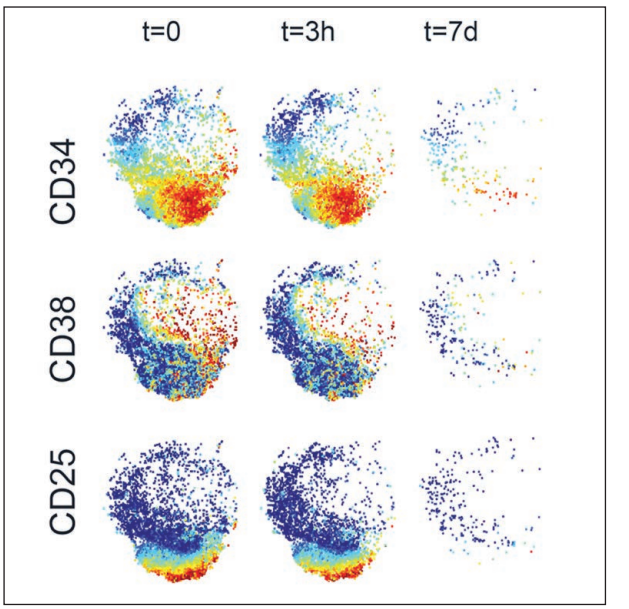
The group has developed an advanced biomarker program for clinical studies. Gjertsen developed a phase I trials unit at HUS, and the impact of CCBIO Seminars and the yearly Symposium led to more phase I clinical trials in Bergen. CCBIO contributed strongly to introducing immunotherapy in cancer, particularly the introduction of immune checkpoint blockers through clinical trials at the trial unit. Materials for advanced biomarker analysis is still being collected and analyzed, and in the coming years, several publications are planned towards liquid biopsy.

Other important outputs and achievements

In 2024, Gjertsen was awarded a five-year KG Jebsen Centre for Myeloid Blood Cancer. In 2021, Gjertsen was awarded the King Olav V's Cancer Research Prize, based on his major research interest in clinical trials, development of targeted therapy and accompanying diagnostics in myeloid leukemia. In 2018, Gjertsen was elected to the Royal Physiographic Society of Lund University (Sweden).

CCBIO significance

The single most important element in the center has been the passionate and deeply involved Scientific Advisory Board, combined with a Centre Director with patience and well-structured leadership. Multiple collaborations have been created, and likely the question of success or societal benefit will not be answered in 5 to 10 years. Within the interest of CCBIO, we have been able to establish a collaboration in immunotherapy and introduced unique cell therapy through the concept of cryoimmunotherapy.



Future perspectives

The CCBIO biomarker concept and the focus on tumor-host interactions have made visible limitations in infrastructure and spawned two small biotech startups: Alden Cancer Therapy and Há Biotechnology. The last biotech, Bjørgvin Technology Group, aims to bring the compassionate diagnostics test in single cell format into effective low toxic therapy to keep aggressive cancer in check.

Upcoming scientific publications will include work on circulating tumor cell determination in peripheral blood combined with single cell immune- and signaling profiling. Single cell profiling will be examined for response evaluation in advanced cancer patients treated with immunological checkpoint blockers as well as in patients surgically treated for colorectal cancer. The immune profile aspect will be used in understanding the most intense and complicated treatment of allogeneic hematopoietic stem cell transplantation. In this interphase together with cryoimmunotherapy, the biomarker aspect of engineered T cells will be established and developed. ••


HELSE BERGEN



Oddbjørn Straume

the tumor biology and clinical trials group

Short bio
Oddbjørn Straume completed his MD in Bergen in June 1996, and the PhD was completed in 2002. After 2002, he worked as an oncologist and researcher at Haukeland University Hospital (HUH), Department of Oncology, combined with a postdoc at the UiB, Department of Pathology. His UiB position is now professor, PI at CCBIO since CCBIO's initiation, and he is currently head of the Department of Oncology at HUH. Straume has extensive clinical experience, comprehensive research expertise and a broad professional network. He has been coordinating investigator in 4 investigator initiated clinical trials, including 1 RCT. In addition, he is PI of more than 12 industry clinical trials.

Brief group presentation and history
The research group was established in 2013 as a CCBIO group. Oddbjørn Straume started his research career in Lars A. Akslen's group as a medical student focusing on biomarkers in melanoma. Later, the focus was expanded to include new tumor biological processes, such as tumor immune responses and tumor dormancy. Later, as a clinical oncologist, these research areas were incorporated in clinical research and clinical trials.

Research focus
The main research goal is to identify predictive biomarkers in clinical materials. The biomarkers under investigation are all related to tumor biological processes and new treatment modalities for cancer patients, such as angiogenesis, tumor immune responses, tumor cell plasticity, epithelial to mesenchymal transition (EMT), and mechanisms associated with the escape from tumor dormancy (i.e. late relapses).

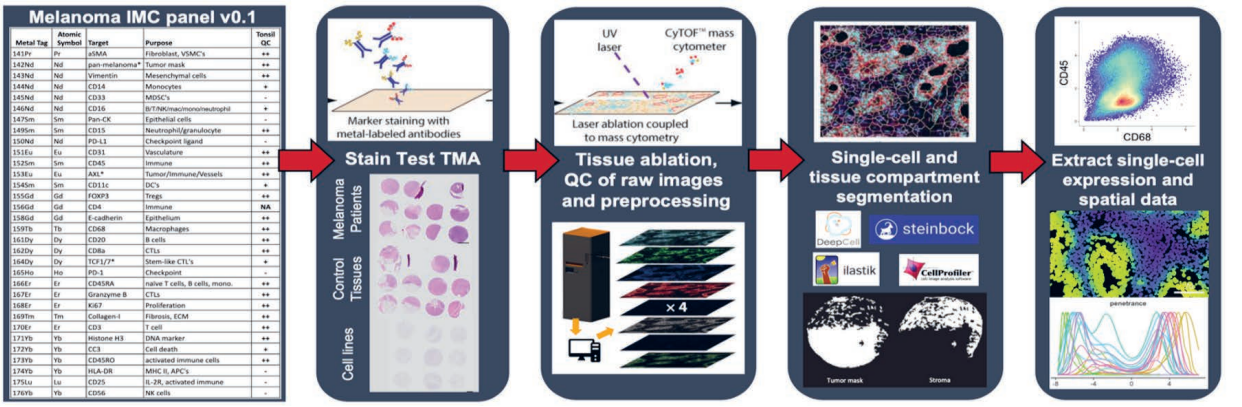
Subprojects
1. Clinical trial I. A phase Ib/II randomized open label study of BGB324 in combination with pembrolizumab or dabrafenib/trametinib compared to pembrolizumab or dabrafenib/trametinib alone, in patients with melanoma. Axl has been linked with both a reduced response to PD-1 blockade and therapy resistance to BRAF directed therapies in melanoma. Bemcentinib is a first-in-class, orally bioavailable, highly selective Axl-inhibitor. BGBIL006 (NCT02872259) was designed to explore whether combinations with bemcentinib are safe and improve overall response rate (ORR) and duration of response. Patients were enrolled between 2017 and 2022. A daily dose of 200 mg Bem was well tolerated in combination with Pem or D/T. Most frequent Bem-related adverse effects were rash, diarrhea, fatigue and increased transaminases. Significant differences in ORR, PFS or OS were not observed between standard treatments and the combinations with Bem. In analyses of baseline biomarkers, the group did not identify subgroups of patients with increased response to combinations with Bem. The following biomarkers predicted improved response to Pem; high CD8+ count high FOXP3 count, high PD-L1 in TIL, high AXL expression in inflammatory cells.

2. Clinical trial II. A national, multicenter, interventional study of ipilimumab in patients with unresectable or metastatic melanoma (IPI4). Ipilimumab was the first immune checkpoint inhibitor to show overall survival efficacy in melanoma. The drug is expensive and is associated with severe adverse effects. Thus, predictive markers for response are needed. The aim of this project is to identify predictive markers of response to ipilimumab in metastatic melanoma. The IPI-4 prospective trial represents the longest reported follow-up of a real-world melanoma population treated with ipilimumab and was recently published. The group has now collected tissue samples from primary tumors and pre-treatment metastatic biopsies and started analyzing the material for predictive markers.

3. Clinical trial III. Efficacy of bevacizumab monotherapy in treatment of metastatic melanoma and predictive value of angiogenic markers. Anti-angiogenic treatments, such as bevacizumab, are widely in use. Still, predictive markers of response are lacking. The aim of this project is to identify predictive markers of response to bevacizumab in metastatic melanoma. This clinical trial has produced several papers describing predictive markers of response. So far, no markers have been regarded as strong enough to move forward to validation. β2-adrenergic signaling is a stress response mechanism that impacts numerous hallmarks of cancer. To the best of our knowledge, the Straume group is the first to show the correlation between strong expression of β2-adrenergic receptor and clinical benefit from bevacizumab.

4. Tumor dormancy project. Importance of physical trauma on time to recurrence after primary treatment of breast cancer. There is evidence to suggest that late recurrences in some tumor types, such as breast cancer, are synchronized and accelerated by systemic signaling in the body. The project is based on the hypothesis that dormant micrometastases can initiate tumor growth following a systemic burst of growth factors after surgery or trauma. By analyzing patient series as well as blood samples from patients undergoing different types of breast surgery or experiencing complications after surgery, the group aims to identify the relation between systemic growth factor signaling and activation of dormant micrometastases. The group has published results confirming a significant correlation between time of surgery, extent of surgery and changes in the recurrence dynamics in breast cancer patients. They have further quantified surgical complications occurring after breast reconstructions in breast cancer patients and show a significant change in recurrence dynamics in patients that experience complications.

Most important results
• Bemcentinib can be safely given to patients in combination with both immune checkpoint inhibitors as well as BRAF/MEK inhibitors.



• The combination of bemcentinib with immune checkpoint inhibitors or BRAF/MEK inhibitors does not increase response rates of survival in patients with metastatic melanoma.

• The quantification of FoxP3 positive regulatory T-Cells in pre-treatment biopsies is potentially a strong predictive marker of response to pembrolizumab.

• Circulating tumor DNA collected in liquid biopsies can provide prognostic information in melanoma patients treated with bevacizumab.

• There is a significant correlation between time of surgery, extent of surgery and changes in the recurrence dynamics in breast cancer patients.

• An augmented stimulating effect on relapse dynamics in patients experiencing complications in the perioperative period as well as in obese patients is demonstrated.

Most important papers

1. Schuster C et al. Beta2-adrenergic receptor expression in patients receiving bevacizumab therapy for metastatic melanoma. *Cancer Med.* 2023. PMID: 37551424.

2. Aamdal E et al. Ipilimumab in a real-world population: A prospective Phase IV trial with long-term follow-up. *Int J Cancer.* 2022. PMID: 34449877.

3. Jansen YJL et al. Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma. *Ann Oncol.* 2019. PMID: 30923820.

4. Forthun RB et al. ctDNA detected by ddPCR reveals changes in tumour load in metastatic malignant melanoma treated with bevacizumab. *Scientific Rep.* 2019. PMID: 31767937.

5.Dillekas H et al. Are 90% of deaths from cancer caused by metastases? *Cancer Med.* 2019. PMID: 31397113.

6. Haaland GS et al. Association of Warfarin Use with Lower Overall Cancer Incidence Among Patients Older Than 50 Years. *Jama Intern Med.* 2017. PMID: 29114736.

7. Dillekas H et al. The recurrence pattern following delayed breast reconstruction after mastectomy for breast cancer suggests a systemic effect of surgery on occult dormant micrometastases. *Breast Cancer Res Tr.* 2016. PMID: 27306422.

Translational, clinical and societal importance

The finding of a negative prognostic role of complications following surgery might be of significant clinical importance, and it adds to the hypothesis that systemic signaling after tissue insult might influence pre-existing dormant occult metastases. The cost-effectiveness analysis of the group's proposed candidates of predictive biomarkers may become part of the total package of validation analyses that we do when assessing the value of new biomarkers, and thus have societal impact.

CCBIO significance

CCBIO has greatly facilitated multidisciplinary collaboration across the different programs between our group and other groups associated with CCBIO. The scientific environment provided by CCBIO has been inspirational and has challenged our group members to think outside the box to find new ways of using biological knowledge and find novel targets for therapy. Also, being part of CCBIO has been beneficial when applying for grants.

Future perspectives

The group is currently establishing infrastructure and group competence to perform state-of-the art methodologies and computational approaches to maximize the impact of biopsy samples obtained from patients participating in clinical trials and to define a new precision medicine approach to improve immunotherapy efficacy for melanoma patients. In addition, they are planning new projects focusing on adaptive mutability as a universal stress response caused by cancer treatment, driving tumor cell heterogeneity and resistance. ••


VARIA



Team 4

ethics, economics and priorities

The aim of this program is to perform studies on the ethics, economics, philosophy and priority challenges in the biomarker field, to contribute to improved education of CCBIO scientists in this dimension of their work including increased self-reflection, and ultimately to influence the public debate and policy making in the expanding area of biomarkers and precision treatment. This team consists of PIs Cairns, Norheim and Strand (chair of this team).





T4

Roger Strand

ethical, legal and societal aspects (elsa) group

Short bio
Roger Strand is professor at the Centre for the Study of the Sciences and the Humanities (UiB); dr. scient in biochemistry (1998); adjunct professor in responsible research and innovation, Centre for Digital Life Norway, NTNU; and co-director of the European Centre for Governance in Complexity.

Brief group presentation and history
This research group was formed with the purpose of creating an interdisciplinary environment within CCBIO to study ethical, legal and societal aspects (ELSA) of contemporary cancer research. With its home at the Centre for the Study of the Sciences and the Humanities (SVT) at the UiB, it originated from, co-existed and acted in synergy with the larger research group at SVT dedicated to responsible research and innovation and anchored in science and technology studies (STS) and philosophy of science. The group has had two main members throughout CCBIO's existence (Anne Blanchard and PI Roger Strand) as well as two PhD candidates (Eirik Tranvåg and Karen Gissum, both in collaboration with other groups). In the second half of CCBIO's 10-year period, the group was strengthened with Adjunct Professor Marta Bertolaso (Campus Biomedico, Rome). In addition, Ina H. Nygaard, Karoline Huse, Irmelin W. Nilsen and Mille S. Stenmarck have been assistant and/or student members of the group.

Research focus
Strand's group has performed research on the ethical, legal and societal aspects (ELSA) of CCBIO's research, distinguishing between two interrelated goals:

1. A better understanding of the developments, expectations, and imaginaries of personalized/precision cancer medicine, including its political economy and ethical and social issues.

2. A better integration of this understanding into practices of "responsible cancer research" in the sense of RRI (Responsible Research and Innovation).

Subprojects
The ELSA group of CCBIO was a small-scale operation that can be seen as one project. They interacted and were tightly linked, however, to several similar RRI projects funded by Horizon 2020 (HEIRRI, TRANSFORM and SuperMoRRI) and the Research Council of Norway (AFINO, Res Publica and ARINA, as well as a number of biotechnology projects with similar ELSA/RRI work packages). They furthermore performed a joint program on the opportunities and challenges of precision cancer medicine with a team of CCBIO ethicists, economists, and biomedical researchers. A particular focus the latter years was the further development of the interdisciplinary research with Bjørge's group, and specifically Karen Gissum's PhD project that integrates dimensions from ELSA and hermeneutical health research into clinical research on ovarian cancer.

Most important results
Strand's group builds insights and intellectual understanding (for peers) and ELSA/RRI awareness, within the consortium and its partners and audiences. The highlight of the group's achievements was the publication of their interdisciplinary research anthology "Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern", edited by Anne Blanchard and Roger Strand and with 17 contributors from the CCBIO ELSA network. The key focus of the publication is the interdisciplinary analysis of the sociotechnical imaginaries of personalized and precision cancer medicine. In general, it can be said that the book elaborated a set of *re-framings* of cancer, drawing on complexity theory, medical philosophy, Daoist philosophy, science and technology studies, post-normal science, and health technology assessment. In this way, the group documented and analyzed ethical and epistemological shortcomings of dominant imaginaries of precision cancer medicine, notably how they rely on overly reductionist understandings of illness and disease and accordingly result in unrealistic promises. By June 2024, the open access e-book version had registered >35k downloads.

Most important papers
1. Blanchard & R. Strand (eds) (2017). Cancer Biomarkers: Ethics, Economy and Society. Megaloceros Press, 148p. https://doi.org/10.24994/2018/b.biomarkers

2. Bremer & R. Strand (eds) (2022). Precision Oncology and Cancer Biomarkers. Issues at Stake and Matters of Concern. Springer, 281p. https://doi.org/10.1007/978-3-030-92612-0

3. T. Völker, R. Slaattelid & R. Strand (2023). Translations of Responsibility. Routledge, 242p. https://doi.org/10.4324/9781003371229

4. MS. Stenmarck, C. Engen & R. Strand (2021). Reframing cancer: challenging the discourse on cancer and cancer drugs — a Norwegian perspective. *BMC Med Ethics* 22, 126. https://doi.org/10.1186/s12910-021-00693-5

5. Blanchard (2016). Mapping ethical and social aspects of cancer biomarkers. *New Biotechnology*, 33(6), 763–772. https://doi.org/10.1016/j.nbt.2016.06.1458

Translational, clinical and societal importance
One of the group's aims was to create a level of ELSA and RRI awareness in CCBIO as such, and to have made a difference on how cancer biomarker research is and will be performed at the University of Bergen. Indeed, it has become an important part of the very identity of CCBIO to maintain considerable diversity, including a multi- and interdisciplinarity that reaches into the social sciences and



the humanities. The focus on ELSA and RRI has been unique to CCBIO as a cancer research center, and has been implemented in other CCBIO activities, such as in a PhD level course, the CCBIO Annual Symposium and in other scientific meetings. Hence, one profound societal impact of CCBIO is the creation of a new generation of scientists with a broad, interdisciplinary outlook that readily combine multivariate molecular information with clinical perspectives, and with economic, ethical, sociological, and philosophical perspectives. This was achieved through the continuous efforts of the ELSA group.

Other important outputs and achievements

One important output from the group has been organizing the PhD level course CCBIO903, Cancer research: Ethical, economic and social aspects. This course has focused on ethical, economical and societal aspects of cancer and cancer research and has given the PhD candidates the tools for systematic reflection on their own and related research as well as methods for assessing the cost benefit of health measures and methods of treatment. The course has focused on aspects such as how to assess the cost-effectiveness of cancer biomarkers, how to make medical decisions when surrounded by risks, uncertainties and even ignorance, what the "good life" can actually mean, and what the future may hold for cancer research. Since the first course in 2015, CCBIO903 has given the young MDs and PhDs a theoretical platform for the difficult decisions they would need to make in their future.

CCBIO significance

Our ELSA research activities on cancer biomarker research and imaginaries of personalized and precision cancer medicine would not have existed without CCBIO. CCBIO has provided both the occasion, substrate, intellectual environment and funding for this research.

Future perspectives

The ELSA group of CCBIO has largely achieved its goals. They are in the phase of translating their work in CCBIO into contributions to the wider field of RRI and governance of science, in a set of publications in 2024/2025. It is also important for the group to take part in the overall endeavor for CCBIO to summarize, analyze and synthesize the accumulated scientific progress that CCBIO has led to over its 10 years of existence. ••





John Cairns

the health economics group

Short bio
John Cairns is Professor of Health Economics at the London School of Hygiene & Tropical Medicine (since 2004) and adjunct professor and PI at CCBIO (since 2013).

Brief group presentation and history
The work on the economics of cancer biomarkers started in 2013 with Professor Oddvar Kaarboe (UiB) and Cairns developing an economic model of the relationship between the developers of cancer biomarkers and drug manufacturers. In 2015, Mikyung Kelly Seo and Ana Beatriz Mateus D'Avó Luís were recruited to PhD positions, Kelly based in the LSHTM and Beatriz in the UiB. Jiyeon Kang, also based in the LSHTM, joined in 2018.

Research focus
Health economics in CCBIO started with a dual focus on the economic evaluation of cancer biomarkers and on understanding the incentives to combine biomarkers with patented medicines. Over time, the emphasis has increasingly been on obtaining a better understanding of the cost-effectiveness of cancer biomarkers and of decision making regarding the adoption of new cancer therapies. Particular attention has been paid to the evaluation methods used and the contribution of different types of data (such as health outcomes recorded in clinical trials and real-world data).

Subprojects
1. How cancer biomarkers change the cost-effectiveness of different therapies.
Seo was awarded her PhD by LSHTM in 2020 for her thesis titled "Economic evaluations of companion cancer biomarkers for targeted therapies", supervised by Cairns and Jan Erik Askildsen (UiB). Seo reviewed methodological approaches and biomarker characteristics considered in existing economic evaluations and conducted a cost-effectiveness analysis of a novel biomarker (HSP27 expression). She also developed a practical guide to modeling the cost-effectiveness of companion biomarker tests.

Cancer biomarkers for targeted therapies in mCRC improve the cost-effectiveness of targeted therapies. However, this does not ensure that the therapies themselves are cost-effective. While companion biomarkers reduce therapy costs, the savings are not necessarily sufficient to make these treatments cost-effective. The studies that evaluate biomarkers have often restricted attention to the cost of tests and do not always consider the characteristics of the test or the prevalence of the marker.

2. 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.
This work took place in cooperation with the Bergen Centre for Competition Law and Economics (BECCLE). The thesis by D'Avó Luís titled "Essays on Economic Incentives and Implications of Biomarker Tests" (supervised by Tommy Staahl Gabrielsen and Julie Riise, UiB) was successfully defended in early 2021.

3. Use of real-world data in the appraisal of oncology drugs.
Kang was awarded her PhD (at LSHTM) titled "Improving economic evaluation and decision-making for oncology drugs using real-world data" in January 2023. She built a unique database of 229 oncology appraisals undertaken by the UK-based National Institute for Health and Care Excellence (NICE) during 2011–2021, drawing on the evidence submission made by manufacturers, the independent report of the Evidence Review Group, and the final guidance issued by the Appraisal Committee. Her thesis included papers detailing how real-world data has been used to inform decision making, testing a series of hypotheses regarding the use and acceptability of real-world data in NICE appraisals, and an analysis comparing the use of data in appraisals of targeted cancer therapies and non-targeted cancer therapies.

The identification and analysis of the limited role played by real-world data in actual appraisals of oncology medicines, in contrast to the widespread enthusiasm for increased use of real-world data, is an important output from this research. Also, the group is making progress in understanding how decision-making processes regarding the adoption of new health technologies and the economic evaluations of cancer drugs interact.

4. Use of health economic information to inform healthcare decision-making.
The final subproject led by Cairns focused particularly on the adoption of new health technologies. This included a study of how molecular targeted therapies and immune checkpoint inhibitors for the treatment of non-small cell lung cancer have been assessed. Clear differences were observed between the appraisal of checkpoint inhibitors and that of molecular targeted therapies, at least in the context of non-small cell cancers, deriving from the more limited clinical data and the more restricted application of targeted medicines.

Most important results
The cost-effectiveness of biomarker-guided therapies was more likely to be driven by the characteristics of corresponding drugs rather than those of companion cancer biomarkers. Although, one interesting finding was how inadequately the impact of the performance characteristics of cancer biomarkers on cost-effectiveness has been studied.

D'Avó Luis and Seo collaborated on a paper assessing the impact of cancer biomarkers on health outcomes in Norway. Their results suggest that biomarker tests improve health by



ensuring that the right treatment is given to the right patient and that the effect is stronger for cancer types for which fewer drugs are available.

Managed Access Agreements are increasingly being used to improve access to treatments where the evidence of clinical effectiveness is too uncertain to recommend routine commissioning. The Cancer Drugs Fund [CDF] in England provides drugs for several years while additional data are collected before a final review of the drug takes place. An analysis of the first twenty-four drugs to exit the CDF highlighted the important role played by longer follow-up of patients in the original clinical trials used to support the introduction of these drugs and the very limited role played by the data collected from patients receiving the drugs provided through the CDF.

Most important papers

1. Seo MK, Cairns J. How are we evaluating the cost-effectiveness of companion biomarkers for targeted cancer therapies? A systematic review. *BMC Cancer* 2021. PMID: 34470603.

2. D'Avó Luis AB, Seo MK. Has the development of cancer biomarkers to guide treatment improved health outcomes? *European Journal of Health Economics* 2021. PMID: 33783662.

3. Cairns, JA. Assessing the Cost-Effectiveness of Molecular Targeted Therapies and Immune Checkpoint Inhibitors. In: Bremer, A., Strand, R. (eds) *Precision Oncology and Cancer Biomarkers*. Human Perspectives in Health Sciences and Technology, vol 5. Springer, Cham, 2022. doi.org/10.1007/978-3-030-92612-0_11

4. Kang J, Cairns J. "Don't Think Twice, It's All Right": Using Additional Data to Reduce Uncertainty Regarding Oncologic Drugs Provided Through Managed Access Agreements in England. *Pharmacoeconomics – Open* 2023. PMID: 36123583.

5. Kang J, Cairns J. Cross-sectional analysis of use of real-world data in single technology appraisals of oncologic medicine by the National Institute for Health and Care Excellence in 2011–2021. *BMJ Open* 2024. PMID: 38485485.

CCBIO significance

Health economics is an integral part of the Ethics, Economics and ELSA Research in CCBIO. Being part of CCBIO has provided support for three PhD students to research different aspects of the economics of cancer biomarkers and has facilitated greater focus on the economic evaluation of cancer therapies. Cairns collaborated successfully to provide the CCBIO903 course *Cancer Research – Ethical, Economic and Social Aspects* in 2015, 2016, 2018, 2019 and 2021, as part of the CCBIO Research School for Cancer Studies. Cairns finds it was stimulating to develop health economics teaching for non-economists, with CCBIO colleagues who are experts in the broader issues underlying cancer research. The Cairns group also contributed four chapters to *Cancer Biomarkers: Ethics, Economics and Society* (ed. Blanchard & Strand), and *Precision Oncology and Cancer Biomarkers* (ed. Bremer & Strand). Being part of CCBIO provided repeated opportunities to discuss important economic issues with CCBIO colleagues coming from quite different disciplinary backgrounds.

Future perspectives

Future work will involve further analysis of the rich oncology drug database, particularly focusing on the maturity of overall survival data and its impact on economic evaluation and decision making. It is planned to extend the work on molecular targeted therapies and immune checkpoint inhibitors from non-small cell lung cancer to all cancers where these treatments have been introduced. ••


CCBIO



Ole Frithjof Norheim

the bergen centre for ethics and priority setting in health (BCEPS)

Short bio
Ole F. Norheim is an MD (University of Bergen, 1991), Dr. Med. (University of Oslo, 1998) and a professor of medical ethics and philosophy of science at the Department of Global Public Health and Primary Care, University of Bergen (UiB). He currently directs the Bergen Center for Ethics and Priority Setting in Health at UiB and has been affiliated to CCBIO since 2016. Norheim is also an adjunct professor of global health at the Department of Global Health and Population, Harvard TH Chan School of Public Health (2015–2024).

Norheim's research interests include priority setting in health, high-cost medical care, ethical theories of distributive justice, inequality in health, and how to achieve Universal Health Coverage and the Sustainable Development Goal for health in low- and middle-income countries.

Norheim served as Head of the Norwegian Biotechnology Advisory Board (2019–2023) and has chaired the World Health Organization's Consultative Group on Equity and Universal Health Coverage (2012–2014) as well as the third Norwegian National Committee on Priority Setting in Health Care (2013–2014). In Norway, Norheim has contributed regularly with op-eds in national newspapers, often giving interviews in radio, television and podcasts.

Brief group presentation and history
Norheim's research group was established in 2009 under the name "Research Group for Global Health Priorities" in 2009. The Bergen Centre for Ethics and Priority Setting was established in 2019 with support from the Trond Mohn Foundation, Norad, and the University of Bergen.

A key theme for BCEPS throughout this period has been how to set priorities for high-cost medicine in the era of precision medicine. In close collaboration with CCBIO's ELSA team (research on the ethical, legal and social aspects of cancer biomarkers, led by Prof. Roger Strand) and the health economist John Cairns, BCEPS has worked on issues related to health technology assessment and the ethics priority setting for new cancer therapies.

Research focus
BCEPS aims to explore and promote ethically acceptable, fair and efficient priority setting in health. The main research questions relate to how cancer biomarkers can inform and improve health care priority setting. First, how is our ethical thinking about treating people as equals challenged when biomarkers and other individual characteristics stratify patients into smaller and smaller sub-groups, creating a weaker evidence base for deciding who should be offered new and potentially life-saving treatments, and second, how to define severity of disease, especially for cancer drugs.

The third Norwegian National Committee on Priority Setting in Health Care (2014), appointed by the government, promoted a value framework that combines efficiency and fairness through a new definition of the worse off in health: those with the most severe conditions measured as absolute QALY shortfall. This innovation, first implemented in Norway's publicly funded health care system — where cost-effectiveness thresholds are modified by severity of disease — was also (in 2022) adopted by the National Institute for Health and Care Excellence (NICE) in the UK. Giving additional weight to health benefits in the most severe conditions allows for more equitable access to treatment. This also allows for unequal treatment when severity of disease differs.

Subprojects
Eirik Joakim Tranvåg's PhD project "Precision and Uncertainty: Cancer biomarkers and new perspectives on fairness in priority setting", with Ole Frithjof Norheim and Roger Strand as supervisors, was the main subproject in Norheim's CCBIO team. Tranvåg successfully defended his thesis in September 2021.

A second subproject (also part of Tranvåg's thesis) was on cost-effectiveness, severity of disease, cancer drugs and reimbursement policies in Norway. In this subproject, Tranvåg and colleagues were able to study confidential drug price information used for drug appraisals and coverage decisions in Norway. They explored how drug coverage decisions within the Norwegian specialist health sector were made and assessed whether they were in accordance with the decided principles of cost-effectiveness and fair distribution of health outcomes.

Most important results
• Together with the promise of precision oncology comes uncertainty about evidence. Part of this uncertainty can be averted, but much of it is linked to fundamental methodological features.

• Precision oncology and cancer biomarkers appear to be well integrated in the Norwegian priority setting system, but there are also fundamental concerns about how fairness can be ensured in priority setting as uncertainty increases.

• Increasing uncertainty calls for a wider perspective on fairness than currently reflected in the priority setting practice. A stronger emphasis on procedural aspects of fairness would give a more robust and fair priority setting system.

• The study on cost-effectiveness, severity of disease, and cancer drugs demonstrated how concerns for efficiency and fair distribution of health can be implemented systematically into drug appraisals and reimbursement decisions. New, expensive drugs are expected to escalate health care costs in the years to come, and it may be feasible

to control costs by negotiating the prices of new drugs while appraising both their cost-effectiveness and how their health benefits are distributed.

Most important papers

1. Tranvåg EJ et al. Appraising Drugs Based on Cost-effectiveness and Severity of Disease in Norwegian Drug Coverage Decisions. *JAMA Netw Open* 2022. PMID: 35767256.

2. Tranvåg EJ et al. Rationing of Personalised Cancer Drugs: Rethinking the Co-production of Evidence and Priority Setting Practices. In A. Bremer, R. Strand (eds.), *Precision Oncology and Cancer Biomarkers*, Human Perspectives in Health Sciences and Technology 5, https://doi.org/10.1007/978-3-030-92612-0_14.

3. Tranvåg EJ et al. Precision medicine and the principle of equal treatment: a conjoint analysis. *BMC Med Ethics* 2021. PMID: 33971875.

4. Tranvåg EJ et al. Clinical decision making in cancer care: a review of current and future roles of patient age. *BMC Cancer* 2018. PMID: 29743048.

5. Hernæs UJV et al. Distribution-Weighted Cost-Effectiveness Analysis Using Lifetime Health Loss. *Pharmacoeconomics*. 2017. PMID: 28625004.

Translational, clinical and societal importance

The study on cost-effectiveness, severity of disease, and cancer drugs demonstrated that cost-effectiveness and severity of disease are systematically implemented and used in appraisals and that the Norwegian method may be a feasible strategy to control rising drug prices. The article was important for Norwegian health policy discussions and received considerable media attention when published.

Tranvåg's work, with Roger Strand, on promoting the procedural aspects of priority setting was recognized by his invitation to be a member of a government appointed expert group advising on "Trust in priorities — increased transparency, participation and competence", led by BCEPS Professor Ingrid Miljeteig.

Other important outputs and achievements

• After completing his PhD, Tranvåg now works as a senior advisor in The Norwegian Biotechnology Advisory Board, with responsibility for personalized medicine, bioethics and other relevant themes for biotechnology and ethics.

• Norheim became an elected member of Norwegian Academy of Science and Letters in 2021.

• In 2022, BCEPS was granted Centre of Excellence status (SFF) by the Norwegian Research Council.

CCBIO significance

Being part of a center where skilled and motivated researchers from diverse backgrounds convene and collaborate has proven to be highly productive. Within the ELSA group and CCBIO at large, the exchange of experiences and knowledge has greatly benefitted the BCEPS team. Additionally, CCBIO's dedication, commitment, and willingness to invest in young researchers have been exceptional. The experience gained from CCBIO, and the acquisition of leadership skills have been pivotal for BCEPS in its transition into a Centre of Excellence.



Future perspectives

BCEPS will continue to explore ethical frameworks and methods for fair and efficient priority setting. Of particular relevance is the ongoing project, led by Norheim and Audun Brendbekken, on high-cost therapies and priority setting, with a focus on orphan drugs against rare diseases. The project applies both qualitative and quantitative methods in following orphan drugs from public deliberation to clinical rationing. Priority-setting is challenged by the high cost and long-term evidence uncertainty of orphan drugs. The aim is to gain knowledge on public preferences for orphan drugs and on the mechanisms for clinical rationing of orphan drugs. Findings will add to literature gaps and be relevant to clinicians, decision-makers, and patients. ••





Inge Jonassen

translational bioinformatics group

Short bio

Inge Jonassen is a professor of informatics at the University of Bergen (UiB), and since 2021 he is the Head of the Department of Informatics. Jonassen obtained his PhD from the UiB in 1996 and has since 2002 been a full professor at the same university. Jonassen's research field is bioinformatics where he performs research into development of algorithms and tools, and he contributes to collaborative projects towards marine biology, ecology and medicine. He has been central in building the Computational Biology Unit (CBU), a research center at the UiB, and a national research infrastructure for bioinformatics, since 2014 having status as a national node of the pan-European research infrastructure ELIXIR, an ESFRI landmark. Jonassen was central in building the NORBIS national research school for bioinformatics and Digital Life Norway, a national center for research and innovation in biotechnology. Jonassen is member of the portfolio board for groundbreaking research at the Research Council of Norway, scientific delegate to the board of the European Molecular Biology Laboratorium (EMBL), member of the board of ELIXIR, and member of the Norwegian Academy of Science and Letters and the Norwegian Academy of Technological Sciences.

Brief group presentation and history

The Jonassen group was established around 1997 when Jonassen joined the University of Bergen as associate professor in bioinformatics. When the Computational Biology Unit was formed in 2002, Jonassen, as the head of CBU, moved his group to this unit. CBU was formally organized as part of Unifob/Uni until 2013 when it moved to the University of Bergen and became hosted by the Department of Informatics. Jonassen has been part of CCBIO as an associate investigator since the launch of CCBIO in 2013.

Research focus

The group has developed algorithms and tools for analysis of molecular biology data including DNA and protein sequences, protein structure, gene expression and genotyping data, single-cell data including CyToF and Imaging Mass Cytometry data. The contributions from the group include seminal work in automatic discovery of motifs in biological sequences and structures, algorithms and tools for analysis of microarray and RNA-seq data and for discovery and analysis of genomic variants. The group has been active in collaborative projects pursuing a variety of research questions in basic biology, ecology and medical sciences. The group has applied and developed statistical and machine learning methods along with techniques from knowledge representation and graph algorithms to help find patterns and regularities in molecular biology data. Within the cancer field, Jonassen has developed innovative algorithms and tools to help identify biomarkers in the form of gene and protein expression patterns linked with cancer sub-types, prognosis, and response to medication.

Subprojects

1. Disentangling cell type composition from bulk tumor gene expression data.

In expression studies where gene expression is measured in samples from the tumor microenvironment, differences in expression between samples from different patients may arise from difference in cell type composition from sample to sample. The Jonassen group developed and applied a novel computational method to perform deconvolution of expression data (Dimitrakopoulou et al., *BMC Bioinformatics* 2018).

2. Using single cell to predict response to treatment of acute myeloid leukemia (AML).

In an ERA-PerMed project AML_PM (coordinated by Jonassen), the group developed novel ways to utilize machine learning and systems biology modeling to help predict treatment response of individual patients. In one publication resulting from this (Tislevoll et al., *Nature Commun* 2023), they found that reduction of certain molecules (ERK 1/2 and phosphorylation) is a predictor of patient 5-year overall survival in this cohort.

3. Computational analysis of spatial data on cancer tissue microenvironments.

In order to understand spatial organization of tissue microenvironments and the interactions between different cell types, their internal state, and use this to help select treatment for individual patients, one can utilize imaging mass cytometry technology, such the Hyperion Imaging System. The Jonassen group developed novel methods to analyze such datasets using a graph-based representation of tissue images to describe features of the cellular organization and introduced novel utilities that can be used for data-driven patient-risk stratification (Ehsani et al., *Bioinformatics Advances* 2023).

Most important papers

1. Dimitrakopoulou K et al. Deblender: a semi−/unsupervised multi-operational computational method for complete deconvolution of expression data from heterogeneous samples. *BMC Bioinformatics* 2018. PMID: 30404611.

2. Tislevoll BS et al. Early response evaluation by single cell signaling profiling in acute myeloid leukemia. *Nat Commun.* 2023. PMID: 36611026.

3. Ehsani R et al. LOCATOR: feature extraction and spatial analysis of the cancer tissue microenvironment using mass cytometry imaging technologies. *Bioinform Adv.* 2023. PMID: 37881170.

Translational, clinical and societal importance

In context of CCBIO, the Jonassen group has focused on development and use of novel computational methods translating molecular level data for understanding tumors



and their microenvironment, the variation between patients, and patterns linked with prognosis, cancer subtypes, and treatment response. During the CCBIO project period, the Jonassen group has worked with analysis of high-throughput data derived from single cells and from bulk tissue. For bulk tissue, a key question is how each sample is composed in terms of cell types since expression differences observed between samples could be largely the result of variation in cell type composition rather than differences in gene expression in tumor cells or in specific immune cells. To help disentangle the data, the group developed a computational method called *Deblender* for de-convolution of gene expression data and estimation of cell type proportions across a set of samples. In practice, Deblender and other computational methods have shortcomings, and with new technology becoming available, the group rather focused on analyzing data obtained for single cells directly. In collaboration with the Gjertsen group and others, they developed methods for analyzing CyToF data and applied these to leukemia samples. They also obtained additional European funding to pursue a personalized medicine project aimed at integrating systems biology and machine learning methods to help tailor treatment of individual patients. One result was published in *Nature Communications* and was highlighted in the news on national television — demonstrating how CyToF data derived short time after treatment could help predict longer-term treatment response. In another line of investigations, for solid tumors focusing first on breast cancer, they worked with the Akslen group on analysis of imaging mass cytometry data obtained using the Hyperion Imaging System and published the *LOCATOR* method for analyzing such type of data. This shows promise for use of spatial protein level data to understand tumor microenvironments and develop novel types of biomarkers.

The methods development of the Jonassen group lays the foundation for deriving novel insights across cancer types and improves the knowledge basis for CCBIO researchers to plan experimental and computational approaches towards improved understanding of tumor biology and improved patient treatment.

CCBIO significance

For the Jonassen group, being part of CCBIO has been important in providing long-term tight collaboration with experimental cancer groups applying novel methods for data production presenting computational challenges and opportunities. It has also meant access to novel data and possibilities for experimental validation of computational findings and of publishing in venues requiring such validation. Being linked with CCBIO has also been important to help inform research infrastructure work in context of ELIXIR Norway, which has been under Jonassen's leadership during most of the CCBIO CoE period.

Future perspectives

With rapid advancements in technologies enabling new data generation and within artificial intelligence during recent years, we now see new opportunities on the computational side. For example, it may be possible to utilize AlphaFold generated models combined with novel imaging technologies to zoom further into molecules and systems playing central roles in cancer development. Furthermore, it may be possible to combine single cell methods with structure models and imaging data to develop novel drug leads and biomarkers. ••





international faculty

The CCBIO International Faculty consists of internationally high-ranking scientists within relevant fields of cancer research. Most of them have 10% adjunct professor or researcher positions at CCBIO. The early establishment of such firm collaborative ties has increased CCBIO's ability to perform cutting-edge research by conducting joint projects, facilitating the transfer of knowledge, and by receiving high-level strategic advice and support. This has successfully strengthened CCBIO's collaborative networks as well as its research. Another important aim has been to enable CCBIO's Research School to organize research-based courses at the highest level and to enable co-supervision and exchange of PhD candidates and postdoctoral fellows.

The International Faculty network was formally established in 2016, and most members have served from then until now, except for Ritva Heljasvaara (2016–2021), Jeffrey Pollard† (2021–2023), Thorsten Schlomm (2016–2017), and Carina Strell (2021–2022). Strell was recruited to CCBIO as a fulltime PI in 2022. Arne Östman and Jean Paul Thiery were recruited in 2015, and Marta Bertolaso in 2020.

In 2023, CCBIO's International Faculty numbered 13 affiliated investigators, and CCBIO clearly feels that this unique group has strongly supported the center's many activities and efforts.



Frédéric Amant

Frédéric Amant, PhD and MD, received his medical degree from the University of Leuven (KU Leuven), Belgium in 1992, completed his specialty training in obstetrics & gynecology in 1998, and his subspecialty training in gynecologic oncology in 2000. He is currently a specialist at the University Hospitals Leuven, full professor at the Faculty of Medicine, Catholic University Leuven, full professor at the Faculty of Medicine, University of Amsterdam, the Netherlands, honorary professor at University of Pretoria, South-Africa, head of the Scientific Unit of Gynecologic Oncology, Catholic University Leuven, head of the Scientific Unit of Gynecologic Oncology, Netherlands Cancer Institute, Amsterdam, and council member of the European Society of Gynecological Oncology. In Leuven he heads the scientific research section of his specialty.

Research interests and important results

Frédéric Amant's research focuses on rare women's cancer conditions thereby covering 2 main programs, i.e. research on (i) cancer in pregnancy and (ii) mechanisms of drivers and resistance in (rare) gynecological cancers. This research relies on clinical studies as well as on a unique series of patient-derived models of gynecological cancers. Together, the investigator-driven research programs converge into the overarching aim to translate cutting-edge research data into clinical benefit for patients suffering from these conditions.

To spearhead research on the rare condition of a cancer diagnosed in pregnancy, Frédéric Amant established the International Network on Cancer, Infertility and Pregnancy (INCIP; www.cancerinpregancy.org), now being the world's only international registry of its kind and harboring unique data and biomaterials from >3.000 pregnant cancer patients. Frédéric Amant's INCIP-embedded studies have led to the development of novel treatment guidelines and a major paradigm shift in the management of pregnant cancer patients. This has positioned him as the world's leading expert for cancer-in-pregnancy research. Very recently, his team developed a web-based software (Advisory Board Cancer Infertility Pregnancy, coined AB-CIP; www.ab-cip.org) to offer remote and free multidisciplinary support to physicians that lack expertise to manage pregnant cancer patients, which is envisioned to enable further distribution of knowledge worldwide.

Amant is driven by the need to address urgent clinical questions related to the treatment management of patients affected by (rare) gynecological cancers. His thesis on uterine sarcomas was the first in a lab previously focused on diabetes and endometriosis, and he started a new oncology-related theme which led to the creation, within the department of Oncology at Catholic University Leuven, of the Gynecological Oncology unit, which he successfully leads since 2005.

As a gynecologist oncologist, he dedicated his research activities to the study of (rare) cancers in women, focusing on difficult to treat/rare gynecological tumors. To increase the translatability potential of the findings obtained in the lab, Frédéric Amant invested and will continue to devote resources in developing new patient-derived preclinical models, both *in vitro* (organoids and explant cultures) and *in vivo* (xenograft models), as he did when he in 2012 founded TRACE, the tumor xenograft platform at the Catholic University Leuven.

At Catholic University Leuven, he founded the Fund for Innovative Cancer Research (FIKO), a platform today upgraded as a fundraising unit of the Leuven Cancer Institute (LKI), and he is co-founder of ENITEC, the European Network on Individualized Treatment of Endometrial Cancer.

His position as chair of the working group of rare gynecological cancers at the European Reference Networks-EURACAN allows him to build a unique and cross-border cooperative platform gathering together European specialists and experts for the diagnosis and treatment of (rare) gynecological cancers. Due to the low incidence and the limited (pre-)clinical data available, pharma companies are reluctant to invest resources for studies dedicated to such conditions, despite their high clinical need. This is why he is actively recruiting funding to support investigator-initiated clinical trials aimed at improving the surgical/therapeutic management and the quality of life of patients.



> CCBIO has always been a source of inspiration both on a personal and professional level. The organization should be congratulated for the development of this exciting program which so many researchers benefited from.

Research collaboration with CCBIO

The Amant group contributed enthusiastically to MOMATEC I, a prospective study on endometrial cancer combining serum and endometrial biopsy biomarkers and clinical data. This successful international collaborative study, initiated in Bergen, is a source of valuable new data focusing on predictive markers for lymph node involvement and survival in a large set of patients. Following up on this, his team supported the continuation of this collaboration in the framework of MOMATEC II. This second Bergen initiated study tailors surgical treatment of endometrial cancer based on biomarkers and needs more international support. In addition, the Amant team exchanged their experience with the CCBIO researchers regarding relevant preclinical models, including patient derived xenografts, to validate experiments. Also, PhD students did benefit from this collaboration through exchange programs.

CCBIO significance

CCBIO has always been a source of inspiration both on a personal and professional level. During the annual meetings, the combination of state-of-the-art sessions in combination with a strong focus on junior researchers and PhD students resulted in very interesting discussions in a safe environment. The low threshold for junior researchers to meet experts in the field ultimately contributed to productive science. The MOMATEC program we contributed to is one of the largest European projects in endometrial cancer and changed the way we did research, leading to innovative insights. The program was also ideal to exchange students participating in the same type of research, allowing them to grow personally and scientifically. The organization should be congratulated for the development of this exciting program which so many researchers benefited from. ••



Rameen Beroukhim

Rameen Beroukhim received his AB in Physics in Philosophy at UC and his M.Phil. and PhD from the University of Cambridge as a Churchill Scholar and subsequently a Glaxo Dorothy Hodgkin Scholar. He returned to the United States to receive his MD from UCSF, where he also completed internship and residency in medicine as a molecular medicine fellow. He specialized in medical oncology at the Dana-Farber Cancer Institute/ Massachusetts General Hospital joint fellowship program. At the Dana-Farber Cancer Institute and Broad Institute, he did postdoctoral research in cancer genomics under the mentorship of Bill Sellers and Matthew Meyerson. In addition to running a research laboratory, he sees patients with brain cancers in the Dana-Farber Cancer Institute Center for Neuro-Oncology. He has been part of the faculty at the Dana-Farber Cancer Institute and Harvard Medical School since 2006, currently as an associate professor of medicine. He is also an associate member of the Broad Institute and a member of the Bioinformatics and Integrative Genomics (BIG) Program at Harvard Medical School. He received a V Scholar Award from the V Foundation for Cancer Research, Distinguished Scientist Award from the Sontag Foundation, Team Science Award from the American Association for Cancer Research, and the 2022 "Mentor of the Year" award from the Dana-Farber Postdoctoral and Graduate Student Association. He is also a member of the American Society of Clinical Investigation.

Research interests and important results

Dr. Beroukhim's research interests have been: 1) to understand alterations in chromosome structure across all types of cancer, including how they arise and their consequences on tumor evolution and generating therapeutic dependencies; 2) to apply genomics tools to understand how brain tumors develop, progress through treatment, and might be treated better; and 3) with his collaborators at CCBIO, to understand how endometrial cancers develop, metastasize, and progress through treatment — again, with an interest in how patients might be treated more effectively. He has developed many widely used computational methods to study tumor evolution and has discovered novel oncogenes, tumor suppressor genes, and whole classes of therapeutic dependencies. His work has led to national and international clinical trials and drug discovery platforms in biotechnology and pharmaceutical companies.

Research collaboration with CCBIO

Dr. Beroukim's work with members of CCBIO began when he was a new postdoctoral fellow in 2004 and has focused primarily on using genomics tools to understand endometrial cancer. Together, they published the first large-scale integrated genomic analysis of endometrial cancer, which identified novel prognostic biomarkers and resulted in a therapeutic patent. They conducted the first large-scale genetic analysis of endometrial cancer progression from pre-malignant lesions through metastasis, where they found that different metastases tend to arise from the same tumor subclone — a finding that has since been replicated in other cancers. They are currently working to understand how endometrial cancers gain resistance to the most commonly used therapeutic, carboplatin.

Dr. Beroukhim has attended and given talks at multiple CCBIO retreats, taught CCBIO courses, and have hosted CCBIO scientists in his laboratory including Professor Camilla Krakstad during her sabbatical year, as well as three postdoctoral fellows of Drs. Salvesen and Krakstad as well as one graduate student. One of his laboratory members subsequently moved to join Dr. Krakstad's laboratory within CCBIO. He also deposited a rug from DFCI in Dr. Krakstad's office, unbeknownst to her (and to her great chagrin). He continues to meet with CCBIO members online at least weekly to plan out experiments and interpret their results.

CCBIO significance

My laboratory's focus on endometrial cancer is entirely the result of our collaborations with CCBIO. Our interactions with CCBIO have brought new ideas and blood to our laboratory and has provided my laboratory members with a unique view of science on an international scale. Frankly, my interactions with CCBIO members have been among the most fun parts of my work. I hope to continue to work closely with CCBIO scientists for many years to come! ••



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Our interactions with CCBIO have brought new ideas and blood to our laboratory and has provided my laboratory members with a unique view of science on an international scale.





Marta Bertolaso

Marta Bertolaso is Full Professor of Philosophy of Science and Human Development at University Campus Bio-Medico of Rome, Italy. Her expertise in philosophy of science, scientific practice and ethics, with a strong scientific background, has allowed her to promote and collaborate in interdisciplinary research and educational programs on complex organized systems and human development. After an initial training and experience in the nineties at the National Tumor Institute in Milan (Department of Molecular Biology); at the Department of Anatomical Pathology, San Giovanni Vecchio Hospital, Turin (Italy); and at the Candiolo Cancer Institute (IRCCS), Turin, she concluded a PhD in Bioethics and Philosophy of Science at Campus Bio-Medico of Rome. Additionally, she has been trained in philosophy of life sciences during fellowships at the Department of History and Philosophy of Science, Pittsburgh, PA, USA; at the Konrad Lorenz Institute (KLI) for Evolution and Cognition Research, Klosterneuburg, Vienna, Austria; at Egenis (the Centre for the Study of Life Sciences), University of Exeter (UK); at the Centre of Biomedical Humanities of the Department of Experimental Oncology of IEO, University of Milan; and at the Institute d'Histoire et de Philosophie des Science et des Techniques (IHPST), Paris, France.

Research interests and important results

Professor Bertolaso's expertise in the philosophy of cancer and of scientific practice has allowed her to promote and collaborate in interdisciplinary research and educational projects. She is currently focusing her work on the integral development of adaptive systems and evolutionary processes. Knowledge derived from cancer biology and the relational epistemology that characterize it is becoming relevant also in order to understand better important features of the current ecological and organizational transitions and open new questions about the use of data and digital tools in these scenarios as well. Social impact and emerging educational challenges for sustainable innovation are also the focus of her contribution in institutional and international programs for a sustainable society. Among other commitments, she currently collaborates with the Italian Ministry of Environment and Energy Security (MASE) within the bioeconomy field, she is a full member of the Académie Internationale De Philosophie des Sciences, and board member of the European School of Oncology, Switzerland/Italy. Marta Bertolaso is also Editor in Chief of Springer Series on "Human Perspectives in Health Sciences and Technology" and of the Italian Rubettino Series on "Fattore Umano & Complessità". Since 2006, Marta Bertolaso is Board Director of the Home Renaissance Foundation (London) and member of the Scientific Committee for the Health and Primary Care field.

Research collaboration with CCBIO

Her collaboration with CCBIO relies upon the work she did on cancer research and cancer biology during the last three decades. In particular, she is focusing on the assumptions and epistemological foundations for an adequate identification and implementation of biomarkers for the diagnosis and treatment of cancer. Her aim has been to expand viewpoints, make the most of empirical results and speed up the process toward better therapeutic approaches, and by that possibly bridge the gap between scientific work and theoretical understanding. In collaboration with Roger Strand, she has done epistemological analyses of CCBIO projects and related volumes, seeking a more comprehensive understanding of empirical results from the CCBIO teams. Results from these opportunities following research activities in practice have been collected and mentioned in recent years' publications and in different contexts (academic, policies, cultural, etc.). She has contributed to the CCBIO Annual Symposium and several other CCBIO events, such as the meetings in the INTPART project Bergen-Harvard Cancer Studies: A Partnership for Excellent Education and Research (2019 and 2024), as well as teaching at the CCBIO PhD course CCBIO903, Cancer Research — Ethical, Economic and Social Aspects.

CCBIO significance

Working with young students and researchers has been of particular interest, stimulus and relevance for me, for the overall activity also in developing philosophical reflections on epistemic virtues such as critical thinking, pluralism, contextual decision making, etc. in the scientific practices. Moreover, the interdisciplinary teamwork I have experienced in CCBIO inspired me and one of my collaborators in Rome to promote a spin-off on new therapeutic strategies based on tumor reversion processes with research, regulatory and educational goals. ••

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Jean-Christophe Bourdon

Dr. Jean-Christophe Bourdon obtained his PhD in cellular and molecular biology in 1997 from the Paris XI University, France. He is currently a senior lecturer at the School of Medicine at the University of Dundee, where he leads the p53 laboratory. Previously, he served as co-director of the Inserm-European Associated Laboratory at Toulouse University, France (2006–2010), and at the CNRS-European Associated Laboratory at University de Lorraine, Nancy, France (2012–2018). In 2012, he was awarded a prestigious fellowship from the Breast Cancer Campaign.

Dr. Bourdon is internationally recognized for his pioneering work in the field of p53 isoforms and cancer. His team was the first to demonstrate that the tumor suppressor TP53, the most frequently mutated gene in cancer, expresses at least twelve different isoforms (p53α, p53β, p53γ, Δ40p53α, Δ40p53β, Δ40p53γ, Δ133p53α, Δ133p53β, Δ133p53γ, Δ160p53α, Δ160p53β, Δ160p53γ) through alternative splicing, transcription initiation, and translation initiation. This discovery has significantly impacted cancer research and expanded the scope of the p53 field to include ageing and degenerative diseases.

Research interests and important results

Dr. Bourdon's research interests encompass both fundamental and translational studies. His lab aims to elucidate the molecular mechanisms by which p53 isoforms influence cell fate in response to various cellular signals and treatments. On the translational side, his work focuses on establishing p53 isoforms as predictive biomarkers in cancer and other degenerative diseases and identifying therapeutic compounds targeting p53 isoform pathways.

Notably, Dr. Bourdon's lab demonstrated that the Δ133p53β isoform promotes cancer cell invasion independently of TP53 mutation status and is associated with increased cancer recurrence and mortality in breast cancer patients. This isoform also plays a critical role in epithelial-to-mesenchymal transition (EMT) by promoting global genome epigenetic reprogramming in both wild-type and mutant TP53 contexts.

Additionally, Dr. Bourdon's lab discovered a novel role for the Δ133p53α isoform in regulating T lymphocyte function. T cells expressing Δ133p53α exhibit enhanced proliferative capacity, superior cytokine secretion, and improved tumor-specific killing *in vitro* and in mouse tumor models. Δ133p53α was found to restore antitumor responses in senescent T cells, suggesting potential applications in cancer immunotherapy and the treatment of immunosenescence-related diseases.

Furthermore, his lab's analysis of p53 isoform expression in multiple myeloma (MM) clinical samples demonstrated that incorporating p53 isoform expression levels into the current cytogenetic-risk classification significantly improved prognostic value. High-risk MM patients with elevated levels of Δ133p53 and Δ160p53 isoforms had notably longer survival compared to those with lower levels of these isoforms.

Research collaboration with CCBIO

Through a close partnership within CCBIO, Dr. Bourdon and Professor Bjørn Tore Gjertsen have established a long-standing collaborative research project. This collaboration has involved exchanging students (master and PhD students) through short stays in the laboratories in Dundee and Bergen, as well as sharing expertise, protocols, and reagents. Their joint efforts have focused on developing p53 isoforms as biomarkers in cancer, particularly in acute myeloid leukemia (AML), and identifying new therapeutic compounds targeting p53 isoform pathways.

Dr. Bourdon has developed a comprehensive panel of antibodies specific to various p53 isoforms, allowing for precise determination of p53 isoform expression in tumor samples. This has been particularly valuable in mass cytometry analysis using the Hyperion Imaging System at CCBIO. This state-of-the-art technology integrates time-of-flight mass spectrometry with metal-tagged antibodies, providing quantitative insights into protein subcellular localization and expression levels. Dr. Bourdon has actively contributed to analyzing data generated by Professor Gjertsen's team, facilitated through video calls and short visits.

In collaboration with Professor Gjertsen, Dr. Bourdon has co-supervised a PhD student at CCBIO, investigating the modulation and function of p53 protein isoforms in AML. The PhD project examined the modulation of p53



> This partnership has provided opportunities to test novel compounds developed at CCBIO, further understanding of cell responses to treatment, and contributing to the broader goals of improving cancer diagnosis and therapy.

protein isoforms in leukemic cells treated with the AXL kinase inhibitor bemcentinib (BGB324), a novel anticancer and anti-metastatic inhibitor developed at CCBIO. The publication is under preparation and should be submitted in 2024. The PhD student successfully obtained the degree in 2021, an outcome that would not have been possible without the CCBIO partnership.

Dr. Bourdon has regularly given seminars at the University of Bergen and has been honored twice as an invited speaker at the CCBIO symposium. Similarly, Professor Gjertsen has given seminars at the University of Dundee. Their partnership has also enabled the organization of an international p53 isoform conference in Bergen (2017). This collaboration has led them to apply for a Synergy ERC grant within the Nordic AML group, with the outcome expected in 2025.

CCBIO significance

The collaboration with CCBIO has been invaluable for both Dr. Bourdon and Professor Gjertsen. It has enabled the extension of research on p53 isoforms into clinical applications and facilitated the development of new predictive biomarkers and therapeutic targets. This partnership has provided opportunities to test novel compounds developed at CCBIO, further understanding of cell responses to treatment, and contributing to the broader goals of improving cancer diagnosis and therapy.

Looking ahead, Dr. Bourdon is eager to continue expanding the use of p53 isoforms as predictive biomarkers in collaboration with Professor Gjertsen, explore the molecular mechanisms underlying cell responses to new treatments, and develop innovative diagnostic tools within the Nordic AML group. ••



Rolf A. Brekken

Professor Rolf A. Brekken received his BA in biology from Luther College in Decorah, IA and his PhD from UT Southwestern Medical Center. His graduate studies in Dr. Philip Thorpe's laboratory were focused on developing novel therapies that target the vascular compartment of tumors. Dr. Brekken performed postdoctoral studies under Dr. E. Helene Sage at the Hope Heart Institute in Seattle where he investigated the function of the matricellular protein SPARC in angiogenesis and tumor progression. He was recruited back to UT Southwestern in 2002 as the Effie Marie Cain Scholar in Angiogenesis Research and joined the Department of Surgery and the Hamon Center for Therapeutic Oncology Research. He is currently a Professor in the Departments of Surgery and Pharmacology. He is the Deputy Director of the Hamon Center for Therapeutic Oncology Research and Director of the Cancer Biology Graduate Program at UT Southwestern.

Research interests and important results

Professor Brekken's laboratory is focused on understanding how the tumor microenvironment effects therapeutic efficacy. The microenvironment of tumors contributes significantly to the development, metastatic spread, and resistance to systemic therapy of cancer. Angiogenesis, extracellular matrix (ECM) remodeling and immune suppression are dominant characteristics of the microenvironment of solid tumors and are the general areas of focus for the laboratory. The Brekken lab studies these themes in the context of therapy in robust preclinical models of cancer.

The lab currently consists of approximately five individuals including two research scientists, one clinical trainee, and two technical staff members. Two junior faculty (Drs. Huocong Huang and Alex Kim) have their research efforts embedded in the Brekken group, and their labs participate in Brekken lab meetings. Thus, the total research effort in Brekken's laboratory space encompasses seven individuals and three PIs. The three groups interact/collaborate effectively. The specific projects among the three groups are diverse but overlap significantly in biology and technical execution and therefore foster a collaborative environment within the overall laboratory.

The laboratory is active in pushing for translation of new modalities for cancer therapy. For example, two therapeutic antibodies Dr. Brekken helped develop have been tested in cancer patients. Further in collaboration with academic and industry partners, the lab has participated in the preclinical validation of multiple therapeutic agents that have moved to clinical testing.



Research collaboration with CCBIO

Professor Brekken has an active and longstanding collaboration with Professor Jim Lorens on the function of Axl in tumor progression. The collaboration is focused on Axl biology and the efficacy of Axl inhibition using small molecules, specific Axl mAbs and strategies to prevent γ-carboxylation of Gas6. In collaboration with Dr. Jim Lorens, the Brekken Lab validated the efficacy of Axl inhibition with bemcentinib in preclinical models of pancreatic cancer, laying the foundation for a clinical trial testing bemcentinib and chemotherapy in pancreatic cancer patients. In addition, the Brekken lab participated in studies investigating Axl inhibition with bemcentinib as



> CCBIO has been a source of new ideas and new interactions as well as an opportunity to strengthen ties with existing collaborators.

a strategy to enhance the efficacy of immune checkpoint blockade in lung cancer, resulting in current clinical studies being driven by BerGenBio ASA. Dr. Brekken has also collaborated with Drs. Nils Halberg and Emmet Mc Cormack to investigate the microenvironment of pancreatic cancer. Additionally, he has a joint project with Dr. Randy Watnick at Harvard, which developed through connections made at CCBIO and involves Professors Lars A. Akslen and Jim Lorens.

Further, through interactions that were initiated at CCBIO, multiple trainees/visiting scientists have spent 3–6 months in Dallas working on joint projects, and two trainees from the Brekken Lab spent time training/working in Bergen. Thus far, CCBIO collaborations have resulted in 11 publications, 3 submitted manuscripts and multiple grant applications.

CCBIO significance

Dr. Brekken has been a regular attendee and participant in the CCBIO Annual Symposium since 2013. Highlights from the meetings are centered on the spectacular setting at Solstrand, listening to talks from local and international speakers as well as trainee presentations, and enjoying the company of friends talking science. CCBIO has been a source of new ideas and new interactions as well as an opportunity to strengthen ties with existing collaborators. Interactions at CCBIO have helped focus the direction of research in the Brekken Lab over the years and provided inspiration to propose innovative approaches to address unmet needs in the area of cancer therapeutics. It has been an honor to be part of the international faculty of CCBIO. The program has been a resounding success. ••



Hani Gabra

Professor Hani Gabra earned his science and medical degrees from the University of Glasgow in 1987 and completed a PhD in Molecular Oncology in 1996 and specialist oncology training at the Cancer Research UK, University of Edinburgh in 1998. His clinical specialist background is in medical oncology with a focus on gynecological cancers, particularly ovarian and uterine cancer.

Professor Gabra is an Emeritus Professor in Medical Oncology and Consultant Medical Oncologist at Portsmouth Hospitals University NHS Trust. He is also Founder and Chief Scientific Officer for the preclinical stage biotech company, Papyrus Therapeutics Inc.

Professor Gabra has held numerous prestigious positions, including Cancer Research UK Professor of Medical Oncology and Director of the Ovarian Cancer Action Research Centre at Imperial College London. He was subsequently VP and head of the Clinical Discovery Unit at AstraZeneca in Cambridge and Chief Medical Officer for BerGenBio ASA. His contributions to cancer research have been recognized with memberships and fellowships of many international societies.

Research interests and important results
Professor Gabra's research focuses on the molecular mechanisms of ovarian cancer, with significant contributions to understanding drug resistance and the development of personalized medicine. His work has resulted in the identification of novel biomarkers and therapeutic targets, leading to over 200 peer-reviewed publications and impactful clinical advancements. In particular, he is focused on the development of OPCML and the IgLON family of proteins as novel anti-cancer therapeutics through a novel approach of extracellular tumor suppression therapy.

Research collaboration with CCBIO
Professor Gabra's collaboration with CCBIO has particularly been with Professor Jim Lorens, engaging in translational research around AXL and the IgLON family of proteins, as well as collaborations into gynecological cancers.

Over the years, Professor Gabra has been deeply involved in CCBIO activities, including participating in courses, conferences, and mentoring programs. His efforts have particularly focused on supporting young researchers, leading workshops, and contributing to educational programs designed to enhance research skills among early-career scientists.



CCBIO significance
The collaboration with CCBIO has been a cornerstone of Professor Gabra's research, providing access to a vibrant research community and cutting-edge resources. This relationship has not only facilitated significant advances in his work on ovarian cancer but also enriched his professional development through valuable networking and knowledge exchange opportunities. ••



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Mark LaBarge

Mark LaBarge studied genetics at the University of California, Davis, and earned his PhD in molecular pharmacology at Stanford University in 2004. He was an American Cancer Society Postdoctoral Fellow at the Lawrence Berkeley National Laboratory where he developed novel technologies for functionally dissecting microenvironment-stem cell interactions. He is currently professor at the Department of Population Sciences, deputy director of the Center for Cancer and Aging, and director of postdoctoral training at the Beckman Research Institute at City of Hope National Cancer Center, California.

Research interests and important results

Professor LaBarge specializes in human mammary epithelial cell culture technology and breast cancer susceptibility, particularly in relation to aging and microenvironment biology. His research primarily focuses on understanding how the aging process affects the mammary gland, increasing its vulnerability to cancer initiation. A significant portion of his work involves developing a model system to study aging and cancer in human solid tissue, specifically in the mammary gland. Collaborating with Martha Stampfer, he has established best practices for culturing normal mammary epithelial cells and pioneered organotypic culture and bioengineering techniques that enable the modeling of complex, multilineage microenvironments in culture.

One of the key resources stemming from Professor LaBarge's work is the Human Mammary Epithelial Cells (HMEC) Aging Resource, a growing collection of normal breast tissue from which they derive primary HMEC and stromal fibroblast cultures. With tissue samples from over 500 women, they have established more than 100 primary HMEC strains, alongside matched fibroblast and adipose samples, creating a highly valuable repository used by researchers worldwide. For over 15 years, his team has developed essential cell growth media for primary human epithelial cells (USP11,293,008). Their culture systems effectively maintain the transcriptional, epigenetic, and biochemical characteristics associated with both lineage and chronological aging, as observed *in vivo*.

Professor LaBarge's work has identified several new hallmarks of aging and susceptibility in breast tissue, earning him the Era of Hope Award from the United States Congressionally Directed Medical Research Program. His research revealed that aging-related changes in luminal cells are predictable, while neighboring myoepithelial cells exhibit increased transcriptional variability, likely driving the predictable changes in luminal and progenitor cells. In heterochronous organoid cultures, the biological age of luminal cells is influenced by the chronological age of the surrounding myoepithelial cells. This led to the discovery that modulating certain cell-cell communication pathways may delay the aging process.



His research consistently demonstrates that luminal cells serve as sensitive markers for breast cancer risk. Molecular changes in luminal cell keratin intermediate filaments and lineage-specific transcription factors act as breast-specific biomarkers for biological age and cancer risk. His team has shown that these hallmarks of aging can be used in breast cancer prevention trials to identify interventions with biological efficacy. Their ultimate goal is to identify molecular targets and biomarkers for breast cancer



> In my opinion, many researchers have greatly benefited from this initiative, and the organization should be commended for designing such a thoughtful and impactful program.

prevention, with a particular focus on the aging-related acquisition of stem cell properties by luminal epithelial cells due to dysregulation of key stem cell pathways and associated genes and proteins.

Research collaboration with CCBIO

Professor LaBarge has a decade-long collaboration with Professor James Lorens resulting in more than ten manuscripts on topics of aging, stem cell states, and cooption of stem cell states by cancer cells. LaBarge has made regular contributions to the CCBIO Annual Symposium and co-mentored doctoral candidates from the CCBIO program. With Professor Lorens and his trainees in CCBIO, they delved deeply into the aging process using single cell proteomic methods which identified acquired changes in mammary progenitor cells that cause them to ignore regulatory cues from the microenvironment (*Cell Reports* 2018). Analysis of stem and progenitor cells in human mammary epithelia led the international team to discover that the AXL receptor is used by multipotent epithelial cells to regulate differentiation into more mature states. They answered a longstanding question as to why AXL was coopted by breast cancers, because it allows the cancer cells access to gene programs that are typically reserved for stem cells (*iScience* 2020). Most recently, the LaBarge and Lorens labs are focusing their collaborative efforts on understanding the impacts of age- and risk-dependent changes in cytokeratin expression, and how that rewires signaling pathways into transformation-susceptible cellular states that can be identified by simple mechanical measurements.

CCBIO significance

CCBIO has been a remarkable influence, both professionally and personally. The program's focus of fostering interactions between seasoned experts and early-career researchers created an inviting and open environment for meaningful exchanges. The annual meetings, featuring cutting-edge sessions, consistently sparked stimulating conversations and nurtured productive scientific work. In my opinion, many researchers have greatly benefited from this initiative, and the organization should be commended for designing such a thoughtful and impactful program. ••



Ian Mills

Professor Mills studied biochemistry at the University of Oxford and went on to earn his PhD in molecular and cellular physiology at the University of Liverpool in 2000. He was then an MRC-funded postdoctoral researcher until 2003, working on clathrin-mediated endocytosis in the Laboratory of Molecular Biology in Cambridge. In 2003, he was recruited as a senior research associate (2003–2006) and subsequently became an associate scientist (2006–2010) establishing a CRUK-funded translational research program to identify drivers of prostate cancer progression. This period led to the identification of novel androgen receptor target genes that support adaptations in prostate cancer metabolism, glycosylation and the unfolded protein response. These remain areas of significant biological interest within Professor Mill's research group. He has had other ties to Norway apart from CCBIO, as PI/group leader at the Norwegian Centre for Molecular Medicine, Nordic EMBL Partnership, University of Oslo, in 2010–2015.

Mills is currently professor in translational prostate cancer biology at Queen's University Belfast; Fellow of Linacre College, Oxford, Interim Head of Department, Nuffield Department of Surgical Sciences, University of Oxford; John Black Professor of Prostate Cancer, Nuffield Department of Surgical Sciences, University of Oxford; and member of the Board of Trustees of Linacre College, Oxford.

Research interests and important results

Over the last 20 years, Mills has led the first tissue-based studies to map androgen receptor binding sites in prostate cancer, showing that the genome-wide distribution of sites changes as the disease progresses, with implications for the biological processes regulated by the androgen receptor. This is important because the androgen receptor remains the primary molecular drug target for the treatment of prostate cancer and identifying stage-specific co-dependent biologies provides a route to develop better biomarkers of treatment response and also combinatorial treatments. Metabolism provides a considerable scope for drug repurposing/repositioning, and prostate cancer cells are characterized by aberrant lipid metabolism and the capacity to withstand stress arising from increased anabolic metabolism. In this context, Mills has shown that calcium calmodulin-dependent kinase kinase 2 (CAMKK2) is an important regulator both of glycolytic flux and of vesicular flux through the secretory pathway and to lysosomes. Mills has also shown that impairing that flux enhances stress in the endoplasmic reticulum and that other prostate cancers alleviates stress by activating distinct axes of the unfolded protein response at different phases in disease progression. In addition, glycosylation, and in particular OGlcNAcylation, maintains the activity and stability of oncogenic factors such as c-Myc and the capacity of cancer cells to transcribe and efficiently process transcripts. Impairing these stress-relieving biologies creates therapeutic vulnerabilities for example to inhibitors of cyclin-dependent kinases such as CDK9, and cancer driven by c-Myc are more susceptible to these interventions. These interventions in turn lead to the production of misprocessed transcripts that can be immunogenic. Eliciting an effective immune response is a further challenge in the treatment of prostate cancer and ongoing work is exploring how an aberrant type 1 interferon response may contribute to this. Beyond these molecular discoveries, Mills has also contributed collaboratively to identifying blood-based protein biomarkers such as LRG1 and in deriving polygenic hazard scores for the improved risk stratification of prostate cancer. More recently, he has collaborated on spatial transcript profiling to identify and characterize early copy-number unstable clones in clinical disease. Future work will define how the biologies and molecular targets defined pre-clinically will relate to these clonal hierarchies, and how that knowledge might be used to restrict disease progression.

Whilst these are key contributions to his field, Professor Mills feels that perhaps his greatest achievement has been in mentoring early career researchers. In so doing it's important to support your mentees in carrying research themes with them and enabling them to use those as pillars for their own career development.

CCBIO collaboration and activities

In setting up his group in Oslo in 2010, Mills was introduced to Professor Karl-Henning Kalland, and their discussions on the transcriptional regulation in prostate cancer evolved into Mills' affiliation with CCBIO. Mills has contributed as speaker at three of CCBIO's Annual Symposia and presented some of his transcriptomic and spatial work to the CCBIO Scientific Advisory Board.



> Effective translational research requires international collaboration and teamwork. CCBIO is one of the few entities to be resourced to support that on a scale that permits international faculty to share ideas and data within Norwegian researchers across a range of fields and cancer type.

This was coincident with Dr. Carina Strell's recruitment to Bergen with whom Mills has shared interests in using these approaches to characterize the early pre-cancerous states of hormone-dependent cancers. This led to a number of informal discussions during Dr. Strell's start-up phase in Bergen. Mills has also contributed to the shortlisting of applicants for postdoc positions with Professor Kalland's group. In addition, he co-authored a book chapter within *Biomarkers of the Tumor Microenvironment* (Springer 2022) edited by Professors Akslen and Watnick. During the course of his International Faculty appointment, Mills has published 79 articles, many affiliated to CCBIO with a particular emphasis on metabolic imaging/spatial profiling and biomarker development.

CCBIO significance

CCBIO has provided me with a valuable opportunity to remain connected to Norwegian research having rotated out of my position at NCMM Oslo into Faculty positions in the UK. Effective translational research requires international collaboration and teamwork. CCBIO is one of the few entities to be resourced to support that on a scale that permits international faculty to share ideas and data within Norwegian researchers across a range of fields and cancer type. That has helped define new and relevant research questions for me and that has doubtless been reciprocal. These connections will continue for a long, long time but it is also important that similar structures are maintained to preserve this culture of shared experience for the next generation of committed researchers. ••



Klaus Pantel

Professor Klaus Pantel did his MD at the University of Cologne in 1986, his Dr. Med. at the University of Cologne in 1987 and his Dr. Med. Habil. at the Ludwig-Maximillians-Universität in 1995. He is currently Director of the Institute of Tumor Biology at the University Medical Center Hamburg-Eppendorf and Full Professor (C4) of Medicine at the University Hospital Eppendorf (UKE), University of Hamburg, Germany.

Research interests and important results
Professor Pantel has done pioneer work in the field of cancer micrometastases, circulating tumor cells and circulating nucleic acids (ctDNA, microRNAs). His expertise is particularly on disseminating tumor cells as biomarker of treatment efficacy. This work provides new insights into the biology of early tumor cell dissemination in cancer patients with particular emphasis on the identification of the putative metastatic founder cells ("stem cells") and the regulation of cancer dormancy responsible for late relapses in breast cancer patients. Pantel is currently a top ranking internationally renowned scientist within the field of personalized medicine and in particular within the rapidly developing field of liquid biopsies.

Professor Pantel currently has 672 PubMed-registered publications, many published in Nature Cell Biology, Nature Reviews Cancer, Nature Biotechnology, Lancet Oncology, Nature Rev Clin Oncol, Nature Medicine, Nature Communications, Cancer Cell and Cancer Research. His h-index is currently 141. He has coordinated the European TRANSCAN group "CTC-SCAN", the European IMI consortium CANCERID (www.cancer-id.eu) on blood-based "Liquid Biopsies" and has established a clinical micrometastasis research network at the University Cancer Center Hamburg with a clear focus on diagnosis and treatment of solid tumors. Pantel has been the scientific coordinator of EU projects: CANCER-ID IMI EU, 01/2015–12/2019, 60 calendar months, EU Innovative Medicines Joint Undertaking (IMI JU) Call with more than 32 European partners; LIQUOPSY, 05/2014–04/2016, EU/BMBF (Federal Ministry of Education and Research), 3 European partners and the TRANSCAN ERA-Network 06/2013–05/2016, EU/BMBF (Federal Ministry of Education and Research) with 6 European partners.

In 2019 he received his second ERC Advanced Investigator Grant (2019–2024), INJURMET, and was highlighted in the journal *Die Zeit* as "Person of the Month."

He has served on several national and international evaluation panels awarding grants and awards such as the Deutsche Forschungsgemeinschaft, Deutsche Krebshilfe, Roggenbuck-Foundation, European Commission/European Research Council, American Association of Cancer Research or Metastasis Research Society.

Pantel has received numerous highly prestigious awards as exemplified by (1) the ERC (European Research Council) Advanced Investigators Grant and (2) the American Association for Cancer Research (AACR) Outstanding Investigator Award for Breast Cancer Research.



He is also founder and one of three key organizers of the 1st–14th International Symposium on Minimal Residual



> The interaction with the CCBIO members, the scientific collaboration and contact with young investigators have been highly stimulating and useful.

Cancer (Paris, Osaka, Athens, Hamburg, San Francisco, Oslo, Berlin, Munich, Nice) in addition to co-organizer and invited speaker to numerous international meetings, including key plenary address at the Annual Meeting of the American Association for Cancer Research (20 000 participants), where he has the reputation of being an excellent speaker and teacher.

During his career, Professor Pantel has supervised more than 30 PhD students and more than 25 postdocs. Presently he supervises 5 PhD students and 6 postdocs.

Over the past 25 years, Professor Pantel has served at various advisory panels for academic institutions (e.g., University of Cambridge; University of Manchester; Champalimaud Research Foundation, Portugal) and pharmaceutical companies (e.g., Veridex/Janssen; Roche, Sanofi, Alere) as well as on the Editorial Boards of peer-reviewed journals such as Cancer Res, Clin. Cancer Res, or Breast Cancer Res. He has provided advice on the quality of past/ongoing projects and future research directions as well as the selection of researchers for open positions.

CCBIO collaboration and activities

Professor Pantel has a broad collaboration with CCBIO, most recently in a prospective non-randomized phase I trial of metastatic castration resistant prostate cancer, published in 2023. Here, he collaborated among others with Liv Cecilie Vestrheim Thomsen, Waqas Azeem, Lars A. Akslen, Bjørn Tore Gjertsen and Karl-Henning Kalland. The trial shows that dendritic cell based cryoimmunotherapy associates with clinical variables and changes in T-cell receptor expression.

Currently, collaboration with Professor Christian Beisland and his team at the Department of Urology, Haukeland University Hospital and with Professor Karl-Henning Kalland, CCBIO in the INJURMET ERC project, is ongoing with examination of patient blood and biopsy prostate samples with the aim to clarify the extent and nature of dissemination of CTCs during prostate biopsies and prostatectomy.

Pantel has regularly participated at the CCBIO Annual Symposia and given several keynote talks at these meetings. He was co-organizer of the CCBIO Satellite Symposium on Liquid Biopsies which took place the day before the CCBIO Annual Symposium, May 22, 2018, at Solstrand outside of Bergen. He has also given additional talks and webinars for the students and researchers at the medical campus of the University of Bergen.

CCBIO significance

The interaction with the CCBIO members, the scientific collaboration and contact with young investigators have been highly stimulating and useful. ••



Randolph S. Watnick

Randy Watnick received his PhD in biochemistry and biophysics from Columbia University in 1999, and was a postdoctoral fellow with Dr. Robert Weinberg, Whitehead Institute, Cambridge, MA, until 2003. Dr. Watnick is currently assistant professor at the Department of Surgery, Harvard Medical School and research associate in the Vascular Biology Program (VBP) at Boston Children's Hospital.

Research interests and important results

Watnick's laboratory is focused on understanding the interactions between the tumor and its microenvironment that regulate the progression of breast cancer. Specifically, they have identified a novel TNBC CSC population that possesses all the consensus CSC properties of chemoresistance, sphere formation, and tumor initiation. Critically, the Notch1^{hi} CSC population are the first CSCs that differentiate *in vitro* to give rise to all the cell types present in the parental tumor population. Disrupting this interaction by silencing TAp73, or deleting the acetylation site of p53 abrogates chemoresistance, sphere formation and tumor metastasis. These findings provide the first functional mechanistic requirements for the tumor-initiating and chemoresistant properties of breast CSCs. Importantly, this work has revealed that the CSC properties of the Notch1^{hi} cells are dependent on the non-canonical, cleavage-independent Notch1 pathway.

Moreover, Watnick developed and was an integral part of the pre-clinical and clinical development of a peptide therapeutic agent. Recruitment is currently underway for a phase 2/3 trial to assess the effectiveness of this therapy in GBM (NCT03970447). This peptide was licensed to Vigeo Therapeutics, a company Watnick co-founded and led the scientific advisory board through IND-enabling studies into clinical trials. Based on his experience in the field of drug development, they believe that by targeting the non-canonical Notch1 pathway, they will be able to more effectively treat triple negative breast cancer patients by sensitizing CSCs to chemotherapy. Thus, overcoming one of the major hurdles to current treatment modalities.

CCBIO collaboration and activities

For the past 19 years, Watnick has been collaborating with Professor Lars A. Akslen on multiple research projects. His collaboration with the Akslen group has been fundamentally important in establishing and validating biological and biochemical observations made in Watnick's laboratory in patient samples. Specifically, this collaboration helped to establish a role for both prosaposin and PRSS2 in disease progression and survival in multiple indications and helped to build the foundation for clinical trials for a prosaposin-derived peptide developed in Watnick's lab, which is currently in a phase 2/3 registration trial for GBM. This collaboration has led directly, or indirectly, to seven peer reviewed papers in high-impact journals, including Cancer Discovery, Science Translational Medicine, Nature Communications, and PNAS.

Throughout the years, Watnick has presented his lab's research at the CCBIO Annual Symposium on eight occasions. He has also been teaching at the CCBIO Scientific Writing Seminar on six occasions. Additionally, he has been an instructor in the course on Cancer Biology both remotely and in person. Finally, Watnick finds that one of the most gratifying activities to have taken part in, has been mentoring young MD and PhD students in his laboratory as part of the CCBIO–VBP INTPART program. To date, he has mentored three students and a fourth will be coming to Boston in October 2024 to work in his lab.



CCBIO significance

In summary, my relationship with CCBIO has been tremendously rewarding on both a professional and personal level. Not only have I been able to engage in collaborations and helpful discussions that have pushed my research forward, I have also made many very good friends who have made Bergen feel like a second home to me. ••



> In summary, my relationship with CCBIO has been tremendously rewarding on both a professional and personal level.





Therese Sørlie

Therese Sørlie received her PhD from the University of Oslo in 2000 under the supervision of Professor Anne Lise Børresen-Dale, and she joined Professor David Botstein's group at Stanford University as a postdoctoral fellow from 2001. After returning to Norway in 2005, she continued her research in the Department of Cancer Genetics and has led her own research group since 2012. From 2017 she has been the head of the Department of Cancer Genetics, Institute for Cancer Research at Oslo University Hospital. She is also an adjunct professor at the Institute of Clinical Medicine, University of Oslo.

Research interests and important results

During her postdoctoral work at Stanford, Sørlie worked on molecular classification of breast cancer. Her contribution during this time pioneered gene expression profiling of tumors and has resulted in a classification scheme for breast cancer that is implemented in international guidelines for the treatment of breast cancer. In Norway, this classification is now implemented through the participation in two clinical studies, EMIT and OPTIMA. Her early work on breast cancer classification has continued to influence her research. The group now focuses on studying breast cancer heterogeneity and identifying the molecular mechanisms underlying breast tumor initiation and progression to the intrinsic molecular subtypes, including the transition from DCIS to invasive breast cancer. Lately, her group has been involved in several projects on endometrial cancer with the aim of identifying new biomarkers for this patient group. Her research group has expertise in molecular biology and bioinformatics and they use mouse models and patient cohorts in their studies.

CCBIO collaboration and activities

The collaboration with CCBIO and Lars A. Akslen was rooted in a mutual interest in breast cancer, and particularly the importance of the tumor microenvironment for tumor progression. Tumor growth is influenced at all stages of development by the surrounding tissues, the cells of the immune system, circulating particles and even the microbiome. Sørlie's recent work on endometrial cancer has in addition led to a collaboration with Camilla Krakstad, to identify blood-based predictive markers for tumor progression and response to therapy. Interactions with CCBIO have also facilitated a collaboration with Carina Strell, leading to common ongoing projects.



CCBIO significance

The connection to CCBIO and its Director Lars A. Akslen during these years has been important for the research group. Additionally, Akslen has served as a mentor for my career development. Our mutual interest in early breast cancer and DCIS in particular, has led to many fruitful discussions that have been motivating for our research. ••



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Jean Paul Thiery

Professor Jean Paul Thiery is a high-ranking international researcher currently located in Singapore and China. He held the position of director of research at the Centre National de la Recherche Scientifique (CNRS), Paris, until 2010. From 1995 to 2003, Jean Paul Thiery established and headed the Cell Biology Department of the Institut Curie. He was the inaugural director of the Department of Translational Research at the Institut Curie Medical Division from 2003 to 2006. In October 2006, he moved to Singapore where he was deputy director of the Systems Biology Division at the Institute of Molecular Cell Biology until November 2011 and chief scientific officer of the Experimental Therapeutics Centre of A*STAR until April 2011. He was then appointed professor and head of the Department of Biochemistry of the Yong Loo Lin School of Medicine at the National University of Singapore (NUS). Concurrently, he remained research director at IMCB A*STAR, senior principal investigator at the Cancer Science Institute and associate principal investigator at the Mechanobiology Institute (MBI) at NUS. Since July 2015, Jean Paul Thiery is emeritus research director at the CNRS research unit "Matter and Complex Systems" in Paris. He also holds a research director emeritus position at the Institut Gustave Roussy in Villejuif, the largest comprehensive cancer center in Europe. Jean Paul Thiery has been a Toh Chin Chye Visiting Professor at the School of Medicine at NUS. He was also a distinguished visiting professor at the Li Ka Shing Faculty of Medicine of Hong Kong University.

Thiery is currently the chief scientist of Biosyngen Pte Ltd Singapore, a cell-based immunotherapy company; he is also the cofounder and chairman of Biocheetah Pte Ltd Singapore, a company focusing on the diagnostics of urological cancers. He is a scientific advisory board member of Papyrus Inc. USA together with Professor James Lorens. This company is involved in elucidating the function of OPCML as a suppressor of AXL function in mesenchymal-like carcinoma.

Research interests and important results

Thiery's research has for many years focused on unraveling mechanisms governing epithelial mesenchymal transition (EMT) in carcinoma. Recent studies made in collaboration with CCBIO members allowed him to investigate the role of hypoxia in lung adenocarcinoma. These studies showed that targeting EMT transcription factors or directly inhibiting TGF-beta receptor signaling rendered carcinoma cells more susceptible to cognate cytotoxic T lymphocytes (Terry et al. 2017). They identified the role of several tyrosine kinases including Src, receptor tyrosine kinases, and the SHP2 phosphatase in the control of TGF-beta receptor activation of the EMT programs (Sim et al. 2019; Lai et al. 2023). With CCBIO collaborators, Thiery focused on the tyrosine kinase surface receptor AXL in controlling immune escape in carcinoma cells undergoing EMT. They found that AXL is overexpressed in lung adenocarcinoma cells undergoing EMT under hypoxic conditions. These cells cannot establish a functional immunological synapse and thus become refractory to cytotoxic T lymphocytes and to NK cells. Inhibition of AXL kinase activity by bemcentinib restores the immune response through induction of expression of I-CAM1 and ULBP1. Inhibition of AXL in lung cancers should improve cell-based immunotherapies (Terry et al. 2019). Then, they found that lung adenocarcinoma acquiring resistance to EGFR tyrosine kinase inhibitors is caused by AXL signaling inducing autophagy. Inhibition of Axl kinase restores susceptibly to EGR inhibitors. (Engelsen et al. 2022). They also investigated the potential role of glycolysis in lung adenocarcinoma refractory to EGFR inhibitors. Pyruvate dehydrogenase (PDH) is a potential target since it acts as a gatekeeper between glycolysis and oxidative phosphorylation. Its activity is downregulated by PKDH phosphorylation. To circumvent the excess production of lactate, the dichloroacetate PDHK1 inhibitor was used in combination with EGFR TKIs and/or ionizing radiation to restore the therapeutic activity of EGFR inhibitors in lung adenocarcinoma cell lines (Dyrstat et al. 2021). The role of AXL was also investigated in normal breast development and breast cancers. AXL expression confers stem-like properties in mammary epithelial cells; its expression is required to reconstitute mammary glands in transplantation experiments. Axl is also involved in the clonogenic development of breast cancers by sustaining stemness (Engelsen et al. 2020).



> My affiliation with CCBIO was very instrumental in our research program on epithelial-mesenchymal transition in carcinoma.

CCBIO collaboration and activities

Professor Thiery has been collaborating with CCBIO in the work with identification of AXL receptor tyrosine kinase as a critical signal transduction in epithelial-mesenchymal transition in carcinoma, with the contribution of AXL signaling in immune escape, and the discovery of AXL as a driver in mammary stem cell maintenance in normal tissue and in cancer development.

Thiery has participated in most CCBIO Annual Symposia at Solstrand. He was a lecturer at three of these conferences and served as chair at two other conferences, and he gave a plenary seminar lecture at CCBIO in December 2020. His collaboration also included mentoring of Dr. Agnete Engelsen through these years and organizing her postdoctoral training at Gustave Roussy Comprehensive Cancer Center in Villejuif France.

CCBIO significance

My affiliation with CCBIO was very instrumental in our research program on epithelial-mesenchymal transition in carcinoma. We explored with the team headed by Professor James Lorens the role of AXL in immune escape. I also learned a great deal with other CCBIO team leaders and affiliated members. The Solstrand annual meeting allows direct contact with the speakers and CCBIO members in a relaxed atmosphere. I have had multiple discussions exploring collaborative studies, particularly with Rolf Brekken, a long-term collaborator of James Lorens. My discussion with the CCBIO Director Lars A. Akslen was also very fruitful as he is a world expert in molecular pathology. I contributed to his two books on the subject with a foreword in *Biomarkers of the Tumor Microenvironment: Basic Studies and Practical Applications* (2017) and a foreword and chapter in *Biology and Biomarkers of the Tumor Microenvironment* (2nd edition), 2022. In sum, my affiliation with CCBIO contributed to my research programs in identifying mechanisms driving the progression of carcinoma. ••



Arne Östman

Arne Östman trained as PhD student at the Ludwig Institute for Cancer Research (LICR) in Uppsala under the supervision of Carl-Henrik Heldin. Following a postdoc with Nick Tonks at Cold Spring Harbor Laboratory, he was group leader at LICR 1993–2003, before joining Karolinska Institutet in 2004 where he was appointed professor in 2006. He has published more than 170 original research articles, reviews in e.g. Nature Reviews Cancer and Cancer Cell, and has trained approximately 40 PhD students and postdocs. He directed the STARGET center-of-excellence 2006–2016 and is since 2020 member of the Nobel Assembly and has been adjunct member of the Nobel Committee in 2023 and 2024.

Professor Östman is currently professor of molecular oncology at the Department of Oncology-Pathology, Karolinska Institutet.

Research interests and important results

Östman's research during the last 20 years has centered on mechanistic and translational studies on the tumor microenvironment with special focus on cancer-associated fibroblasts (CAFs) and PDGF receptor signaling. The studies have uncovered novel molecular mechanisms whereby CAFs stimulate tumor growth, angiogenesis and metastasis. Collaborative analyses of large well-annotated tumor collections have identified novel prognostic and therapy-predictive CAF-derived biomarkers. More recently, advanced multiplex-based methods for tissue profiling have identified novel multi-marker-defined CAF subsets with differential associations to driver mutations, immune features and outcome.

CCBIO collaboration and activities

As member of the CCBIO International Faculty, Östman has contributed to the annual Solstrand meetings as speaker, as session chair, as participant in program discussions and as host. Östman has also co-authored chapters in both editions of the review collections edited by Akslen & Watnick on biomarkers of the tumor microenvironment. A spin-off of the CCBIO engagement is the SCANPATH meeting series, initiated by Östman & Akslen. Seven highly interactive meetings have been held since 2016 where Norwegian, Swedish and Finnish cancer researchers have presented novel findings in the field of human tissue-based explorative and translational cancer research.

Regarding collaborative research, Östman has, based on the CCBIO position, received three rounds of funding from the Norwegian Cancer Association, and also funding from the Western Norway Regional Health Authority. This funding has supported postdocs and one bioinformatician, which has performed a set of studies in close collaboration with the group of Lars A. Akslen. Studies have identified novel vessel features associated with outcome in ER+ breast cancer.

Novel and ongoing ambitious studies are using the imaging mass cytometry (IMC) method, using the Bergen-based Hyperion Imaging System, for discovery of novel CAF subsets and their associated niches. These collaborative studies, including Akslen and other partners, have significantly contributed to novel directions in the research fields of the Östman group.



CCBIO significance

To be part of the CCBIO International Faculty, and to get the chance to do research in this environment, has been very rewarding, an honor and a pleasure. I am highly sympathetic to the CCBIO atmosphere where high academic ambitions, and genuine translational intentions, are key ingredients. The efforts of the leadership to increase international connections, and the early investment in imaging mass cytometry, are bold initiatives which possibly will have long-lasting impact. ••



> To be part of the CCBIO International Faculty, and to get the chance to do research in this environment, has been very rewarding, an honor and a pleasure.



summary of research activities 2013–2024

In accordance with our vision and aims, CCBIO's research has been structured in the following areas: basic research (**team 1**), biomarker discovery and validation (**team 2**), clinical studies (**team 3**) and societal studies (**team 4).** After a brief overall introduction and review as a backdrop, a short summary of the research will be given for each group, followed by some concluding remarks.

I. CCBIO activities in brief

CCBIO aims to discover, validate and translate cancer biomarkers to improve our understanding of tumor mechanisms, promote accurate diagnosis and stratification of cancer patients, and inform precise, cost-effective and responsible treatment of cancer.

In particular, CCBIO is focusing on the tumor microenvironment (TME), and how tissue context can instruct aggressive tumor traits and predict cancer behavior and prognosis, by functional analysis and protein biomarkers. The center studies how crosstalk between the tumor cells and TME reflects functional cancer complexity and heterogeneity.

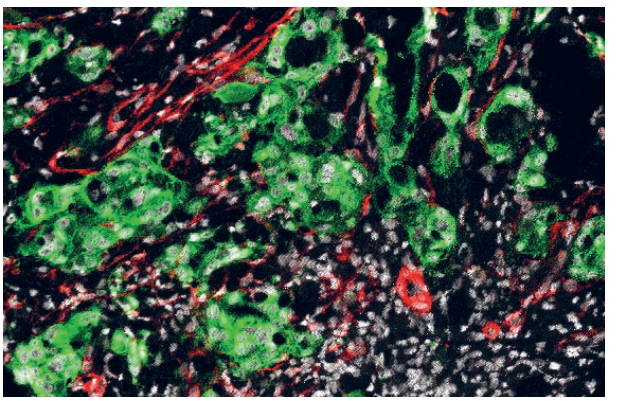
During 2013–2024, multiple projects have been performed, with results at different levels, from basic studies of important tumor mechanisms to extensive mapping of cancer tissues and liquid biopsies, with novel findings of biomarkers with an ability to improve patient stratification.

The center has performed and participated significantly in many clinical trials, with biomarker programs and use of new protocols for how such studies can be performed. CCBIO has also analyzed how to fund and prioritize cancer treatment as well as how biomarkers and various models for drug reimbursement relate to the pharma industry, and guidelines for studies of cost-effectiveness have been presented.

Altogether, around 1000 papers have been published, and 105 PhD theses have been defended by candidates from the CCBIO teams.

1.Biomedical and clinical results

Basic studies: Several groups have established and developed novel experimental models to do mechanistic studies and drug screening, such as organoids, PDX-models and establishment of human cancer-derived cell lines (breast, endometrium, lung, ovary, prostate, vulva). Models of cancer-nerve interactions have been established.



Examples: Preclinical CD37 and CA125 directed CAR-T have been established, and CD24-based fluorescence guided surgery is reported. For high-grade ovarian cancer and pancreatic cancer, a novel decellularized porcine tissue *in vitro* platform is developed for experimental studies. A model for stepwise tumor development in prostate cancer is established, revealing a key IL-6/STAT3 differentiation loop and importance of transcription factors (AR, β-catenin). This model is used in drug screening, and blocking of Wnt/β-catenin by axitinib is identified by drug repurposing. The relationship between Axl and

immune responses and therapy resistance is focused in several projects. Studies have been performed on matrix biology and the α11 integrin molecule, a collagen receptor, including development of novel antibodies suitable for archival tissues and imaging mass cytometry (IMC), and an ITGA11-Cre mouse strain is developed. As an example of the emerging field of cancer neuroscience, models for studies of breast cancer cells interacting with neural cells are established, with the first study published.

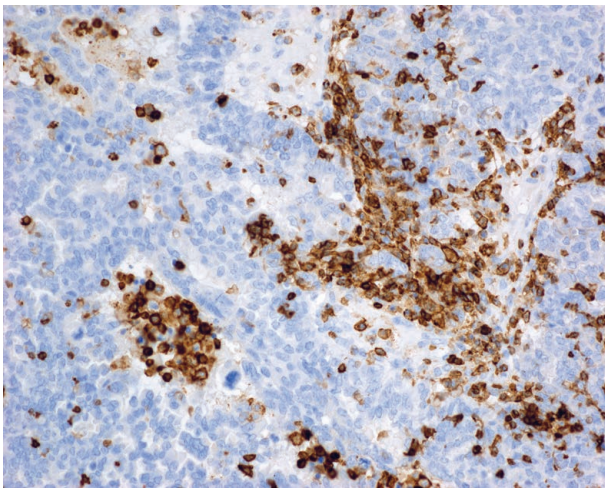
Biomarker mapping: A large number of papers report on the discovery and validation of novel cancer biomarkers, using tissue samples or liquid biopsies, from clinical cohorts and trial studies. Such markers have been validated to show improved patient stratification by multivariate survival analyses.

Examples: Regarding solid cancers, extensive results have been presented on gynecologic and breast cancers, as well as some data on melanoma, oral cancer, and prostate tumors (Axl, breast cancer proteomic signatures, hypoxia markers, age signatures, HER2, immune-markers like FOXP3 T-cells, PD1-PDL1, TCR deep sequencing, and miR-204, MSH6, vimentin). Some of these markers have been examined or included in clinical trials. Indications of a new relationship between FOXP3 and response to immunotherapy in advanced melanoma have been observed, and a novel Axl isoform (Axl3) has been discovered. Data on breast cancer-neural interactions are published, showing induction of aggressive tumor features by neural cells. Also, new results on circulating biomarkers have been reported from trial studies (ctDNA, CTC).

Functional biomarkers in leukemia and lung cancer (single cell signaling mapping by mass cytometry; PD1-PDL1 by PLA, proximity Ligation Assay) have been reported. High-dimensional biomarker studies using Imaging Mass Cytometry (IMC) enabling single cell spatial analytics of the tissue landscape have been reported. In ovarian cancer trials, changes in multifunctional cytokines and immune response markers have been studied in preclinical models and reported as promising for treatment stratification.

Clinical studies: In addition to multiple clinical cohort studies (retrospective), CCBIO teams have organized or participated significantly in around 20 clinical trials, attempting to improve treatment and pre-treatment stratification by companion biomarkers.

Examples: In prostate cancer, the early CryoIT trial using cryo-immunotherapy for advanced prostate cancer, by dendritic cells, revealed responses and several promising predictive biomarkers (TCR deep sequencing, CTCs). Anti-Axl treatment is applied in several trials and shown to restore PD-1 blockade sensitivity of STK11/LKB1 mutant lung cancer (NSCLC) through expansion of TCF1+ CD8 T-cells. In advanced melanoma, anti-VEGF monotherapy has shown efficacy, with expression of beta-2 adrenergic receptors (β2-AR) indicating predictive value. Strong expression of Activin A, interleukin-1β, and urokinase-type plasminogen activator receptor in metastases, as well as vascular metrics, are significantly associated with overall response to bevacizumab in metastatic melanoma. In leukemia studies, single cell analysis of signaling circuits is reported as very promising functional biomarkers for early response prediction as a basis for adaptive treatment.



Societal studies: Biomedical projects are integrated with ethics and economics research, focusing on how to fund and prioritize expensive cancer diagnostics and treatment, in a responsible way, in the era of expanding and costly personalized medicine. Economic evaluations of drug use and applied biomarkers are performed, also looking at models for drug reimbursement. Several papers and PhD theses have been produced. Societal studies contribute to self-reflection and intellectual awareness (ELSA/RRI) in the CCBIO environment.

2. Innovation and patents

Several of the projects have led to issued or pending patents, for example on prostate cancer (cryo-immunotherapy), breast cancer (stromal proteomics signatures), novel antibodies for diagnostic and therapeutic purposes (Axl, α11, NPM1), and drugs for leukemia. Regarding companies, some have been founded by CCBIO teams and collaborate with CCBIO: KinN Therapeutics (2004), tailored preclinical oncology services for the development of novel anticancer compounds; Alden Cancer Therapy AS (2013), dendritic cell immunotherapy combined with cryoablation against cancer; Hà Biotechnology AS (2019), nanobody design and production; Bjørgvin Therapeutics Group AS (2024), small molecule design, production, clinical development for cancer therapy. Several investigators have collaborated closely with BerGenBio, a clinical-stage biopharmaceutical company developing innovative drugs for aggressive diseases, including cancer.

3. Educational results

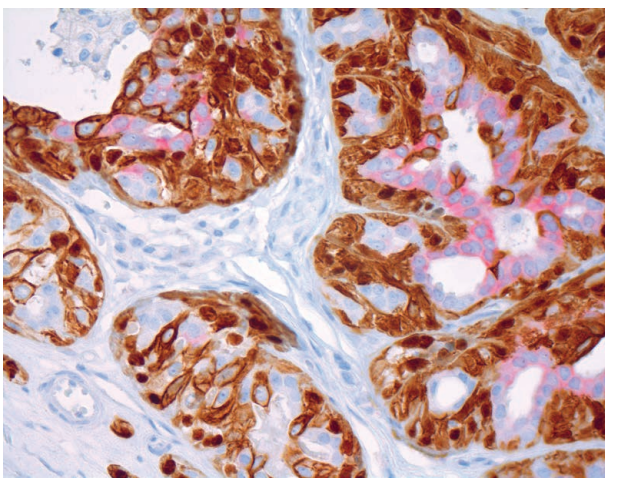
From the start, science education and outreach have been important for CCBIO. The CCBIO Research School for Cancer Studies was established as the first research school focusing on cancer in Norway. Twelve core courses have been established, most of them being held annually or every second year, with topics ranging from biomarker methods to clinical trials, scientific writing and communication, innovation, as well as ethics and economics.

Also, a Masterclass program was established to mentor the most promising young scientists, with 10 candidates in each cycle. The research school has been widely acclaimed and appreciated by the students and is open to all students at UiB and outside. All courses have also been opened up as ECTS-giving courses for master level students, and for the general scientific public for attendance and transfer of knowledge without ECTS, thereby ensuring maximum output.

4. Communication and outreach

CCBIO has been very active in public dissemination with more than 500 media appearances, e.g. in commentaries and interviews in newspapers and television, as well as more than 250 popularized presentations and events, e.g. a multi-year theatre-based program in cancer biology for school children.

In addition to more than 1000 publications, CCBIO has published the following books: 2017: Roger Strand, Anne Blanchard (eds): *Cancer Biomarkers: Ethics, Economics and Society*. 2017: Lars A. Akslen, Randolph S. Watnick (eds): *Biomarkers of the Tumor Microenvironment - Basic Studies and Practical Applications*, Springer. 2022: Anne Blanchard and Roger Strand (eds): *Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern*, Springer. 2022: Lars A. Akslen and Randolph S. Watnick (eds): *Biomarkers of the Tumor Microenvironment*, Springer (2nd ed., textbook).



5. Organization of seminars and meetings

CCBIO established from the beginning a framework of various meetings: monthly research seminars with invited speakers mainly from abroad, special seminars with guest presentations (e.g. by visiting opponents), annual symposia in May each year (international meeting, 200–250 participants), four junior scientist symposia per year (organized and chaired by postdocs and young researchers), and mini-symposia (2–3 presentations with panel discussion). The annual symposia have been especially valued, being a high-density research meeting with time for crosstalk and bonding as a basis for novel collaborations.

In addition to CCBIO-internal meetings, researchers have been active in organizing external meetings, such as the P53 isoforms conference, Bergen (2017), and the Nordic AML meeting, Bergen (2023). In 2016, Akslen & Östman founded the SCANPATH meeting, a network gathering for pathology-based researchers using tissues and novel techniques, with annual meetings (80–120 participants) and increasing collaboration. As a collaboration with the Vascular Biology Program and Harvard Medical School (Boston), two meetings have been organized (the CCBIO–VBP Research Meetings; 2019, 2024).

6. Awards and accolades

CCBIO researchers have received multiple awards over the years, for example for presentations at meetings and congresses. In 2021, Gjertsen was awarded the King Olav V Cancer Research Prize. In 2023, Akslen received the Helse Vest Research Award (second time). In 2023, Norheim was awarded a CoE from the RCN: Bergen Centre for Ethics and Priority Setting in Health (BCEPS), and in 2024, Gjertsen was awarded a five-year KG Jebsen Centre for Myeloid Blood Cancer (C-MYC). The following CCBIO researchers were elected members to the Norwegian Academy of Science and Letters: James Lorens 2020, Ole Frithjof Norheim 2021, and Inge Jonassen 2021. From before, Lars A. Akslen and Rolf Reed are also members. Akslen was elected to Academia Europaea in 2023.

II. Brief summary of research by individual groups

The results referred to below are important for our understanding of tumor complexity by adding information from the tumor microenvironment (TME), including immune response data and information on vasculature and tumor innervation, and by showing the clinical importance of such information. This will improve clinical stratification and enhance precision of treatment, demonstrating an improved cost-effectiveness profile for several tumor types. The reporting of single cell functional biomarker data adds novel value in early response prediction following treatment.



Team 1

Gullberg group: The Matrix Biology Group

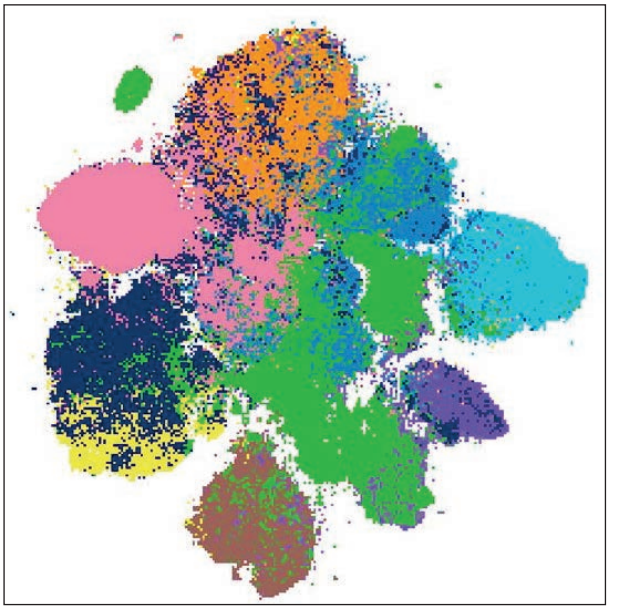
The group has consistently focused on the role of α11β1 integrin in various aspects of extracellular matrix and stroma remodeling in malignant tumors, particular cell-collagen interactions. Further, the group has focused on experimental models, with development and characterization of several novel α11-antibodies and the new fibroblast specific transgenic Cre driver mouse (ITGA11-Cre) strain. Gullberg and collaborators have recently shown how α11 can influence fibroblast migration, as well as proliferation and invasion in malignant tumors (Zeltz et al., *Cancers* 2019; Erusappan et al., *Sci Rep* 2019). The clinical relevance of α11 integrin expression has been reported (Smeland et al., *J Pathol Clin Res* 2020).

Kalland group: The Cancer Immunotherapy Research Group

The group initially focused on understanding prostate cancer development and characteristics, by establishing experimental models, and novel molecular mechanisms of benign prostate basal to luminal cell differentiation were discovered, particularly related to the expression of the androgen receptor (AR) and its target genes. A stepwise prostate tumorigenesis model was then developed without carcinogen use, identifying tumorigenic cells characterized by an IL-6/STAT3 regulatory loop (Qu et al., *Cancer Res* 2013). This model was used in drug discovery, identifying small molecular compounds that inhibit the transcription factors AR, β-catenin, and STAT3 (Qu et al., *PNAS* 2016; Qu et al., *Nature Chem Biol* 2018). In a different line of investigation, Kalland and collaborators organized and conducted an early clinical trial of cryoimmunotherapy for advanced prostate cancer (CryoIT), showing promising clinical response and novel biomarkers (Thomsen et al., *Cancer Immunol Immunother* 2023).

McCormack group: The PreCOS (Precision Oncology) Group

The team's core activities focus on the establishment and application of clinically relevant experimental models (PDX, Hu-PDX, *in vitro* decellularized scaffold platforms) integrated with multimodal molecular imaging strategies. Recently, the group has concentrated on the development of novel immunotherapies (CAR-T and BiTes). The team also reported a novel Axl3 isoform as a potential game changer in the function, localization, and regulation of Axl in cancer (Gelebart et al., *Blood* 2023). In the team's work on CD37 targeted CAR-T, they demonstrate the preclinical efficacy and superiority in AML versus other CAR concepts currently in clinical development. Therapy improvements for ovarian cancer by CD24-targeted intraoperative fluorescence image-guided surgery have also been reported (Kleinmanns et al., *eBioMedicine* 2020).



Team 2

Akslen group: The Cancer Biomarker Group

During the last 10–12 years, the group has mainly focused on proteomics studies of breast cancer, particularly related to the tumor microenvironment, performed by mass spectrometry (whole tissues) and the multidimensional imaging mass cytometry technique (tissue slides). The aim has been to discover and validate novel tissue-based cancer biomarkers for improved molecular grading and patient stratification. The group has reported novel and strong hypoxia-related proteomic signatures of breast cancer stroma (Kjølle et al., *Nat Commun* 2023). Lately, the group has focused on the growing field of cancer neuroscience and reported mutual effects between cancer cells and neural elements of clinical relevance (Bjørnstad et al., *eBioMedicine* 2023; Wik et al., in revision 2024). The role of PRSS2 and Stathmin in regulation of immune response has been published (Sui et al., *Nat Commun* 2022; Askeland et al., *Sci Rep* 2020).

Costea group: The Experimental Pathology Research Group

The group has focused on experimental models for tumor-fibroblast interactions and characterization of fibroblast subgroups. Oral tumors, stratified for HPV-status, and the relationship with vulvar tumors, have been examined in later comparative studies. The identification of two distinct carcinoma-associated fibroblast subtypes with differential roles was reported (Costea et al., *Cancer Res* 2013). It was further published that metabolic reprogramming of normal oral fibroblasts correlated with increased metabolic changes of oral squamous cell carcinoma, preceding their conversion to carcinoma associated fibroblasts (Zhang et al., *Cell Mol Life Sci* 2020). Also, a role of miRNA-204 in regulating invasion was reported from studies of CAFs in oral cancer (Rajthala et al., *Int J Mol Sci* 2021).

Engelsen group: Cancer Cell Plasticity and Therapy Resistance Group
The group has been focusing on exploring how phenotypic plasticity interferes with therapeutic efficacy and immune cell-mediated tumor cell killing. They reported how Axl targeting abrogates autophagic flux and induces immunogenic cell death (Lotsberg et al., *J Thoracic Oncol* 2020). Further, the importance of Axl as a driver of stemness in normal mammary gland and breast cancer was presented (Engelsen et al., *iScience* 2020). Heterogeneity of tumor tissue organization and stromal cell interactions was reported by single-cell analysis (Lotsberg et al., *Front Oncol* 2022).

Krakstad group: The Bergen Gynecologic Cancer Research Group
The group has focused on studies of various classes of biomarkers in gynecologic tumors, in particular endometrial and cervical cancer, combining basic and translational studies. PDX models and organoids have been established. Results on single-cell analysis have indicated low epithelial vimentin expression as a marker of recurrent disease in low-stage endometrial cancer (Lien et al., *eBioMedicine* 2023). Studies of mismatch repair markers, in particular MSH6, and prognosis were reported (Berg et al., *Br J Cancer* 2022), in addition to the biomarker value of HER2 expression in endometrial cancer (Halle et al., *Br J Cancer* 2018; Krakstad et al., *JAMA Oncol* 2024).

Lorens group: The Tumor Plasticity Group
The group has focused on the Axl receptor and in particular its role in tumor cell plasticity and immune regulation in malignant tumors. It was reported that Axl is a driver of stemness in normal mammary gland and breast cancer (Engelsen et al., *iScience* 2020). The group also found that Axl targeting overcomes human lung cancer cell resistance to NK and CTL-mediated cytotoxicity (Terry et al., *Cancer Immunol Res* 2019), and that small-molecule inhibition of Axl targets tumor immune suppression and enhances chemotherapy effects in pancreatic cancer (Ludwig et al., *Cancer Res* 2018). Lorens is a co-founder of BerGenBio ASA and has facilitated interactions with the company.

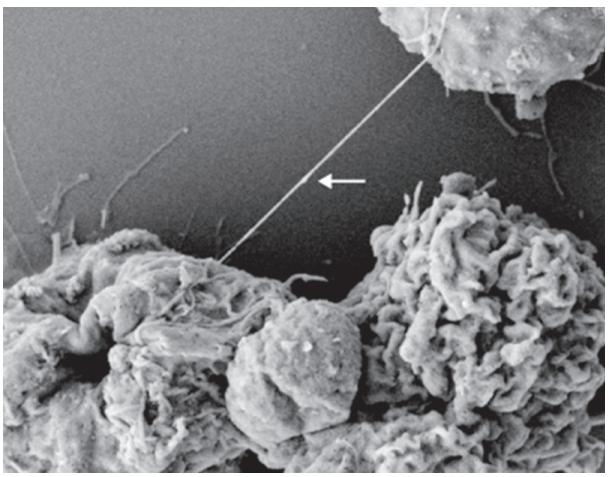
Strell group: The Early Breast Cancer Group
The focus of the group has been to study characteristics of early breast cancers, including non-invasive tumors like DCIS, by using advanced and integrated spatial mapping of genetic and proteomic alterations. Moreover, the aim is also to develop clinically relevant treatment stratification models for women with early-stage breast cancer. The importance of immune response patterns for the progress of DCIS was reported (Schiza et al., *Eur J Cancer* 2022), and the group found that high PDGFRb expression predicts resistance to radiotherapy in DCIS (Strell et al., *Clin Cancer Res* 2021). Recently, the use of beta-blockers was found to protect patients with DCIS from tumor recurrence (Strell et al., *BCRT* 2024).

Wik group: Breast Cancer of the Young – Bergen (BCY-B)
The group has focused on molecular and clinico-pathologic differences between breast cancers among young patients compared to the older group, and how findings can eventually be relevant for therapy stratification. Results have been presented on increased proliferation in breast cancer of the young, and on a proliferation related gene signature focusing on age differences (Ingebriktsen et al., *Br J Cancer* 2022; Svanøe et al., *Int J Cancer* 2024). Also, the presence of age-related immune phenotypes has been reported (Ingebriktsen et al., *Mod Pathol* 2024).

Team 3

Bjørge group: The INOvA Group
The group has focused on experimental and clinical approaches to advance the treatment of aggressive high-grade ovarian cancer based on molecular profiling, partly in collaboration with the McCormack group. Reports on novel immune profiling of the tumor microenvironment of high-grade ovarian cancer have been presented (Anandan et al., *Cancers* 2021; Torkildsen et al., *Front Immunol* 2024). Also, the group reported that CD24-based intra-operative imaging might improve experimental surgical treatment of ovarian cancer (Kleinmanns et al., *eBioMedicine* 2020).

Gjertsen group: Signaling-Targeted Therapy Group
The focus of the group has been to apply single-cell immune and signaling profiling for early response evaluation of myeloid leukemia patients, as well as therapy development using single-cell analysis as companion diagnostics. The use of early single-cell signaling profiling for response prediction, as a functional biomarker, was reported for AML patients, paving the way for adaptive treatment (Tislevoll et al., *Nat Commun* 2023). Single-cell analysis of CML patients have also been presented for a trial setting (Gullaksen et al., *Haematologica* 2017). The use of multiplexed antibodies for improved *in vivo* imaging of AML cell xenografts was described (McCormack et al., *Blood* 2013).



Straume group: The Tumor Biology and Clinical Trials Group
The group has focused on predictive biomarkers in clinical materials and trials, with reference to processes like angiogenesis, tumor immune responses, tumor cell plasticity, and escape from tumor dormancy (i.e. late relapses). Related to dormancy and late recurrences, the team reported that the recurrence pattern following breast reconstruction after mastectomy for breast cancer suggests a promoting effect of surgery on escape from tumor dormancy (Dillekås et al., *BCRT* 2016). In a trial of metastatic melanoma treated with bevacizumab monotherapy, liquid biopsies for ctDNA indicate changes in tumor load following therapy (Forthun et al., *Sci Rep* 2019). From the same trial, the group reported that expression of β2-adrenergic receptor in tumor tissue from patients was associated with clinical benefit (Schuster et al., *Cancer Med* 2023). Indications of a new relationship between FOXP3 and response to immunotherapy in advanced melanoma have been observed (ESMO 2023; meeting abstract).

Team 4

Cairns group: The Health Economics Group
The group has focused on health economics in CCBIO and started with a dual focus: on the economic evaluation of cancer biomarkers, and on understanding the incentives to combine biomarkers with patented medicines. The team has published several papers on biomarkers and cost-effectiveness of cancer therapy. It was reported that in general, cancer patients have benefited from biomarker testing (D'Avó Luis & Seo, *Eur J Health Econ* 2021). Papers on the use of RWD (real world data) on processes of drug appraisals have been presented (Kang & Cairns, *BMJ Open* 2024). In colorectal cancers, biomarkers were mostly found to be cost-effective (Seo & Cairns, *PLoS One* 2018). In 2021, Seo & Strong presented guidelines for conducting biomarker cost-effectiveness assessments (Seo & Strong, *PharmacoEconomics* 2021).

Norheim group: The Bergen Centre for Ethics and Priority Setting in Health (BCEPS)
The group's aim has been to explore and promote ethically acceptable, fair and efficient priority setting in health. The main research questions relate to how cancer biomarkers can inform and improve health care priority setting. The team reported how concerns for efficiency and fair distribution of health can be implemented into drug appraisals and reimbursement decisions (Tranvåg et al., *JAMA Netw Open* 2022). The use of biomarkers in priority setting has been presented, alongside patient characteristics like age, physical function and comorbidity. (Tranvåg et al., *BMC Med Ethics* 2021), and the importance of patients' age in these decisions has been reported on (Tranvåg et al., *BMC Cancer* 2018).

Strand group: Ethical, Legal and Societal Aspects (ELSA) Group
The group has focused on ethical, legal and societal aspects (ELSA) of CCBIO's research, concentrating on improved self-reflection and increased RRI awareness (i.e. responsible research and innovation). This has been mirrored by continuous efforts in research and education, in general as well as directed towards specific topics and PhD projects. The team is responsible for the CCBIO903 course on *Cancer research: Ethical, economic and social aspects.* A major output is the book published in 2022 by Springer: Bremer A & Strand R (eds) (2022). *Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern*.

Bioinformatics and Big Data

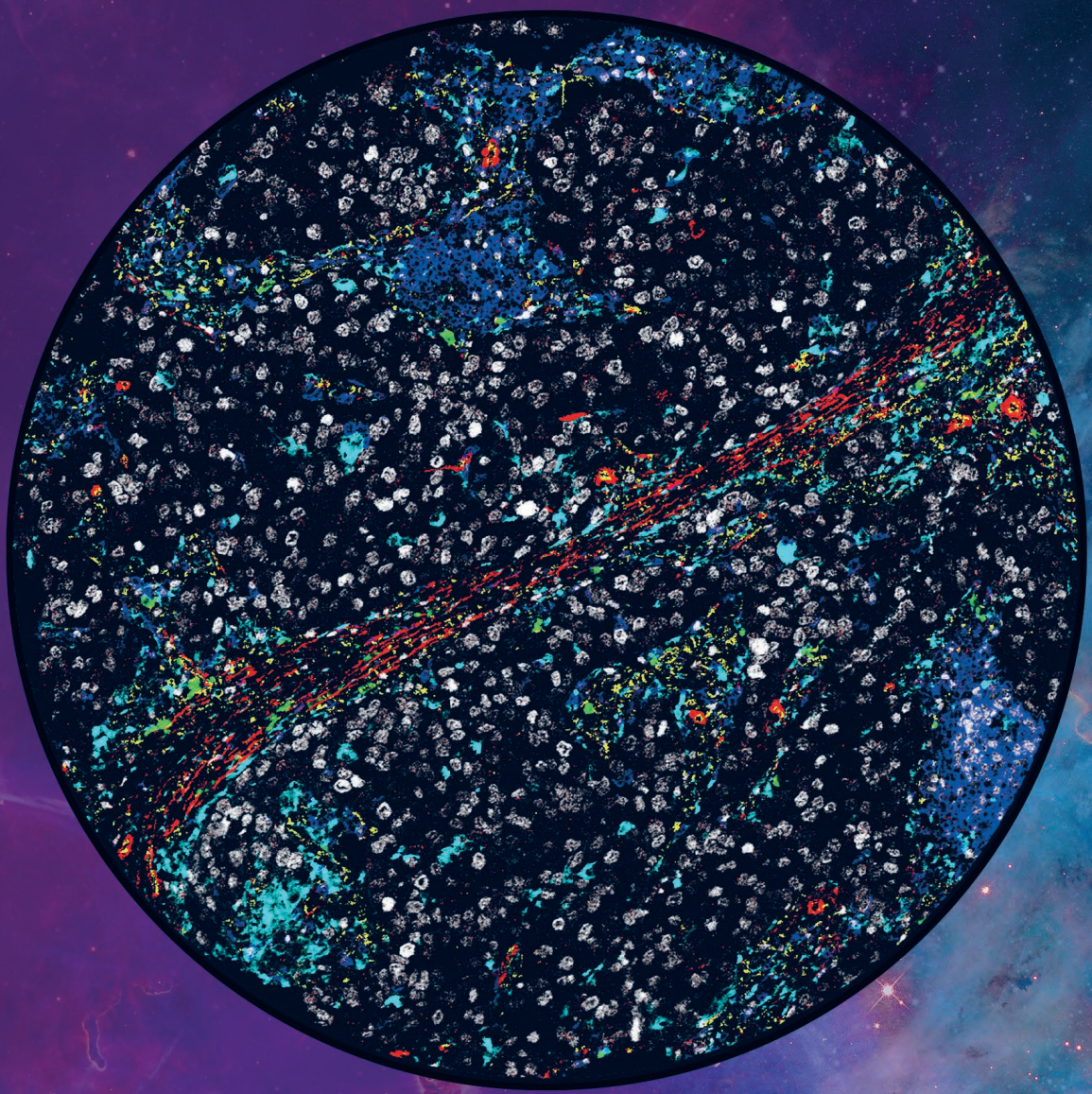
Jonassen group: Translational Bioinformatics Group
The group has developed algorithms and tools for analysis of molecular information including gene expression and single-cell data (CyToF, Imaging Mass Cytometry). A novel computational method of deconvoluting expression data to account for tissue heterogeneity and distribution of cell types was reported (Dimitrakopoulou et al., *BMC Bioinformatics* 2018). The group presented novel ways to utilize machine learning and systems biology modeling to help predict treatment response of individual patients (Tislevoll et al., *Nat Commun* 2023). Also, the group developed new methods for spatial analysis by imaging mass cytometry using graph-based representation of tissue images (Ehsani et al., *Bioinform Adv* 2023).

III. Concluding remarks

CCBIO has entailed multiple contributions in the field of cancer biomarkers — to other researchers, patients, and to society — with around 1000 papers published, 105 PhD theses defended, and multiple other contributions by educational efforts, public dissemination, and policy engagement.

Novel data have been reported on basic tumor drivers and mechanisms related to tumor cells as well as the essential tumor microenvironment. Further, data on single protein biomarkers, proteomic and transcriptomic signatures, and immuno-profiling have been published, leading to better understanding of cancer biology. Many of the biomarkers have been derived from clinical cohorts, and improvement of patient stratification has been shown. Several biomarkers are tested in clinical trials, and novel pathology-based markers have been included in national guidelines. Our data have been made available to the research community at large.

Our main goal for the coming years is two-fold: to continue our deep profiling of malignant tumors, and to increase the pace of moving results to the patients, by innovation projects and guideline processes. ••



Microcosmos meets Macrocosmos - the Emergence of Cancer Singularities

The image demonstrates the cellular composition and complexity of a basal-like breast cancer. Tissue has been stained with a 38-plex antibody panel using imaging mass cytometry.
(Photo: Kenneth Finne/Lars A. Akslen, CCBIO)

comments on CCBIOs self-evaluation

Text: Roger Strand & Lars A. Akslen

The backdrop
The resources channeled towards Norwegian Centres of Excellence both from the RCN and the host institutions, are both considerable in size and given on generous and flexible terms. Our final report is a "*thank you for the funding*" to all our supporters, including private agencies like the Norwegian Cancer Society.

Approaching the end of CCBIO's CoE period, the CCBIO principal investigators therefore embarked on a self-evaluation, attempting to observe ourselves through the looking glass, but hopefully without falling too deep into the rabbit hole. Through interviews and self-reflection, we have tried to take the bird's perspective to gain some overview and insight into the CCBIO landscape.

Methodologic approach
This self-evaluation exercise was conducted with the methodological approach of *evaluative self-inquiry* (de Rijcke et al., 2019; Völker, Mazzonetto, et al., 2023). During August–November 2022, Lars A. Akslen and Roger Strand (CCBIO Director and PI for Societal Studies, respectively) conducted conversations with all CCBIO principal and associate investigators. These conversations followed a semi-structured guideline whereby each investigator reflected on the main strengths and weaknesses of CCBIO and its outcomes, both at the center level and with respect to one's own group and work. Preliminary findings were presented and discussed with the CCBIO Scientific Advisory Board in 2023 and 2024.

The point of departure: The scientific vision of the CCBIO proposal
In asking "*what have we been doing these years?*", CCBIO's original CoE proposal (2012) provides a key point of departure. We proposed a restructuring of cancer research by gathering a rather wide set of cancer research groups mainly in Bergen around the goals of discovering, validating and translating functional cancer biomarkers, mainly at the proteomics level.

In terms of scientific vision, the proposal focused on the importance of tumor-microenvironment (TME) interactions in cancer progression and treatment responses, since this was considered to be understudied at the time, thereby highlighting the complexity of such communications both as an explanation for limited treatment success and as providing resources for new diagnostic and clinical opportunities. This complexity was contrasted with what the proposal explicitly criticized as a "linear focus" on gene mutations and alterations.

Also, the proposal put forth a series of theoretical concepts designed to account for TME complexity, including "cancer landscapes", "contextual cancer codes" (referring to TME interactions by which tumor cells become aggressive), and "molecular taxonomies and forecasts" of cancer. This vision was anchored in the arguably bold assumption that "the tumor cell's ability to respond to contextual signals in the microenvironment determines progression and patient survival" (CCBIO proposal).

The proposal included by its own initiative *social science and humanities (SSH) research* into the potential ethical, social, and economic perspectives of its own practice. It anticipated that the application of biomarkers could raise new issues about fairness and justice as well as cost-effectiveness. Accordingly, the CCBIO team would include researchers within the field of so-called ELSA (ethical, legal, and social aspects) research and health economics.

The pre-proposal was shortlisted and received praise for its "novel approach to unravel the mechanisms of carcinogenesis — in sharp contrast to the usual concentration on genetic mutation as the driving force of malignancy" (letter from the RCN, 1 June 2012). The full proposal received a very favorable evaluation that also appreciated the novelty and boldness of the scientific vision, understood as "the hypothesis that tumor cells are educated by the microenvironment to behave aggressively".

The thematic range of the CCBIO research output has been wide, and the focus was somewhat narrowed down in the second 5-year period (2018–23), in part due to significant investments in mass cytometry instrumentation for spatial and single-cell analytics.



The concept of excellence

The concept of *excellence* resides at the very core of our inquiry. As a Centre of Excellence, in what sense, and to what degree, may the results and the modes of operation of CCBIO be said to have been excellent? What does it take to plan and perform, develop and keep, and teach and learn excellence? More fundamentally, what *is* scientific excellence? These questions have been part of strategic discussions within CCBIO throughout its existence.

Concepts of excellence are not politically innocent as they may shift the focus of research practice, for example, away from topics of great local importance in a particular society, towards topics that are more easily published in international journals with high-impact factors (Stilgoe, 2014). In practice, there are tensions between the yearning for scientific prestige in a world of basic research, exemplified by publications in *Nature* or *Science*, and the context of being a translational research center with a clear aim to improve clinical practice and meet patients' needs also at a national and regional level. Thus, there must be struck a balance between these two ambitions.

Further, it is useful to distinguish between an *output-centered concept of excellence* that is defined mainly by the merits of research outputs such as scientific publications and rights to intellectual property, and an *organization-centered concept* that includes activities such as research education, management and leadership, and engagement with stakeholders and the wider public (Hellström, 2011).

Already in 2018, midway into the 10-year CoE period, CCBIO organized an open event at the University of Bergen to have a broader debate on the notion of *scientific excellence*, with invited scholars from Harvard University and Lund University. A central issue was whether CoEs are meant to establish, promote, or strengthen excellence, or whether excellence is a prerequisite for funding, upon which other qualities are meant to emerge, such as critical mass, or transformation of the research environment or research field. The seminar largely confirmed the notion that excellence appears in many forms (Lamont, 2009) and that this affords sufficient conceptual flexibility and adaptability to satisfy the needs both of academics and research policymakers (Hellström, 2011).

Further, in the case of Norway and the RCN CoE funding program, it appears that there has been a mixture of those two purposes, and perhaps with differing mixing proportions, across the funding cycles and the funded centers.

CCBIO was conceived as an example of the latter, i.e. already excellent environments that set out to create new research collaborations at the University of Bergen (and the university hospital, as well as national and international research environments), in keeping with the original CoE application. The added value promised by CCBIO was a restructuring of cancer research that could have scientific and social impact beyond Bergen and Norway.

Thus, as is clear from this report, CCBIO has endorsed a broader, organizational concept of excellence that includes a view of the social responsibility of science.

Translational research output with "normal impact"

The question of *impact* has been with us during the evaluative inquiry and indeed throughout the existence of CCBIO. It could be argued that it is too early to discuss the impact of ongoing research. The impact concept itself is tied to conventional intervention logic, assuming there has to be a direct linear causal and temporal flow from inputs and interventions to activities, and then further on in terms of *outputs → outcomes → impacts*. Considering the complexity of translational processes in biomedical research, a proper, robust assessment of the clinical impact of CCBIO research should wait until the 2030s.

In the discussion on the use of research assessment, a distinction has been drawn between *"normal"* and *"extraordinary" impact* (Sivertsen & Meijer, 2020). Cases of extraordinary impact are those that receive extremely high visibility in public or scientific media. Sivertsen and Meijer warned against exaggerated emphasis on extraordinary impact because it is not clear that research with such visibility is what actually creates the larger scientific or social impact in the long term, and because such cases will be rare and make up a small part of the research.

In CCBIO, the goals, as stated in the proposal, are conceived more in terms of normal impact – *of providing ever more biomarkers through a gradually refined biological understanding of TME interactions,* in contrast to extraordinary impact. Hence, an implicit notion of scientific *quality* was proved important in the evaluative inquiry. *Scientific quality* is a concept that takes the internalistic perspective and sees e.g. citations more as a sign of recognition than as evidence of effect.

In the evaluative conversations, several PIs highlighted as a strength of CCBIO that the research output has covered the range of translational biomedical research, from basic, preclinical studies to translational discovery of biomarkers and clinical trials. This was also in line with what was envisioned in the proposal.

The evaluative conversations confirmed that the translational aspect has been important also in studies of model systems at the cellular and molecular levels. In our self-understanding, a lot of CCBIO research falls within "Pasteur's Quadrant", that is, it can be categorized as research that combines a strong interest in fundamental understanding with a high consideration of use (Stokes, 1997).

In the evaluative conversations, PIs shared examples of CCBIO research work that they considered significant and of high quality, although not necessarily major stand-alone discoveries. This perception is consistent with our bibliometric exploration, with the existence of some highly cited papers, with a fifth or sixth of CCBIO papers being published in high-impact journals, and an aggregated citation analysis that showed CCBIO papers to be well cited relative to world averages.

Breadth versus research focus

Reflections on how to strike the *balance between breadth and focus* came up time and again during the evaluative inquiry. Some PIs reflected on how some of their international collaborators or other Norwegian CoEs have chosen to work towards narrowly defined scientific goals and organized themselves with strict, hierarchical leadership towards those goals. The following is an excerpt from an evaluative conversation between the director and one of the PIs:

Director: Are there weaknesses in CCBIO?
PI: Not easy to say. We've done a lot of good stuff, a lot of collaboration. We could possibly have had fewer projects and more focus at an earlier stage. It can become a bit too much business as usual. Maybe we should have had one project where everyone participated? But that being said, students and postdocs collaborate at their level. We never defined a $10 million moon shot.

Director: Yes, going from a CCBIO "network" to something more in-depth. But perhaps it also takes 5–10 years to define the moonshot?

PI: Maybe a moonshot in CCBIO2.0? Delve deep to solve one problem?

As witnessed by the excerpt, the balance between breadth and focus is an issue that goes beyond the question of extraordinary impact and the political economy of research. It is fundamentally a matter of scientific vision and choice.

The PIs did identify individual studies, findings, and outputs that they considered particularly important in terms of scientific quality. Among these, we find ongoing clinical studies that were described as "crescendos" and "tour de force biomarker analysis", in which also the preclinical research in CCBIO is being translated into clinical research.

The already mentioned narrowing and sharpening in research focus during the second 5-year period (2018–23) was clearly perceived in the PI group. In part, this was connected to leadership decisions such as financial investments in imaging and flow mass cytometry instrumentation and the use of internal calls for funds. In part, it was understood as the need for research interests to converge and for collaborations to develop organically.



In general, opinions on where to locate the balance between breadth and focus varied, though without expressions of strong disagreement. Most agreed that a strong, narrow focus (*"a moonshot"*) would have required a steeper hierarchical organization and performance-driven, strict leadership. Some PIs expressed that they might have welcomed that (at least to some degree) while others already experienced CCBIO leadership as quite strict. We may think of this as a choice in degree of hierarchical control but also as a reflection of the underlying conditions, including the CoE instrument itself, which is designed to promote curiosity-driven, fundamental research, and the organizational culture which still values a high degree of autonomy especially at the PI level.

Creation of new collaborations

From the CCBIO leadership perspective, an important dimension of its organization-centered approach to excellence was the creation of new research collaborations within CCBIO as well as with strong international research groups. In the evaluative conversations, most PIs expressed that they had developed new and important scientific collaborations both within CCBIO as well as with CCBIO's international faculty.

One PI described such a collaboration as a "CCBIO baby" that went "fantastically well". Several PIs attributed these collaborations directly to the existence of CCBIO and the particular style of leadership within CCBIO. Four factors appear important: First, the Director made direct efforts to facilitate scientific contact and collaboration. This took the form both of "soft" measures like creating arenas for interaction and discussion and by way of "hard" measures like setting an increasing degree of cross-group collaboration as a prerequisite to get CCBIO funding for projects. Second, approximately 20% of the budget was reserved for novel collaborations and emerging strategic areas, the so-called "strategic fund". Third, investments were made in joint infrastructure, in particular the mass cytometry facility. Finally, the group of PIs spent time together in a variety of meetings and events and gradually built trust and a sense of community.

The significance of international faculty and scientific events

A unanimous conclusion from the evaluative inquiry was the positive evaluation of CCBIO's scientific outreach, in the sense of its scientific events and how the center had reached out and affiliated internationally leading cancer researchers. More than a dozen such researchers (mainly from the USA and Europe) were included as "international faculty" in adjunct professorship positions. They received CCBIO researchers for incoming stays and visits, and they also made research visits themselves to Bergen to work with and mentor CCBIO researchers. International faculty took a very active part in scientific events such as the CCBIO symposia, seminars, and research education.

Most CCBIO PIs highlighted the international faculty as a success factor that contributed to open cancer research in Bergen up toward the larger world. Their presence, also at the CCBIO events such as the symposia and the ongoing

seminars, inspired and created new collaborations at a high scientific level.

The annual symposium stands out as the pinnacle of all CCBIO meeting activities, as a scientific event that attracts internationally leading capacities and an institution that has created a sense of identity, self-confidence, and pride in the CCBIO community as well as catalyzing high-level international collaboration. It is reasonable to assume that there has been a synergy between the investments in international faculty and the symposia, with our adjunct professors taking their share of ownership for the success of these events. Also, the monthly CCBIO seminars (which mostly have featured invited guests, including the international faculty) are very positively evaluated by the CCBIO PIs.

The research school
During the evaluative conversations, the CCBIO research school was often brought forth as one of the main achievements of CCBIO. Especially, during the second CCBIO period, it was seen as developing into a comprehensive research school for the new generation of cancer researchers at an advanced level that Norway had not seen before. It was (and still is) the only cancer research school in Norway. All courses are open for national and international participation and, for maximum effect, also open for master-level students.

The PIs describe that junior researchers have received training of exceptional quality and comprehensiveness and furthermore that they have developed a wide and mature intellectual scope and a sense of community and identity beyond their own group. Some PIs reflected on the long-term effect of the research school in *promoting better research* with more widely qualified practitioners, either in research or in other management and leadership positions beyond the research itself. Seeing this as an added value of CCBIO is once again an expression of a broad, organization-centered approach to excellence.

The inclusion of social sciences and the humanities
CCBIO has been quite unique in the Norwegian context as a biomedical CoE with a rather strong element of social sciences and the humanities (SSH) research already from the beginning. Several CCBIO PIs highlighted how SSH research had increased awareness of the ethical and societal aspects of cancer research and cancer treatments.

The health economists and medical ethicists who participated in CCBIO mainly focused on performing excellent research within their own disciplines, on CCBIO-relevant topics, and with occasional collaborations with biomedical groups within the center (see e.g. Kang & Cairns, 2022, 2023; Tranvåg et al., 2022). The science and technology studies (STS) group subscribed to an RRI — Responsible Research and Innovation — approach that aimed at integrating and embedding RRI principles within the biomedical research itself. Their consultancy function became rather strong as RRI often was translated into what has been called "the everyday responsibility of accountability and care" (Völker, Slaattelid, et al., 2023). Interestingly, a mode of RRI developed where the SSH scholar qua "RRI person" influenced conversations and decisions by being present as a sort of "critical friend" (Blanchard & Strand, 2024) and thereby played an important role within the CCBIO model.

CCBIO adding value to the PIs
Several PIs emphasized the utility of *CCBIO as a brand and as an identity*. The brand was perceived as important, e.g. in funding applications, and its importance was connected to CCBIO's increasingly positive reputation and visibility also internationally. For some PIs, the brand itself was seen as an important reason for a continuation of CCBIO after its CoE period.

Finally, the role of CCBIO as an *intellectual impulse* was highlighted. In part, this was ascribed to the high quality of the scientific events of CCBIO as well as the interaction with the Scientific Advisory Board. For some, albeit not for all PIs, however, CCBIO came to be their main scientific community and collegium. For the PIs, the continuation of CCBIO is a question not merely of bridge funding or brand but also one of scientific identity and commitment.

The CCBIO model
Following our self-evaluation, it is clear that at the core of the *"CCBIO model"* there is a broad, organization-centered approach to excellence and a desire to strike a balance between top-down defined research focus and bottom-up, curiosity-driven research breadth and diversity.

The broad notion of excellence was realized in the research school, the proliferation of new research collaborations within campus as well as abroad with the aid of the international faculty, the active outreach profile of the center, and the inclusion of SSH. Also, a key element of the CCBIO model was that from the outset in 2013, 20% of the funds were set aside for funding of emerging collaborations and promising research avenues. This approach created flexibility and agility, and from 2015 onwards, all allocation of funding was done on a per-project application basis, with increasing demands for strategic relevance and complementary collaboration. In this way, funding was increasingly used to support emerging "hot projects" with well-defined internal and external collaborations as well as compliance with core scientific concepts and strategies of CCBIO, rather than "splitting the spoils".

The administrative organization was lean while at the same time consciously aiming for the same notion of excellence in administrative support. This was at times demanding given the level of ambition of collaboration, communication, and



education activities. From the administrative perspective, the expediency (or lack thereof) of administrative processes at the department and faculty levels, sometimes emerged as a challenge to excellence that called for specific measures.

Apparently, *our self-evaluation of the CCBIO model is positive*. We found it fit for purpose and believe that several of its elements can and should be retained in the next, post-CoE, phase of CCBIO (the CCBIO2.0 phase). In deeming it "fit for purpose", we emphasize the correspondence between the scientific vision of CCBIO, its approach to excellence, and its organizational model.

As explained, CCBIO had a scientific vision that contained an element of *paradigm shift,* focusing on the complexities of tumor-microenvironment interactions. This is why the CCBIO model was fit for purpose, in that it presented a balance and synergy between *top-down governance and bottom-up creativity*. ••

Some concluding remarks

Based on our experience during the CCBIO CoE period, including some of the reflections above, there are a few potential lessons to be shared. We assume that the relevance for others is highly context-dependent.

Research funding organizations (RFOs). The most obvious lesson with relevance for RFOs is that CoEs come in different forms. Notably, CoEs may aim for excellence in a narrow or broad sense. As explained above, there should be a correspondence between the CoE model and function, and its structure. In other words, the scientific vision, strategy, and organizational model should be well aligned. Intellectually flat imaginations of RFOs' role, such as "to maximize groundbreaking research in Norway" may underperform by neglecting their considerable influence and power and instead need to act in a very targeted manner, as a change agent. Careful funding decisions on CoEs can release synergies and produce added value but they require a keen eye for how the instrument is used and the composition of CoE portfolios.

CCBIO is an example of a CoE that operated with a broad definition of excellence, focusing a lot on *sustainable science culture and diversity*. We believe the self-evaluation has indicated that CCBIO performed well by its own criteria. Notably, there is a need for responsible quantification, as recommended by the San Francisco declaration (DORA 2012), as well as the continued development of better research assessment and evaluation methodologies of the qualitative as well as the quantitative type.

One such methodology is *evaluative self-inquiry*, used by CCBIO for self-evaluation. While being less suitable for independent, external ("summative") assessment, its strength lies in how it helps build a common understanding in processes of formative assessment.

Host institutions. CCBIO has been hosted by the University of Bergen, mainly at the Faculty of Medicine. The evaluative self-inquiry has led to reflections on potential improvements in what we termed the "CoE-microenvironment interactions". We believe that these lessons might have value also beyond the local context.

In hindsight, the issue of co-localization was not sufficiently addressed and resolved, neither prior to application nor in the establishment phase nor during the midway evaluation. The CCBIO structure was therefore closer to a network than a one-site center that was originally intended. Since the allocation of lab space and offices touches fundamentally upon the very basic interests, e.g. of the departments involved, proper discussions and attention to such issues appear to be very much a host responsibility to be addressed appropriately at the institutional level.

The inter-department and inter-faculty organization of CCBIO resulted in *scientific added value* and was instrumental to the scientific vision itself. It posed some administrative challenges that CCBIO had to solve in order to maintain excellence in its organization. We believe the University of Bergen could continue to improve its organizational capacity to cater to the particular needs of different types of CoEs as well as to coordinate action between departments and faculties.

The CoE itself is a vehicle for research strategy. For instance, CCBIO has added value to UiB's research by creating new ways of research collaborations across departments and faculties and thereby restructuring the local research community. It developed innovations in research education through its research school, and it conducted research internationalization in a systematic and strategic fashion. The possible lesson for the host (UiB) is to give proper attention to CoEs as vehicles for its own strategic development and not just a source of research funding. This is also a matter of engaging in the so-called "exit" or post-CoE-funding strategies.

Other researchers. The CCBIO story is one example that a distinct, bold, and possibly counter-current theoretical concept at the core of a CoE proposal may succeed. Indeed, this is one way of realizing "groundbreakingness". A clear underlying research concept favors effective communication of the proposal but more importantly — as witnessed in the case of CCBIO — it can also give a clear direction to the research that creates a space for strategic decisions during the operational phase.

There should be a correspondence between the type of scientific vision at the core of the CoE, the organizational model of the CoE, and one's own success criteria, as exemplified in the choice between narrow and broad conceptions of excellence and the balance between normal and extraordinary impact. There is no one right approach. Instead, CoE design should be *fit for purpose*.

Taking the *fit for purpose*-maxim and other centers' experiences as a point of departure, CoEs are quite distinct from departments and big research groups. Hence, attention should be given to negotiations with the host institution at an early stage, to tailor a setup for each individual CoE. This includes much more than pure budgetary issues — such as co-localization, administrative procedures, and routines. Establishing some "rules of engagement" in writing can be a cornerstone.

Taken together, our advice is to map out as many aspects as possible for reflection and interaction within the PI group as well as with the institutions and units involved. We believe that this will maximize the odds for success. ••

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comments on organization

A Centre of Excellence (CoE) is not a department, not a research group and not a big research project. It entails elements of all three, but is something entirely different, making it challenging to incorporate and organize within the standardized institutional frameworks.

CoEs are usually inherently multi-disciplinary, often spanning across several departments, faculties and even organizations. They also have the longest funding horizon in Norway, 10 years of economic predictability and funds nobody can take away. This is quite unique in our national research landscape. So how did we organize CCBIO to make the most out of this privileged position?

Upon contacting existing CoEs to learn from their experience, it became clear that there are many potential pitfalls. Several CoEs had experienced a high level of conflict with their host departments, draining both money and energy from their research efforts. From our point of view, it would be a pity if the center grant and the privileged situation it created should become a bone of contention or even a battleground.

The Romans managed to keep their internal peace, their *pax romana*, in a diverse cross-cultural empire for centuries. So, it should really be possible to ensure a semblance of *pax ivestigationis* in and around a cross disciplinary center for a mere decade. But how could we achieve that?

So, let's be honest. It's about power, i.e. the ability to make others act in a different manner than they would otherwise have done. So, how to gain full control over the resources granted to CCBIO, while at the same time making friends rather than enemies? Should we choose hard power or soft power? Well, both, but with a preference for the softer variant. In the end, CCBIO combined some old and new maxims into its own variant, and decided to "*smile, talk softly, bring gifts and carry a big stick*" (inspired by Theodore Roosevelt et al).

Let's be honest, again. People may want to do the right thing, but especially if times are perceived to be hard, people think with their stomachs. So, knowing that your department or faculty is contributing towards the RCN's top research program and excellent science is all good and well, but maybe not enough. Positive reinforcers and incentives are needed and also constitute a much more efficient way of wielding power than mere arm twisting. Hence, we aimed to set CCBIO up so that the departmental leadership and administration would perceive the hosting of CCBIO activities as being clearly beneficial to their department (*… smile, talk softly*). Then we had to deliver on the promises over time so that the departments felt they were constantly getting something they really wanted (*… bring gifts*). We also had to make it clear that in case of departmental misbehavior, we would be willing to withdraw and relocate resources to other departments (*… carry a big stick*). In case of faculty level- or institutional misbehavior, we also had to signal or preferably prove our willingness to twist arms, e.g. by voicing a breach of contract directly to the RCN (*… carrying an even bigger stick*).

Luckily, the RCN had already realized that with so many resources comes the risk of being raided. Without talking about the dynamics of privilege and envy, let's just say that the RCN had inserted into its contracts that a CoE shall have a "*high degree of scientific and administrative independence*" — and that this proved to be a very necessary precaution.

So, how to set this up without CCBIO becoming too much of a continuous battleground? Machiavelli stated that bad things should be done all in one go, whereas good things should be spaced out. In this way, people will feel safe and remember the good stuff. Hence, instead of handling problems as day-to-day skirmishes, we moved to confirm CCBIO's independence initially in one single effort, in relation to faculty and department levels, thereby clearing the air and paving the way for positive and friendly day-to-day interactions when moving forward. This needed to take place while CCBIO still had "hard power", preferably in the form of a "nuclear option".

In retrospect, this is what we did: During the spring of 2013, the faculty's administrative leadership, quite publicly, attempted to shape CCBIO according to the perceived needs of the line organization, by locating all positions and funds at a single department. As CCBIO was to be a cross-disciplinary center with activity at four faculties and seven departments, this did not appear to be appropriate,



as it would likely violate the RCN contract. This strained situation was used to establish a more lasting "treaty" with the Faculty of Medicine and the three medical departments. This took the form of written "*rules of engagement*" that was signed by the CCBIO director and the head of departments, and also endorsed by CCBIO's local council where the dean was chair and the director of the Haukeland University Hospital was represented.



This signed document, in short, described CCBIO as a cross-disciplinary center organized in a matrix structure across seven departments and four faculties, and that CCBIO should have full control over its resources while the departments catered for day-to-day administration of funds and personnel. In more detail, it also spelled out:

• The practical implications of the RCN's contract terms, giving CoEs a high degree of scientific and administrative independence.

• CCBIO's organizational aims, e.g. avoiding conflicts of interest with the line organization, handling cross-department activities seamlessly and using as many resources as possible directly on research, while also giving CCBIO's researchers the best possible administrative support.

• Defining the role and authority of the center director and administrative leader, e.g. that the director could decide on recruitment and the administrative leader could instruct the department's administrative personnel whenever they were involved in CCBIO matters.

• The authority and role of heads of department and the center director in different types of HR processes.

• That as a main rule, positions and funds would be located at the department where the research activity was to take place.

• That the departments would receive the RCN overheads or similar and that dissertations and publications would be addressed to CCBIO as well as the respective departments, crediting the departments fully. In return, the departments would conduct all routine administration and take the risk of deficits on PhD and PD positions.

Having this agreement in writing and signed by heads of departments, made sure that it was practically impossible to remember the terms arbitrarily, or for the organization to "forget" the agreement when leaders and staff were replaced. We thus forestalled most of the misunderstandings and conflicts bound to arise over such a long period and with much money involved. It also enabled us to quickly solve the few issues arising, as in most cases it sufficed to send the agreement to the person in question. We believe that this procedure acted to prevent a significant number of challenges and problems. The signed agreement catered for clarity and good relations with the involved departments throughout the full 11-year period (2013-2024).

During the second half of CCBIO's CoE period, we were to an increasing degree asked for advice by other centers and CoEs countrywide. We take this as proof that research organization is not merely some nuisance that needs to be done. Rather, organization is one of the main pillars upon which all activity involving groups of humans is based, and medical research is definitely a group effort. Hence, excellent science very much depends on excellent organization.

Clearly, we did not invent the wheel from scratch. We based ourselves both on prior knowledge and experience, transferred from persons and other centers, and also from within CCBIO. We owe our colleagues a lot for sharing their advice. ••




ORGANIZATION
OF THE
CENTER

comments on educational activities

In a world where everything moves faster, and the threshold for what represents a high standard constantly goes upwards, conducting excellent research often resembles racing the proverbial *Red Queen*. If you just run, you stand still and if you stand still, you actually go backwards. There are many factors outside of the direct effort and energy put into conducting research that decides whether you run faster than the others.



Basic strategy
Creating a competitive center characterized by excellence resembles the process of carefully erecting a building. You'll need to select a good spot, lay the foundation, erect the supporting structure "stone by stone" and set up "behind-the-walls" piping and wiring. This takes time and effort.

As we submitted our Centre of Excellence (CoE) application in 2012, the PI group already had comprehensive experience from previous work, in running groups, collaboration, international networking, and in using resources and platforms on campus. The Research Council of Norway (RCN) agreed that the *groundwork* was sound. CoEs are in practice awarded to already excellent research environments, but with the expectation that the center organization, grant and 10-year period of grace will trigger output not otherwise possible. Importantly, one of the key promoters of excellent research is excellent education.

Core educational activities
How did we deliver on the expectation of excellent education? We started out by actively strengthening our educational *foundation* even before CCBIO's official starting date. This took the form of establishing a strategic community by creating activities that would act as a basis for education by interaction, e.g. the CCBIO Annual Symposium, monthly research seminars and Junior Scientist Symposia. Then, in 2014, the *CCBIO Research School for Cancer Studies* (RSCS) was announced and opened. Initially, the RSCS mainly focused upon the methodological skills explicitly needed to fulfil CCBIO's research ambitions in the years to come. Later, the perspective widened, and the number of courses increased gradually.

CCBIO went one step further, applying for external funding for educational measures, receiving a total of 9 mill NOK (INTPART I and II and an Olav Thon grant). We used these funds to (1) establish international courses of extremely high quality together with our partners from the Vascular Biology Program (VBP) at Boston Children's Hospital and Harvard Medical School, (2) establish a program of lab visits to the VBP in Boston with the aim to transfer state of the art skills to the UiB, and (3) giving master students access to all RSCS courses and (4) extensive resources for their own research projects far beyond what would otherwise have been possible. Within the fields influenced by this additional external funding, we are confident that we have offered the highest quality of cancer research education in Norway, possibly also in Northern Europe.



Ethical and societal perspectives
Already from the outset we realized that today's world is complex, and we might need an "inner compass" to navigate properly in the contemporary science landscape. Hence, we initiated a resource intensive course in *Ethical,*



Economic and Social Aspects. This was CCBIO's first effort to provide our up-and-coming researchers with deeply rooted self-reflection.

Generic skills

CCBIO also included a package of so-called transferrable skills, e.g. scientific writing, science infographics, communication, how to design a "science pitch" and presentations, and mentoring of young and promising candidates, these skills being omnipresent and essential in our everyday conduct of activities, but not immediately visible. Building upon the success of such activities, courses related to patient involvement, running of clinical trials, and biomedical innovation have also been included.



Career challenges

Transitioning from post-postdoc to a faculty position is an inherent challenge in today's academic institutions, and very frustrating for many younger colleagues and talents. CCBIO has, notably through its *Masterclass Program* for future research leaders, tried hard to ease growing pains and transitional issues by providing know-how and coping strategies, e.g. in grant writing, navigating the system, leading research groups and in networking, and not least by setting up a mentoring program. We have also, through inspirational lectures and group sessions with extremely successful researchers like Bob Langer and Bruce R. Zetter, provided cases on how to overcome friction and resistance and move on to success. One important take-home message is to learn *when to stand your ground*. Another key message is to know the fine balance between *persistence and obstinacy*, and also the distinction between *persistence and perseverance*.

Taken together, we believe that CCBIO's targeted educational efforts have provided its researchers with a well-founded basis of methodological and transferrable skills on a very high level and an arsenal of coping strategies and resilience. Assuming that everyone else work as hard as they can, this gives our up-and-coming research leaders the best possible chances of getting ahead by running smartly rather than just hard. Hence, excellent research and *beating the Red Queen* is very much about education. Finally, having been copied by others, CCBIO will now have to run even smarter. ••

comments on communication and outreach

It is easy to forget that *communication and dissemination* is an important part of the universities' *third mission* after research and teaching, i.e. generating knowledge outside academic environments. CCBIO has focused strongly on this from the outset, making it one of our cornerstones.

CCBIO has five major communication and outreach aims:

- Bringing updated knowledge and understanding to the population
- Being a visible flagship for cancer research
- Strengthening CCBIO as a brand
- Good internal communication
- Recruiting the best

In retrospect, how well did we meet our goals?

Initial strategy
Apart from a very active mass media profile around our opening symposium, CCBIO initially also focused on consolidating internal communication and basic forms of external communication. CCBIO's webpages have been an important part of internal communication and our visibility strategy. After the initial phase, CCBIO decided to use the UiB web platform and to work with the Department of Clinical Medicine's communications responsible. This proved fruitful far beyond the initial expectations.

External communication
Our media strategy has been developed over the years in collaboration with the Faculty of Medicine's communications unit and was invaluable to CCBIO from the outset. The amount of coverage received around the opening symposium was on a level so impressive that the UiB's central communications unit was rather taken aback when informed it was of our own making, having believed it must have been a very lucky coincidence.



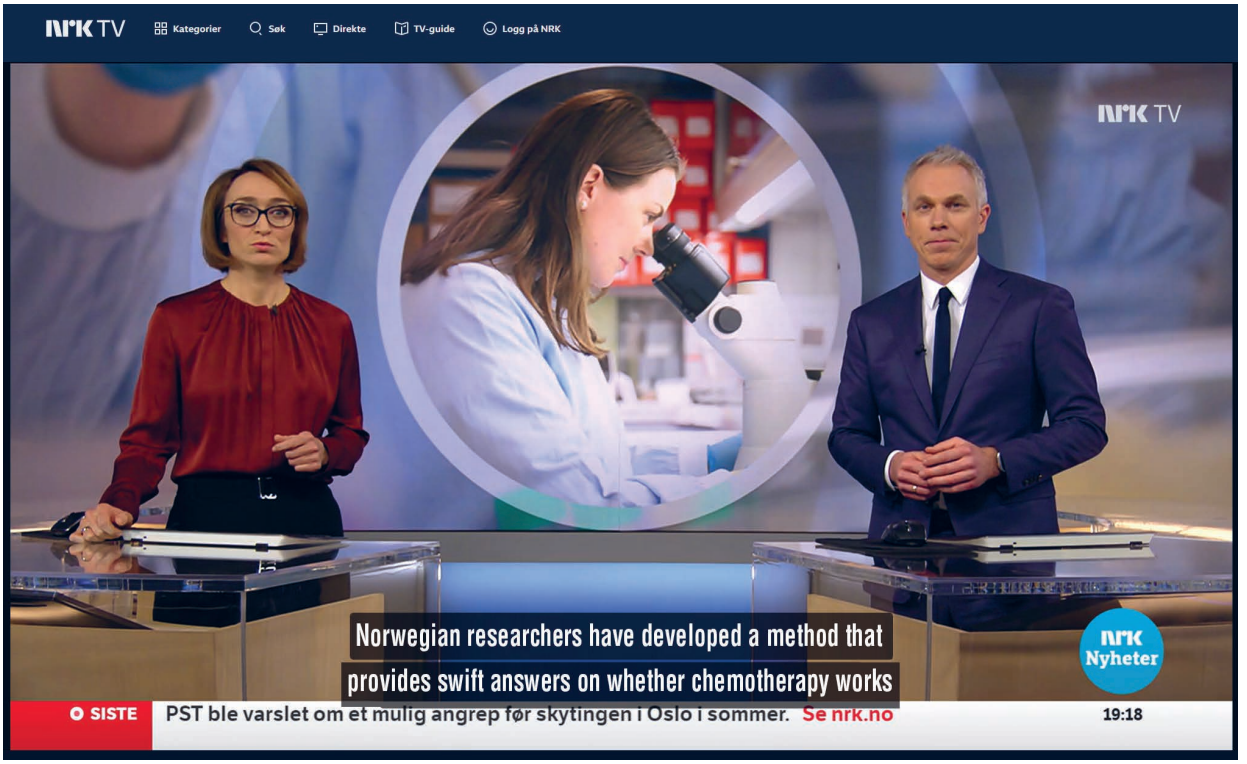
The steady work, focus and training in media relations, and our media advisor support in contact with mass media, resulted in more than 500 media appearances. In this way, CCBIO communicated to the wider public its important research discoveries on biomarkers and precision cancer therapies, expert commentaries on the research results of others, patient case stories, and it's participation in the public debate concerning ethics and prioritization.

Further, CCBIO has used the Faculty of Medicine's social media channels throughout the CoE period, promoting our scientific findings, our researchers, happenings and media appearances, and we have recently opted to additionally establish our separate channels. This is to make sure the audience understands that CCBIO will continue as a flagship center beyond the CoE period (CCBIO2.0).

CCBIO prioritized to have a strong presence at the National Science Week (Forskningsdagene) in Bergen, a regional research fair mainly for pupils ranging from primary school throughout high school. CCBIO's stands were very well visited, and PhDs and PDs as well as the director took part in research fair events. CCBIO also arranged and took part in public debates directed towards adults, e.g. in collaboration with the Norwegian Academy of Science and Letters at Litteraturhuset in Bergen.

Communication towards children
As we believe dissemination towards children should be more focused upon than is often the case, we entered into a collaboration with Henriette Christie Ertsås, a CCBIO PhD graduate who is also a trained actor. Initially she performed her already established and cancer-related interactive plays for schoolchildren on CCBIO's behalf. Then, in 2019, she approached the CCBIO leadership with the idea of popularizing the CCBIO book *Biomarkers of the Tumor Microenvironment*. The result was, to our knowledge, the first popularized interactive theatre play based on a cancer-related textbook, performed more than 100 times mainly for children aged 10–14 years, in schools and at Forskningsdagene.

Internal communication
Internal communication was established and maintained through newsletters, 4–6 issues per year, round-mails and through our many meeting points. This applies to staff



meetings on all levels, the monthly research seminars where cross-team mingling was encouraged over pizza, as well as more ad hoc research meetings and mini-symposia.

The CCBIO Research School was integrated into CCBIO's other communications activities and intentionally set up to bring young researchers from different fields together, e.g. making sure there are group assignments in all classes where relevant. CCBIO's Annual Symposium was established as an important meeting place and "retreat" for all staff, also connecting them with local, national and international collaboration partners outside of CCBIO.

Annual report

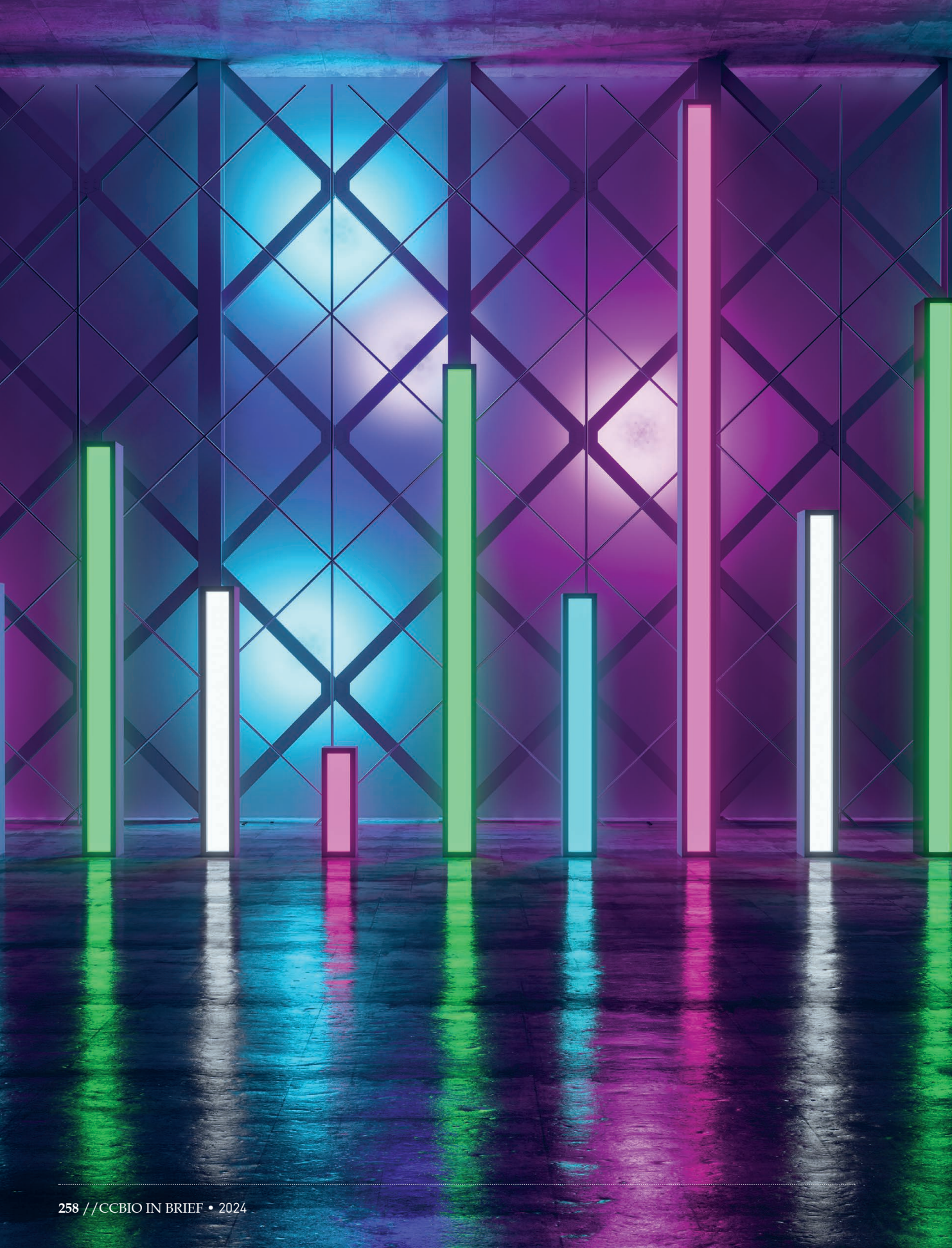
In addition to the use of webpages and mass media, another important hybrid internal-external communication format has been the annual report. The quality of this publication, now more of a book, has developed year by year, in close collaboration with our long-time photographer and designer. These reports provide an excellent overview and documentation of CCBIO's efforts throughout.

Some reflections

In combination with CCBIO's graphic profiles, we believe the above activities have contributed towards making CCBIO as recognizable a brand as possible within our field. This conscious effort has made the university, departments and our own groups recognize and actively seek out CCBIO's events, and also make the CCBIO name and our core concept recognizable in the media and by current and potential future collaborative partners nationally and internationally. It seems to us that CCBIO is now a firmly established brand associated with high quality cancer research and education, as befitting a Centre of Excellence.

Our evaluators, e.g. the CoE Midway Evaluation Panel and our Scientific Advisory Board seem to concur that our communication and dissemination activities have been very successful. We experience that the involved staff take pride in being part of CCBIO as we head for CCBIO2.0. Notably, we find that later-coming centers of excellence and similar have looked to CCBIO for inspiration, as a source of best-of-practice and often copying our activities and style. We choose to read this as a solid vote of confidence from our peers.

Apart from fulfilling this part of our *third mission*, we also believe that our dissemination efforts, in more tangible terms, have increased our ability to recruit high level collaborators as well as new staff at the highest possible level. As an example, upon announcing positions, we have had well above 100 applicants to single PhD positions, enabling us to recruit among the very best candidates. In their own turn, these recruitments have not only enabled high level publications but have also enabled us to cater well for CCBIO's aftergrowth, ensuring a continuation of our achievements moving forward to CCBIO2.0. ••




CCBIO
Infographics
2013–2024

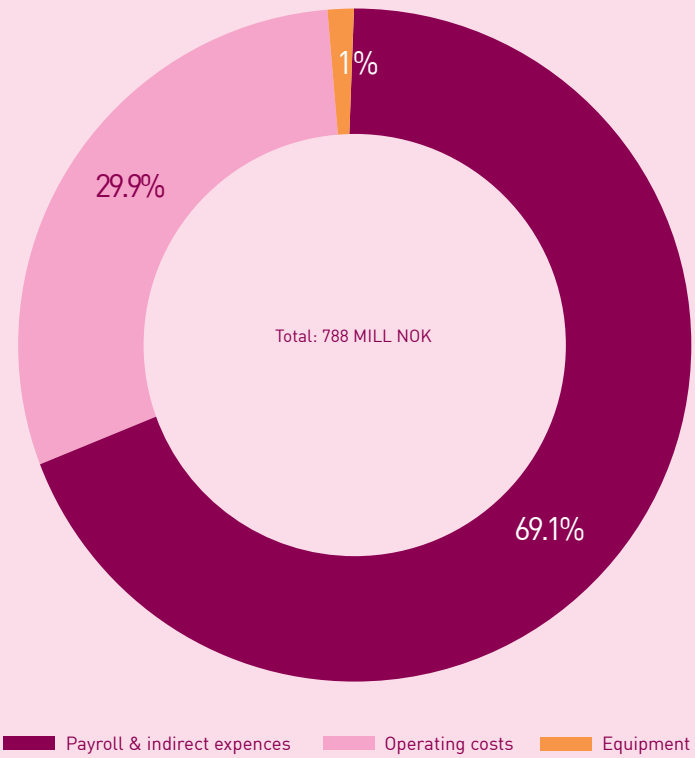
facts and figures 2013-2024

PERFORMANCE INDICATORS

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	Total
Publications	76	71	77	85	94	81	79	79	126	123	97	46	1034
Completed PhDs	6	5	5	10	12	9	8	15	8	11	8	8	105
Media appearences	39	11	32	31	54	40	68	54	54	54	51	21	509
External funding MNOK	7	22	23	36	34	32	27	30	27	34	36	19	326
External funding as % of total	55%	38%	41%	50%	43%	43%	35%	39%	37%	40%	42%	46%	41%

CCBIO's scientific production has been on a high level throughout its CoE period, with 105 PhDs completed and more than 1000 scientific papers and book chapters. The output of PhDs peaked in 2020 followed by a very high number of publications in 2021-22 as the previous years' long-term efforts came to fruition in the form of scientific papers. Our considerable amount of media appearances, more than 500, is one of the indicators showing that CCBIO has taken its third mission activities (beyond research and teaching) very serious, putting a lot of effort into the various forms of dissemination and outreach. CCBIO's external funding, outside of the CoE grant, is well above twice the budgeted amount and illustrates a high success rate with funding agencies, totaling 326 MNOK and 41% of the total 788 MNOK used in CCBIO's CoE period July 2013 to June 2024.

FUNDING 2013-2024

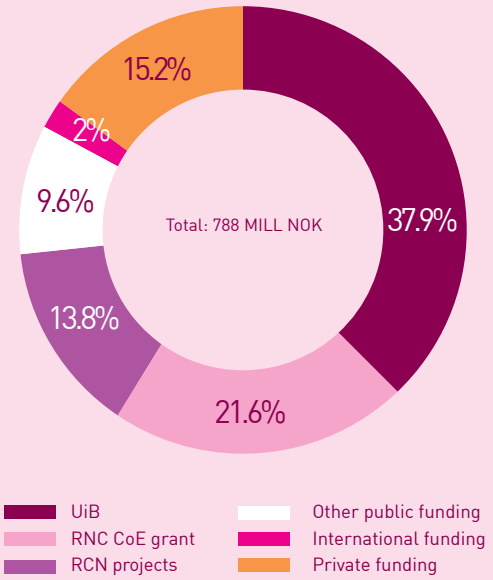


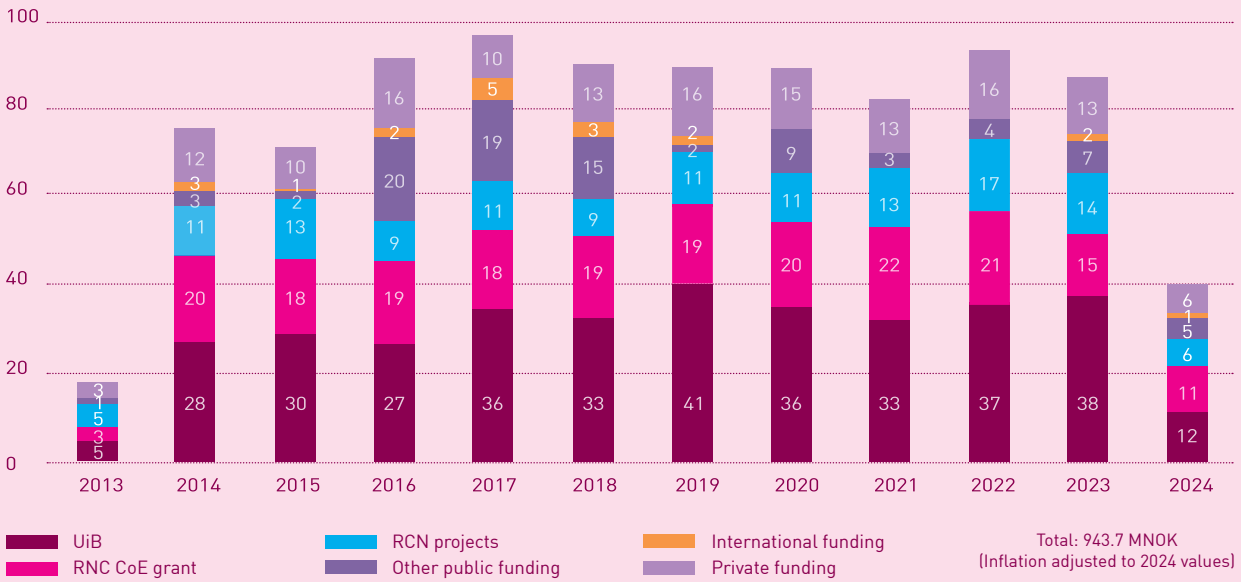
COST TYPES

Research in general is labor-intensive, and 69% of CCBIO's 788 MNOK in expenses from July 2013 to June 2024 were related to the upkeep of our highly qualified staff. A CoE within cancer biomarkers is, however, also a technology- and laboratory intensive venture. In our accounting this is expressed by almost 30% of our expenses being related to operating costs in various forms. This encompasses everything from pipettes and antibodies to the use of high-tech equipment, e.g. in core facilities at the UiB. Initially, we budgeted with purchase of research services from external vendors. Looking back, we are very happy that our own faculty and university as well as the Trond Mohn Research Foundation (TMF) decided to fund the purchase of the groundbreaking Hyperion Imaging System. This, in combination with the core facilities at Haukeland Campus, enabled CCBIO to channel its funds locally rather than buying services from commercial companies. The resulting effective use of funds, and economic cross-fertilization within the UiB has put CCBIO in an excellent position to keep up its level of research moving forward.

FUNDING SOURCES

During CCBIO's CoE period of July 2013 to June 2024, own contributions from the UiB constituted the largest share of funding with 298 MNOK (38%) of the total. This includes both "fresh funding", i.e. funds under direct control of CCBIO and in-kind own contribution in the form of faculty positions, overheads and depreciation of major equipment units used by CCBIO. The generous and very flexible CoE grant made up the second largest share of our funding with 170.3 MNOK (21.6%) of the total. Considering that the CoE grant had a 10-year horizon and was part of CCBIO's base funding, we illustrate other project funding from the RCN as a separate category with 108.9 MNOK (13.8%). Other public funding, 75,4 MNOK (9.5%), is mainly from Helse Vest RHF (the Western Norway Regional Health Authority). Private funding, 119.5 MNO (15.2%), is project funding and contribution towards equipment given by foundations and trusts, of which 83% is from the Norwegian Cancer Society. The Bergen-based Trond Mohn Research Foundation (TMF) has provided targeted funding for equipment, as well as for CCBIO's aftergrowth through its Starting Grant Program. Interestingly, CCBIO's private funding is in aggregate larger than the project funding from the RCN outside of the CoE grant and equivalent to more than two thirds of CCBIO's CoE funding from the RCN. *We are deeply grateful towards the generous individuals making voluntary donations towards research in general and cancer research in particular.*





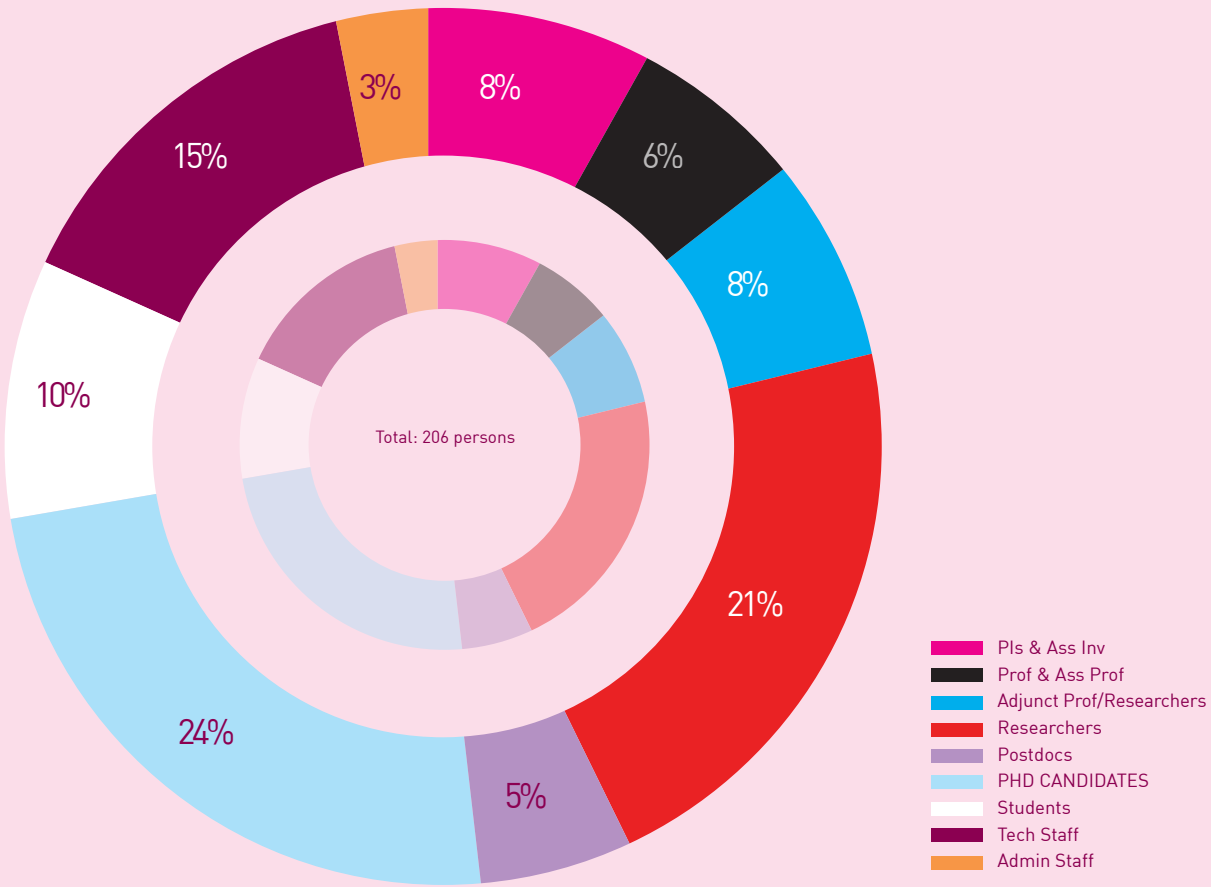
Total: 943.7 MNOK
(Inflation adjusted to 2024 values)

RESOURCES USED

In 2013 every NOK was worth almost 1.4 times its value in 2024. When illustrating CCBIO's use of resources over an extended 11-year CoE-period, we have therefore adjusted for inflation with point of departure in the 2024 NOK value. The inflation adjusted overview of total resources, and our funding sources, shows that CCBIO's 788 MNOK used amounts to almost 950 MNOK in 2024 values. When looking at the table, the half year effect created by starting in July 2013 and finishing in June 2024 is obvious. CCBIO used the second half of 2013 to quickly and efficiently recruit the first batch of key personnel, as is indicated by the resources used in 2014. CCBIO's peak use of resources in 2016-2017 illustrates CCBIO's high success rate with funding agencies and foundations. The peak of CoE- and UiB funding used in 2019 shows the overlap between the first and second 5-year CoE period.

The pandemic-related reduction in activity in 2020-2021 caused a major delay in operating costs. Our staff was barred from performing their duties by the lab bench, equipment broke down with no outlook for repairs and even pipettes were hard to come by. However, since the Norwegian universities refrained from using temporary layoffs when lab work was made impossible, the gravity of the situation for lab-based research is only partly illustrated in our accounting. The delay in activities in turn contributed towards the continued high level of UiB and CoE funds used in 2022, 2023 and 2024.

HUMAN RESOURCES



STAFF OVERVIEW 2023 (HEADCOUNT)

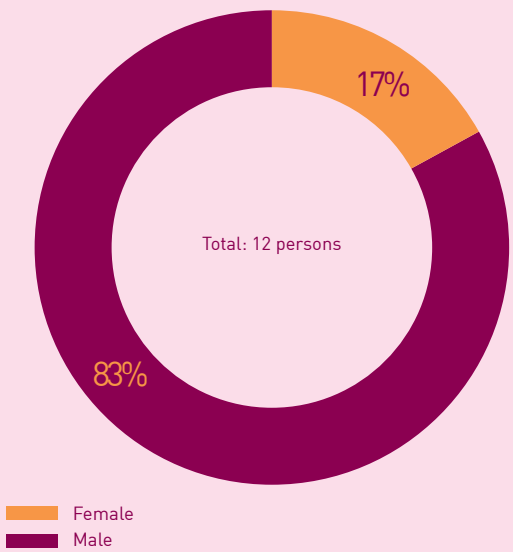
As a representative snapshot of CCBIO in full operation, we have chosen to show you a staff overview from 2023. This year is quite representative of CCBIO's balanced composition of 200+ junior- and senior researchers and support staff throughout its CoE period. To strengthen the ground for major breakthroughs and high-level publications, we have focused increasingly on prolonging and developing the projects of top tire younger researchers. During its second 5-year period, CCBIO recruited younger, predominantly female, investigators as associate PIs, over time giving them full PI status. We have given them bridging funds for salaries and supported their efforts to solicit their own funding portfolios and establishing their own independent groups. Through the CCBIO Masterclass program, two batches, each of around 10 selected younger researchers, received targeted training to prepare them to become CCBIO's future group leaders. CCBIO's international network of 14 adjunct professors and researchers ensured excellent access to high-level collaboration, advice, and tuition for CCBIO's researchers.



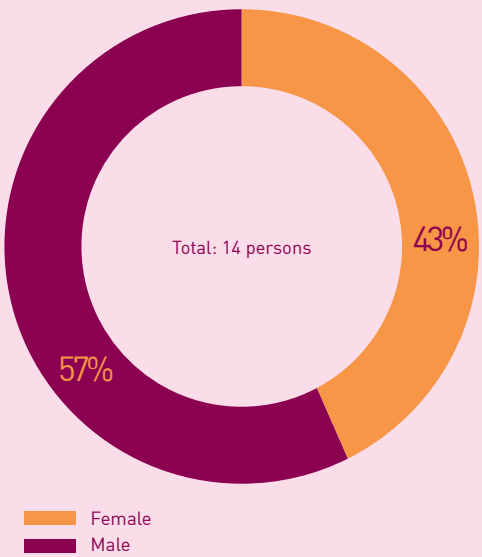
GENDER DISTRIBUTION 2023 (HEADCOUNT)

Among the persons involved in CCBIO, a stable majority are women, and of PhD students and postdocs about 60% are female. Among senior researchers, the female share is steadily increasing year by year and is currently almost half the total. CCBIO's active recruitment of excellent female staff during its second CoE-period has further increased the female part of its principal- and associate investigators from 17% in 2013 to 43% in July 2024. Throughout its CoE period, CCBIO undertook no gender based affirmative action and was among the first at the UiB to insist on removing the clause encouraging women to apply for PhD and PD positions. Recruitment of faculty has been done purely on merit, and among more junior staff and future group leaders also on perceived potential. Looking back over the years in general and at the development among PIs in particular, it is quite clear that by now the pool of female talent is such that merit-based recruitment is sufficient to gradually improve the gender balance in CCBIO's top tire.

CCBIO PIs 2013

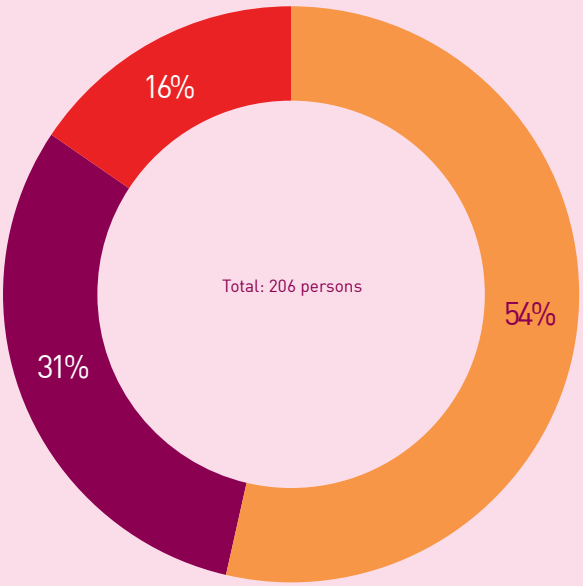


CCBIO PIs 2024



INTERNATIONALIZATION

(Staff country of origin)



STAFF COUNTRY OF ORIGIN 2023

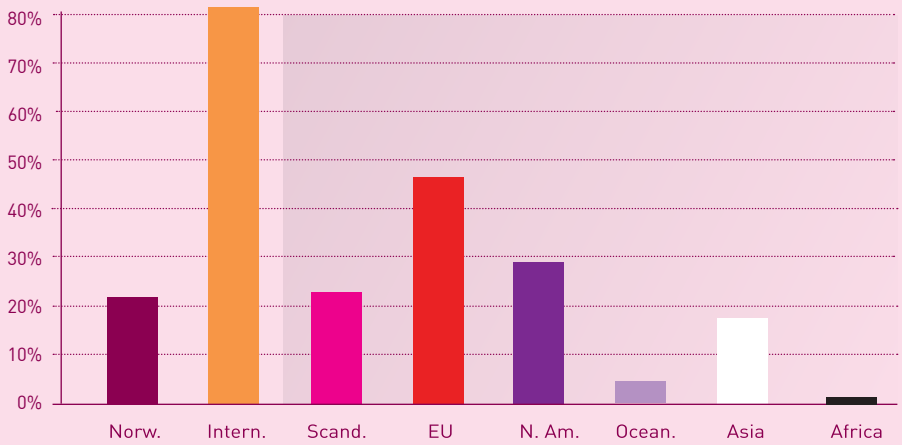
Of CCBIO's overall staff in 2023, 47% had other citizenships than Norwegian, and 73% of its postdocs and 44% of PhDs originated from outside of Norway. Of CCBIO's international PhDs, half originated from Asia and Africa. Among CCBIO's senior researchers, 45% are foreign nationals. With minor variations, the tendency from 2023 holds true for the whole CoE period, making CCBIO a truly internationally staffed Norwegian Center of Excellence.

- NORWAY
- Other Western Countries
- Africa & Asia

INTERNATIONALIZATION

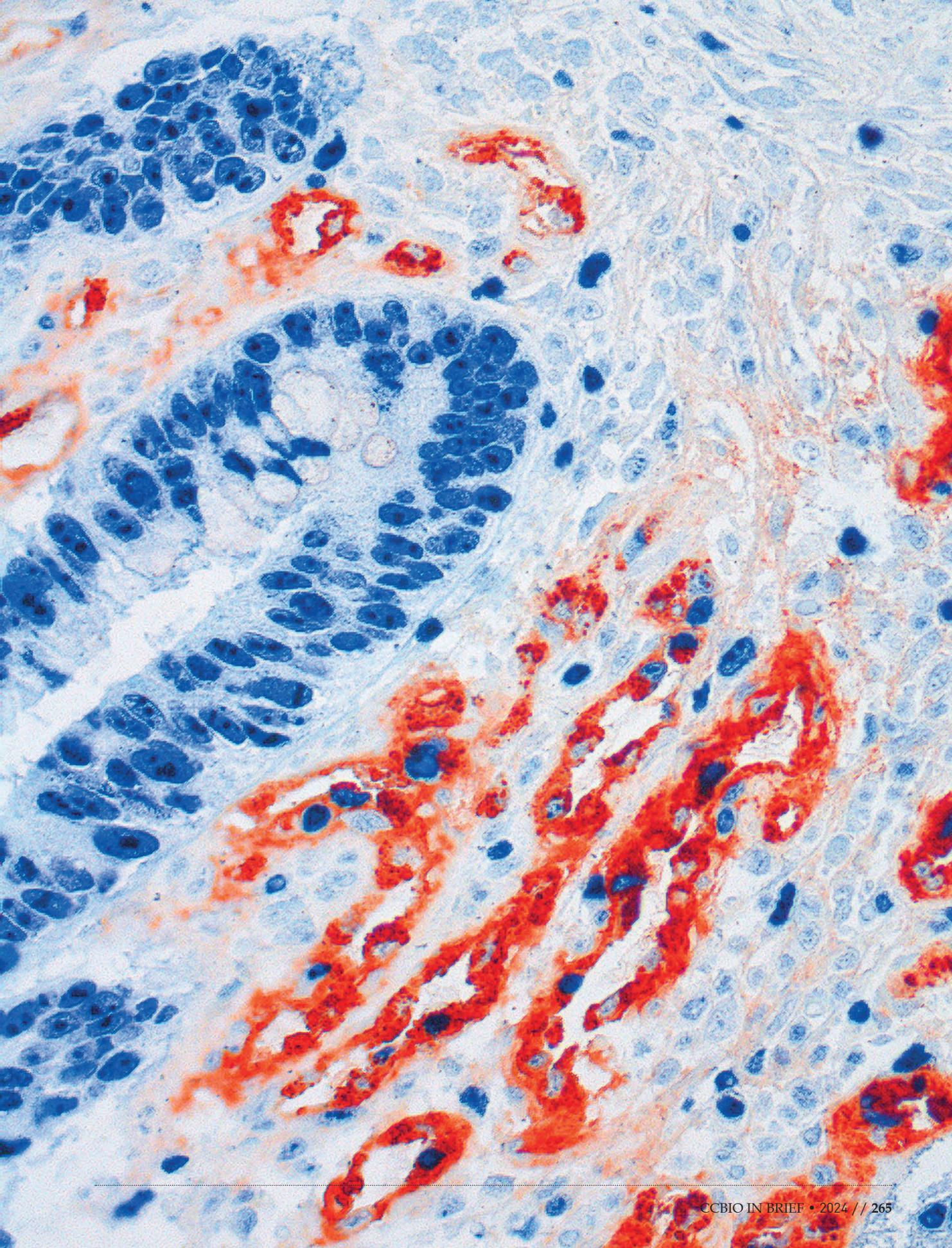
(Co-authorships)

- Norway
- International, over all
- Scandinavia
- Europe
- North America
- Oceania
- Asia
- Africa



INTERNATIONAL COLLABORATION 2023

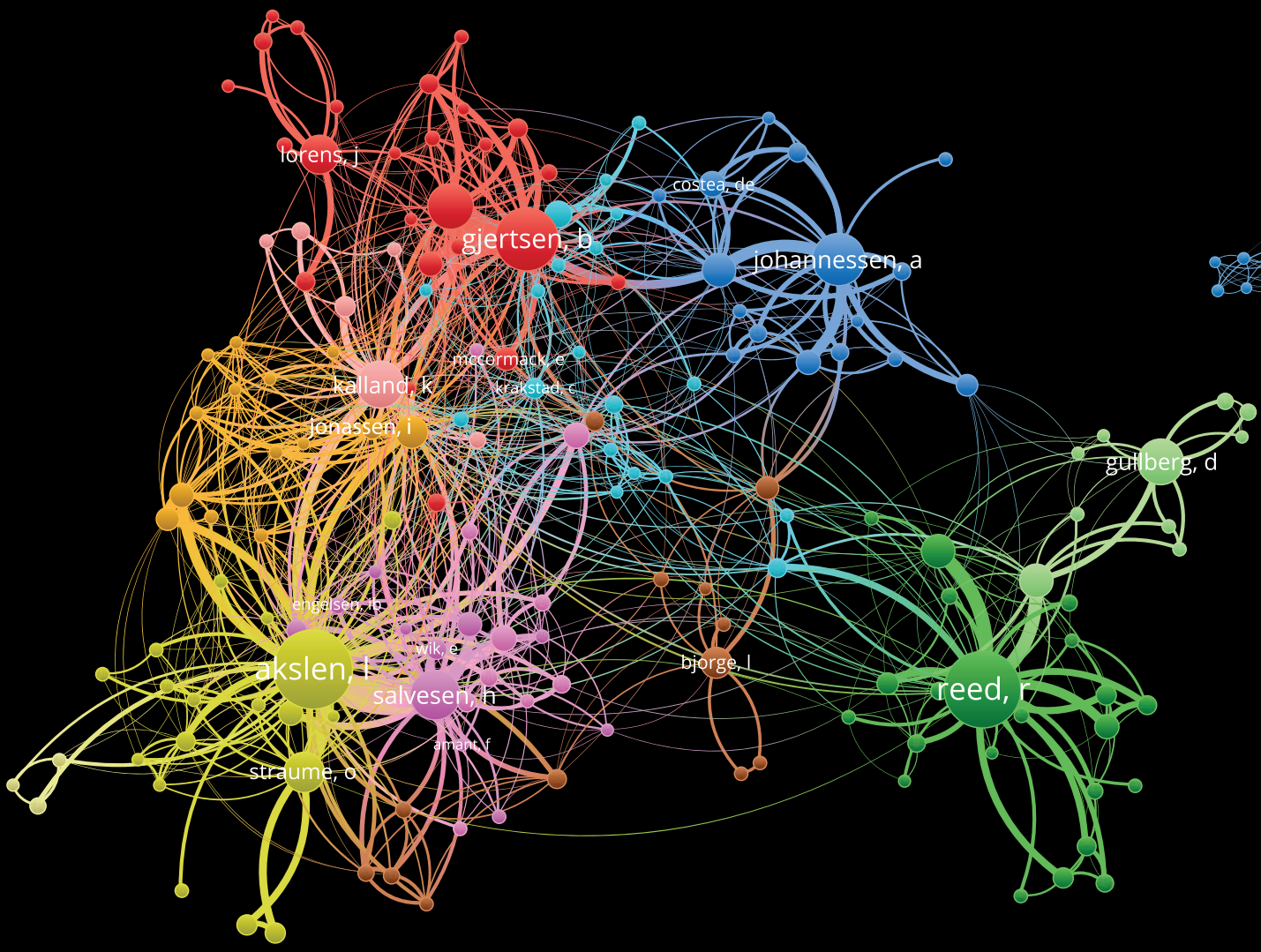
CCBIO's research continues to become increasingly internationally integrated through both formalized- and publication-based networks. The share of publications with co-authorships by researchers from other Norwegian universities decreased from 35% in 2020 to 29% in 2022 and 22% in 2023, and solely Bergen based publications now stand at a mere 10%. CCBIO's ever stronger international networks on the other hand generate an increasing number of publications with co-authors from international institutions, rising gradually from 58% in 2019 to 82% in 2023. Further, the subdivision of international co-authorships into six regions (grayed out background) demonstrates that CCBIO collaborates with institutions from all major regions worldwide. If we then add up these six columns, we reach 124%. By comparing this total with the 82% in the "international summarized"-category, we can conclude that the average international CCBIO publication in 2022 had co-authors from more than one worldwide region, being truly multi-regional. If we then look at the numbers behind the statistics, we also observe that many of the publications have co-authors from several countries within each region. CCBIO has clearly experienced a strong increase in its international research collaborations throughout the CoE period, both widening and deepening in scope. This is of course partly due to the general tendency towards increasing international research collaboration but most of all it reflects CCBIO's strategic choices.

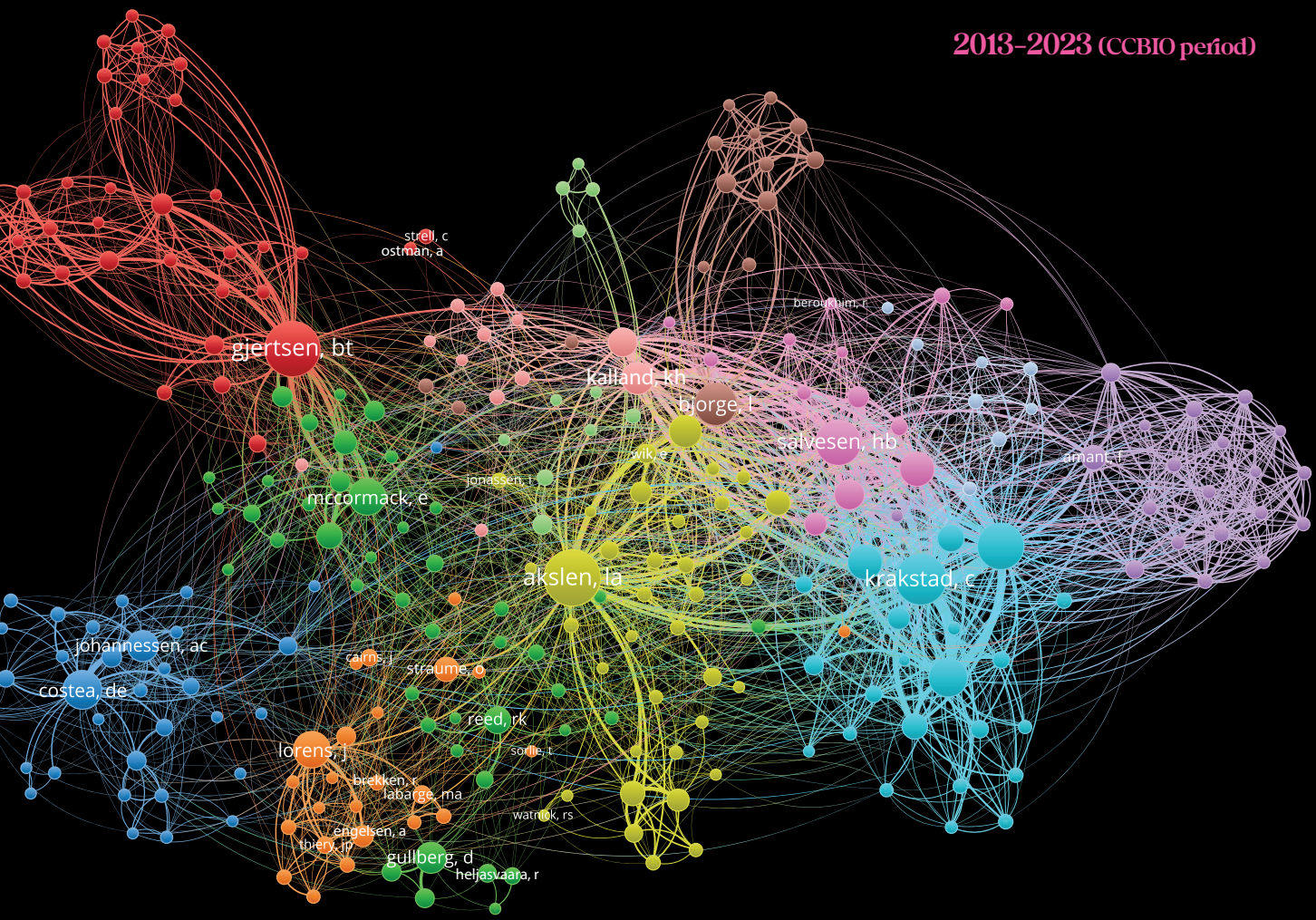


The CCBIO pattern

This bibliometric network review of collaborative patterns based on author lists of publications by CCBIO's biomedical PI's tells a story about the developing relations between PIs and also with the CCBIO international faculty. During the main centre of excellence (CoE) period (2013 – 2023), a much stronger integration between these research environments has evolved. This fits with our impression of increased and tighter collaborations within CCBIO, including our affiliated international networks. Thus, CCBIO did bring together already excellent research environments and tied them together to a much stronger and productive enterprise than just adding individual strands of activity. Notably, CCBIO's researchers have actively integrated their international faculty and other researchers during the CoE period. Different aspects of this are covered in the text of this report including the Facts & Figures section, as well as in the figures of the following pages.

2008–2012 (pre-CCBIO period)





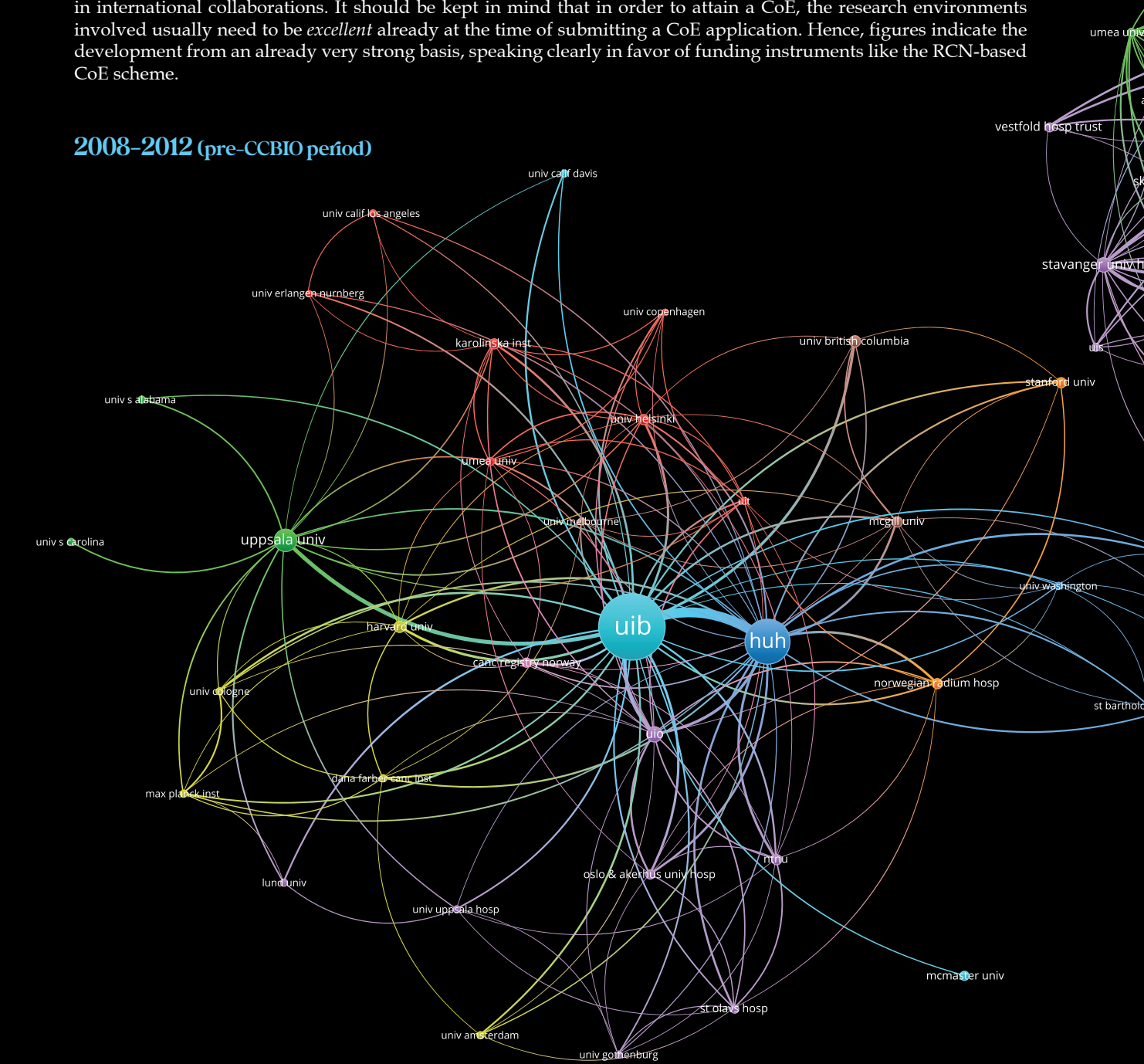
How to interpret the figures

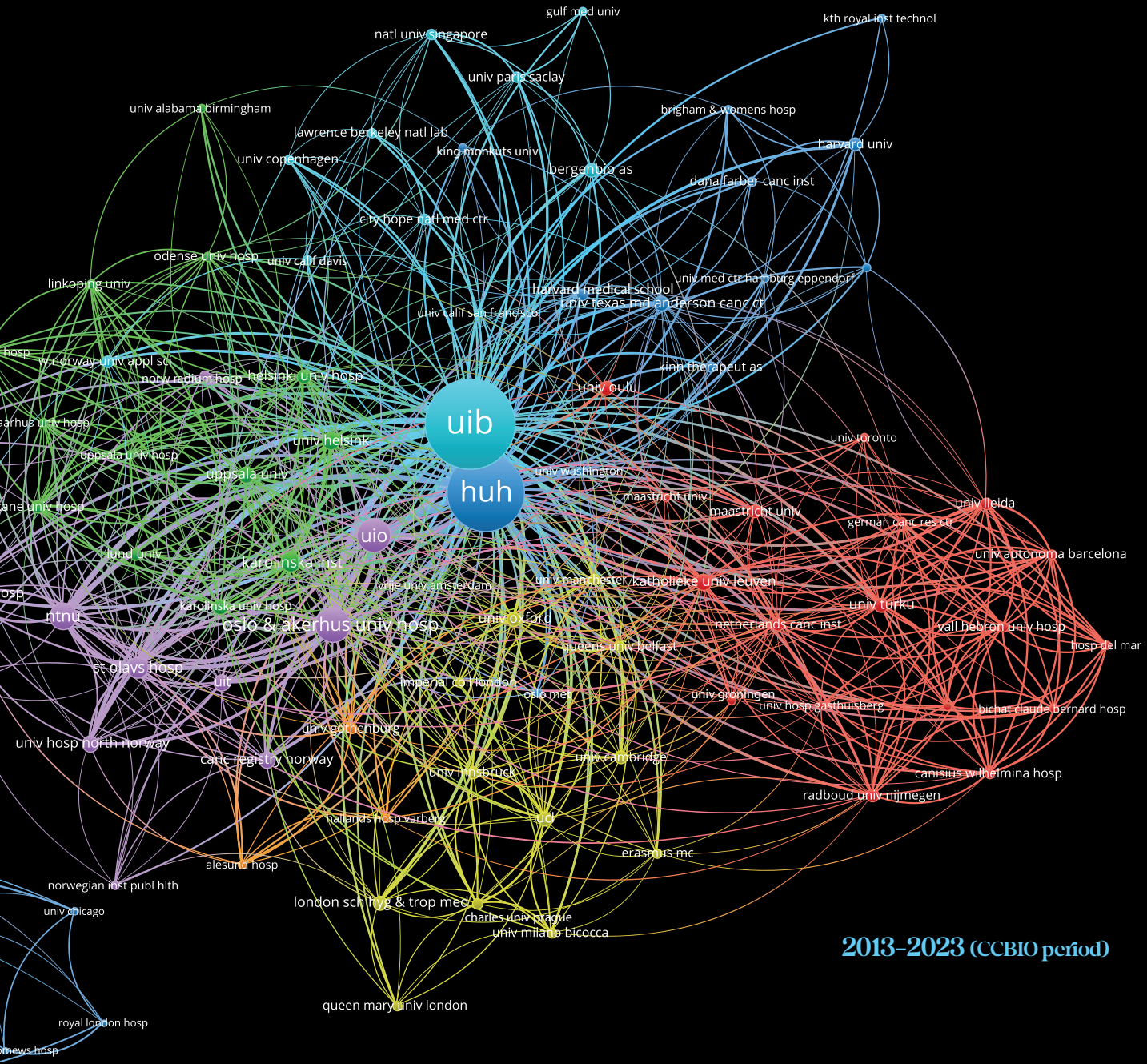
PIs and international faculty are labelled. Each circle is an author (many of them named). Authors with 5 or more publications, and articles with 50 or fewer authors, are included. Cluster colors give an indication to how authors are grouped (based on co-authorships). Node size indicates number of publications, while lines indicate co-authorships, with thicker lines indicating more co-publications. Line thickness is relative on each map and cannot be directly compared between maps. Distance between nodes is not a direct measure of strength of relationships.

The CCBIO Collaborative Cosmos

The figures reflect two bibliometric reviews of the institutional affiliation of authors on CCBIO's biomedical PI's publications during the years before CCBIO was established (2008-2012) and during CCBIOs main tenure as a CoE (2013-2023). In the figure, the CCBIO PIs are made up by the two clusters named "uib" (University of Bergen) and "huh", (Haukeland University Hospital in Bergen). This is mainly due to most CCBIO PI's having shared appointments or funding and activities also at HUH, thereby being obliged to report both affiliations. However, HUH has not been a formal partner in the CCBIO enterprise. Despite the difference in the number of years for the two figures, the tendency is obvious. There is a strong development both in terms of number of publications and a remarkable increase in international collaborations. It should be kept in mind that in order to attain a CoE, the research environments involved usually need to be *excellent* already at the time of submitting a CoE application. Hence, figures indicate the development from an already very strong basis, speaking clearly in favor of funding instruments like the RCN-based CoE scheme.

2008–2012 (pre-CCBIO period)





How to interpret the figures

The thickness of the lines reflects the strength of relations between authors, and the size of the dots illustrate the number of authorships. Distance between various circles gives a rough indication of the relative frequency of co-authorships between the institutions. For the figures to be generally comparable and for the CoE period figure to be readable, only institutional affiliations with a minimum of 6 occurrences are included, and publications with more than 25 co-authors, in effect network publications, are excluded. Hence, the figures demonstrate collaborative relations with publications containing a strong CCBIO contribution.

dissertations 2013–2024

Dissertations have been included from the start of CCBIO (inaugural symposium on May 30–31, 2013) until the formal end date on June 30, 2024; a few theses submitted shortly after the end date have also been listed.

2013



YI QU
Generation of a stepwise prostate carcinogenesis model. A study of epithelial to mesenchymal transition and malignant transformation of prostate primary epithelial cells. Supervisors: Karl-Henning Kalland, Xisong Ke and Anne Margrete Øyan. Defense date: May 29, 2013.



ELISABETH WIK
Endometrial carcinoma: a step closer to individualized therapy? Exploring transcriptional alterations in relation to prognostic biomarkers. Supervisors: Helga B. Salvesen and Lars A. Akslen. Defense date: September 30, 2013.



JØRN SKAVLAND
Risk stratification and therapy response monitoring by phosphoprotein profiles in acute myeloid leukemia. Supervisors: Bjørn Tore Gjertsen and Øystein Bruserud. Defense date: August 30, 2013.



HANNE HASLENE-HOX
The microenvironment in human ovarian carcinoma - characterization through proteomic analysis of tissue interstitial fluid. Supervisors: Helge Wiig, Olav Tenstad, and Helga B. Salvesen. Defense date: October 11, 2013.



EVEN BIRKELAND
Mutations and gene amplifications in endometrial carcinomas. Clinical characteristics and potential targets for therapy related to KRAS, MYC, ATAD2, PIK3CA and FGFR2 alterations. Supervisors: Helga B. Salvesen and Camilla Krakstad. Defense date: September 20, 2013.



HANNE EKNES PUNTERVOLL
Molecular studies of sporadic and hereditary cutaneous malignant melanoma. Supervisors: Lars A. Akslen and Anders Molven. Defense date: December 11, 2013



2014



AMANI HAMZA A. OSMAN
Characterization of the tumor stroma and stem cell niche in oral squamous cell carcinoma. Supervisors: Anne Christine Johannessen and Daniela Elena Costea. Defense date: February 20, 2014.

TARIG AL-HADI OSMAN
Cancer stem cell-related markers in normal and neoplastic oral mucosa; a study on human samples and experimental models. Supervisors: Daniela Elena Costea and Anne Christine Johannessen. Defense date: June 4, 2014.



HENRICA MARIA JOHANNA WERNER
Clinical and molecular markers in endometrial cancer. Studying prognostic and predictive biomarkers that can help to individualize therapeutic decisions. Supervisors: Helga B. Salvesen and Jone Trovik. Defense date: May 20, 2014.



CRINA ELENA TIRON
The Role of the Axl Receptor Tyrosine Kinase in Breast Cancer. Supervisor: James B. Lorens. Defense date: June 20, 2014.



ØYSTEIN HELLAND
Ovarian Cancer: A clinical challenge requiring basic answers. Development of an orthotopic ovarian xenograft model accessible to surgical intervention and exploring the role of Treg in evasion of immune destruction. Supervisors: Line Bjørge, Bjørn Tore Gjertsen and Emmet McCormack. Defense date: May 23, 2014.



2015

IDA WIIG SØRENSEN
Molecular Characterisation of Integrin a 11 Function. Supervisors: Donald Gullberg and Marion Kusche-Gullberg. Defense date: February 12, 2015.



LIV CECILIE VESTRHEIM THOMSEN
Preeclampsia specific genetic risk factors and shared predisposition with cardiovascular disease. Supervisors: Line Bjørge, Anne-Charlotte Iversen, Rigmor Austgulen, Ottar Nygård and Eric K. Moses. Defense date: March 13, 2015.



LENE ELISABETH MYHREN
Cell death induction by free and encapsulated cancer drug candidates. Supervisors: Stein Ove Døskeland, Lars Herfindal and Bjørn Tore Gjertsen. Defense date: October 16, 2015.



KATARZYNA WNUK-LIPINSKA
The role of Axl signaling in phenotypic plasticity in normal and neoplastic epithelial cells. Supervisors: James B. Lorens and David Micklem. Defense date: April 7, 2015.



2016

JENNY HILD AASE HUSBY
Functional imaging to promote individualized and targeted therapy in endometrial cancer. Supervisors: Ingfrid S. Haldorsen and Helga B. Salvesen. Defense date: February 5, 2016.



METTE LØKELAND
Implementation of medical abortion in Norway 1998–2013. Supervisors: Line Bjørge and Ole Erik Iversen. Defense date: April 17, 2015.



HIMALAYA PARAJULI
Role of integrin α11 in oral carcinogenesis. In vitro and in vivo studies. Supervisors: Daniela Elena Costea, Anne Christine Johannessen and Donald Gullberg. Defense date: April 29, 2016.



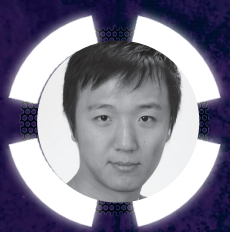
FANNY PÉLISSIER

The Role of Age in Cellular Responses to Microenvironmental Cues as a Breast Cancer Susceptibility Factor. Supervisors: James B. Lorens and Mark LaBarge. Defense date: May 9, 2016.



GØRIL KNUTSVIK

Biomarkers in breast cancer, with special focus on tumor cell proliferation. Supervisors: Lars A. Akslen and Ingunn M. Stefansson. Defense date: October 31, 2016.



HENGSHUO LIU

Expression and mechanosensitivity of integrin alpha 11 in the tumour microenvironment. Supervisors: Donald Gullberg and Rolf Reed. Defense date: September 16, 2016.



LAVINA AHMED†

Axl as a Biomarker in Breast and Lung Cancer. Supervisors: Lars A. Akslen, David Micklem and Hawa Nalwoga. Defense date: November 2, 2016.



INGVILD LØBERG TANGEN

Hormone signaling related factors as biomarkers in endometrial cancer. Supervisors: Camilla Krakstad and Helga B. Salvesen. Defense date: October 7, 2016.



ELISE AASEBØ

Mass spectrometry-based proteome quantification in leukemic cells from acute myeloid leukemia patients. Supervisor: Frode S. Berven, Frode Selheim, Marc Vaudel and Bjørn Tore Gjertsen. Defense date: November 4, 2016.



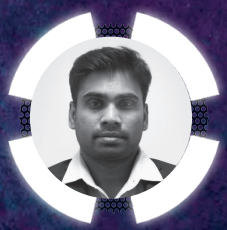
CORNELIA SCHUSTER
Investigation of predictive markers in patients with metastatic melanoma treated with bevacizumab. Supervisors: Oddbjørn Straume and Lars A. Akslen. Defense date: November 22, 2016.



MARIA OMSLAND
Investigation of the intercellular structure tunneling nanotube (TNT) in leukemia. Supervisors: Vibeke Andresen and Bjørn Tore Gjertsen. Defense date: February 3, 2017.



ANDRÉ SULEN
Leukocyte p38 and p53 proteins after environmental exposure; variation, associations and applicability. Supervisors: Bjørn Tore Gjertsen, Jörg Assmus and Bjørg Eli Hollund. Defense date: December 9, 2016.



PUGAZENDHI MURUGAN ERUSAPPAN
Molecular Aspects of Integrin α11 Function. Supervisors: Donald Gullberg and Helge Wiig. Defense date: May 5, 2017.



2017

JAN ROGER OLSEN
Context dependent transcription factor regulation in normal and malignant cell differentiation. Supervisors: Karl-Henning Kalland, Xisong Ke and Anne Margrete Øyan. Defense date: January 27, 2017.



KAREN KLEPSLAND MAULAND
Context-related biomarkers in endometrial cancer – a study with focus on obesity and genomic alterations. Supervisors: Henrica MJ Werner, Helga B. Salvesen, Erling André Høivik and Jone Trovik. Defense date: June 9, 2017.



ANNA BERG
Molecular alterations and diagnostic imaging in premalignant and malignant endometrial lesions for improved diagnosis and treatment. Supervisors: Ingfrid Haldorsen, Camilla Krakstad and Henrica MJ Werner. Defense date: June 22, 2017.



STEFAN HINZ
Mechanisms of AXL mediated cell plasticity and drug resistance. Supervisors: James B. Lorens and Gro Gausdal. Defense date: September 8, 2017.



INGA REIGSTAD
Investigation of different aspects of the tumor microenvironment as determinants of tumor development and progression. Supervisors: Linda Stuhr and Rolf Reed. Defense date: June 22, 2017.



MARIT VALLA
Molecular subtypes of breast cancer: incidence and prognosis. Supervisors: Anna M. Bofin, Signe Opdahl and Lars A. Akslen. Defense date: October 12, 2017.



SURA AZIZ
Biological and clinico-pathologic markers in breast cancer. With focus on histologic features, markers of proliferation and angiogenesis. Supervisors: Lars A. Akslen and Elisabeth Wik. Defense date: June 27, 2017.



KRISTI KRÜGER
Markers of angiogenesis and the basal-like phenotype of breast cancer. Supervisors: Lars A. Akslen and Elisabeth Wik. Defense date: November 8, 2017.



MARI KYLLESØ HALLE
Molecular alterations suggesting new treatment strategies in uterine carcinomas. Supervisors: Camilla Krakstad and Jone Trovik. Defense date: November 10, 2017.



STEIN-ERIK GULLAKSEN
Single cell signalling and immune profiles in chronic myeloid leukemia. Supervisors: Bjørn Tore Gjertsen, Jorunn Kirkeleit and Emmet McCormack. Defense date: March 23, 2018.



GRY SANDVIK HAALAND
Investigations of the cancer therapeutic and protective effects of warfarin-mediated inhibition of the receptor tyrosine kinase AXL. Supervisors: James B. Lorens and Oddbjørn Straume. Defense date: November 17, 2017.



HENRIETTE CHRISTIE ERTSÅS
The effects of ageing on microenvironment-contextual epithelial cell signalling. Supervisors: James B. Lorens and Rein Aasland. Defense date: April 6, 2018.



2018

TOR AUDUN KLINGEN
Vascular invasion by tumor cells, and other prognostic factors in a population-based breast cancer study. Supervisors: Lars A. Akslen and Elisabeth Wik. Defense date: February 20, 2018.



MARIA RAMNEFJELL
Prognostic biomarkers and clinico-pathologic characteristics in non-small cell lung cancer. A study with special focus on tumor-vascular interactions. Supervisors: Lars A. Akslen and Lars Helgeland. Defense date: April 10, 2018.



EMILIA HUGDAHL
Prognostic and molecular markers in primary and metastatic cutaneous melanoma. Supervisors: Lars A. Akslen and Rita Grude Ladstein. Defense date: April 20, 2018.



LAWRENCE FRED SEMBAJWE
EXT Proteins: Role in Heparan Sulfate Assembly and in Tumor Biology. Supervisors: Marion Kusche-Gullberg, Donald Gullberg and Helge Wiig. Defense date: August 24, 2018.



WAQAS AZEEM
Regulatory patterns in prostate cell differentiation – investigation of transcription factors AR, GATA2 and NKX3-1. Supervisors: Karl-Henning Kalland and Xisong Ke. Defense date: June 1, 2018.



TINA FONNES
Preclinical models and molecular biomarkers - tools to improve treatment in endometrial carcinoma. Supervisors: Camilla Krakstad, Emmet McCormack and Bjørn Tore Gjertsen. Defense date: November 30, 2018.



ISRAA ABDULRHMAN AHMED
Identification of prognostic biomarkers for oral squamous cell carcinoma. Study on human samples and experimental models. Supervisors: Daniela Elena Costea, Anne Christine Johannessen and Dipak Sapkota. Defense date: June 26, 2018.



2019

KATHARINA BISCHOF
Rethinking Gynecological High-Grade Serous Carcinoma. Portraying the p53 isoform landscape and development of a new preclinical tool for optical imaging in xenograft models. Supervisors: Line Bjørge, Emmet McCormack, Bjørn Tore Gjertsen and Stian Knappskog. Defense date: February 8, 2019.

dissertations 2013–2024



MARIA RYSSDAL KRABY
Tumor Vasculature in Subtypes of Breast Cancer. Supervisors: Anna Bofin, Signe Opdahl, Lars A. Akslen and Hege Russnes. Defense date: February 13, 2019.



KJERSTI TEFRE DAVIDSEN
The Receptor Tyrosine Kinase Axl in Tumour Phenotyptic Plasticity and Acquired Resistance to Cancer Targeted- and Immunotherapy. Supervisors: James B. Lorens and Oddbjørn Straume. Defense date: June 21, 2019.



MARIA LIE LOTSBERG
The role of AXL and the microenvironment in cancer cell plasticity and therapy responses. A study in non-small cell lung cancer models. Supervisors: James B. Lorens, Lars A. Akslen and Agnete S.T. Engelsen. Defense date: April 29, 2019.



SAMEER BHARGAVA
Mammographic screening among immigrant women in Norway; disparities in attendance and selected screening outcomes. Supervisors: Solveig Hofvind, Kåre Moen and Lars A. Akslen. Defense date: November 1, 2019.



SAHBA SHAFIEE
Translational Development of Preclinical Models and Therapies in Myelodysplastic Syndromes (MDS). Supervisors: Emmet McCormack, Astrid Olsnes Kittang and Bjørn Tore Gjertsen. Defense date: June 20, 2019.



SIGMUND YTRE-HAUGE
Advanced imaging biomarkers in endometrial cancer. Supervisors: Ingfrid S. Haldorsen, Jone Trovik and Helga B. Salvesen. Defense date: December 11, 2019.



KATRIN KLEINMANNS
Rethinking High-Grade Serous Ovarian Carcinoma: Development of New Preclinical Animal Models for Evaluation of Image-guided Surgery and Immunotherapy. Supervisors: Emmet McCormack and Line Bjørge. Defense date: December 13, 2019.



HILDE RENATE ENGERUD
Molecular markers to predict prognosis and guide therapy in endometrial cancer. Supervisors: Camilla Krakstad and Jone Trovik. Defense date: February 7, 2020.



2020

JAHEDUL ALAM
Novel Insights into Integrin α11 Expression and Function. Supervisors: Donald Gullberg, Rolf K. Reed and James Lorens. Defense date: January 13, 2020.



CAROLINE BENEDICTE NITTER ENGEN
Exploring the boundaries of precision haemato-oncology – The case of FLT3 length mutated acute myeloid leukaemia. Supervisors: Bjørn Tore Gjertsen, Emmet McCormack and Øystein Bruserud. Defense date: February 14, 2020.



MARTIN PILSKOG
Predictive biomarkers for response to treatment with sunitinib in renal cancer patients. Supervisors: Oddbjørn Straume, Christian Beisland and Lars A. Akslen. Defense date: January 23, 2020.



TONE HOEL LENDE
Proliferation in operable breast cancer. Aspects of prognostication and relevance of carbohydrate metabolism. Supervisors: Håvard Søiland, Emiel AM Janssen, Jan PA Baak and Lars A. Akslen. Defense date: March 6, 2020.

dissertations 2013–2024



TORMOD KARLSEN BJÅNES
Drug delivery in pancreatic cancer. Supervisors: Bettina Riedel, Jan Schjøtt and Emmet Mc Cormack. Defense date: March 6, 2020.



HANNA ELISABETH DILLEKÅS
Importance of physical trauma on recurrence of breast cancer. Can tissue trauma synchronize growth of dormant micrometastases? Supervisors: Oddbjørn Straume, Svein Arthur Jensen and Olav Mella. Defense date: June 4, 2020



HARSH NITIN DONGRE
Biomarkers and preclinical models for more precise diagnosis and personalized treatment of oral and vulva carcinomas — Study on human samples and experimental models. Supervisors: Daniela Elena Costea, Line Bjørge and Anne Christine Johannessen. Defense date: April 30, 2020.



EDUARDA GUERREIRO
Isolation and characterization of extracellular vesicles – Molecular couriers from cancer cell lines, and saliva and tear fluid from patients with primary Sjögren's syndrome. Supervisors: Tine Merete Søland and Daniela Elena Costea. Defense date: June 12, 2020.



YAPING HUA
Discovery and characterization of novel STAT3 and androgen receptor inhibitors in prostate cancer cells. Supervisors: Karl-Henning Kalland and Xisong Ke. Defense date: May 4, 2020



RAGNHILD HAUGSE
Endothelial cell signaling and sonoporation. Supervisors: Spiros Kotopoulis, Emmet McCormack and Anika Langer. Defense date: June 17, 2020.



NAZAR GAFAR ABDULRAHMAN MOHAMED
Biomarker Identification in Oral Squamous Cell Carcinoma. Study on Cohorts of Patients from Sudan. Supervisors: Daniela Elena Costea, Anne Christine Johannessen, Ahmed Sulaiman and Elisabeth Sivy Nginamau. Defense date: June 19, 2020.



MIKYUNG KELLY SEO
Economic evaluations of companion cancer biomarkers for targeted therapies. Supervisors: John Cairns and Alec Miners. Defense date: December 2020.



SISSEL DYRSTAD
A study on metabolic rewiring in cancer cell plasticity. Supervisors: Karl Johan Tronstad, Gro Vatne Røsland and Jim Lorens. Defense date: August 21, 2020.



2021

ANA BEATRIZ MATEUS D'AVÓ LUÍS
Essays on Economic Incentives and Implications of Biomarker Tests. Supervisors: Tommy Staahl Gabrielsen and Julie Riise, with contributions from Lars A. Akslen, Roger Strand, John Cairns and Kelly Seo. Defense date: February 12, 2021.



EHSAN HAJJAR
Next generation leukemia diagnostics and therapy through p53 isoforms. Supervisors: Bjørn Tore Gjertsen, Vibeke Andresen and Sigrun Margrethe Hjelle. Defense date: December 17, 2020.



ELVIRA GARCÍA DE JALÓN VIÑEGRA
Preclinical molecular imaging in oncology – From chemical synthesis to clinical translatable applications. Supervisors: Emmet Mc Cormack and Bengt Erik Haug. Defense date: June 25, 2021.

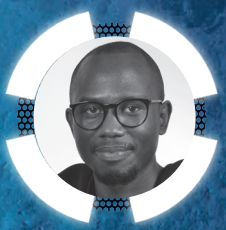
dissertations 2013–2024



SHAMUNDEESWARI ANANDAN
Rethinking High-Grade Serous Carcinoma: Development of new tools for deep tissue profiling. Supervisors: Line Bjørge, Emmet McCormack and Liv Cecilie Vestrheim Thomsen. Defense date: June 25, 2021.



EIRIK JOAKIM TRANVÅG
Precision and Uncertainty. Cancer biomarkers and new perspectives on fairness in priority setting decisions in personalized medicine. Supervisors: Ole Frithjof Norheim, Roger Strand, Lars Andreas Akslen and Trygve Ottersen. Defense date: September 24, 2021.



MOSES MUSIIME
Novel tools and assays for the study of integrin α11 expression and function. Supervisors: Donald Gullberg and Daniela Elena Costea. Defense date: September 24, 2021.



DAVID ERIK FORSSE
Novel preoperative biomarkers and evaluation of altered treatment strategies to improve outcome for endometrial cancer patients. Supervisors: Camilla Krakstad and Jone Trovik. Defense date: October 1, 2021.



HILDE YTRE-HAUGE SMELAND
Role of integrin α11β1 in breast cancer. Supervisors: Linda E. Birkhaug Stuhr, Lars A. Akslen, Donald Gullberg and Rolf K. Reed. Defense date: September 24, 2021.



ASTRID BØRRETZEN
Epithelial-mesenchymal transition, angiogenesis, and molecular markers in aggressive prostate cancer. Supervisors: Ole Johan Halvorsen, Lars A. Akslen and Christian Beisland. Defense date: October 22, 2021.

2022



CALUM LEITCH
Identification and development of small molecule therapies for the treatment of acute myeloid leukaemia. Supervisors: Bjørn Tore Gjertsen and Vibeke Andresen. Defense date: February 11, 2022.



YING CHEN
The tumor microenvironment in breast cancer: A study of stromal elastosis, tumor immune cells, vascular invasion, and the relation to detection mode. Supervisors: Lars A. Akslen, Elisabeth Wik and Tor Audun Klingen. Defense date: April 8, 2022.



SUSHMA PANDEY DHAKAL
Prognostic roles of proliferation- and differentiation-related proteins in oral leukoplakia and oral squamous cell carcinoma. Supervisors: Dipak Sapkota and Daniela Elena Costea. Defense date: February 18, 2022.



HEGE FREDRIKSEN BERG
Organoid models and novel biomarkers for improved treatment of endometrial cancer. Supervisors: Camilla Krakstad and Erling Høivik. Defense date: April 22, 2022.



NUHA MOHAMMED GAAFAR MOHAMMED
Prognostic biomarkers and tumour immune microenvironment characterization in oral squamous cell carcinoma. Supervisors: Daniela Elena Costea, Anne Chr. Johannessen, Elisabeth Sivy Nginamau and Tarig Osman. Defense date: March 25, 2022.



RIDHIMA DAS
Novel Methods and Sources for Regeneration of Oral Mucosa. Supervisors: Daniela Elena Costea, Anne Christine Johannessen, Mihaela-Roxana Cimpan and Salwa Suliman. Defense date: June 16, 2022.



SILJE KJØLLE
Tumor microenvironment in breast cancer progression. A mass spectrometry-based proteomics study for biomarker discovery and validation. Supervisors: Lars A. Akslen, Kenneth Finne and Heidrun Vethe. Defense date: August 30, 2022.



JIYEON KANG
Improving economic evaluation and decision-making for oncology drugs using real-world data. Supervisors: John Cairns and Alec Miners. Defense date: December 13, 2022.



HILDEGUNN SIV AASE
Digital Breast Tomosynthesis - the future screening tool for breast cancer? Supervisors: Solveig Hofvind and Ingfrid S. Haldorsen. Defense date: October 31, 2022.



SUSHIL DHAKAL
AXL targeting to enhance tumor Type 1 interferon response and potentiate chemo-immunotherapy. Supervisors: James Lorens and Niels Aarsæther. Defense date: December 16, 2022.



CECILIE ASKELAND
Biomarkers of aggressive breast cancer with emphasis on tumor-stroma crosstalk. Supervisors: Lars A. Akslen, Elisabeth Wik and Ingunn Stefansson. Defense date: December 9, 2022.



2023

BENEDICTE SJO TISLEVOLL
Single-cell protein profiling in early therapy response evaluation of acute myeloid leukemia by mass cytometry. Supervisors: Bjørn Tore Gjertsen and Vibeke Andresen. Defense date: January 19, 2023.



KRISTINE ELDEVIK FASMER
MRI and 2- [18F] FDG PET/CT for staging, prognostication, and tailoring treatment in endometrial cancer. Supervisors: Ingfrid Haldorsen and Camilla Krakstad. Defense date: January 20, 2023.



LOUISE BERGSJØ SAND
Synthetic studies toward [18F]-fluorination of solid-supported silyl ethers. Supervisors:Bengt Erik Haug, Ole Heine Kvernenes and Emmet McCormack. Defense date: May 25, 2023.



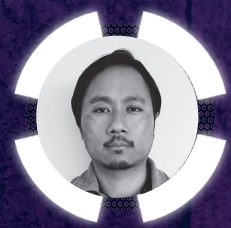
MARIA KATHRINE TVEITARÅS
Immunotherapy and HBOT – from bench to bedside. Supervisors: Linda Stuhr and Rolf K. Reed. Defense date: January 20, 2023.



CECILIE FREDVIK TORKILDSEN
Rethinking High-Grade Serous Ovarian Carcinoma: Comprehensive Bioprofiling for Enhanced Identification of Surgical Phenotypes and Treatment Outcomes. Supervisors: Cecilie Vestrheim Thomsen, Line Bjørge and Ragnar Kvie Sande. Defense date: September 29, 2023.



NEHA RANA
Immunomodulatory effects of mesenchymal stromal cells and calcium phosphate scaffolds in bone regeneration - Preclinical and clinical studies. Supervisors: Kamal Mustafa, Bjørn Tore Gjertsen, Sonia Gavasso and Salwa Suliman. Defense date: February 24, 2023.



SAROJ RAJTHALA
Functional and Prognostic Role of MicroRNAs in Cancer Associated Fibroblasts and Stroma in Oral Squamous Cell Carcinoma. Supervisors: Anne Christine Johannessen, Daniela-Elena Costea and Dipak Sapkota. Defense date: November 23, 2023.



LISE MARTINE INGEBRIKTSEN
Breast cancer of the young: Exploring age-related breast cancer biology. Supervisors: Elisabeth Wik, Lars A. Akslen and Erling Høivik. Defense date: November 30, 2023.



OLE VIDHAMMER BJØRNSTAD
Neural Interactions in the Breast Cancer Microenvironment. Supervisors: Heidrun Vethe, Manuel Carrasco, Dimitrios Kleftogiannis and Lars A. Akslen. Defense date: May 31, 2024.



2024



VICTORIA XENAKI
Nanosafety aspects: Dental health care workers' perception of nanomaterials and in vitro nanotoxicity assessment using new approach methodologies. Supervisors: Anne Nordrehaug Åstrøm, Mihaela Roxana Cimpan, Daniela Elena Costea and Ileana-Mihaela Cuida Marthinussen. Defense date: May 23, 2024.

CHRISTIANE HELGESTAD GJERDE
Development of Advanced 3D Ovarian Carcinoma Models. Supervisors: Line Bjørge, Emmet McCormack and Katrin Kleinmanns. Defense date: June 24, 2024.



HASSAN ALI
Stemness and osteogenic differentiation of induced pluripotent stem cells generated in xeno-free conditions. Supervisors: Kamal Mustafa, Daniela Elena Costea, Helge Ræder and Salwa Suliman. Defense date: May 24, 2024.



KAREN ROSNES GISSUM
Unveiling the Complexities: Patients' and Healthcare Providers' Perspectives on Understanding and Managing Ovarian Cancer. Supervisors: Line Bjørge, Roger Strand, Ingvild Vistad, Sigrunn Drageset and Liv Cecilie V. Thomsen. Defense date: June 28, 2024.



HILDE EIDE LIEN
Single cell expression patterns in endometrial cancer and novel biomarkers for improved treatment. Supervisors: Camilla Krakstad, Lars A. Akslen and Ingfrid Salvesen Haldorsen. Defense date: September 13, 2024.

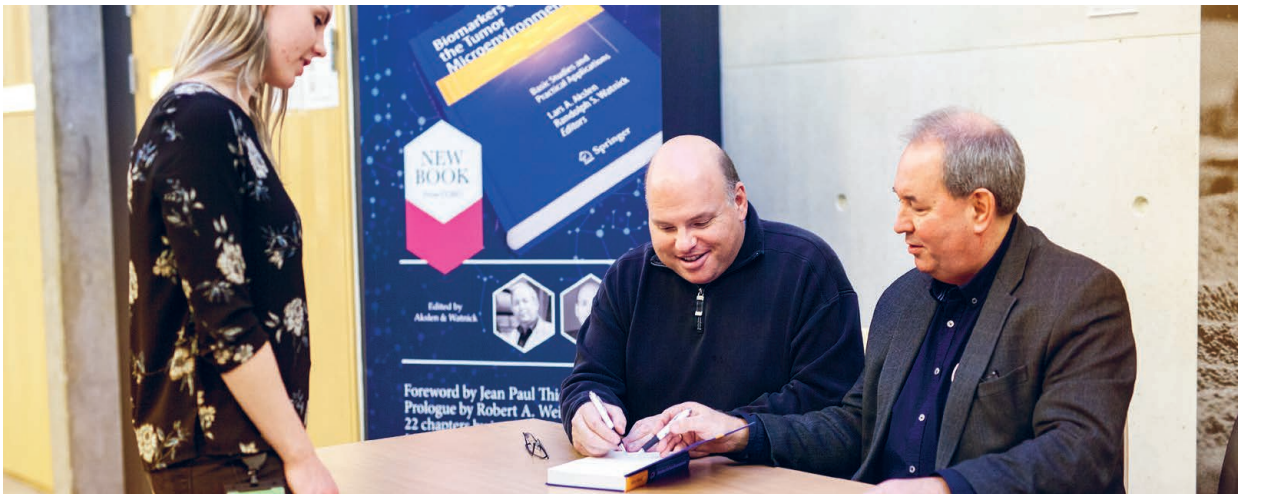


AUSTIN RAYFORD
Studies on the effect of AXL inhibition in non-small cell lung cancer. Supervisors: James B. Lorens, Agnete Engelsen and David Micklem. Defense date: October 11, 2024.



STURLA GRØNDAL
Mechanisms of Immune Dysregulation through AXL Receptor Tyrosine Kinase Signalling in Cancer and Fibrotic Diseases. Supervisors: Jim Lorens and Silke Appel. Defense date: October 14, 2024.

CCBIO books



CCBIO has published four books through coordinated research activities and cross-field collaboration and contributed strongly to a fifth.

Cancer Biomarkers: Ethics, Economics and Society

The first book, published in April 2017, entitled *Cancer Biomarkers: Ethics, Economics and Society*, is edited by **Roger Strand** and **Anne Blanchard (Bremer)** from the CCBIO ELSA group, with contributions from several CCBIO investigators. A slightly updated version was made available through a second printing (June 2018).

This book is intended to stimulate reflections on how we design and perform biomarker research. On top of basic and clinical projects, bringing in these additional aspects could have the power to intensify our reflection on our own activities. This goes to the core of the RRI-concept, *i.e.*, to perform responsible research and innovation.

In more detail, the book focuses on cancer management undergoing a shift from a "one-size-fits all" approach to more personalized precision medicine. One way of tailoring cancer treatment is through biomarkers: molecular alterations found in the patient's tissues and body fluids (*solid and liquid biopsies*). The book reflects upon the promise of cancer biomarkers and asks questions such as: How may the complexity of cancer biology impede the robustness of biomarkers in the clinic? How should one draw the line between the various sub-groups of patients for personalized treatment? How can one evaluate the cost-effectiveness and fairness of personalized cancer treatments? By bringing together authors from the fields of science and technology studies, medical ethics and philosophy, health economics and oncology, the book aims to give a critical yet accessible overview of some of the key social, ethical and economic issues that surround cancer biomarkers. Bruce Zetter, Charles Nowiszewski Professor of Cancer Biology in the Department of Surgery, Harvard Medical School, commented: *"The book should be required reading for oncologists, medical students, graduate students and especially for those who make policy decisions regarding the use and reimbursement of cancer biomarkers."*

The book can be obtained e.g. from Amazon.

Biomarkers of the Tumor Microenvironment - Basic Studies and Practical Applications

The same year, in August 2017, CCBIO with editors **Lars A. Akslen** and **Randolph S. Watnick** published *Biomarkers of the Tumor Microenvironment – Basic Studies and Practical Applications*, at Springer Publishing. Several CCBIO investigators and affiliated professors contributed.

In 2022, this book was published in a new and extended format as a Springer textbook: **Lars A. Akslen** and **Randolph S. Watnick** (eds): *Biomarkers of the Tumor Microenvironment*. The considerably enlarged second edition deals with the most important aspects of the tumor microenvironment, providing an in-depth analysis of the interactions that take place between normal and malignant cell types. It provides a rather exhaustive scrutiny of the phenotypes and organization of various tissue components, decoding the roles enacted by vascular cells, stromal fibroblasts, immune cells, and neural cells within the tumor microenvironment. The book provides insight into the clinical relevance of important signaling systems. The advent of new technologies is also discussed, with reflections on how these methods are being used in the discovery and validation of new biomarkers towards their inclusion in clinical trials and application in the clinic.

Biomarkers of the Tumor Microenvironment is aimed at cancer researchers from various backgrounds and research

pathologists in the cancer field, particularly those using advanced morphology techniques and models focusing on the crosstalk between different cell types in tumors.

This textbook can be obtained through Springer, and is also available in open access, with more than 52 000 accesses by June 2024. A 3rd edition is currently in the planning phase.

Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern

2022 also saw the publication of the interdisciplinary research anthology *Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern*, edited by **Anne Blanchard** and **Roger Strand** and with 17 contributors from the CCBIO ELSA network. The book's key focus is the interdisciplinary analysis of sociotechnical imaginaries of personalized and precision cancer medicine. This volume reflects on matters of social and ethical concern raised in the daily practices of those working in and around precision oncology. Each chapter addresses the experiences, concerns, and issues at stake for people who work in settings where precision oncology is practiced, enacted, imagined or discussed. It subsequently discusses bioethical dilemmas, scientific challenges and economic trade-offs, the need for new policies, further technological innovation, social work, as well as phenomenological research.

This volume takes a broad actor-centered perspective where, whenever cancer is present, the range of actors with issues at stake appears almost unlimited. This perspective and approach open the possibility for further in-depth and diverse questions, posed by the actors themselves, such as: How are cancer researchers navigating biological uncertainties? How do clinicians and policymakers address ethical dilemmas around prioritization of care? What are the patients' experiences with, and hopes for precision oncology? How do policymakers and entrepreneurs envisage precision oncology? These questions are of significant interest to a broad audience, including cancer researchers, oncologists, medical ethicists and philosophers, social scientists, patients and health economists.

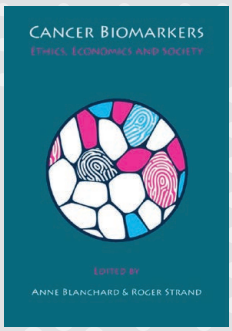
This edition can be obtained through Springer, and is also available in open access, with more than 36 000 accesses by June 2024.

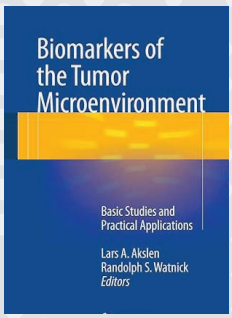
Pathology and Pathologists Through 100 Years. The Norwegian Society of Pathology 1923–2023 (in Norwegian)

CCBIO was also strongly involved when the Norwegian Society of Pathology celebrated its 100th anniversary and in that connection published a book covering the Society and its activities through 1923–2023. The book *Faget og foreningen gjennom 100 år* (in Norwegian, 450 pages) was edited by CCBIO's Director **Lars A. Akslen** together with **G. Cecilie Alfsen** and **Ying Chen**. It contains a brief history of the pathology field in Norway, an overview of the society, and presentations of hospital units, university departments and private labs as well as national registry functions. The committee for the event and for the *100th Anniversary Symposium: Updates and Future of Pathology* was chaired by Akslen.

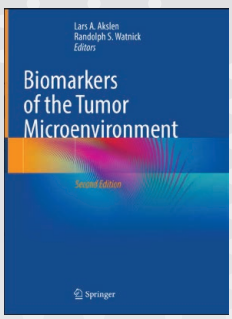
The book can be obtained by email to cecilie.alfsen@medisin.uio.no or to lars.akslen@uib.no. ••

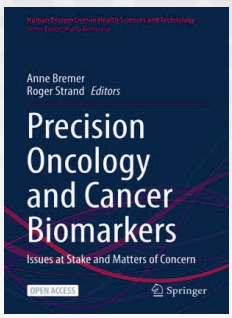
CCBIO Books











CCBIO archive

Key elements in the history of CCBIO are well documented on our website (ccbio.no). Numerous reports and stories on scientific results, educational activities, communication cases and appearances in the media can be reviewed and reflected on. Here you will find some highlights.

CCBIO Website



Newsletters



Research Groups



Comments from Bruce R. Zetter



The 2022 Holberg Prize Interview (Jasanoff and Strand) (video)



The Hyperion Imaging System



CCBIO Annual Symposia



News Archive



CCBIO Research School



Advice from Carl-Henrik Heldin



Special Seminar by CCBIO and the Holberg Prize
Holberg Laureate, Sheila Jasanoff and Stephen Hilgartner



The Laser Microdissection System



Annual Reports



Opinions



CCBIO in a Nutshell (video)



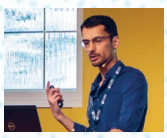
Bob Langer at the CCBIO Annual Symposium



Want to book a performance?



Upcoming CCBIO Symposium






Centre for Cancer Biomarkers
Norwegian Centre of Excellence – University of Bergen
ANNUAL REPORT 2021
20
ANNUAL REPORT
22



CCBIO in pictures


2013
2024

















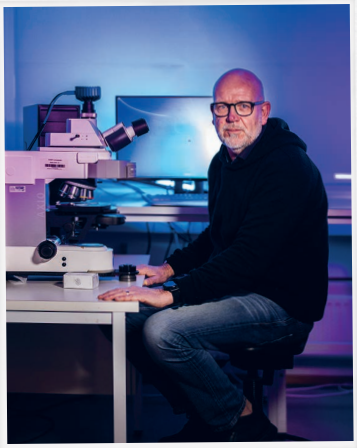





NANSEN!










































CCBIO
in pictures
2013







14 | nyheter

BERGENS TIDENDE TORSDAG 30. MAI 2013

Opnar nytt kreftsenter

Med status som senter for framifrå forsking håper Centre for Cancer Biomarkers (CCB) å løyse kreftgåta.

BIVIND DIGERNES
TOR ANDRE (foto)
visnd.digernes@bt.no

I november blei det klårt at CCB ved Universitetet i Bergen (UiB), som einaste kreftforskingssenteret denne runden, fekk status som senter for framifrå forsking (SFF). Løyvinga er på heile 17 millionar kroner årleg over ein femårsperiode, med moglegheit for utviding for fem nye år. I morgon er det tid for opning av det nye senteret.

Kan utvide

Midlane fører til at senteret kan intensivere forskinga dei har jobba med tidligere, ved å betre forståinga, diagnostikken og behandlinga av kreft.

– Dette betyr at vi kan utvide repertoaret av analysemetodar og utvide pasientgruppa vi forskar på. Meir pengar gjev oss moglegheita til å utforske noko svært nytt og spanande, seier leiar Lars A. Akslen ved senteret.

– Kva betyr det for senteret at de har fått status som senter for framifrå forsking?

– Det er ei stor ære og ein fantastisk anerkjenning. Ein må også vere litt lokalpatriot og seie at det er bra at vi har dette i Bergen, og at ikkje alt kjem til hovudstaden, seier Akslen muntert.

– Ein revolusjon

Spesielt med CCB er at dei forskar på såkalla biomarkørar knytta til mikromiljøet, som er viktige eigenskapar ved kreftsvulstane. Dette er eit lite undersøkt felt innan kreftforskinga, hevdar Akslen.

– Biomarkørane er fyrtårn som viser korleis ein skal behandle svulsten, og meir kunnskap om desse er noko av det som kan føre til ein revolusjon innan kreftbehandlinga, seier han.

Ved å lære meir om biomarkørane, kan ein drive betre og skreddersydd kreftforsking, og dermed tilpasse ei spesifikk behandling til kvar enkelt pasient.

– For å behandle ein kreftsvulst effektivt, må ein truleg ha behandling som både angrip kreftcellene og forsyningslinjene i mikromiljøet. Om ein gjer dette samtidig, reduserer ein faren for å at kreften sprer seg betydeleg, seier han.

– Knivskorp konkurranse

Det ligg stor nasjonal og internasjonal prestisje å få SFF-status.

– Det er en knivskarp konkurranse, og berre dei aller beste får midlar. Grunnen til at CCB vann er kvaliteten i forskingsplanane, seier divisjonsdirektør Anders Hanneborg i vitskaps-divisjonen hos Forskingsrådet.

– Dette er kanskje eit av dei mest spanande forskingsområdane i medisin i dag.

Av 149 søkarar, var det berre 13 som fekk midlar.

– Dei fleste SFF-senter utvidar gamle raskt, og aktiviteten er ofte tre-firedobla i løpet av nokre få år.

Internasjonalt samarbeid

Tre institutt ved Medisinsk-Odontologisk Fakultetet ved UiB er involvert i senteret. Dekan Nina Langeland ved fakultetet er svært nøgd med opninga.

– Det gjer noko med dei andre fagmiljø at nokon får denne anerkjenninga. Eg trur det er viktig inspirasjon for andre miljø, og at fleire tør å søke på dei mest konkurranseutsette forskingsumidlane, seier Langeland.

Fleire grupper ved fakultetet har søkt tidlegare, utan gjennomslag.

– At kreftforskingsmiljøet i Bergen blir vurdert som betre enn mange andre plassar, er veldig bra.

I morgon har senteret opningsseremoni med store internasjonale kreftforskarar frå amerikanske prestisjeuniversitet til stades.

– Dette er viktige samarbeidspartnarar, og det er svært gunstig for oss at dei støttar senteret. Det betyr mykje for å styrke forskinga, og i tillegg bidrar dei med kunnskap og opplæring til dei nye forskingskandidatane, seier Akslen.

fakta
kreft

- Samlenemning på rundt 200 ulike svulstformer. Ved kreft har det oppstått mutasjonar i arvestoffa til ceilene, slik at ceilene deler seg ukontrollert.
- Kreft er den vanlegaste dødsårsaka i Noreg etter hjarte- og karsjukdommar. I 2010 blei 28.271 nordmenn diagnostisert med kreft. Av desse var 53 prosent menn og 47 prosent kvinner.
- Dei vanlegaste kreftformene for menn er prostatakreft, lungekreft, og tjukk- og endetarmskreft. For kvinner er brystkreft mest utbredt, følgt av tjukk- og endetarmskreft og lungekreft.

KJELDE: KREFTFORENINGA



TIL KRIG MOT KREFT: *Centre for Cancer Biomarkers (CCB) forskar på utvikling av skreddersydd kreftbehandling. – Kunnskap om biomarkørar kan føre til ein revolusjon innan kreftbehandlinga, seier senterleiar Lars Akslen.*



FORSKARTRIUMFE: Professor James Lorens kjemmer med fire av hans PhD-stipendiater. Fra venstre Kekeritzte Wood-Lorens, Henriette Straub, Fanny Petresen og Cinna Tron. FOTO: KYRRE SVERTAG, UiB

Bergensforskere fant ny kreftmedisin

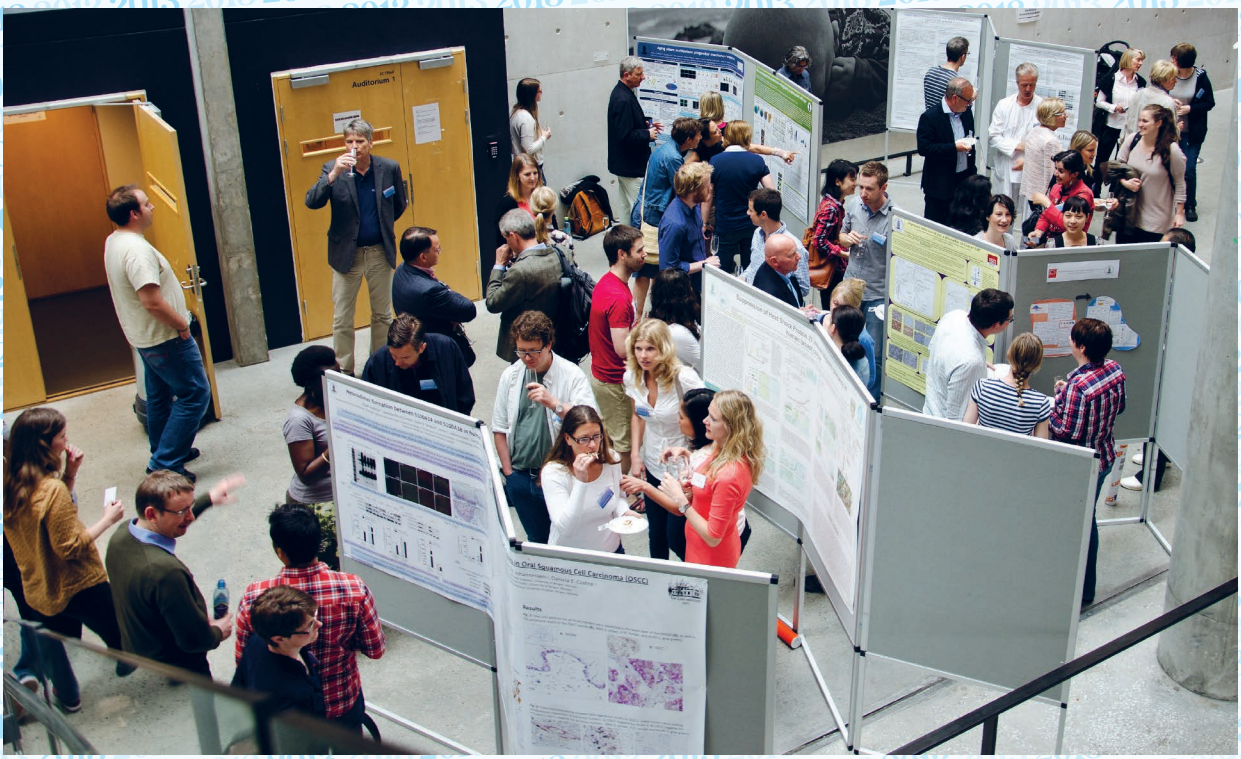
Forskere fra Bergen har utviklet ny medisin som kan hemme spredning av brystkreft.










Auditorium 1









PROSJEKTLEDERNE: Senteret har ni prosjekter, med hver sin prosjektleder. Fra venstre: Bjørn Tore Gjertsen, Karl Henning Kalland, Anne Christine Johannessen, Lars A. Akslen, Helga B. Salvesen, Oddbjørn Straume, Donald Gullberg, James Lorens og Rolf Reed var ikke til stede da bildet ble tatt. FOTO: JAN M. LILLEBØ

Skarpskytterne

365 gode nyheter

En av årets beste helsenyheter i Bergen er etableringen av det nye Senter

SENTER FOR KREFTMARKØRER



31.05.13: BA – "new cancer hope"



04.06.13: VG – "How cancers can sometimes limit their own spread". T study represents an example of successful collaboration in translation cancer research.



01.06.13: TV2 – opening day of CCBIO, Dr. Akslen commenting on the opening of CCBIO and targeted cancer therapy.

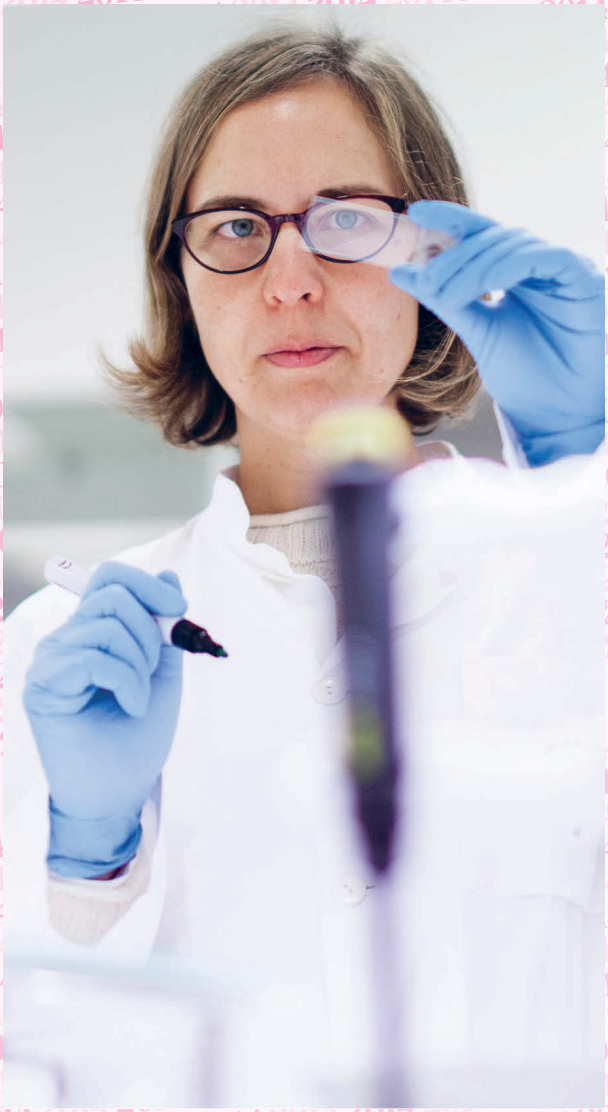


27.12.13: Aftenposten: "Breakthrough in gynecologic cancer research"




CCBIO
in pictures
2014






MEG!
MAT!
Jeg skal bli flere!
Jeg skal aldri dø!
Kreftceller er egoister
og tenker
derfor bare på seg selv
Personalized
cancer medicine
Biomarkers
Tumor biology
Angry cells







Molekylærbiolog Henriette Christie Ertås fra Kreftforeningen spiller skuespill med engasjerte elever. Hun prøver å få dem til å forstå hvor slitsomt og kaotisk det er å være cellearbeider når personen man er «inni» har falt ned fra et tre og slått foten. Foto: VIDAR LANGELAND

Cellekaos på Festplassen




















Angry cells
Klarer du å ta knekken på kreftcellene uten å skade de normale?
Det er dette vi forsker på
Bli med å forske!
Flytt dere!
Oxygen!
MAT!
Jeg skal aldri dø!












CCBIO
in pictures
2015



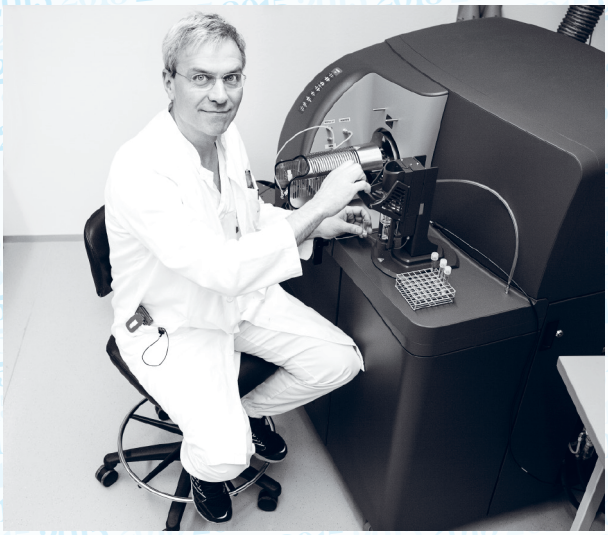





















SE
REFTCELLER
HER


✓ Angiogenesis related genes in the sig
✓ Associates with aggressive tumor feat
survival







FREDAG



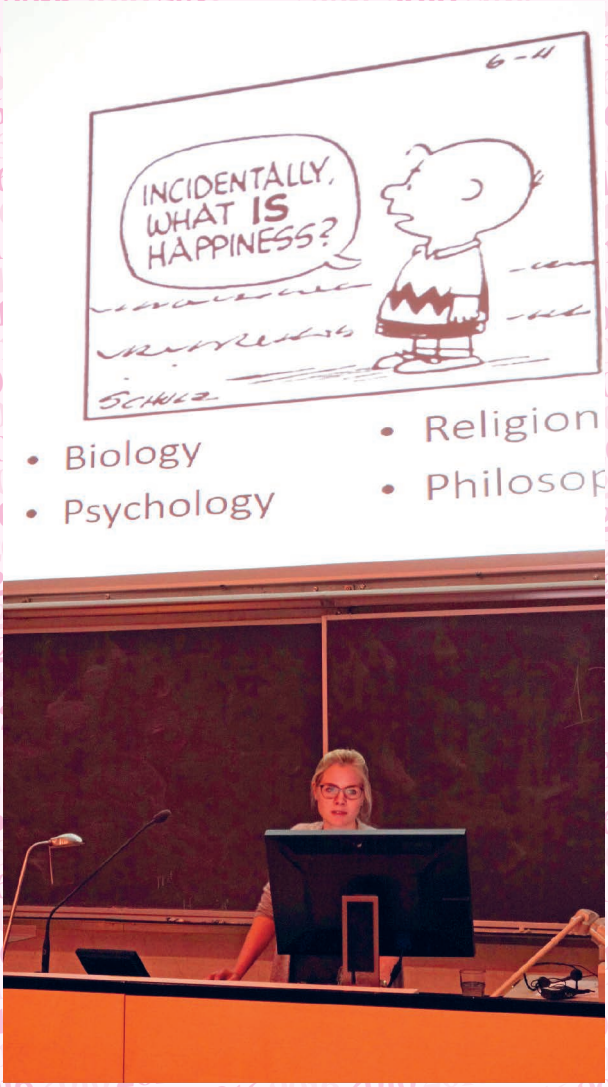
KREFTFORSKER I VERDENSKLASSE

Ålesunderen Lars A. Akslen har erklært krig mot kreftsvulstene. Med en krypskytters presisjon søker han seg inn mot kreftcellenes egenskaper for å tilintetgjøre dem.



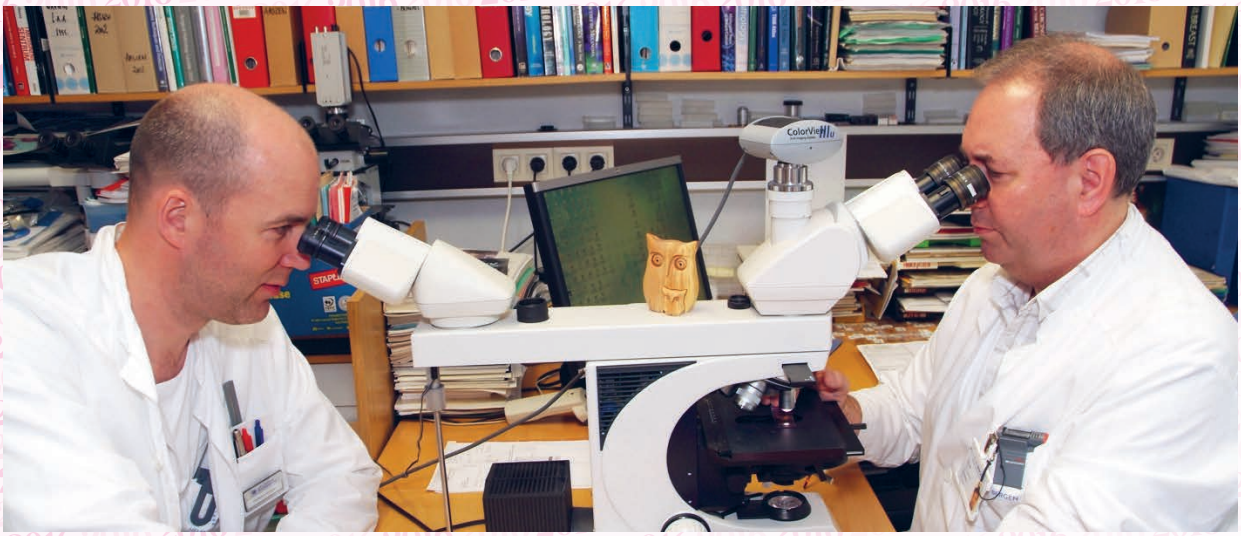

CCBIO
in pictures
2016




INCIDENTALLY, WHAT IS HAPPINESS?
• Biology
• Psychology
• Religion
• Philosop

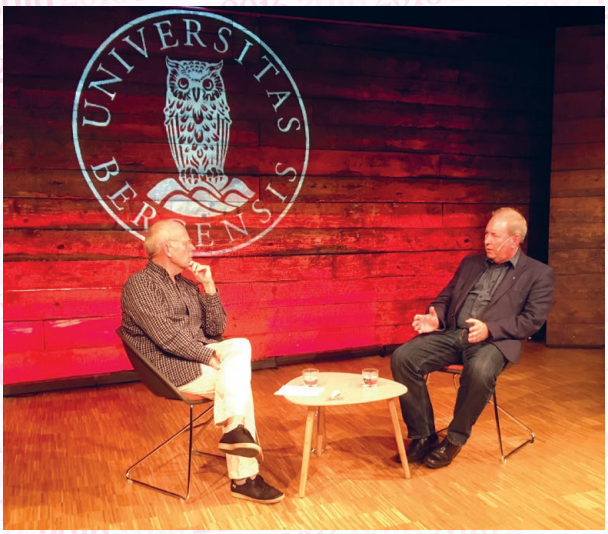



MAPPING
MAPPING








UNIVERSITAS
BERGENSIS




CCBIO
4th Symposium
2016
MAY 10-11
Solstrand (Bergen - Norway)















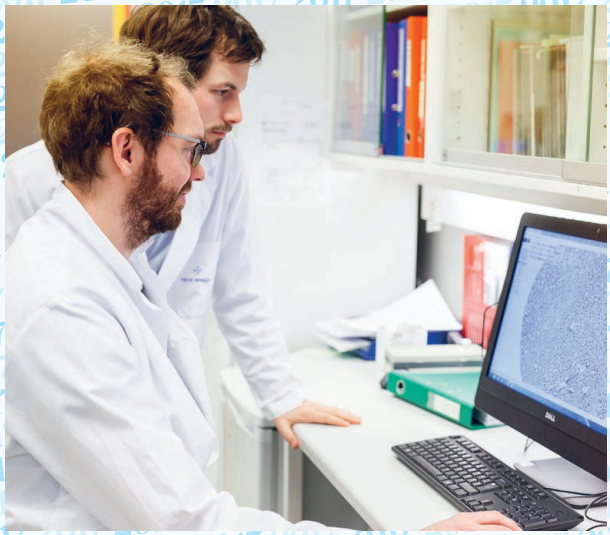

biology


CCBIO
in pictures
2017














GRANDTERMINUS












We don't always notice our own mistakes
I
LOVE
PARIS IN THE
THE SPRINGTIME




Centre for Cancer Biomarkers
NEW BOOK





















12 ET MAGASINET | LØRDAG 22.–SØLL 2017

PÅ ET BORD LIGGER PUSLEBITENE spredt utover. Foran sitter Kristin Taraldsen Grannes sammen med barnebarnet Hans Richard Idtun (3 1/2 år).

Hans kan ofte treste på dette vite hun puslet sammen med Hanna. At ville er også jobben hans som kreftforsker.

– Kreftforskning er som å samle inn mange biter, og så forsøke å sette dem sammen til et mønster, sier Grannes.

– Hvor er vi i dag?

– Vi ser mer fortsatt ikke er tydelig bilde. Kreft er et utmyntende ikonen mediem. Og in mer vi får vite, desto mer tydelig blir det hvor mye vi ikke vitenen.

Grannes er professor ved Universitetet i Bergen med i Form punktdeler og prøve å sette dem sammen. Ofte i prosjekter der de samarbeider med forskerkollegar over hele verden. I denne artikkelen møter dig noen av de lokale kreftforskerne.

Kristin Taraldsen Grannes kommer med store lidenskaper. Hun vokste ut som et opt landvid. Når forskerlig som motivasjon, understreker Aleksen.

I 2012 startet hun CCBIO, Bergen Center for Cancer Biomarkers, hosten for kreftforskerne er i dagsti av Universitetet i Bergen og Haukeland universitetssykehus.

CCBIO samlokaliserer noen av studiene i kreftforskningen. Her studerer. De kan enge hvordan kreftcellene oppfører seg i cvrolen – og i mere omgang hvilke medisiner som vil kunne virke på dem.

– Vi har en unik mulighet her hvor vi prøver ut cyniskmene selv når vi er en bestemt kreftcellene. Også evaluere et av hverdagliga. Den lagemiddelkonsensen har vanskelig for å virke slik. Det kreiser seg ikke å i lage medisiner til et like antall pasienter, sier Aleksen.

I ANDRE ENDEN STUDIE hos dr. Gjertrud Lundervold i Laura en av kreftcellene her kreften for kreftmekanisme blir identifisert. Hvem var cellen, andre var mer stabil. Han cellen seg sparsomhet. Hvorfor var det slik? Og hvordan oppførte kreftcellene seg sammen med cellene og omkrets, som også er en del av kreftsvulsten?

– Det er mange spørsmål vi ønsker å svare. De kan sammenligne disse med slektninger. De ønsker signaler til vevet rundt og forteller hvordan det skal oppføre seg. De får altså mennene med seg på galoppen, sier Aleksen.

Det 20–30 år siden var det ikke så stor interesse for å studere kreftcellene i sin helhet. Men i dag vet for forskerne at dette har stor betydning.

– Når en kreftcelle sauer inn på kroppens omgivelser, må en stamme alle hensyn. Dette kan både vi få likheten spredning, det er noe vi jobber mye med.

Det er nettopp dette Laura Aleksen og flere som hvilke cellekarakterer som er mer til stort aggressive eggcelle i kreftcellene.

– Jo mer vi vet om hvorfor dette skjer, jo større mulighet har vi til å behandle effektivt, selv i vanskelige tilfeller, sier Aleksen.

FORSKERNE VET I DAG at det er ulikheter vanlig i kreftcellene. Og at det ikke nødvendigvis er hvilket organ kreften befinner seg i, som er avgjørende for hvordan den vil.

– I dag studerer vi som hovedsakelig eller hovedsakelig. Men en svulst i brystet kan være mer lik en svulst i tarmen enn i et annet brust. Det kan være større biologisk likhetsgrad mellom to svulster i hudkreft og tarmkreft, sier Aleksen.

OPTIMALISERT BEHANDLING MED MINDRE BIVIRKNINGER

Kristin Taraldsen Grannes, professor Rolf Bjerkvig, Hans kan det egentlig noe for mye å se hvor kreftforskning i et fire kjøtter er vanlig?

– Det er jeg ikke KG, Johnne Beate Tvenne Kosmerik Cancer og har gjennom et år bygget opp et samarbeid med et forskningsmiljø i Luxemburg.

Bjerkvig er også bygge-direktør og leder dermed 60 forskere som alle jobber med å kunne forenkle biomarkører i cancer og effekter og, både et kliniske medikamentbehandlingen.

– Vi samarbeider nå med en av de største institusjonene i Europa som forsker på biomarkører, sier professor Rolf Bjerkvig.










Med_UiB @medofak_uib · 21. apr.
Calle Heldin Vice-President @ERC_Research and Chair @NobelPrize 5 TIPS to become SUCCESSFUL CANCER RESEARCHER bit.ly/2p2rJnP @UiB
3: Select an excellent place


What makes a manuscript memorable?


flere!
aldri dø!
Kreftceller er egoister
og tenker
derfor bare på seg selv










CCBIO
in pictures
2018










































CCBIO
in pictures
2019














B16 Melan
GFP
neuropilin2
Boston Childre









































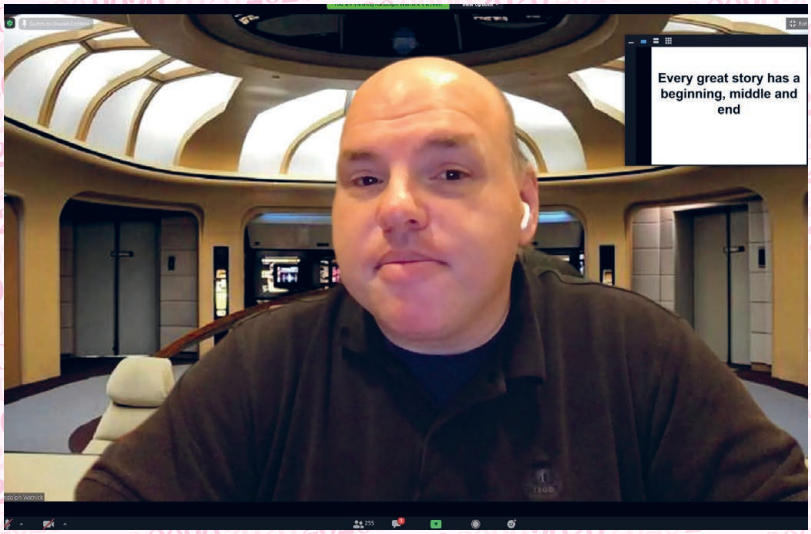

CCBIO
in pictures
2020










Every great story has a beginning, middle and end












CCBIO
in pictures
2021


Falch
Lecture
Presentation














Scientific Practice – Dichotomies


Psychosis Research Group
Centre for Cancer Biomarkers
for helse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2022



























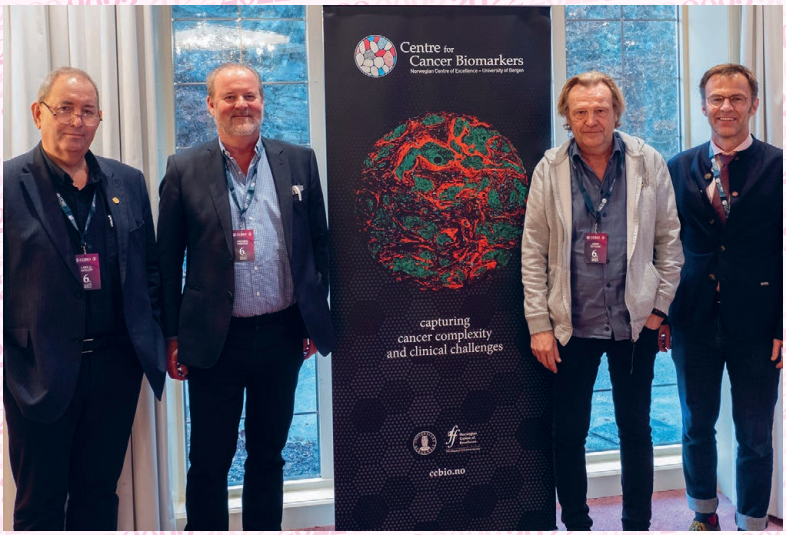
Centre for
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Norwegian Centre of Excellence – University of Bergen
capturing
cancer complexity
and clinical challenges
ccbio.no











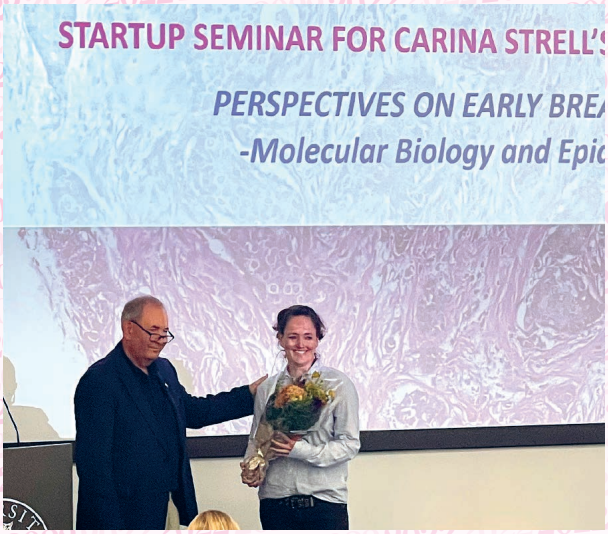











STARTUP SEMINAR FOR CARINA STRELL'S
PERSPECTIVES ON EARLY BREA
-Molecular Biology and Epid





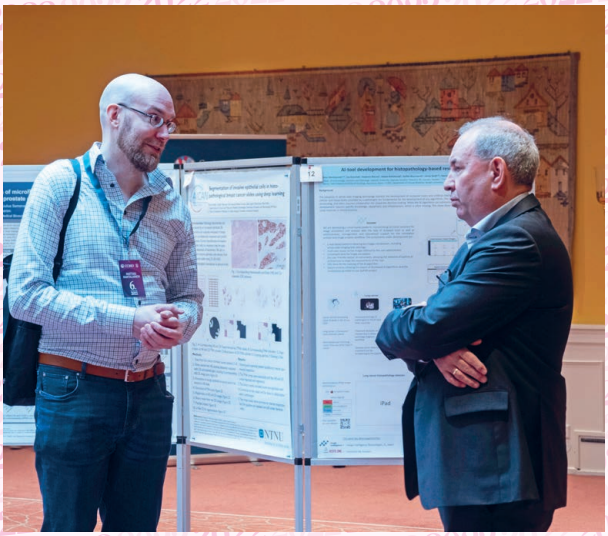





Precision
Oncology




17




14














CCBIO
in pictures
2023










Giuseppe Floris
Best Poster Presenter
35th European Congress of Pathology


Hyperion
Imaging System


CCBIO
Anny
LeBlanc










ANNE BLANCHARD
ROGER STRAND






CCBIO
Cornelia
Schuster








CCBIO


Books from CCBIO


Centre for Cancer Biomarkers
11th CCBIO ANNUAL SYMPOSIUM
10 2023 - Bergen, Norway




Age-related phenotypes in breast cancer
a population-based study
Background
Methods


Novel preoperative bi
evaluation of altered trea
to improve out
for endometrial can
David Forsse,
Gyn onc dept, Bergen
NFOG
NFOG20
NFOG


Centre for Cancer Biomarkers
11th CCBIO ANNUAL SYMPOSIUM
MAY 8-10
SOLSTRAND // BERGEN // NORWAY


Applications of ovarian cancer organoids for
and overcoming treatment resistance


CCBIO
Ramees
Bernukhins










11th CCBIO Annual
Symposium 2023








Centre for
Cancer Biomarkers




-10, 2023










CCBIO
in pictures
2024





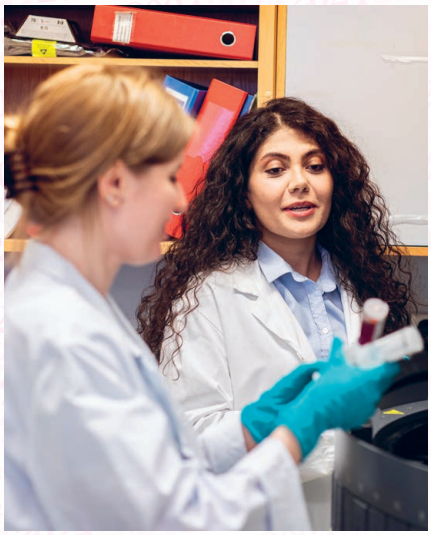

























Bergen Centre for Ethics and Priority Setting in Health
Ingvild Fossgard Sandøy, Deputy director
B·CEPS






13th
CCBIO
SYMPOSIUM
2025
13
14
MAY






Sekretari
224












CCBIO
Speedtalk Prize




ccbio Newsletter








ional diagnostics fo
cancer ther
Patrick Micke
Uppsala University







Founding Principal Investigators 2013

From the left: *Bjørn T. Gjertsen, James B. Lorens, Karl-Henning Kalland, Anne Chr. Johannessen, Lars A. Akslen, Rolf K. Reed, Helga B. Salvesen, Oddbjørn Straume, Donald Gullberg.*



Annual Symposium May 30–31, 2013

Some Principal Investigators and Invited Speakers: ***From left to right:*** *John Cairns, Oddvar M. Kaarbøe, Ate van der Zee, Christopher C. W. Hughes, Oddbjørn Straume, Rolf Brekken, Arne Östman, Lars A. Akslen, George N. Naumov, Randolph Watnick, Bruce R. Zetter.*



Annual Symposium March 25–26, 2014

Principal Investigators and Invited Speakers: ***From left to right:*** *Lars A. Akslen, Oddbjørn Straume, Helga B. Salvesen, Mark LaBarge, Therese Sørlie, James B. Lorens, Anne Christine Johannessen, Karl-Henning Kalland, Johanna Ivaska, Bruce R. Zetter, Randolph Watnick, Valerie M. Weaver, Rolf K. Reed, Donald Gullberg, Roger Strand, Kjetil Taskén, John Cairns, Bjørn Tore Gjertsen, Ian Mills, Taina Pihlajaniemi.*



Annual Symposium May 19–20, 2015

Principal Investigators and Invited Speakers: ***From left to right:*** *Roger Strand, James B. Lorens, David Tuveson, Nils Halberg, Ravi Bhatia, Bjørn Tore Gjertsen, Bruce R. Zetter, Helga B. Salvesen, Arne Östman, Randolph Watnick, Donald Gullberg, Inge Jonassen, 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.*



Annual Symposium May 10–11, 2016

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



Annual Symposium April 10–19, 2017

Principal Investigators and Invited Speakers: ***Upper row, from left to right:*** *Janine Erler, Ritva Heljasvaara, Jeanette Wood, Jean Paul Thiery, Salem Chouaib. Thomas Arnesen, Jean-Christophe Bourdon, John Cairns, Angela Nieto, Oddmund Nordgård, Krister Wennerberg, Randi Hovland, Erling Andre Høivik and Ole Frithjof Norheim.* ***Third row, from left to right:*** *Randolph Watnick, Rolf A. Brekken, Daniela E. Costea, Camilla Krakstad, Therese Sørlie, Elisabeth Wik and Eirik Tranvåg.* ***Second row, from left to right:*** *Carl-Henrik Heldin, Diane Bielenberg, Kristin Taskén, Line Bjørge, Emmet McCormack and Frédéric Amant.* ***Front row, from left to right:*** *Spiros Kotopoulis, Karl-Henning Kalland, Rolf K. Reed, Bjørn Tore Gjertsen, Lars A. Akslen, Anne Christine Johannessen, Donald Gullberg, James Lorens, Roger Strand and John Heymach.*



Annual Symposium May 23–24, 2018

Principal Investigators, Invited Speakers and Main Organizers: ***Upper row, from left to right:*** *Hani Gabra, Leonard Fleck, Elisabeth Wik, Randolph S. Watnick, Liv C. V. Thomsen, Daniela E. Costea, Ulf Landegren, Gry S. Haaland, Hrvoje Miletic, Kenneth Finne, Thomas F. Meyer, Carina Strell, Frederic Amant, Rolf A. Brekken, Bruce R. Zetter, Ragna Breines, Mark LaBarge.* ***Middle row, from left to right:*** *Jean-Paul Thiery, Richard Hynes, Camilla Krakstad, William N. William Jr., Arne Östman, Fanny A. Vatter, Jean-Christophe Bourdon, Therese Sørlie, Eirik Tranvåg, Ritva Heljasvaara, Line Bjørge, Ian G. Mills, John Cairns, Ole W. Petersen.* ***Front row, the left to right:*** *Oddbjørn Straume, Rolf K. Reed, Roger Strand, James B. Lorens, Lars A. Akslen, Anne Christine Johannessen, Karl-Henning Kalland, Inge Jonassen, Emmet McCormack.*



Annual Symposium May 13–14, 2019

Principal Investigators, Invited Speakers and Main Organizers: ***Upper row, from left to Right:*** *Geir Olav Løken, Rolf Brekken, Randy Watnick, Jean Christophe Bourdon, Hani Gabra, Alea Mills, Eric B. Haura, Marta Bertolaso, Carina Strell, Ian Mills, Teijo Pellinen, Nick Tobin, Sonia Gavasso, Caroline Heckman, Agnete Engelsen, Yves Aubert, Mark LaBarge, Xisong Ke, Omid Farokhzad.* ***Middle row, from left to right:*** *Ritva Heljasvaara, William D. Foulkes, Arne Östman, John Cairns, Jean Paul Thiery, Duanqing Pei, Vicky Seewaldt.* ***Front row, the left to right:*** *Karl-Henning Kalland, Emmet McCormack, Bob Löwenberg, Donald Gullberg, Line Bjørge, Lars A. Akslen, Camilla Krakstad, Jim Lorens, Jonathan Irish, Bjørn Tore Gjertsen, Roger Strand, Elisabeth Wik, Oddbjørn Straume.*



Annual Symposium May 19–20, 2021

From the top left: *Lars A. Akslen, Elisabeth Wik, Geir Olav Løken, Hans Clevers, Camilla Krakstad, Liv Cecilie Vestrheim Thomsen, Oddbjørn Straume, Karl-Henning Kalland, Daniela Costea, Klaus Pantel, Else Driehuis, Lewis Au, Agnete Engelsen, Amir Aref, Morag Park, Bernd Bodenmiller, Bjørn Tore Gjertsen, Cornelia Schuster, Rolf Brekken, Eli Synnøve Vidhammer, Ezra Cohen, Genevieve Boland, Line Bjørge, Anil Sood, Ulf Landegren, Jim Lorens, Jeffrey Pollard, Hani Gabra, Kara Davis.*



Annual Symposium May 10–11, 2022

Principal Investigators, Invited Speakers and Main Organizers: ***Upper row, left to right:*** *Karl-Henning Kalland, Line Bjørge, Matthias Nees, Bjørn Tore Gjertsen, Malin Sund, Hani Gabra, Bob Langer, Roger Strand, Yamila T. Cleuren, Geir Olav Løken, Rolf K. Reed, Jean-Christophe Bourdon, Yves Aubert, Olli Kallioniemi.* ***Middle rows, left to right:*** *Carina Strell, Srinivas Malladi, Marta Bertolaso, Anne Blanchard, Therese Sørlie, Daniel Öhlund, Ingeborg Winge, Sébastien Wälchli, Elisabeth Wik, Mark LaBarge, Bjørn Hofmann.* ***Front row, left to right:*** *Oddbjørn Straume, John Cairns, Ian Mills, Christine Desmedt, Gooitzen van Dam, Rolf Brekken, Lars A. Akslen, Daniela Elena Costea, Donald Gullberg, Jim Lorens, Dominique Chu.*



Annual Symposium May 8–10, 2023

Principal Investigators, Invited Speakers and Main Organizers: ***Upper row, left to right:*** *Roger Strand, Rameen Beroukhim, Karen Rosnes Gissum, Anne Blanchard, Ingeborg Winge, Caroline Engen, Anniina Färkkilä, Linn Getz, Bruce Zetter, Rolf K. Reed, Rolf Brekken, Iain McNeish, Geir Olav Løken, Alexander Swarbrick, Agnete Engelsen, Benno Schwikowski, Oddbjørn Straume, Bjørn Tore Gjertsen.* ***Middle rows, left to right:*** *Ingrid Hedenfalk, Michael Rogers, Ritva Heljasvaara, Caroline Heckman, Mark LaBarge, John Cairns, Brunangelo Falini, Amy LeBlanc, Frederic Amant, Catherine Panabieres, Klaus Pantel, Stephane Terry.* ***Front row, left to right:*** *Ian Mills, Donald Gullberg, Jim Lorens, Robert D'Amato, Line Bjørge, Lars A. Akslen, Elisabeth Wik, Jean Paul Thiery, Carina Strell, Camilla Krakstad, Daniela Costea, Emmet Mc Cormack, Karl-Henning Kalland.*



Annual Symposium May 14–15, 2024

Principal Investigators, Invited Speakers and Main Organizers: ***Upper row, left to right:*** *Kjell-Arne Johansson, Roger Strand, Randy Watnick, Geir Olav Løken, Kenneth Finne, Rolf Brekken, Bruce Zetter, Ian Mills, Raza Ali, Guro Dugstad, Daniela Costea, Göran Jönsson,* ***Middle rows, left to right:*** *Carina Strell, Camilla Krakstad, Anna Vähärautio, Eli Synnøve Vidhammer, Linda Lindström, Patrick Micke, Elisabeth Wik, John Cairns, Karpal Singh.* ***Front row, left to right:*** *Agnete Engelsen, Oddbjørn Straume, Fran Balkwill, Karl-Henning Kalland, Carl Henrik Heldin. Jim Lorens, Jean Paul Thiery, Donald Gullberg, Line Bjørge, Lars A. Akslen.*

THE ADVANCEMENT OF SPATIAL MAPPING TECHNIQUES – POSSIBILITIES AND CHALLENGES
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