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PHOTOS:

Cover image: **Half an inverted carcass of a *Drosophila* larva showing muscles, nuclei, and some fat. Photo courtesy of Alicia Gomez**
Pages 8-9, 34-35: **GIST epithelial stomach cells (GeoMx), Courtesy of Leonardo Meza-Zepeda**
Photo credit (lab photos)**: Per Marius Didriksen, OUS**


Discovery
StereO

Identifying molecular mechanisms that promote or suppress cancer

Even though the covid-19 pandemic hit the world hard in 2021, CanCell's research has continued to advance our knowledge on the basic cellular and molecular mechanisms of cancer. The centre's scientists published 41 articles in 2021 in international journals of high esteem, including papers in top journals such as *Nature and Cell*. Three of CanCell's young scientists defended their PhD theses in 2021, and 8 MSc degrees were obtained. CanCell's MSc/PhD course, "Molecular Cancer Medicine", was implemented with good participation and strong efforts by CanCell's junior scientists as teachers.

CanCell's scientists obtained several scientific breakthroughs in 2021. Some of these were related to one of the centre's main goals, to identify the Achilles' heels of cancers. For example, project leader Kay O. Schink and his co-workers in Harald Stenmark´s group identified the protein Phafin2 as a novel regulator of macropinocytosis, a process that involves large-scale sequestration of extracellular fluid by cells via formation of retracting membrane ruffles. Cancer cells use macropinocytosis to take up proteins from the extracellular space, which can be digested to amino acids that the cells use as nutrients. Kay and his co-workers found that pancreatic cells devoid of Phafin2 fail to take up proteins by macropinocytosis, and they thus fail to utilize extracellular proteins as nutrient source under nutrient-poor growth conditions. This identifies Phafin2 as an Achilles' heel of cancer and raises the possibility that targeting this protein can be used for reprogramming cancer cells into harmless cells.

Another cellular process that is highly relevant to cancer is autophagy, which literally means self-eating. Tor Erik Rusten´s group has previously shown that tumours can induce autophagy of neighbouring cells, resulting in breakdown of macromolecules into small molecules such as amino acids and sugars, which are used to fuel tumour growth. Postdoc Rojyar (Roji) Khezri and her co-workers in Rusten´s group have now found that cancer-induced autophagy is also essential for a systemic cancer-associated wasting syndrome known as cachexia. Cachexia is one of the major causes of deaths of cancer patients, and knowledge about the role of autophagy in this process could provide new strategies to prevent this serious condition. This, and the fact that the paper contained some beautiful imaging, were the reasons why Roji´s paper was featured on the cover of EMBO Journal.

Even though cancer cells can utilize autophagy for their growth, autophagy is actually beneficial to prevent cancer in

Harald Alfred Stenmark
Director, Centre for Cancer Cell Reprogramming

Anne Gjøen Simonsen
Co-director, Centre for Cancer Cell Reprogramming

the first place. In normal cells, autophagy plays a detoxifying role by mediating degradation of damaged mitochondria (mitophagy), which otherwise would produce carcinogenic compounds inside the cell. Moreover, autophagic clearance of mitochondria is believed to play an important role in the metabolic shift (from oxidative phosphorylation to anaerobic glycolysis) often seen in tumors, referred to as the "Warburg effect". It is therefore important to characterize the signals that trigger autophagy of mitochondria and the machinery involved. The labs of Anne Simonsen and Terje Johansen have previously identified proteins that act as "eat-me" signals for damaged mitochondria. In 2021, postdoc Michael Munson and his colleagues in Simonsen´s group identified two kinases that promote mitophagy and in this way protect cells from accumulating carcinogenic compounds.

Autophagy entails sequestration of cytoplasmic objects, such as damaged mitochondria, by a double membrane known as a phagophore. The biophysical principles that govern the bending of phagophores to sequester cargoes have been unknown, but in 2021 CanCell electron microscopist Sebastian Schultz teamed up with an interdisciplinary alliance of autophagy researchers in Norway, Germany and Japan to establish the physics that govern how phagophores sequester liquid-like protein assemblies piecemeal or in one big bite.

CanCell´s junior scientists have also gained attention in other ways in 2021. Marina Vietri received the Early Career Award from Oslo University Hospital, and Kay Schink was awarded "Researcher of the Year" at Institute for Cancer Research. Alf Håkon Lystad received the prestigious Young Research Talents grant from the Research Council, and Helene Knævelsrud received a grant from *Helse Sør-Øst* for hiring a PhD student. Some of CanCell's junior scientists are also writing grants to the European Research Council, and we hope that some will succeed in obtaining these highly prestigious grants.

Several CanCell groups are involved in interdisciplinary research projects through "convergence environments" at the Life Science Programme of the University of Oslo. Two new convergence environments led by CanCell scientists were established in 2021. One of these

41

articles published

08

8 MSc degrees obtained

MNOK **55,5**

55.5 MNOK – new research funding

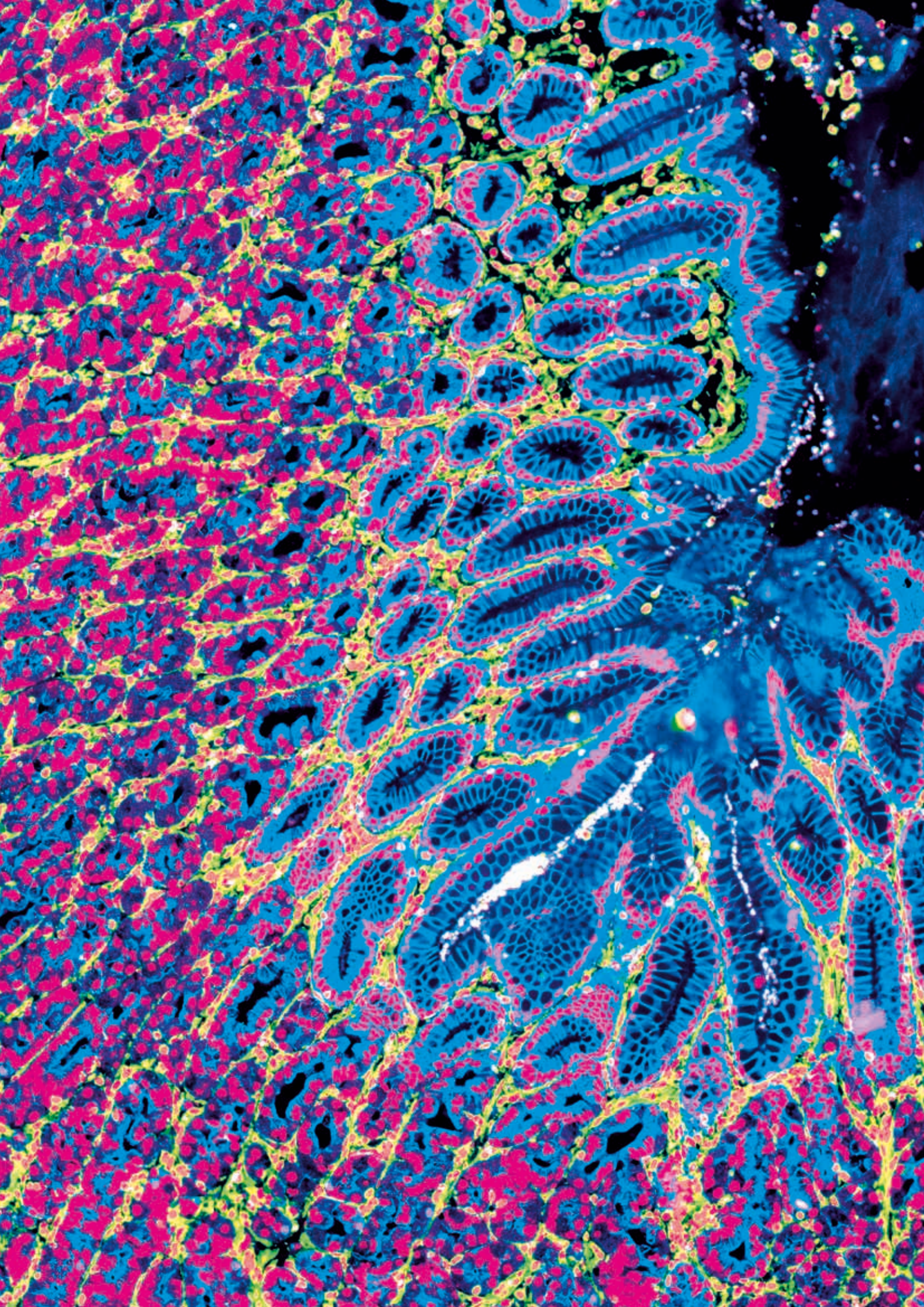
is led by Tor Erik Rusten and focuses on communications between different organs during disease progression. Another is led by Anne Simonsen (with Jorrit Enserink and Helene Knævelsrud as key participants) and is about the role of autophagy in healthy aging.

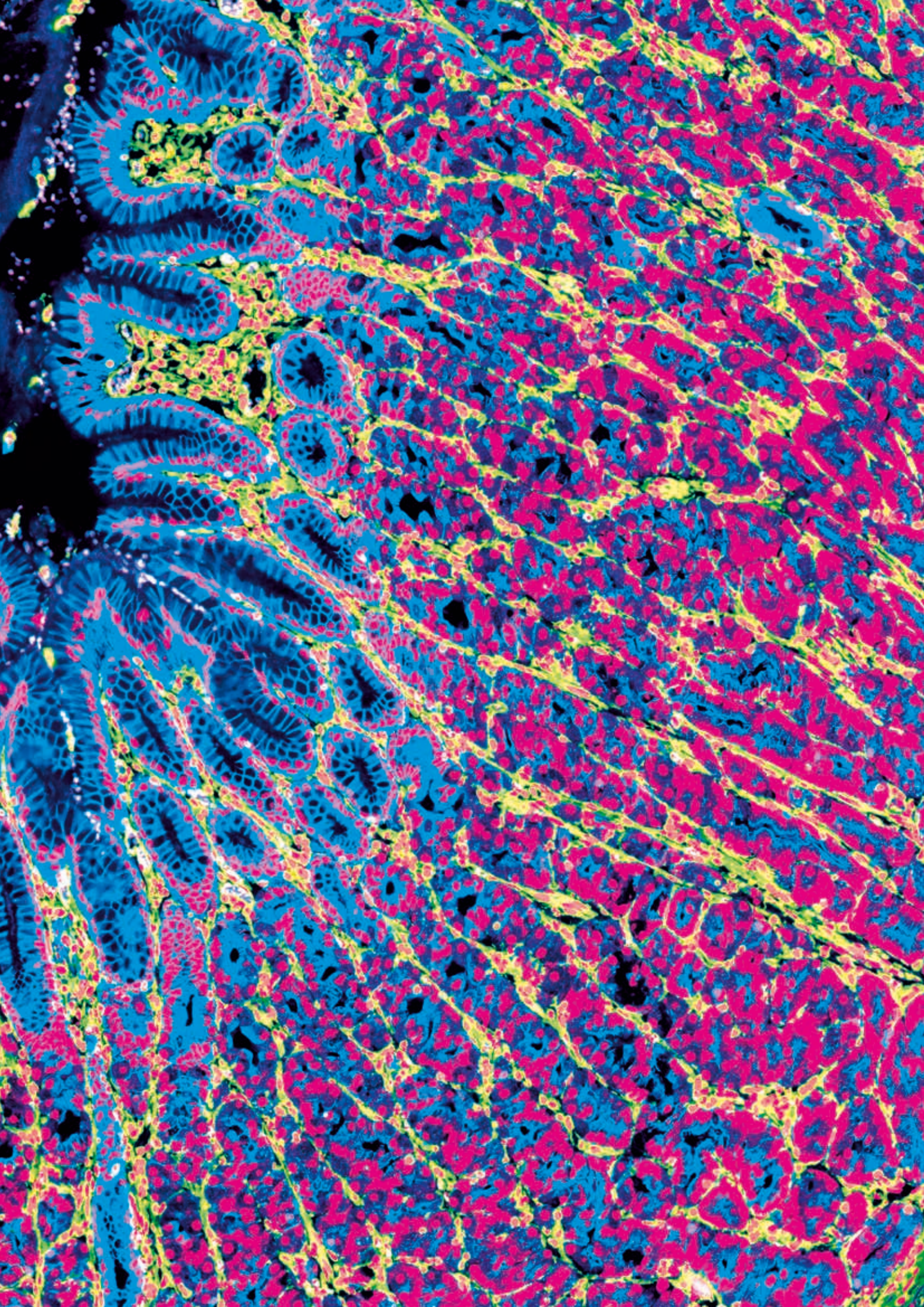
The pandemic has not prevented CanCell´s scientists from collaborating with leading international research groups. Two of the centre´s postdocs, Dagim Tadele and Viola Nähse, are currently on long-term visits at world-leading laboratories in USA and Finland, respectively, funded by mobility grants from the Research Council. CanCell´s scientists are also involved in an INTPART collaboration on cancer cell biology with two leading laboratories in China, and several of CanCell´s scientists are actively involved as coordinators or PIs in EEA or EU projects that involve multiple international laboratories. A donation from Mr. Trond Paulsen via the Radium Hospital Foundation has led to a collaboration between CanCell researchers and a group at the Curie Institute in Paris, and this collaboration has already uncovered new knowledge about mechanisms of cancer cell invasion.

CanCell's international collaborations is mirrored by its highly international staff of some 25 different nationalities. One of the aims of CanCell's Equality Forum is to ensure that no one in the centre feels excluded because of differences in language, religion or ethnic background, and CanCell's potluck dinner in November 2021, where CanCell members served specialties from their regions, was a successful example of an activity that promotes integration.

CanCell´s activities have been disseminated in popularized form via CanCell´s web pages and the Norwegian research web portal forskning.no, as well as through newspaper and magazine articles, blog posts, podcasts, and interviews in the media. An untraditional way of science communication was CanCell´s collaboration with Butoh Encounters for the dance performance "Rebellion of the Cell" in Oslo in November 2021. In order to further strengthening CanCell's dissemination activities, we have hired Pooja Kumari, an experienced scientist with communications background, as communications advisor in 50% position, starting in January 2022.

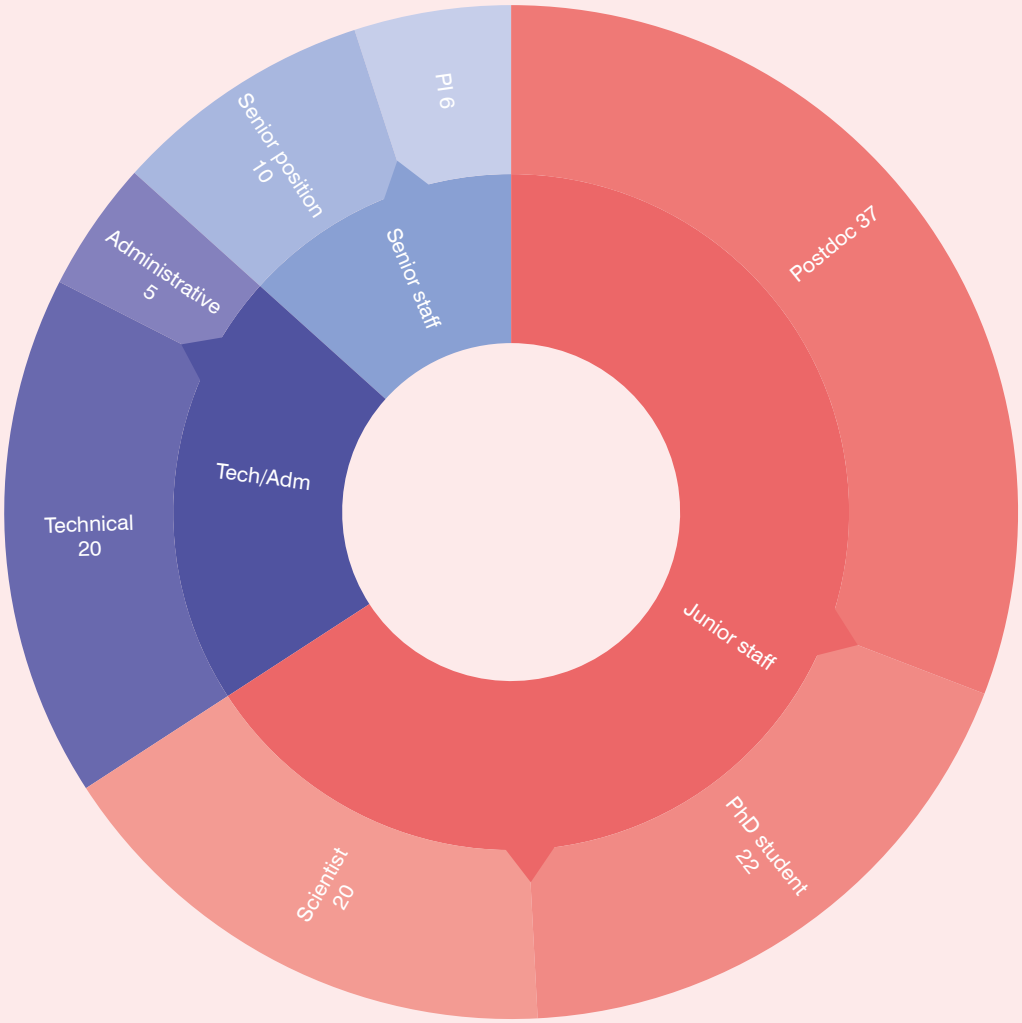
CanCell is fortunate enough to have excellent cooperation with the centre's host institutions, the University of Oslo and Oslo University Hospital. Our hosts provide great laboratory facilities and cutting-edge core facilities, and we appreciate the help from the skilled administrative and technical staff. We are also grateful to the Research Council, which not only provides Centre of Excellence funding, but also funds a number other important projects within CanCell. The regional health enterprise, Helse Sør-Øst, is also acknowledged for providing substantial funding, both to projects and core facilities. Special thanks to the Norwegian Cancer Society for being a long-term sponsor of all CanCell's group leaders. The Cancer Society is CanCell's contact point with cancer patients, and we are grateful to the members of CanCell's User Panel for their feedback and support. With all this support we feel a strong commitment to perform cancer research of the highest standard, and it is our aim that this research will ultimately benefit the future cancer patient.





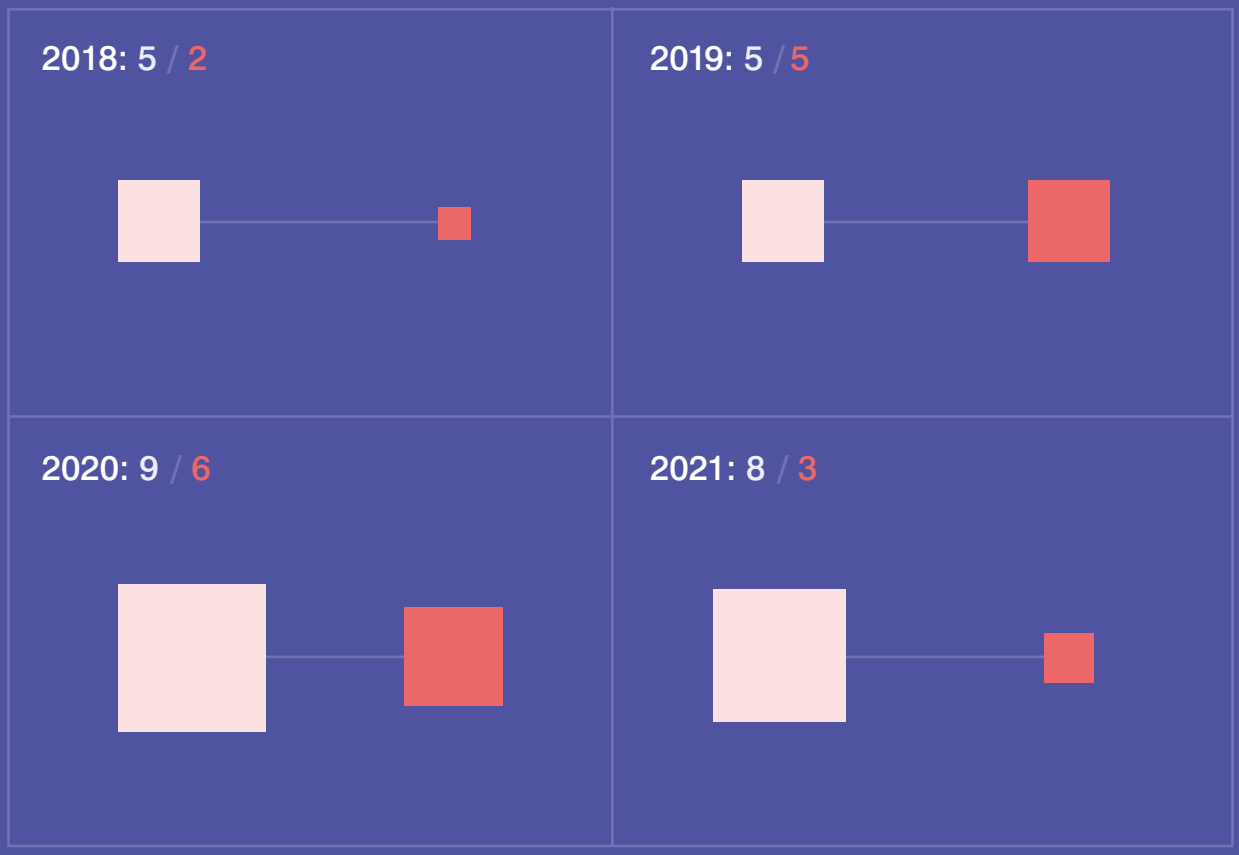
Facts and figures

Staff distribution



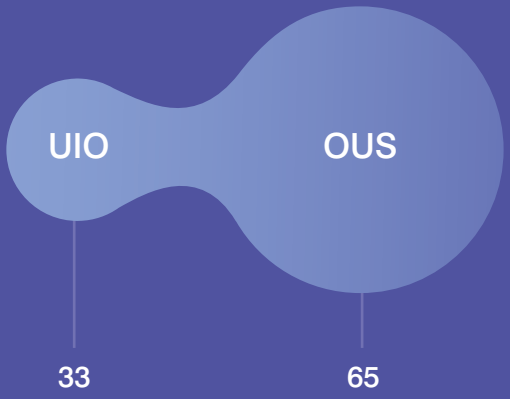
Education

Number of graduates

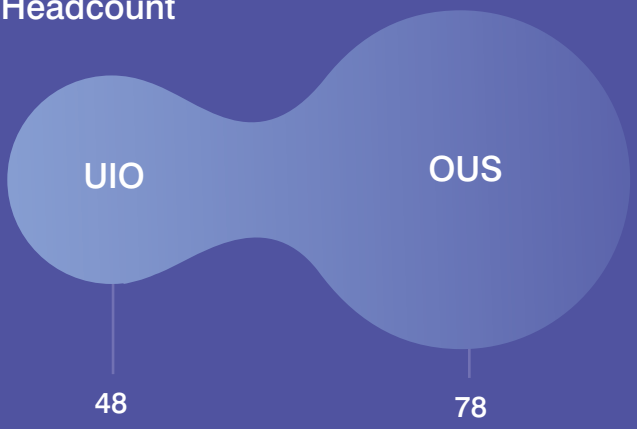


Employment

FTE

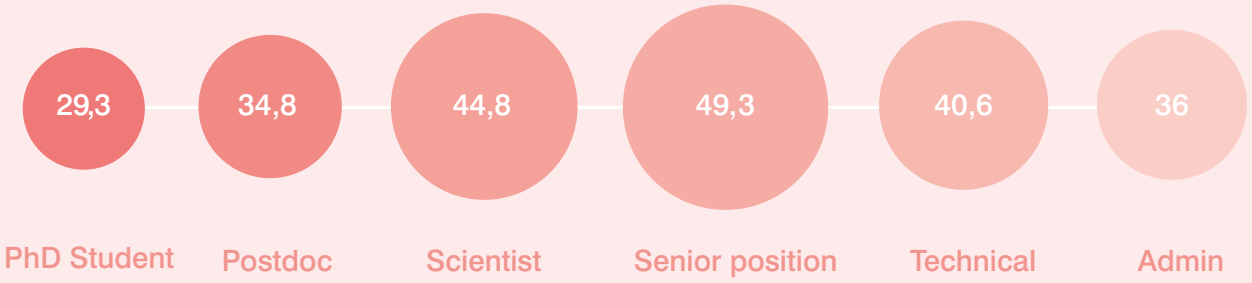


Headcount

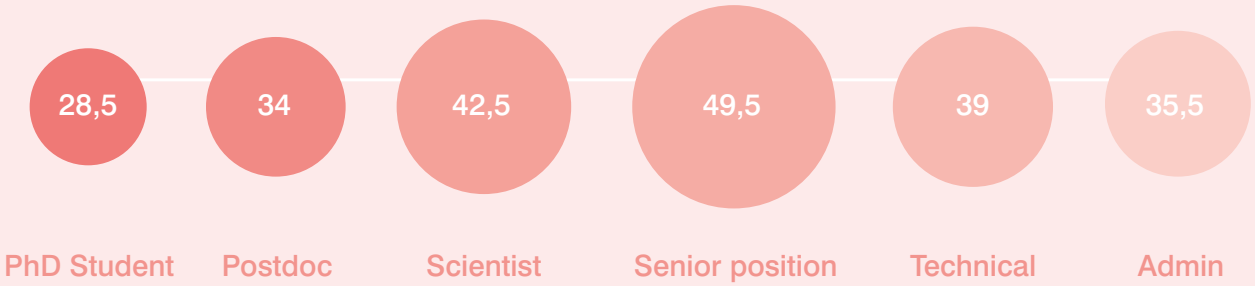


Age/position

Average age

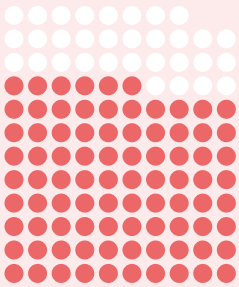


Median age



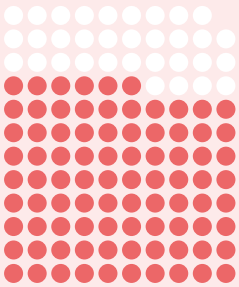
Centre personnel

2018



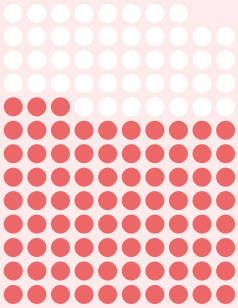
Headcount 118
● FTE 86

2019



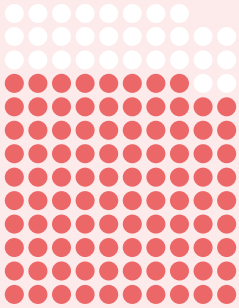
Headcount 119
● FTE 86

2020



Headcount 128
● FTE 83

2021



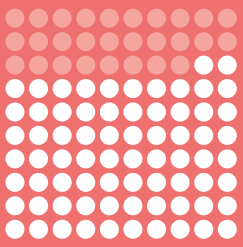
Headcount 135
● FTE 98

Gender balance % per staff level

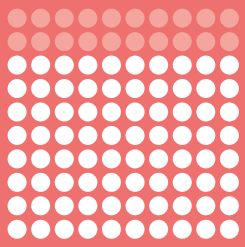
Male Female * 6 PIs counted twice

Tech/Adm: 2021/2020

28% 72%

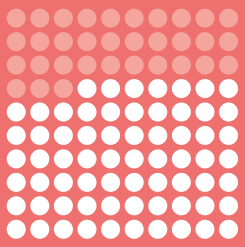


20% 80%

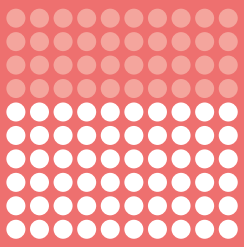


MSc/MD-PhD students: 2021/2020

33% 67%

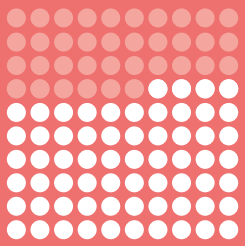


40% 60%

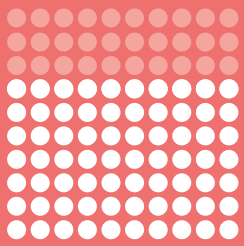


PhD student 2021/2020

36% 64%

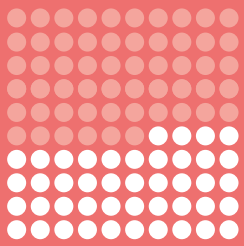


30% 70%

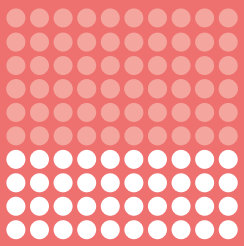


Senior staff: 2021/2020

56% 44%

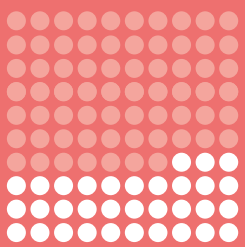


60% 40%

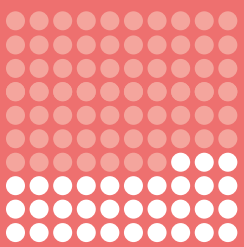


Leadership: 2021/2020

67% 33%

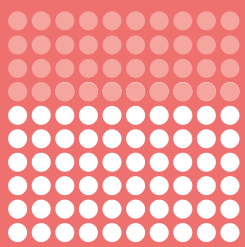


67% 33%

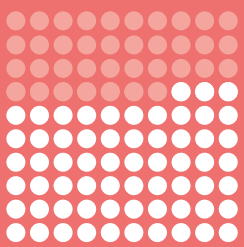


Postdoc/scientist: 2021/2020

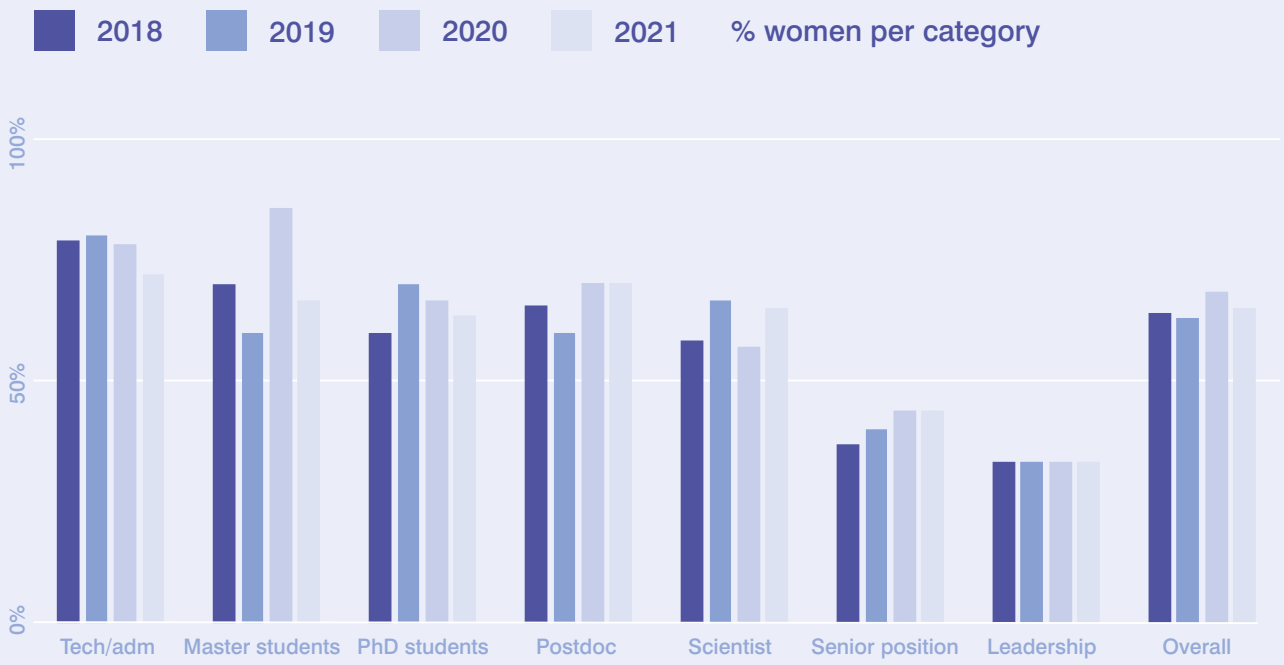
32% 68%



38% 63%

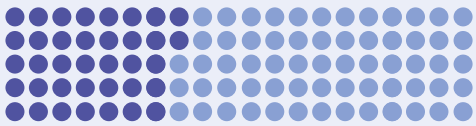


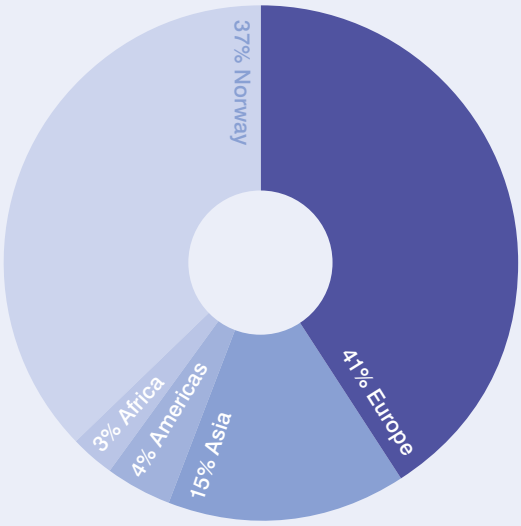
Gender balance development

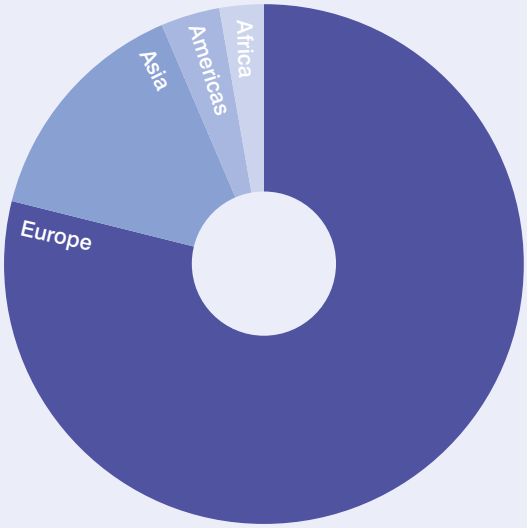


Continent of origin

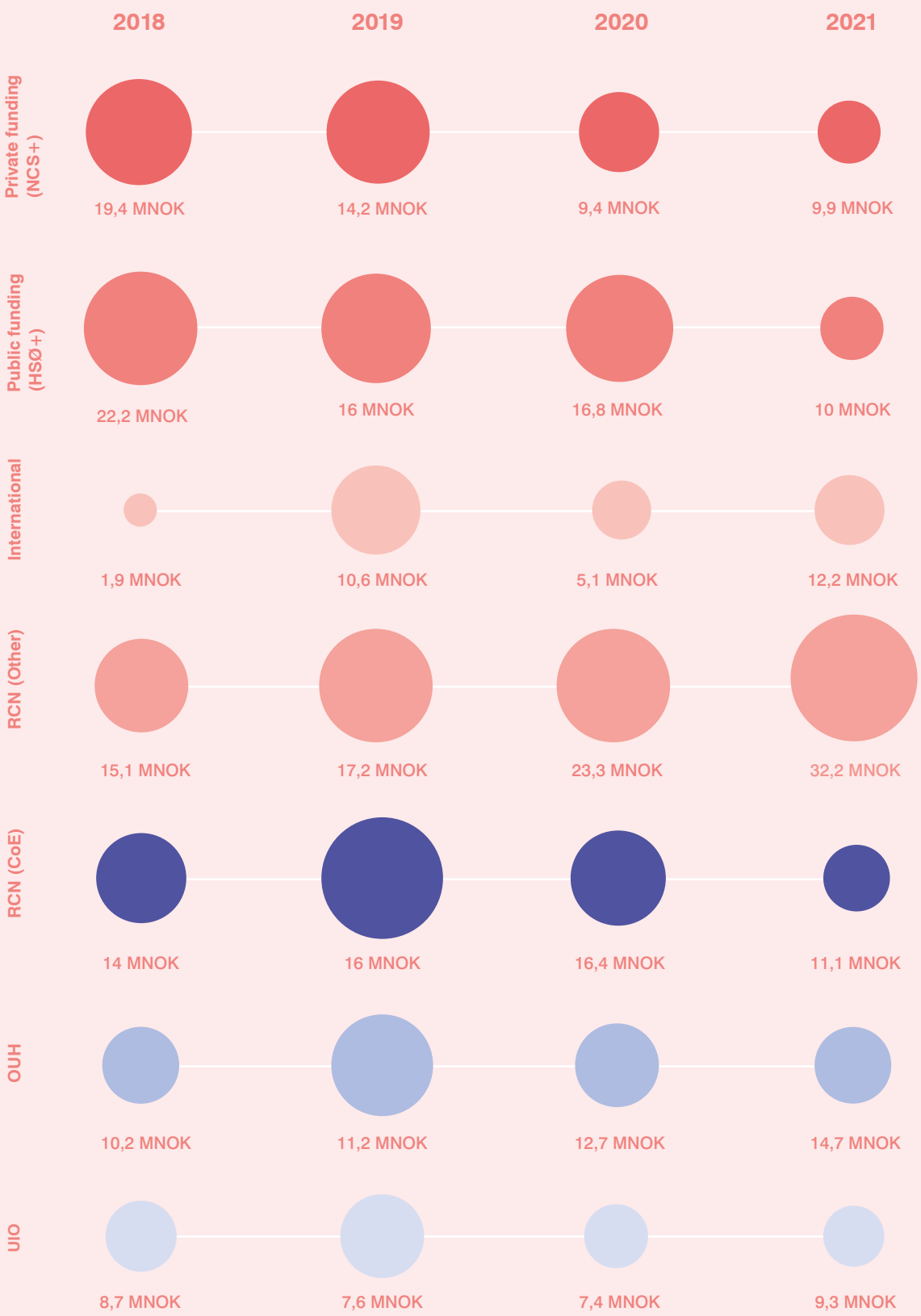
NORWAY 37%
WORLD 63%







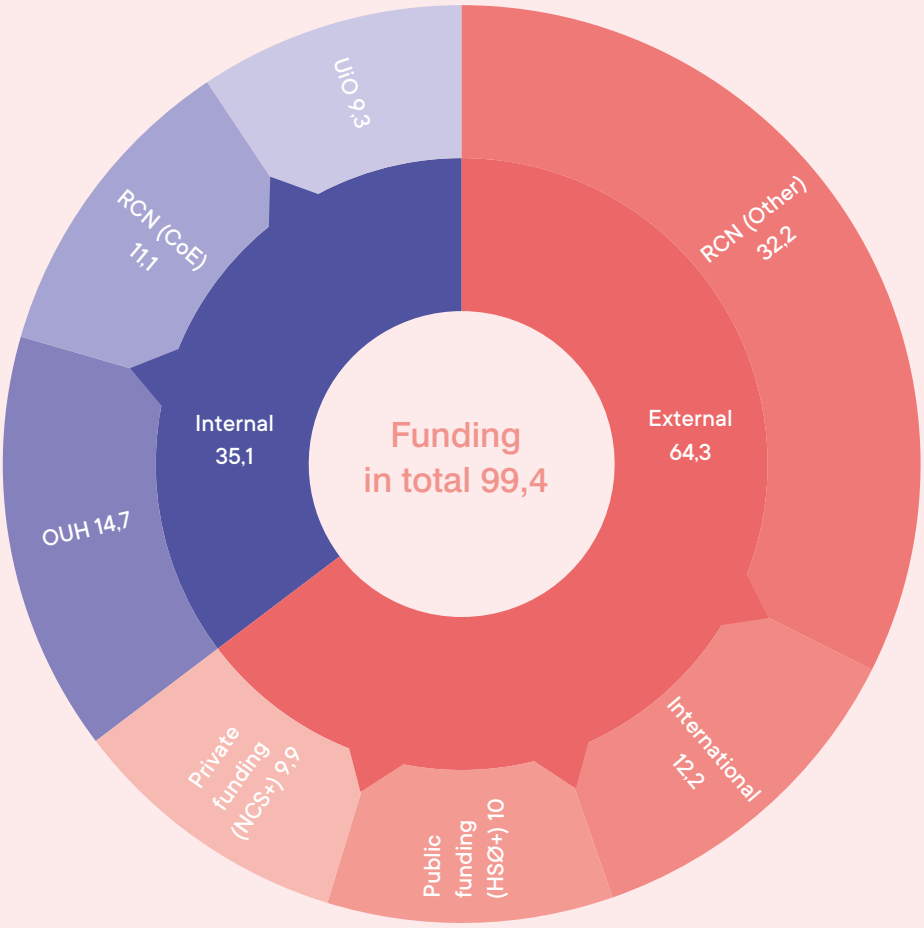
Income


2018
2019
2020
2021
Private funding (NCS+)
19,4 MNOK
14,2 MNOK
9,4 MNOK
9,9 MNOK
Public funding (HSØ+)
22,2 MNOK
16 MNOK
16,8 MNOK
10 MNOK
International
1,9 MNOK
10,6 MNOK
5,1 MNOK
12,2 MNOK
RCN (Other)
15,1 MNOK
17,2 MNOK
23,3 MNOK
32,2 MNOK
RCN (CoE)
14 MNOK
16 MNOK
16,4 MNOK
11,1 MNOK
OUH
10,2 MNOK
11,2 MNOK
12,7 MNOK
14,7 MNOK
UIO
8,7 MNOK
7,6 MNOK
7,4 MNOK
9,3 MNOK

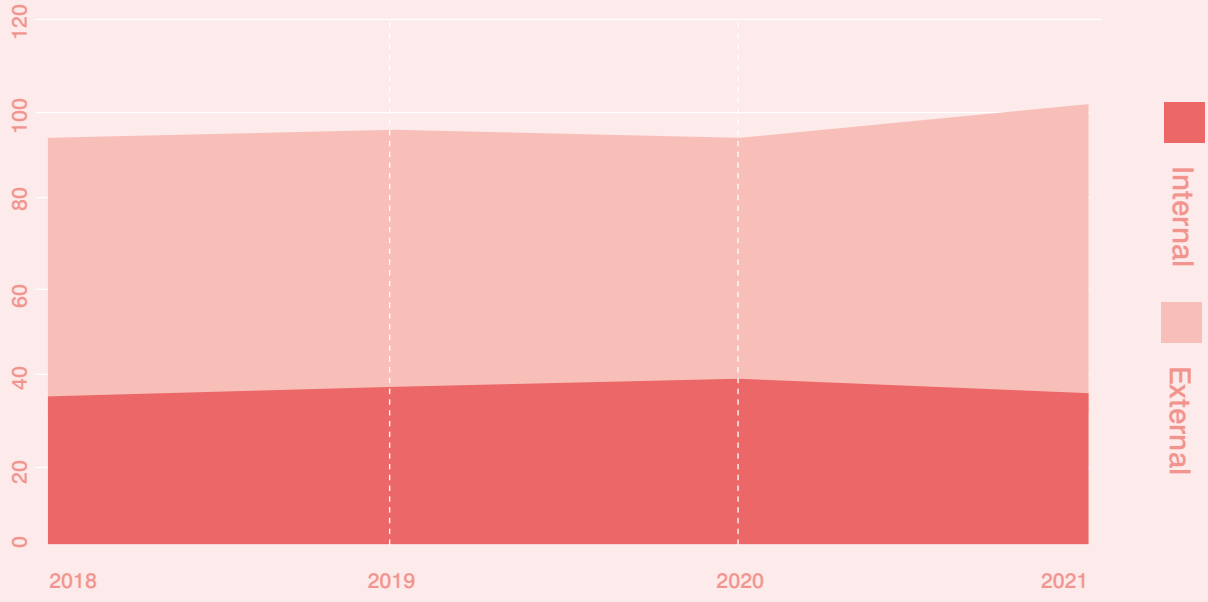
Funding 2021 (MNOK)

Internal: 35.1 MNOK

External: 64.3 MNOK



Funding development (MNOK)



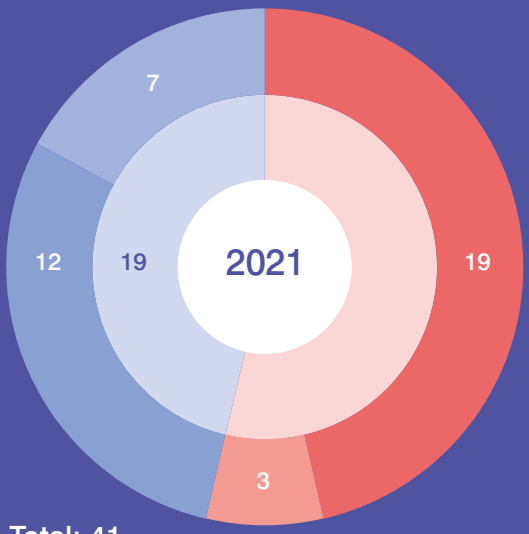
Publications – collaborations

137 publications in total were published from 2018-2021

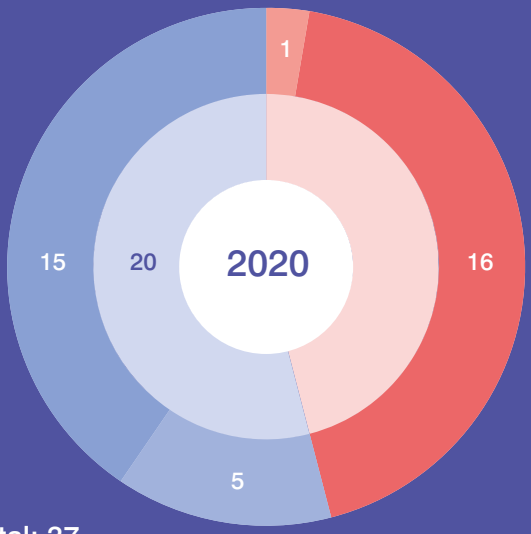
22 were co-publications within CanCell

67 were first/last author from CanCell

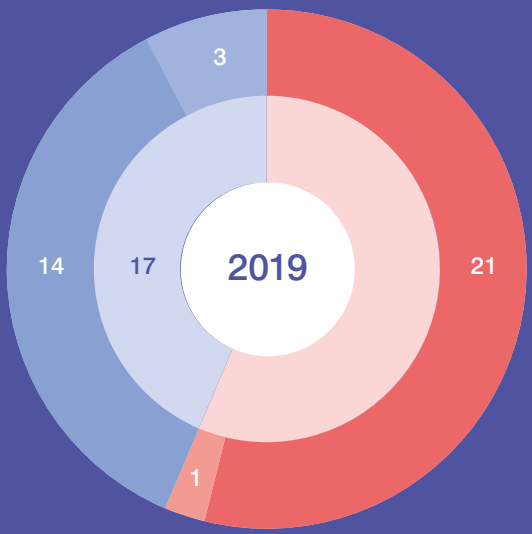
Number of publications and collaborations



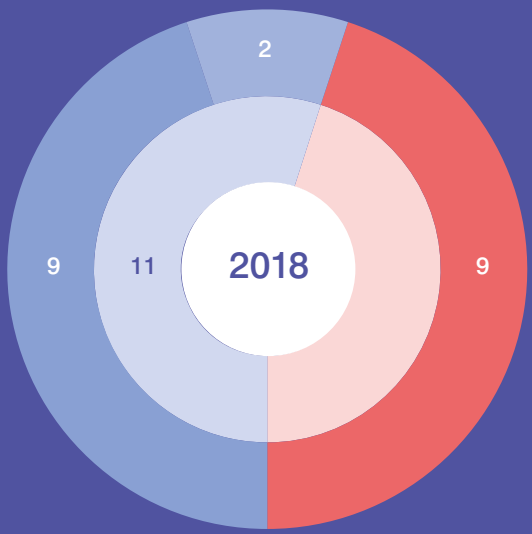
Total: 41



Total: 37



Total: 39



Total: 20

Outside CanCell | Within CanCell | Outside CanCell | Within CanCell | 1st/last author CanCell

Groups

Fun facts

Most students
Enserink Group

Enserink Group had 8 Master students in 2021

Highest educated
Wesche Group

92% of Wesche Group holds a PhD

Most women
Eskeland Group

Eskeland Group consists of 70 percent women

Most project leaders
Stenmark Group

Stenmark Group has seven project group leaders

Most copublications
Simonsen Group

Simonsen Group had four papers co-authorered with other CanCell groups

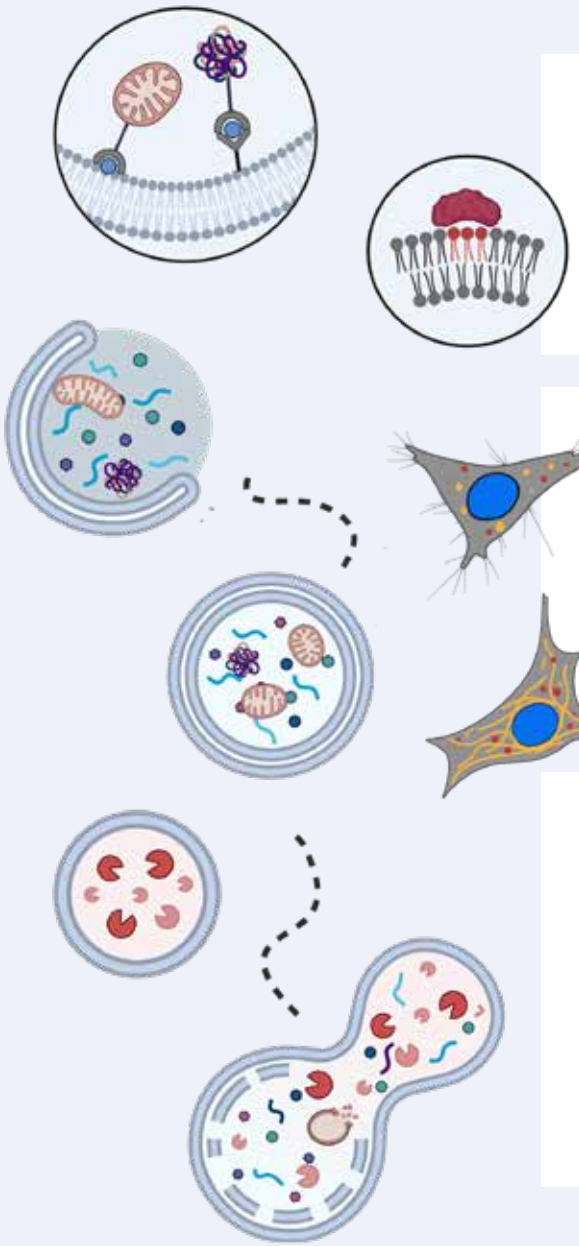
Most funding
Rusten Group

Rusten Group obtained 25 MNOK funding, equivalent of 2.3 MNOK per group member

@simonsen_lab

16 current members | 11 nationalities | 10+ ongoing projects

Simonsen Group
Autophagy



Research Focus

- Mechanisms of cargo selection
- Lipid-binding proteins
- Regulation of Selective Autophagy

Experimental Expertise

- HTP-microscopy screening
- Bioinformatics analysis
- In vitro assays
- In vivo models

Research Outcome

- Identification of novel autophagy regulators
- Characterization of disease-autophagy relationships
- In depth delineation of autophagy pathways

Anne Simonsen (far left) leads the Autophagy research group

The primary focus of the Simonsen Lab is to characterize the mechanisms involved in recognition and clearance of cellular components by autophagy and their role in disease development. Autophagy is a key regulator of tumorigenesis as it protects healthy cells against malignant transformation, e.g. by clearance of dysfunctional mitochondria (mitophagy), but it can also promote tumor cell survival under certain conditions, such as hypoxic stress and chemotherapy. Clearance of mitochondria is also believed to play an important role in the metabolic shift (from OXPHOS to anaerobic glycolysis) often seen in tumors, referred to as the "Warburg effect". The Autophagy group has recently carried out several screens to identify novel regulators of hypoxia-induced mitophagy. We are currently characterizing their function in mitophagy and cancer development using various molecular, imaging and computational approaches, in combination with relevant *in vitro* and *in vivo* cancer models. We expect our results to provide novel insight into the role of mitophagy in the metabolic switch of tumors, with a long-term goal to improve therapeutic treatment for cancer patients.

- Several lipid-binding proteins were identified and characterized as novel regulators of non-selective and selective types of autophagy in the AUTOLIPID project (Toppforsk grant from the Research Council of Norway) (Munson et al, Nat Commun 2021; Ng et al, BioRxiv and two manuscripts in progress).
- Two Marie Sklodowska-Curie Innovative Training Networks (ITN) fellows have been working with lipid-binding proteins involved in endocytosis and secretion.
- Role for HS1BP3, a negative regulator of autophagy, in gastric cancer was investigated in a project supported by the Norwegian Cancer Society.
- In a project funded by Helse Sør-Øst (HSØ), we aim to unravel the mechanisms involved in hypoxia-induced mitophagy and the role of mitophagy in tumorigenesis.
- Provided insight into the localization and functions of BEACH-domain containing proteins (BDCPs) in the endocytic and secretory pathways.
- The Autophagy group gained two new members in 2021, PhD student Anette K Dahl (BDCP project) and Patricia Gonzalez Rodriguez (mitophagy project).
- The whole lab attended the Nordic Autophagy Society meeting in Tromsø in October 2021 and had a fantastic retreat prior to the meeting, including whale watching, northern lights and great food.

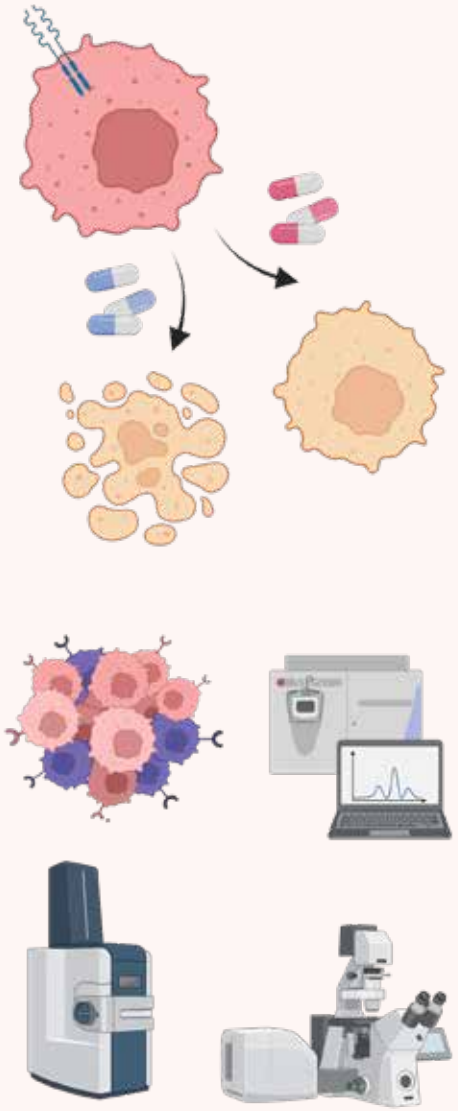
Highlights

- Comprehensive review on mitochondrial quality control: "Quality control of the mitochondrion" (Ng, Wai and Simonsen, Journal of Developmental Cell Biology 2021).
- Demonstration that Autophagy modulates cell fate decisions during lineage commitment (Sharma et al., Autophagy 2021).
- Contribution to a paper identifying a mammalian hybrid pre-autophagosomal structure (HyPAS) that generates autophagosomes (Kumar et al., Cell 2021).
- Members of the group published seven original papers and four review articles in 2021.
- Laura Trachsel Moncho defended her thesis entitled "Lipid-binding proteins in selective and non-selective autophagy".
- PhD student Chiara Veroni visited the Telethon Institute of Genetics and Medicine of Pozzuoli for 3 months.
- Grant from the Norwegian Cancer Society to Anne Simonsen.

@Wesche_Lab

12 current members | 5 nationalities | 10+ ongoing projects

Wesche Group
Molecular Biology of Sarcomas



Research Focus

- Precision medicine
- RTK signalling in sarcomas
- Resistance mechanisms

Experimental Expertise

- Genomics and Proteomics
- Bioinformatic analysis
- In vitro assays
- In vivo models

Research Outcome

- Characterization of novel signalling mechanisms
- Identification of new druggable targets – Precision medicine
- Management of drug resistance

Jørgen Wesche (3rd from left) is the Principle Investigator (PI) of the Molecular Biology of Sarcoma research group

The group has its focus on the development of precision medicine for sarcoma patients. We study the hyperactive signalling of receptor tyrosine kinases (KIT and FGFRs) in gastrointestinal stromal tumours, osteosarcoma and the childhood cancer Rhabdomyosarcoma. Since KIT and FGFRs are frequently mutated in these sarcomas, they can be used as targets for therapies. In order to improve treatment, we are investigating how genetic changes (e.g. mutations or amplifications) affect the signalling within the tumour, and how tumours evolve and become resistant. This will help identify new therapeutic strategies and novel drug targets, ultimately providing better treatment for sarcoma patients.

Group members have broad expertise in basic cell biology, genomics and translational research, bioinformatics and, importantly, the group includes one MD in a shared clinical position. This multidisciplinary approach helps to ensure that basic findings will be translated to clinical use when feasible. In addition, collaborations internationally, nationally and within CanCell, open up exciting possibilities for high-quality research. The group uses advanced technologies, including bulk and single-cell sequencing, to genetically characterize sarcoma patient material to identify and monitor druggable targets. Advanced proteomic methods and imaging are applied to study oncogenic sarcoma signalling. Our work utilizes well-characterised sarcoma cell lines and patient-derived xenograft models to test novel anti-cancer drugs.

- The role of fibroblast growth factor receptor (FGFR) signalling in rhabdomyosarcoma, liposarcoma and osteosarcoma. By detailed understanding of oncogenic FGFR signalling, we aim to identify new strategies to inhibit sarcomas and other cancers dependent on FGFR signalling (Wesche).
- Efficient Low-energy Electron Cancer Therapy with Terbium-161 (ELECTTRA) – targeted radiotherapy of cancers overexpressing FGFRs (Wesche).
- Establish new modalities for sensitive non-invasive monitoring of sarcoma patients by use of "liquid biopsies" (Meza-Zepeda).
- Characterize intratumoral heterogeneity in relation to resistance in GIST, and reveal the molecular determinants linked to imatinib resistance at a single cell level (Meza-Zepeda).
- GIST-Risk, identification of prognostic biomarkers for long term responders in GIST, (Meza-Zepeda).
- Norwegian Sarcoma Consortium (NoSarC) genomic characterization (~300 normal/tumour pairs) of patient material and establishment of patient-derived sarcoma cell lines and xenograft models (Myklebost, Boye and Meza-Zepeda).

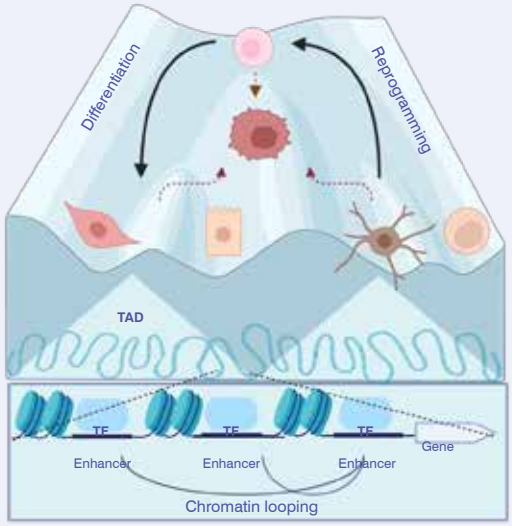
Highlights

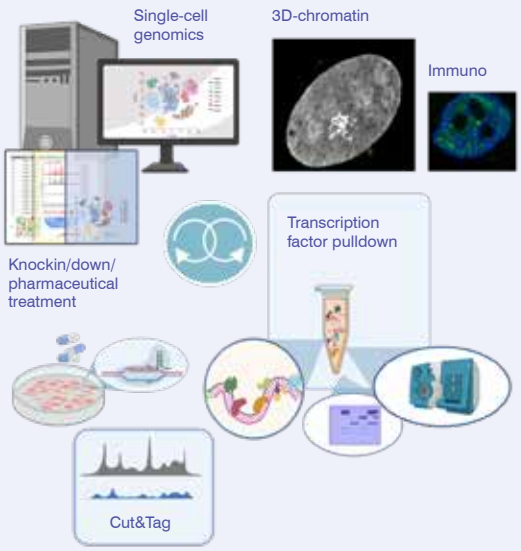
- Members of the group published 15 papers in 2021.
- Obtained funding from the new grant scheme, the Norwegian Cancer Society Pioneer Projects (Wesche). Title of the funded project: Identifying tumour-secreted factors responsible for education of premetastatic niches.

@EskelandLab

9 current members | 3 nationalities | 6+ ongoing projects

Eskeland Group
Chromatin Biology





Research Focus

- Gene regulation in early development and cancer
- Nuclear organisation and chromatin structure
- Histone variants and non-coding genome

Experimental Expertise

- Biochemistry and chromatin analysis methods
- Single-cell genomics
- Imaging
- Bioinformatic analysis

Research Outcome

- Identification of novel Liposarcoma biomarkers
- Transcription factor network in Osteosarcoma
- Web-tool for single-cell ATAC-seq

Ragnhild Eskeland (far left) heads the Chromatin Biology research group

Gene regulation is important for both development and disease. A stem cell has the potential to become any cell in the body and the type of cell it differentiates to, is based on the regulation by the epigenetic landscape that turn specific genes on or off. A differentiated cell cannot normally revert the gene expression program back to the stem cell form that it originated from. However, we only need to add a few transcription factors (Yamanaka factors) to reprogram a differentiated cell into an "induced" stem cell. Similarly, the path of cancer initiation may also rely on few factors. Gaining knowledge of these factors, which function by altering the epigenetic landscape to drive tumorigenesis, will give us clues on how to revert a cancer cell into a non-malignant cell.

The Eskeland group focuses on understanding epigenetic regulation of gene expression during stem cell differentiation and how gene expression is mis-regulated during tumorigenesis or upon treatment with pharmaceuticals. We also develop new tools to understand epigenetic gene regulation better. To detangle the aberrant gene expression programmes and epigenetic driver mechanisms of different cancers such as breast cancer, prostate cancer, osteosarcoma and liposarcoma, we utilize the forefront of methodology in the field including single-cell genomics, CUT&RUN, auxin inducible degron knockdown, transcription factor proteomics, CRISPR-Cas9 editing. Nuclear shape and chromatin organisation are frequently abrogated in cancer, however the underlying mechanisms are poorly understood. We study chromatin organization in liposarcoma to better understand the mechanisms of how higher levels of chromatin compaction is controlled in cancer. We utilize imaging techniques such as fluorescent in situ hybridization, immunohistochemistry, and live-cell imaging of single genomic loci to gain new knowledge of how genes are regulated on a three-dimensional chromatin level. This will be combined with whole genome, long read sequencing and Hi-C to map the global chromatin structure and the underlying genetic landscape. We believe that exploration into the non-coding genome will give us novel knowledge of deregulated gene regulatory mechanisms in cancer. Our multidisciplinary approaches and interdisciplinary collaboration within CanCell will establish knowledge on various aspects of tumour development that may translate this into new patient-centered strategies to fight cancer in the future.

- Identification of transcriptional drivers and biomarkers of Liposarcoma
- Chromatin structure and deregulation in Sarcomas
- Epigenetic regulation of "jumping genes" in embryonic stem cells and cancer
- The role of histone variants in Breast Cancer
- Novel tools for live-cell imaging of genomic loci (RCN FRIPRO 2017-2021)
- Gene regulation and chromatin organisation in Prostate Cancer

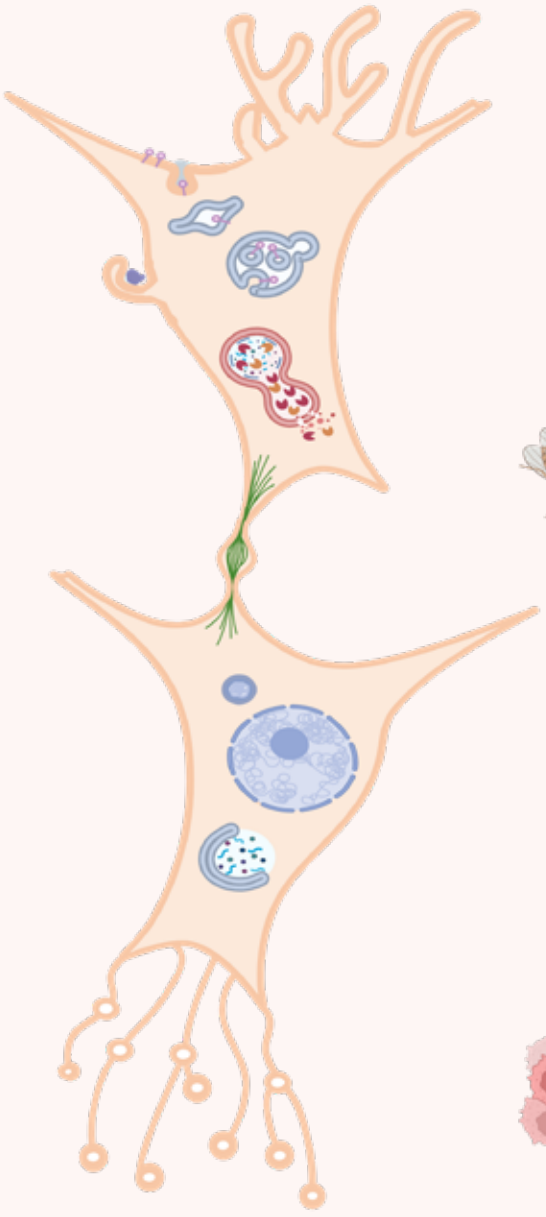
Highlights

- Developed an interactive visualisation tool for single-cell ATAC sequencing data (Sharma et al., Bioinformatics, 2021)
- Identified novel biomarkers for Liposarcoma.
- Mapped the transcription factor network in Osteosarcoma.
- Mari Gornitzka and Emily Martiensen successfully finished their master projects

@harald_stenmark

35 current members | 13 nationalities | 10+ ongoing projects

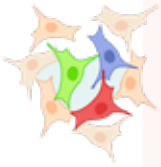
Stenmark Group
Cellular Membrane Dynamics



Research Focus

- Cell invasion and metastasis
- Lysosomal repair
- Macropinocytosis: nutrient and pathogen uptake
- Nuclear envelope, cytokinesis and genomic instability
- Aberrant signalling: receptor downregulation and trafficking
- Autophagy pathways and initiation
- Migrasomes in cancer immunity

Experimental Expertise



- Super resolution & live cell imaging
- CRISPR and transgenic cell lines
- Electron microscopy
- In vivo models & In vitro assays

Research Outcome

- Understanding how membrane dynamics at the plasma membrane, nuclear envelope and endosomes impact on cancer progression
- Identification of novel regulators of cell invasion and cancer cell feeding
- Understanding the mechanisms and importance of autophagy in cancer

Harald Stenmark (front row) is the PI of the Cellular Membrane Dynamics research group

Many of the crucial biochemical reactions in the cell take place at the cell's membranes – the plasma membrane or the membranes of the cell's organelles. These membranes are highly dynamic and undergo continuous budding, fission and remodelling, and alterations in membrane dynamics can affect biochemical reactions. In our group, we try to identify dysregulated membrane dynamics that leads to cancer progression. We are particularly interested in alterations of how the cells internalize large molecules by endocytosis, how they degrade molecules in lysosomes, and how dynamics of the membrane that surrounds the nucleus is regulated.

- Seven project leaders are responsible for specific projects involving themselves and their co-workers:
- The roles of lysosomes and membrane contact sites in cancer cell invasion (Camilla Raiborg)
- Ultrastructural characterization of endocytic and autophagic pathways (Andreas Brech)
- Cytokinesis in development and carcinogenesis (Kaisa Haglund)
- Fibroblast growth factor signalling in cancer (Antoni Wiedlocha)
- Macropinocytosis in nutrient acquisition and pathogen entry (Kay Oliver Schink)
- Nuclear envelope dynamics in genome stability (Marina Vietri)
- Non-canonical autophagy pathways and membrane integrity (Alf Håkon Lystad)

In addition, several other projects are ongoing:

- Mechanisms and importance of lysosome repair (Maja Radulovic)
- Initiation of autophagy (Viola Nähse)
- Migrasomes in cancer immunity (Yan Zhen)
- Autophagy in regulation of cell signalling (Simona Migliano)

The group had a very successful lab retreat at Oscarsborg Fortress in August 2021.

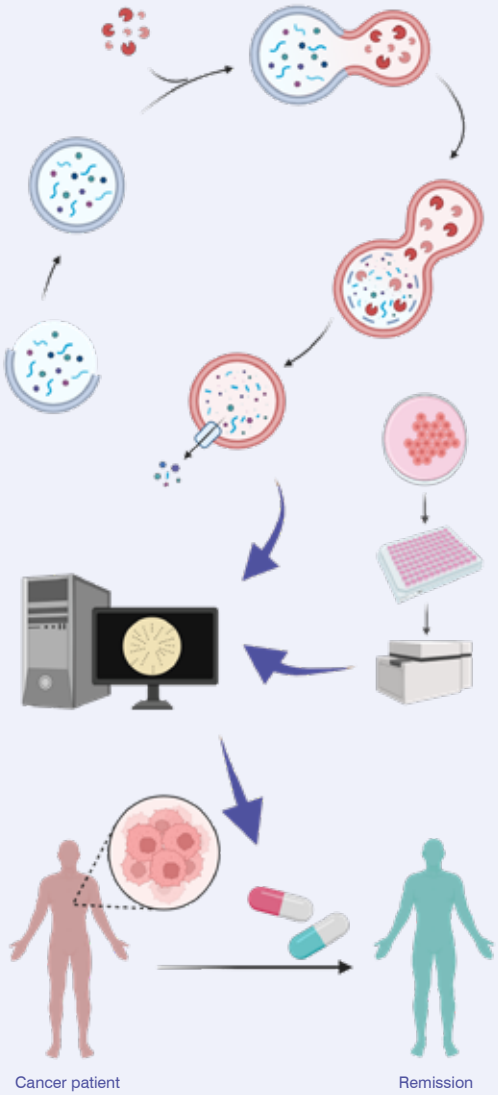
Highlights

- Identification of Phafin2 as an important regulator of macropinocytosis and nutrient acquisition by cancer cells (Schink et al., Nature Communications, 2021).
- Demonstration that the motor adaptor JIP4 is recruited by Phafin2 to early macropinosomes to mediate cargo recycling (Tan et al., Journal of Cell Science, 2021)
- Establishment of the biophysical basis for autophagy of liquid-like protein assemblies (Agudo-Canalejo, Schultz et al., Nature, 2021).
- Demonstration that the PI3P-binding protein SNX4 controls autophagy through regulation of ATG9A trafficking (Ravussin et al., Journal of Cell Science, 2021)
- Review about mechanisms of cellular membrane repair (Zhen et al., EMBO Journal, 2021)
- PhD degrees to Tonje Sønstevold and Kia Wee Tan
- "Young Research Talents" grant from the Research Council to Alf Håkon Lystad
- Kay O. Schink awarded "Researcher of the Year" at Institute for Cancer Research
- Marina Vietri received "Early Career Award" from Oslo University Hospital

@enserinklab

26 current members | 11 nationalities | 8 ongoing projects

Enserink Group
Molecular Cancer Medicine



Research Focus

- Systems overview of autophagy dynamics in context of nutrient stress
- Develop better strategies for patient stratification and novel combination treatments for certain forms of cancer

Experimental Expertise

- High-content microscopy
- Autophagy dynamics in yeast and Drosophila at the systems level
- Bioinformatics tools for analysis of large-scale datasets
- High-throughput drug screening

Research Outcome

- Novel insight into systems level regulation of autophagy dynamics
- Better patient satisfaction
- Precision Cancer Treatment

The research group is lead by Jorrit Enserink (third left, back row) with assistance of Helene Knævelsrud (far right).

The molecular cancer medicine group is supervised by Jorrit Enserink and Helene Knævelsrud. One of the central themes of the group's research is to gain insight into how cells respond to environmental cues, particularly nutrient stress. Organisms often experience periods of limiting amounts of nutrients followed by periods of abundant nutrients. Their cells respond to nutrient stress by reducing anabolic pathways while activating catabolic pathways, such as autophagy. Autophagy needs to be switched off upon nutrient availability as failure to do so results in reduced fitness of the organism. However, how organisms control autophagy dynamics at a systems level is poorly understood. The Enserink team uses budding yeast as a model while the Knævelsrud team uses the fruit fly Drosophila melanogaster, to obtain a comprehensive, systems-wide overview of the cellular pathways that control autophagy during periods of nutrient depletion and repletion. Knowledge obtained from both systems can feed into each other, creating the possibility of potent research synergy that is unique in the field.

The second theme focuses on development of novel strategies for cancer treatment. Towards this, the Enserink team uses high-content drug screens and various bioinformatics methods to identify potential novel strategies for cancer treatment. Systematic drug combination screens are designed to identify synergistic drug combinations for melanoma, breast cancer and acute myeloid leukemia. In addition, the team has developed novel bioinformatics methods to analyze the drug screening data as well as large-scale CRISPR-Cas9 screening datasets to identify potential Achilles' heels of cancer that can be exploited for development of new cancer treatment strategies. The group aims to use the gained information to better stratify patients into high- and low-risk groups. The Knævelsrud team, under this theme focuses on nutrient signaling pathways in various forms of renal cancer with the aim of developing novel forms of treatment.

- Systems analysis of autophagy dynamics in budding yeast and fruit flies
- Mathematical modeling of autophagy dynamics using novel bioinformatics tools and machine learning
- Development of anti-fungal compounds based on metal ionophores that inhibit autophagy
- Targeting autophagy in kidney cancer
- Modeling of leukemia in fruit flies
- Drug combination screening in melanoma, leukemia and breast cancer
- Mapping of genetic networks of leukemia by CRISPR screening and bioinformatics

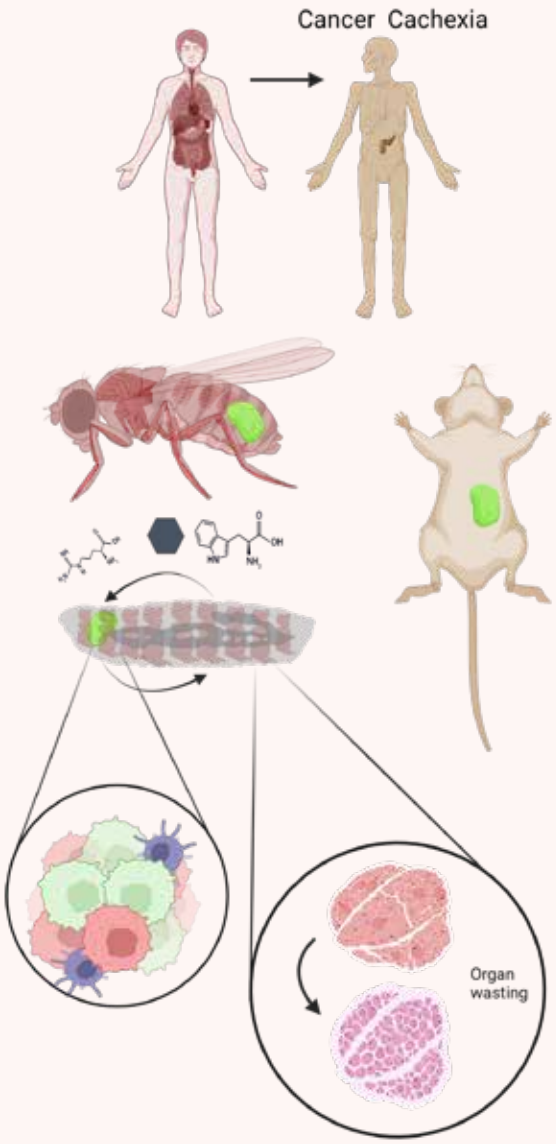
Highlights

- The group (co)published seven articles in 2021, including in Autophagy and Cell Reports.
- Helene Knævelsrud obtained funding from Helse Sør-Øst.
- The group participates in a new Convergence environment, "Autorythm", which is led by Dr. A. Simonsen with H. Knævelsrud as co-leader.
- The group has been involved in numerous public outreach activities during 2021.

@rustenlab

13 current members | 10 nationalities | 4 ongoing projects

Rusten Group
Tumor-Host Biology



Research Focus

- Autophagy and Cancer
- Tumor-microenvironment interaction
- Cancer Cachexia with organ wasting
- Nutrient requirements for tumor growth

Experimental Expertise

- Drosophila genetics
- Tumor models
- Cell signaling
- Vesicle trafficking

Research Outcome

- Insight into cell biology and cell signaling of organ wasting
- Roles of autophagy in tumorigenesis and cachexia
- Definition of tumor- microenvironment interactions driving cell competition tumor growth and progression

The Tumor-Host Biology is headed by Tor Erik Rusten (second from right, back row).

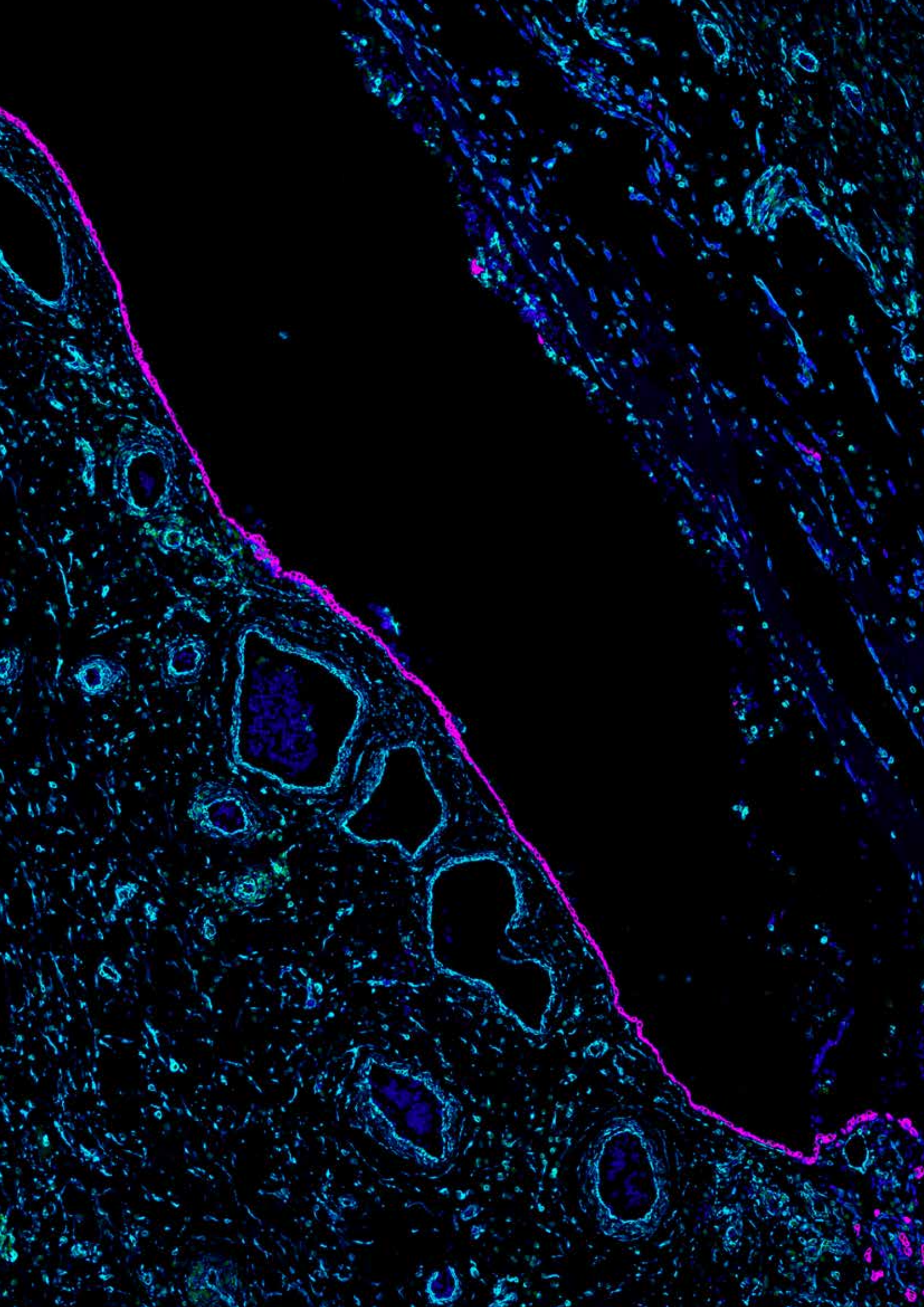
Our overarching interest is to understand the mechanisms by which tumor and host cells mutually engage each other in reciprocal interactions to facilitate carcinogenesis through cell signaling and transfer of nutrients. Tumor-host interactions occur locally in the tumor microenvironment and systemically cause organ dysfunction such as in cancer cachexia - the metabolic reprogramming, and catastrophic wasting of muscle and adipose tissue. We study these processes in the fruit fly animal model system and human organoids.

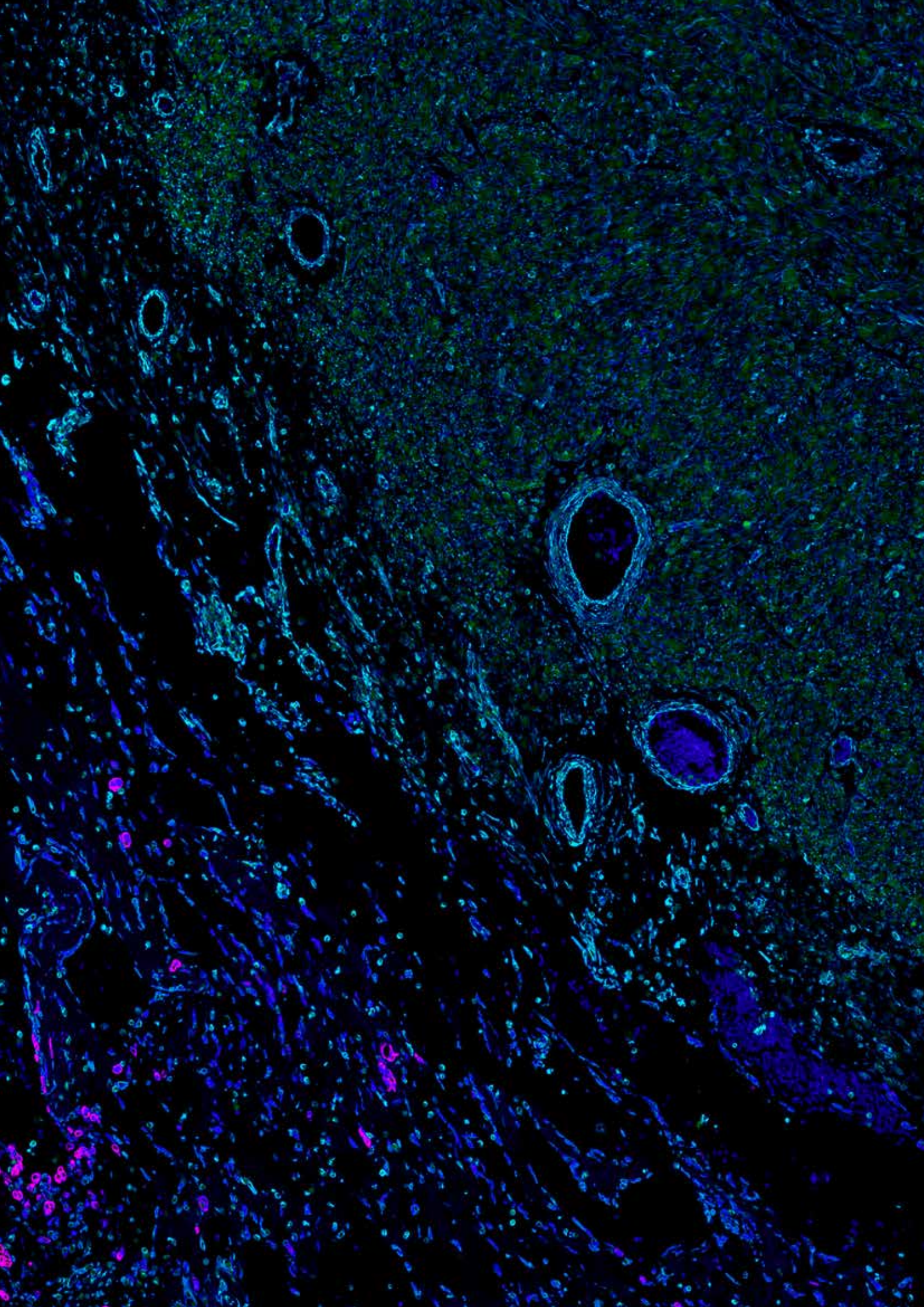
In order to mechanistically understand how tumor and non-tumor cells and organs communicate to foster tumor growth and cause cancer cachexia we develop novel genetic tools in Drosophila. We now have tools in hand to selectively and independently manipulate tumor and either tumor microenvironment or systemic organs in vivo. We employ a wide array of techniques and collaborate with experts in cell biology, genetics, imaging, tumor biology, metabolism, bioinformatics and clinical cancer cachexia in order to survey, measure and mechanistically understand these complex aspects of cancer biology. In parallel to in vivo work in flies, we utilize human organoid and spheroid cell culture to understand cellular mechanisms controlling tumor growth, such as the nutrient exchange between host and tumor, nutrient requirements for tumor growth and mechanisms of cachectic organ wasting. The group members have expertise in cell biology, genetics, molecular biology, Crispr-Cas9 screening, Drosophila, mouse and cell work.

- Deciphering tumor-host biology (2018-2024 "Toppforsk", The Norwegian Research Council) – The projects aims to characterize the reciprocal communication between tumor and host, metabolically and transcriptionally.
- Development of novel genetic tools to enable independent manipulation of tumor and host tissues in order to systematically interrogate what cellular mechanisms are required for tumor-microenvironment interactions that supports tumor growth and cancer cachexia.
- Study the role of inflammation and reactive oxygen species stress signaling on tumor growth, cell competition, and systemic effects.
- Uncovering Nutrient Vulnerabilities to stall Tumor Growth in vivo (2021-2024, South-Eastern Norway Regional Health Authority, and EMBO).
- Modeling Human multi-organ disease-Cancer Cachexia (2022-2025, University of Oslo, Life Science): The project is a collaboration between four labs to establish and utilize multi-organ experimental model system to address mechanisms of human disease that will have relevance to personalized medicine.

Highlights

- Members of the group published four papers in 2021.
- Development of CATSIR, a novel stable carbon isotope labelling and measurement technique that allows precise quantification of the relative contribution of building blocks from food or host tissues to tumor growth in vivo.
- Autophagy is required for cachectic degradation of host tissues and release of nutrients to the circulation and constitute the main source of nutrients for tumor biomass. This supports a central role of autophagy in organ wasting of cachectic cancer patients.
- Obtained funding for a 4-year Life Science Convergence Environment for studying mechanisms of inter-organ communication in Cancer Cachexia (MORGI) using human organoid models. The interdisciplinary work between four labs will commence May 2022: Rusten lab (leader, cancer cachexia), Gareth Sullivan lab (iPS-derived human organoids, Rikshospitalet, Oslo), Yoshiaki Tanaka (Cancer biology/bioinformatics, University of Montreal, Canada), Anne Kjersti Befring (Medical law, University of Oslo).





Highlights

Four excellent papers were awarded as scientific highlights from CanCell in 2021.

Wetting regulates autophagy of phase-separated compartments and the cytosol

Sebastian W. Schultz from the Stenmark group published an article in Nature (Agudo-Canalejo et al., 2021) describing the mechanisms behind autophagy-mediated degradation of membrane less granules or droplets. Such granules are formed via liquid–liquid phase separation and serve as compartment to control biochemical reactions in space and time within the cells. However, how these granules are removed is not well understood. By analyzing, the granules that contain the protein p62 (SQSTM1) in live cells Sebastian and colleagues describe how autophagosomes sequester these droplets. The in vitro experiments suggest that autophagosome-like vesicles form at the surface of protein-free droplets in vitro through partial wetting. Wetting refers to the deformation of droplets by adhesion and the underlying force balance that guides this process is known as elastocapillarity. The role of material properties of droplets and membrane sheets in autophagy was previously undescribed. Thus, this study highlighted the importance of wetting in autophagy.

Lavalamp lustrates how autophagic membranes (green) sequester phase separated molecular assemblies (pink) piecemeal or in one bite (illustration S. Migliano, Agudo-Canalejo et al. 2021)

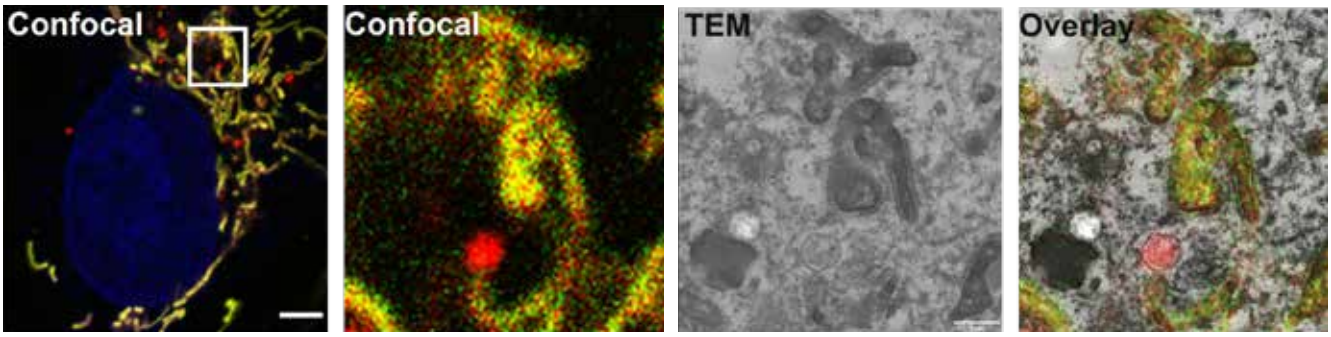
ShinyArchR.UiO: user-friendly, integrative and open-source tool for visualization of single-cell ATAC-seq data using ArchR

Ankush Sharma and members from Eskeland group developed an open-source R based shiny app, ShinyArchR.UiO, to facilitate user-friendly data access and visualization of single cell ATAC-Seq data (Sharma et al., 2021). Assay for Transposase-Accessible Chromatin sequencing (ATAC-Seq) is used to determine genome-wide chromatin accessibility and the integration of this data with gene expression data enables a better understanding of gene regulation. Such datasets at single cell resolution are critical in determination of gene regulatory mechanisms underlying cell-fate determination during development and in disease. The datasets are deposited in repositories but remain inaccessible to those lacking in-depth knowledge of computational programming. ShinyArchR.UiO allows for open access data sharing for wider audiences and can be applied to streamline collaborative efforts for interpretation of massive chromatin accessibility datasets. The app and a demo server with tutorial data sets are available at Github and UiO websites respectively.

- User-friendly
- Integrative
- Open-Source
- Introductory videos

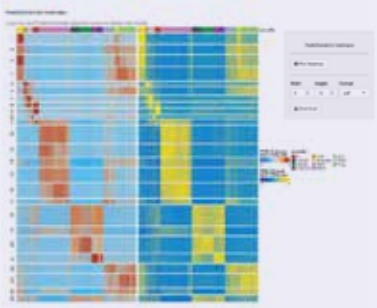
GAK and PRKCD are positive regulators of PRKN-independent mitophagy

Michael J. Munson and colleagues from the Simonsen group identified two lipid kinases, Cyclin G-associated kinase (GAK) and Protein Kinase C Delta (PRKCD), as regulators of PRKN-independent mitophagy (Munson et al., 2021). Mitophagy refers to selective degradation of mitochondria, often damaged due to stress, via autophagy. Depending on the stimuli and cellular contexts, different mitophagy mechanisms can be activated via multiple signaling cascades. One of the better characterized mechanisms is mediated by PINK1 and the E3 ligase PRKN. However, mitophagy can be PRKN independent where other E3 ligases take up the role of PRKN and such a mode plays important roles in response to stress. Several studies have added to the understanding of selective autophagy and the proteins involved in those pathways but the roles of lipids and lipid-binding proteins in cargo recognition and autophagosome biogenesis during selective autophagy remains elusive. The authors examined the role of proteins containing lipid interacting domain in PRKN-independent autophagy specifically by using a fluorescent mitophagy reporter by performing a siRNA screen. They found that GAK and PRKCD are required for efficient mitophagy and their kinase activity is critical for this function. *C. elegans* lacking expression of GAK homolog and zebrafish *prckd* mutants showed significantly lower level of basal mitophagy highlighting the conserved roles of these kinases in mitophagy.



Measuring Mitophagy: Overlay of an TEM section on a confocal image showing a tandem tag mitophagy reporter

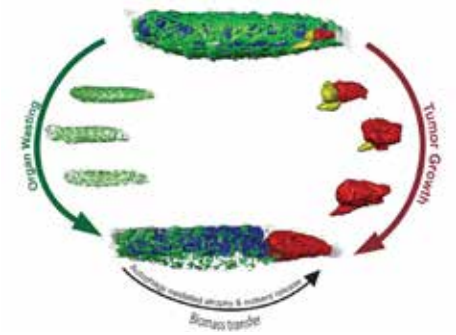
Streamlines collaboration, hypothesis development and interpretation of data



www.github.com/EskelandLab
www.cancell.medisin.uio.no/ShinyArchR.UiO

Host autophagy mediates organ wasting and nutrient mobilization for tumor growth

Rojyar Khezri from Rusten group led a multidisciplinary collaborative project to study the role of systemic host autophagy in tumor growth (Khezri et al., 2021). Using a *Drosophila* malignant Ras driven eye tumor model showing organ wasting, the team quantified tumor growth, organ wasting, metabolic reprogramming to establish a direct link between tumor growth and organ wasting. They performed high-resolution micro computed tomography (μ-CT) to measure the volume of the tumor and other organs while the tumor grew during larval development and employed florescent reporters and backlight microscopy to quantify muscle and fat body changes. Next, to see if increased autophagy is resulting in organ wasting, the authors employed the power of fly genetics. They introduced a mutation in a gene from the autophagy initiation complex (atg13) in the tumor model to stop autophagy and found that those animals displayed complete reversal of weight loss and alterations in body fat and muscle and showed reduced tumor growth. Cell-free serum analysis of animals with malignant tumors showed elevated levels of amino acids and sugars as compared to controls and by carbon tracing the authors showed that the released nutrients from organ wasting are mobilized to the tumor. Thus, the authors conclusively showed that autophagy mediated organ wasting and nutrient mobilization contributes to tumor growth.



Volumetric 3D-representations of micro-computed (μ-CT) tomography sections of a healthy larva (top) and tumor-carrying animal (bottom). Tumors grow 10 times in volume (red) while organ wasting of muscle (green) ensues, mimicking a central hallmark of cancer cachexia in human. Autophagy in host tissues is required for organ wasting and leads to release of nutrients to the circulation that is utilized for tumor growth.

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The year at CanCell

CanCell continued its activities despite of COVID restrictions as far as possible and had several scientific events, mostly still on Zoom. In May, we held our *user panel conference* where prospective grant applicants received feedback from our panellist of patient group representatives. During June, the *semi-annual symposium* hosted one of our SAB members' Professor Pier Paolo Di Fiore (IGEM), Eivind Hovig and several excellent flash talks from junior scientist. In November, we were finally able to meet again and the *annual retreat* at Norefjell was very well received – a record 91 participants discussed, danced, relaxed and enjoyed themselves in the Norwegian mountains. The retreat was followed by a *workshop with CanCell's associated members*: Hovig, Collas, McCormack, Helland, Frigessi and Johansen all met in person. Yngvar Fløisand participated via Zoom. The newest associated member Tuula Nyman (Proteomics) introduced herself at both the workshop and the retreat. The *seminar committee* organized six events throughout 2021; the final two with Irene Miguel-Aliaga (Nov 5) and Ross Cagan (Dec 3) restarted the in-person seminars after eighteen months of online seminars. Previous speakers were Sara Sigismund (Feb 19), Matthew Vander Heiden (Mar 26), Thomas Melia (Apr 23), and Effie Apostolou (May 28).

A scientific- cultural collaboration with *avant garde* Butoh dance group led to an exciting performance where a dancer impersonated/dramatized the life cycle of a cell during cancer development. The séance *"The Rebellion of the Cell"* was performed four times at a theatre in Oslo for an almost sold out audience, including many CanCell members.

As previous years, several of CanCell *Young Scientists Grant* were able to obtain seed grants for collaborative project (up to 300 000 NOK) or minor solo projects (50 000 NOK). During the three years of its existence, 3.2 MNOK of funds has been granted to proponent projects initiated by the Centre's junior scientist across groups. Several of our junior scientists also participated in organizing the University course *"Molecular Cancer Medicine"* over four weeks in October. Young scientists also had crucial contribution through *CYS – CanCell Young Scientists* – organizing two webinars, on grant writing and scientific illustrations. They also were instrumental at the retreat with an excellent social session.

Our own *Equality Forum* continues to play a pivotal role in the cultural and social integration of our centre. They initiated a potluck dinner and had a lunch seminar which both turned out a good crowd.

CanCell collaborators represented at the Butoh dance premiere

Picture from the event 'CRISPR, past, present and future'

Outreach

The center is committed for broader dissemination and public outreach of the research conducted at the center as well as for popular science topics. Towards this, we have dedicated social media accounts on Twitter (@CanCell_UiO), Instagram (cancell_uio) and Youtube (CanCell UiO). We use Twitter to broadcast to the broader scientific community while Instagram is used for internal communication at the center. We are developing our Youtube channel to reach broader audience. In addition to this some CanCell members have established networks with associations, newspapers and podcasts through which they engage in public outreach.

Helene Knævelsrud writes quarterly for a newspaper, Morgenbladet, where she brings out a scientist's point of view on day-to-day matters. She also featured on Framtida Junior as a cancer researcher and interviewed for various podcasts. Among other activities, she also presented her research in the popular annual science festival of Pint of Science. Deservedly, she was awarded as the communicator of the year at the CanCell awards. Pilar Ayuda-Durán is an active member of the Spanish Association for Cancer Research and participates in their outreach activities, webinars and podcasts. She is also the president of the Spanish Researcher Association in Norway and organizes regular outreach events with them of which Science Tapas is very popular. In 2021 she organized a seminar titled 'CRISPR, past, present and future' to which other CanCell members contributed as well. Finally, Ragnhild Eskeland co-authored textbook in Biology, Bios 1, for Videregående skole.

To increase out outreach activities that have a stronger impact, a dedicated 50% communications adviser position was advertised in 2021 and the new adviser has started working from the beginning of 2022.

Twitter:
@CanCell_UiO

Instagram:
cancell_uio

YouTube:
CanCell UiO

The center is committed for broader dissemination and public outreach of the research conducted at the center as well as for popular science topics. Towards this, we have dedicated social media accounts on Twitter, Instagram and YouTube.

Helene Knævelsrud was awarded CanCell Communicator of the Year

Follow us online:

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About CanCell

Centre for Cancer Cell Reprogramming *(CanCell)* was established in December 2017 as a Centre of Excellence appointed by the Research Council of Norway with the University of Oslo (UiO) as host institution. The core funding for the CoE encompasses six years with a possible four years extension based on evaluation. The Centre resides at two different locations: Institute for Cancer Research (ICR) at Norwegian Radium Hospital, Oslo University Hospital (OUS) and Institute for Basic Medical Sciences (IMB) at Domus Medica, University of Oslo (UIO). Regular shuttle bus service connects the nodes. A consortium agreement regulates cooperation between UiO and OUS with the intention to make conditions favourable for fulfilling the scientific aims and strategic plans of CanCell.

Research Groups

Six principal investigators (PIs) and their groups form CanCell: Harald Stenmark (director), Anne Simonsen (co-director), Jorrit Enserink, Tor Erik Rusten, Jørgen Wesche and Ragnhild Eskeland. The PIs have weekly meetings to discuss all issues related to the Centre. Furthermore, eight independent groups or research teams are associated with CanCell. These are the groups of Emmet McCormack, Arnoldo Frigessi, Terje Johansen, Eivind Hovig, Yngvar Fløisand, Åslaug Helland, Phillippe Collas, and Tuula Nyman (from 2021). They all bring distinct complementary expertise to the Centre.

Management

The CanCell PIs acts as executive board for CanCell together with administrative coordinator Anders Øverbye. The Centre management reports to the CanCell Board. The Board is chaired by Dag Kvale (Institute of Clinical Medicine, UiO), with additional members Arne Klungland (Head of Department, Institute of Biosciences, UiO), Åslaug Helland (Head of Research, Division of Cancer Medicine, OUS), and Lene Frost-Andersen (Head of Department, IMB, UiO).

Support staff

CanCell also relies on the support of administrative and technical staff at both locations. The technical staff are invaluable to ensure functions and safety in the laboratories. The administration take care of procurement, budgets, HR-functions and communications.

Read more online

About the centre

Research Groups

Staff

CanCell PIs - from left: Tor Erik Rusten, Jorrit Enserink, Jørgen Wesche, Anne Simonsen, Harald Stenmark, Ragnhild Eskeland

Centre for Cancer Cell Reprogramming (CanCell) was established in December 2017 as a Centre of Excellence appointed by the Research Council of Norway with the University of Oslo (UiO) as host institution

CanCell Associated Members' workshop. From left: Terje Johansen, Emmet McCormack, Ragnhild Eskeland, Arnoldo Frigessi, Philippe Collas, Åslaug Helland, Harald Stenmark, Anne Simonsen, Eivind Hovig, Tuula Nyman, Jorrit Enserink, Tor Erik Rusten.

Years
6/10

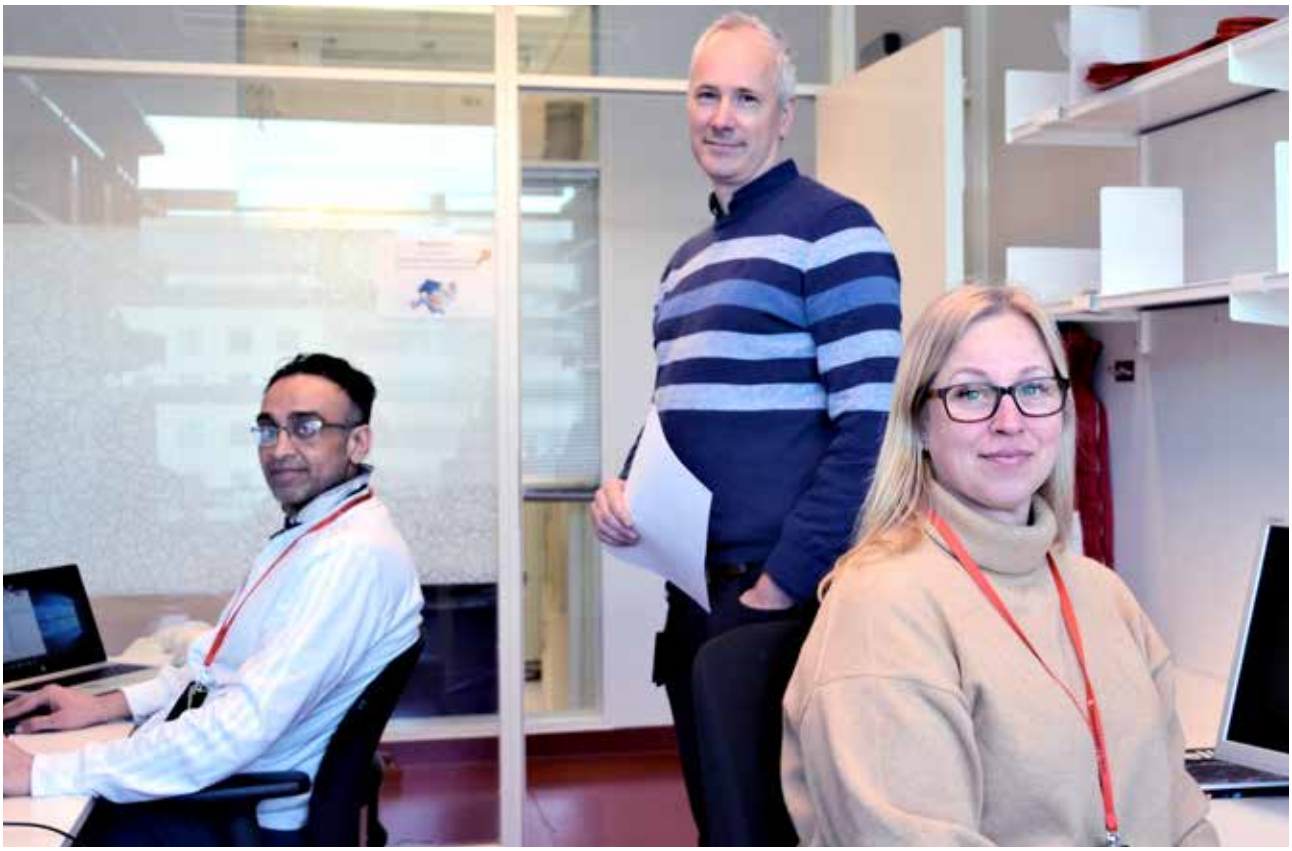
Six years funding guaranteed/ four years further funding pending evaluation

Groups
06

Six principal investigators (PIs) and their groups form CanCell

Groups
08

Eight groups/research teams are associated with CanCell



CanCell admin staff - Abdushakoor Khan, Anders Øverbye (manager) and Nina Karlsrud


REPROGRAMMING CANCER
OMPROGRAMMERING AV KREFT