Cancer Research KI PI-Retreat

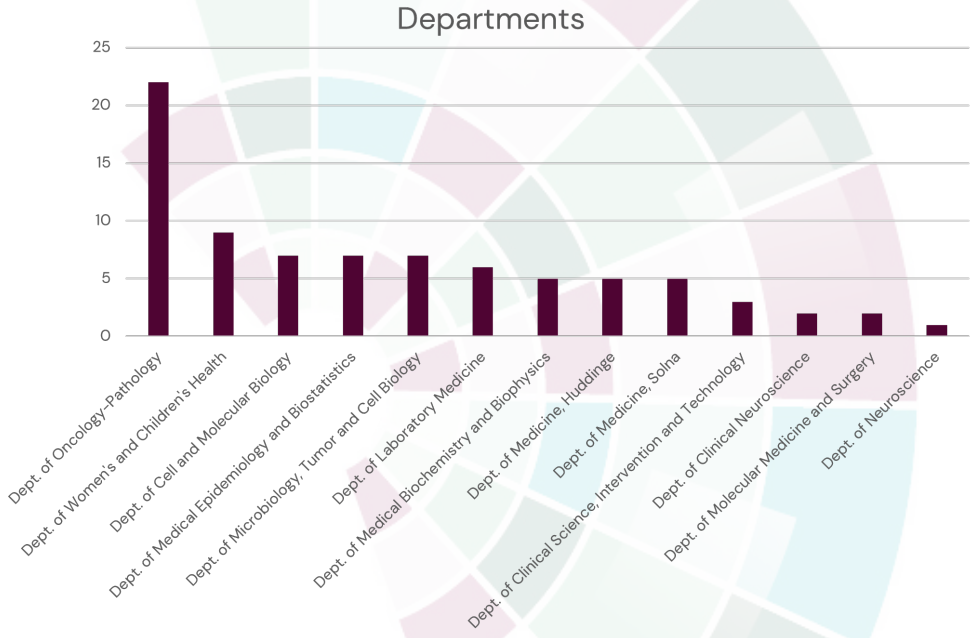
DJURÖNÄSET

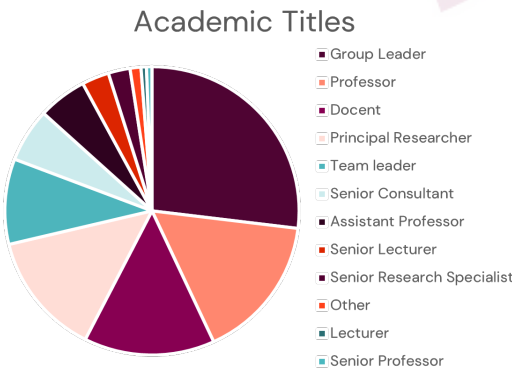
FEBRUARY 17-18, 2025

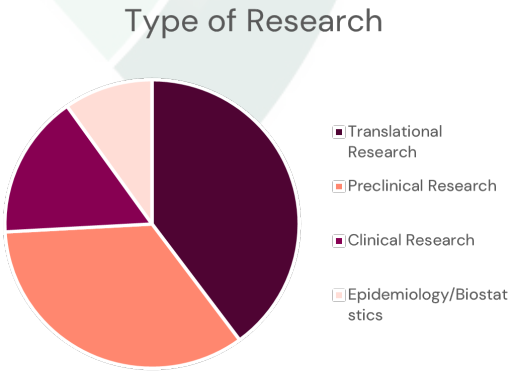
Welcome to the Cancer Research KI PI-Retreat

You are welcome to a 2-day meeting with research presentations and networking opportunities, which is only open for PIs that head research groups at Karolinska Institutet within the field of cancer. The meeting will provide many possibilities for networking with other researchers within the cancer field, opening your scientific horizons, and new possibilities for collaborations and funding initiatives. During the meeting, we will have oral presentations, elevator pitches, and a "Fast-Track Collaboration Challenge".

We are happy to share that we will have 13 departments represented during the PI-retreat, from both Solna and Flemingsberg campuses. Our researchers cover pre-clinical, translational, clinical and epidemiological research areas.

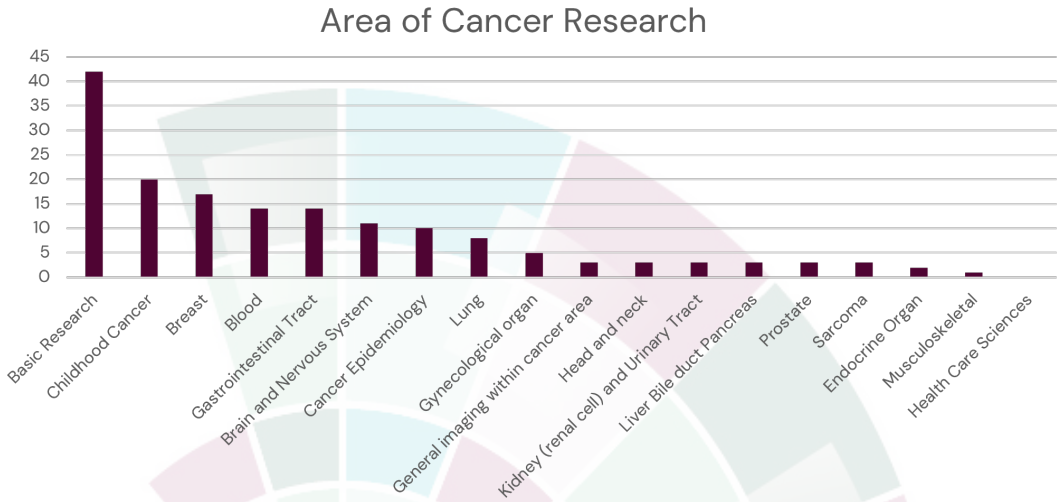






Welcome to the Cancer Research KI PI-Retreat

Moreover, a variety of areas of cancer will be covered.



In this abstract booklet you will find information about the attending researchers, including their research area, their needs for collaboration, a short description of their research, top publications and contact information. Using the search function in the PDF version of the abstract booklet you can easily find people and topics of interest to you. All retreat participants are listed in alphabetical order according to their first names.

We are looking forward to having you on board and we wish you a productive meeting and a pleasant stay!

The Cancer Research KI PI-Retreat
Organizing committee

Linda Lindström
Ninib Baryawno
Dhifaf Sarhan
Liselotte Bäckdahl
Dina Dabaghie
Pablo Martí Andrés
Stefina Milanova
Johanna Mayer

Cancer Research KI (CRKI) in a nutshell

Mission

To aid in the generation of new scientific discoveries that can be rapidly translated into clinical practice for the benefit of patients and society.

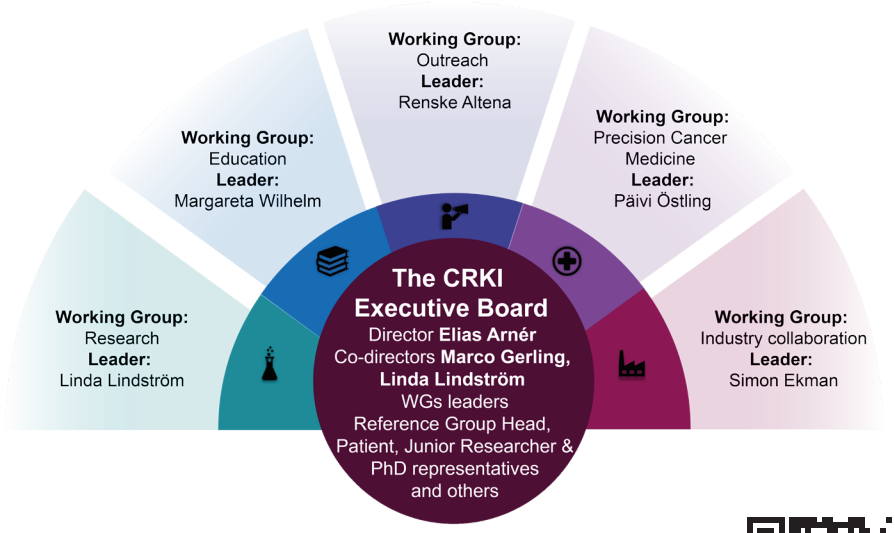
An umbrella organisation for cancer research at Karolinska Institutet

A Strategic Research Programme in Cancer since 2009 (previously StratCan)

An initiative that provides various type of support for all cancer researchers at KI

A hub for communication of cancer research at KI towards the general public

>390 PIs in cancer research at KI 21 Departments



The Executive Board

Elias Arner, Marco Gerling, Linda Lindström, Margareta Wilhelm, Päivi Östling, Simon Ekman, Jonas Fuxe, Matthias Löhr, Renske Altena, Joakim Dilner, Keith Humphreys, Ninib Baryawno, Sara Abu Ajamieh, Lise-lott Eriksson, Patrik Rossi, Lena Sharp, Eva Jolly, Liselotte Bäckdahl, Dina Dabaghie, Johanna Mayer, Stefina Milanova, Pablo Martí Andrés

More information on the website

1-7 Konferenslokaler & hotellrum / Conference & Hotel rooms
8 Seregården
9 Reception, Restaurang Matsalen, Barer / Reception, Restaurant & Bars
10 Skärgårdsspa / Spa
11 Spapaviljongen / Spa treatments

12 Skärgårdskrogen Sjöboden / Restaurant Sjöboden
13 Vedeldad bastu & badtunnor / Wood burning sauna & hot tubs
14 Svit & Längan / Suite & Hotel rooms

A Varm infinitypool / Hot outdoor infinity pool
B Cyklar / Bicycles

C Naturstig / Nature trail
D Badstrand & Äventyrscenter / Beach
E Helikopterplatta / Helipad
F Motionsslinga / Running trail
G Utegymstationer / Outdoor gym stations
H Busshållplats / Bus stop
I Tennisbana / Tennis court
J Folkparken / Outdoor event area

K Ångbåtsbrygga / Steamboat jetty
L Kanoter & båtar / Canoes & boats
M Gästhamn / Guest harbour
N Mötesplats / Meeting spot

P1 Parkering / Parking
P2 Parkering / Parking

Some practical information

TRANSPORT & RETURN

Buses depart from Cityterminalen Monday, February 17th, at 8:30 (the extended terminal building at the Stockholm main railway station), entrance next to World Trade Center, Klarabergsviadukten. Check the monitors for a gate number for our buses "KI till Djurönäset". The bus ride takes approximately one hour. We return to the Stockholm City terminal on Tuesday afternoon, February 18th, approximately 18:00.

ARRIVAL AT DJURÖNÄSET

You will get a name badge when you arrive at the location of the meeting in house 7 (see map). Please, wear the name badge visible throughout the conference. Coffee/tea and sandwiches are served prior to the conference that starts at 09:45. Our luggage will be stored temporarily until check-in time, which will be during the afternoon coffee break at 15:05. On Tuesday, February 18th, please check-out before the morning session at 8:30.

MEETING

The meeting and coffee breaks throughout the day will be held in House 7. All presentations are given 10 min each. Please adhere to the allocated time! In addition, we hope that you will make the best possible use of breaks, free time, lunches and dinner, to connect and discuss possible joint interests with the other PIs attending the meeting!

MEALS

Breakfast, lunch and dinner will be served in the main building (house 9). Those of you who have informed us of special food requests please contact the serving staff in the restaurant. They have received the information beforehand.

INTERNET

Djurönäset's wireless net is free of charge. Log in: djuronaset-guest. In each room both the wireless net and a net cable is available.

LEISURE

At the conference center there is a 25 m swimming pool, a gym and sauna, open between 15:00-23:00. On the evening of 17th, the sea-side wooden sauna will be opened 18:00-23:00.

Monday, February 17

08:30 Bus departs from Stockholm Cityterminalen
09:15 Arrival, coffee and registration

09:45 – 10:10 **Welcome + Presentation of CRKI**
Linda Lindström, Elias Arnér

10:10 – 10:25 **"Fast-Track Collaboration Challenge" Kickoff and Practical Overview**
Dhifaf Sarhan

10:25 – 11:25 **Morning Session 1**
Chairs: Margareta Wilhelm, Galina Selivanova

10:25 – 10:35 Niklas Björkström, Dept. of Medicine, Huddinge
Title: Spatial organization of cytotoxic lymphocytes in the tumor microenvironment as a predictor for treatment response and prognosis in cancer with poor outcome

10:40 – 10:50 Twana Alkasalias, Dept. of Women's and Children's Health
Title: Innovative ex-vivo models for unraveling early cancer initiation in women: Towards targeted prevention strategies

10:55 – 11:05 Kirsty Spalding, Dept. of Cell and Molecular Biology
Title: The impact of adipocyte senescence in breast cancer progression

11:10 – 11:20 Kristina Viktorsson, Dept. of Oncology-Pathology
Title: Non-small cell lung cancer- exploring the Ephrin/Eph signaling axis and extracellular vesicle protein cargo in context of precision cancer medicine and immune checkpoint blockade

11:25 – 11:50 **Coffee Break**

11:50 – 12:50 **Morning Session 2**
Chairs: Keith Humphreys, Therese Andersson

11:50 – 12:00 Anna Johansson, Dept. of Medical Epidemiology and Biostatistics
Title: Identifying risk and prognostic factors for breast cancer in the population-based setting

12:05 – 12:15 Hanna Brauner, Dept. of Medicine, Solna
Title: Determining disease trajectories in cutaneous lymphoma

12:20 – 12:30 Shaohua Xie, Dept. of Molecular Medicine and Surgery
Title: Risk-adapted prevention of upper gastrointestinal cancer

Monday, February 17

12:35 – 12:45 Mattias Rantalainen, Dept. of Epidemiology and Biostatistics
Title: AI-based precision pathology – scalable solutions for cancer patient stratification and phenotyping

12:50 – 13:50 Group Photo + Lunch

13:50 – 15:05 Afternoon Session 1: Personalized Cancer Medicine and Clinical Trials
Chair: Dhifaf Sarhan

13:50 – 14:20 Jeffrey Yachnin
Title: Personalized Cancer Medicine: Not great so far but it can be!

14:20 – 15:05 Panel Discussion (Jeffrey Yachnin, Theodoros Foukakis, Richard Rosenquist Brandell, Anna Johansson, Hanna Brauner, Ingemar Ernberg)

15:05 – 15:35 Coffee Break and Check in

15:35 – 16:50 Afternoon Session 2
Chairs: Nico Dantuma, Hanna Brauner

15:35 – 15:45 Amir Ata Saei, Dept. of Microbiology, Tumor and Cell Biology
Title: Identifying and targeting the tumorigenic functions of oncometabolites in cancer

15:50 – 16:00 Avlant Nilsson, Dept. of Cell and Molecular Biology
Title: Predicting cancer mechanisms with deep learning

16:05 – 16:15 Bennie Lemmens, Dept. of Medical Biochemistry and Biophysics
Title: Direct visualisation and control of DNA replication initiation in single human cells reveals new mechanisms of action of targeted cancer treatments

16:20 – 16:30 Cecilia Williams, Dept. of Medicine, Huddinge
Title: How estrogens regulate sex differences of the colon, its cancer, microbiome, and the immune microenvironment

16:35 – 16:45 Eduardo Villablanca, Dept. of Medicine, Solna
Title: Liver X Receptor unlinks intestinal regeneration and tumorigenesis

16:50 – 17:20 Coffee Break

Monday, February 17

17:20 – 18:00 **Elevator Pitch**

Chair: Stefina Milanova

Adamantia Fragkopoulou
Klas Blomgren
Andreas Lundqvist
Carlos Rodrigues
Daniel Hagey
Hans Grönlund
Hassan Abolhassani
Klas Wiman
Marie Arsenian Henriksson
Nicola Crosetto
Rainer Heuchel
Thomas Helleday
Simon Elsässer

18:00 – 19:00 **Mingle**

19:00 - Late **Dinner, followed by continued mingle**

Tuesday, February 18

07:00 Breakfast and Check-Out

08:45 - 10:00 Morning Session 1
Chairs: Ninib Baryawno, Marco Gerling

08:45 – 08:55 Jean Hausser, Dept. of Cell and Molecular Biology
Title: Machine-learning of cancer-host interactions to target in therapy from multi-omics

09:00 – 09:10 Sergio Martinez Høyer, Dept. of Microbiology, Tumor and Cell Biology
Title: Regulation of normal and malignant hematopoiesis by Group 2 innate lymphoid cells

09:15 – 09:25 Sylvain Peuget, Dept. of Microbiology, Tumor and Cell Biology
Title: Deciphering the links between oncogenic bacteria and cancer for innovative therapies

09:30 – 09:40 Ola Hermanson, Dept. of Neuroscience
Title: Molecular Neurodevelopment and Neuro-Oncology

09:45 – 09:55 Phillip Newton, Dept. of Women's and Children's Health
Title: Understanding and preventing radiation-induced skeletal late-complications

10:00 – 10:30 Coffee Break

10:30 – 11:45 Morning Session 2
Chair: Dhifaf Sarhan

10:30 – 10:40 Magnus Nilsson, Dept. of Clinical Science, Intervention and Technology
Title: Clinical and translational studies on gastric and oesophageal cancer

10:45 – 10:55 Svetlana Bajalica Lagercrantz, Dept. of Oncology-Pathology
Title: Previvors of hereditary cancer risk syndromes with focus on the Swedish gTP53 cohort

11:00 – 11:10 Fredrik Strand, Dept. of Oncology-Pathology
Title: Artificial Intelligence for Breast Cancer Radiology

11:15 – 11:25 Marco Gerling, Dept. of Clinical Science, Intervention and Technology
Title: Cancer invasion fronts: Tumor epithelial interactions and cell competition

Tuesday, February 18

11:30 – 11:45 Thuy Tran, Dept. of Oncology-Pathology
Title: Radiopharmaceutical Developments for Translational Theranostics of Cancer Based on Small Ligands, High-affinity Peptides and Antibodies – From Bench to Bedside

11:45 – 12:45 Lunch

12:45 – 14:00 "Fast-Track Collaboration Challenge": Collaboration and Proposal Formation
Chair: Dhifaf Sarhan

Meet with your assigned partner to brainstorm project ideas, focusing on structure and feasibility.
Deliverable: by 14:00, submit a short pitch (max. 200 characters) through Mentimeter (will be available at the retreat). The pitch should briefly describe the project idea and its potential impact.

14:00 – 14:30 Coffee Break and "Fast-Track Collaboration Challenge": Voting
Please, vote for your favorite pitch using the QR codes availble in House 7

14:30 – 16:00 Afternoon Session 1
Chairs: Twana Alkasalias, Ourania Kostopoulou

14:30 – 14:40 Margareta Wilhelm, Dept. of Microbiology, Tumor and Cell Biology
Title: Identifying molecular mechanisms and therapeutic targets in childhood neural tumors

14:45 – 14:55 Oscar Wiklander, Dept. of Laboratory Medicine
Title: Extracellular vesicle-based liquid biopsy and targeted therapy

15:00 – 15:10 Per Hydbring, Dept. of Oncology-Pathology
Title: Multi-omics uncovers signatures associated with resistance to osimertinib in EGFR-mutant non-small cell lung cancer patients

15:15 – 15:25 Sten Linnarsson, Dept. of Medical Biochemistry and Biophysics
Title: Towards curative reprogramming of human glioblastoma

15:30 – 15:40 Andrea Ponzetta, Dept. of Medicine, Huddinge
Title: Interrogating the immune landscape in gastroesophageal cancer to improve current patient classification

Tuesday, February 18

16:00 – 16:30 Coffee Break

16:30 – 16:50 "Fast-Track Collaboration Challenge": Presentations
Chair: Ninib Baryawno

The top three teams will present their ideas in 5-minute slots (oral or PowerPoint), followed by a 1-minute Q&A session. This will showcase projects to inspire further collaboration or gain broader support.

16:50 -17:00 Conclusion
Linda Lindström

17:15 Bus departs to Stockholm Cityterminalen

Abstracts

Adamantia Fragkopoulou

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Cancer Research Area

- Childhood brain tumours
- Radiotherapy
- Late complications

Key research field interests

- Radiotherapy
- Neuroinflammation
- Cognition
- Tumor growth
- Antisense oligonucleotides

Needs for collaborations

- Machine learning expertise
- Immunology expertise
- Clinical samples

Machine Learning Models of Microglia-Mediated Neuroinflammation Post-Cranial Irradiation to Develop Targeted Antisense Therapies for Pediatric Brain Tumour Survivors

Adamantia Fragkopoulou

Each year, approximately 100 children in Sweden are diagnosed with brain tumours. Although radiotherapy can be life-saving, it often results in long-lasting complications, such as cognitive impairment. Neuroinflammation is thought to play a role in these effects, though its specific dynamics and impact on brain function are not yet fully understood.

We use a mouse model of cranial irradiation (IR) to generate longitudinal single-cell RNA sequencing datasets to profile the cellular responses in the hippocampus, a central brain area in cognition. Our findings unveil a complex sequence of inflammatory events (Osman A. et al., 2020, Cell Reports; Lastra Romero A.#, Preka E.#, et al., in revision, Immunity). Initially, there is an acute inflammation and cell death within 6 hours post-IR, followed by a delayed microglial response two weeks later, coupling interferon signalling to mitotic progression. At the later phases post-IR, we observe progressive microglial loss, a failure of these cells to repopulate, and the emergence of microglia-like cells derived from peripheral monocytes.

Our project employs machine learning to model these microglial dynamics in healthy and irradiated brains (mouse and human). Using in silico simulations, we selectively silence genes or transcription factors governing the microglial lineage specification or immune responses and analyze the downstream consequences, which are later validated in vivo using the putative target-specific knock-out mice. After validating the potential putative targets, we implement therapeutic interventions using the novel target-specific antisense oligonucleotides (ASOs). These ASOs have a favourable safety profile and regulatory approvals by the FDA and EMA. Currently, we focus on intervening with the delayed IR-induced interferon response by targeting the cGAS-STING pathway.

A selection of publications from your group

- Zhou K, Alkis Zisiadis G, Havermans M, **Fragkopoulou A**, Dominguez C, Ohshima M, Osman AM, Rodrigues CFD, Blomgren K. Microglia depletion and repopulation do not alter the effects of cranial irradiation on hippocampal neurogenesis. Brain Behav Immun. 2024 Aug 30:S0889-1591(24)00576-2. doi: 10.1016/j.bbi.2024.08.055. PMID: 39218233
- Preka E, Lastra Romero A, Sun Y, Onetti Vilalta Y, Seitz T, **Fragkopoulou A**, Betsholtz C, Osman AM, Blomgren K. Rapid and robust isolation of microglia and vascular cells from brain subregions for integrative single-cell analyses. Heliyon. 2024 Aug 5;10(16):e35838. doi: 10.1016/j.heliyon.2024. e35838. eCollection 2024 Aug 30. PMID: 39211933
- Zanni G#, Goto S#, **Fragopoulou AF#**, et al. Lithium treatment reverses irradiation-induced changes in rodent neural progenitors and rescues cognition. Mol Psychiatry. 2021 Jan;26(1):322-340. # Equal contribution.

Alexander Espinosa

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Cancer Research Area

- Basic research

Key research field interests

Needs for collaborations

A selection of publications from your group

Alexios Matikas

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Cancer Research Area

- Breast cancer

Key research field interests

- Clinical oncology
- Epidemiology
- Translational research/biomarker discovery
- Biostatistics methods

Needs for collaborations

- Molecular expertise
- Image analysis

Investigating the effect of (neo)adjuvant chemotherapy for early breast cancer: clinical and molecular correlations

Alexios Matikas

Neoadjuvant and adjuvant chemotherapy for early breast cancer improves patient survival, although not all patients respond and can thus be exposed to unnecessary side effects. The overarching goal is to understand the factors and mechanisms that govern response to treatment. In the academic phase 3 trial PANTHER, dose dense and standard interval adjuvant chemotherapy were compared. Long-term follow-up is available, with the primary analysis recently published in JCO and several clinical secondary analyses already submitted for review. RNA sequencing from >600 patients is ongoing, digitized H&E images from >1000 patients are available, whereas multiplex fluorescent immunohistochemistry is underway. The goal is to identify predictive biomarkers for dose dense chemotherapy, a sparsely explored area in the breast cancer literature. At the same time, we explore neoadjuvant treatment for HER2-positive breast cancer in the academic randomized phase 2 trial ARIADNE which is ongoing in Sweden and Norway and will soon open in Belgium and Netherlands. In total, 370 patients are planned to be enrolled and receive either standard chemotherapy and dual HER2 blockade (TCHP) or the revolutionary antibody-drug conjugate trastuzumab deruxtecan, with further treatment individualization according to molecular subtyping. Within ARIADNE baseline, on-treatment and post-treatment biopsies are obtained and cores are both snap frozen for bulk whole exome and RNAseq and dissociated immediately for single-cell analyses. The third focus of my research is based on registry data, where we have constructed and curated a dataset of primary breast cancer with linkage to multiple registries and completed missing data from patient charts to give answers to pertinent clinical questions.

A selection of publications from your group

- Tailored dose-dense versus standard adjuvant chemotherapy for high-risk early breast cancer: end of-study results of the randomized PANTHER trial
  Matikas A, Möbus V, Greil R, Andersson A, Steger G, Untch M, Fornander T, Malmström P, Schmatloch S, Johansson H, Hellström M, Brandberg Y, Gnant M, Loibl S, Foukakis T, Bergh J. Journal of Clinical Oncology 2024. PMID 39018515, IF: 45.3
- A population-based study on trajectories of HER2 status during neoadjuvant chemotherapy for early breast cancer and metastatic progression
  Boman C, Liu X, Eriksson Bergman L, Sun W, Tranchell C, Toli MA, Acs B, Bergh J, Foukakis T, **Matikas A**
  British Journal of Cancer 2024. PMID 38942987, IF: 8.8
- Longitudinal molecular profiling elucidates immunometabolism dynamics in breast cancer
  Wang K, Zerdes I, Johansson H, Sarhan D, Sun Y, Kanellis D, Sifakis E, Mezheyeuski A, Liu X, Loman N, Hedenfalk I, Bergh J, Bartek J, Hatschek T, **Matikas A**, Foukakis T.
  Nature Communications 2024 May 7;15(1):3837. PMID: 38714665, IF: 16.6

Amir Ata Saei

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Cancer Research Area

- Colon cancer
- Liver cancer

Key research field interests

- Mass spectrometry-based proteomics
- Cancer metabolism
- Microbiome
- Drug discovery
- Biomarkers

Needs for collaborations

- We are interested in collaborations at any level. We are especially looking for collaborators with access to clinical material on colon and liver cancers and those on structural biology (NMR, cryo-EM, crystallography) and biophysics.

Identifying and targeting the tumorigenic functions of oncometabolites in cancer

Amir Ata Saei

Targeting cancer metabolism: Colon and liver cancers are among the most prevalent and fatal malignancies worldwide, often characterized by late-stage diagnosis and resistance to conventional therapies, making the development of novel therapeutic strategies crucial for improving patient outcomes. As a hallmark of cancer, dysregulated cellular metabolism is a viable target for developing anticancer therapeutics. We have developed unique proteomics tools to study "oncometabolite-protein" and "host-pathogen" interactions at multiple dimensions. Our aim is to identify metabolic vulnerabilities and develop therapeutic strategies against these cancers. We study the complex interplay between colon cancer cells, intracellular metabolites, microbiome, and microbial metabolites in the gut. We work at the intersection of multiple disciplines including proteomics, metabolomics, cell biology, biochemistry and biophysics and validate our results in relevant in vitro and in vivo model systems and patient material.

Development of novel proteomics tools: The propelling engine for our studies is chemical proteomics that can be used for studying the interaction of molecular entities with proteins. We have developed multiple techniques including Proteome Integral Solubility Alteration (PISA) assay, ProTargetMiner, and SIESTA that can be employed for deconvoluting drug targets, identifying enzyme substrates, studying cell biology and deciphering disease mechanisms. Our latest development is the multifaceted proteomics tool PISA-REX which can inform on the targets at the three dimensions of expression, stability/solubility, and redox state. Finally, we recently introduced a novel patented strategy for enhancing the depth of plasma proteome profiling. Albumin alone constituents 55% of the plasma by mass, and the peptides originating from such abundant protein crowd the mass spectra, hampering the detection of other proteins. Utilizing a small molecule that binds albumin and other highly abundant proteins, combined with nanoparticles that could fish the low abundant proteins, the new strategy leads to a massive increase in the proteomics depth (from couple hundred proteins to 1500). This strategy can potentially identify biomarkers against cancer and other diseases.

A selection of publications from your group

- Ashkarran AA, Gharibi H, Modaresi SM, Sayadi M, Jafari M, Lin Z, Ritz D, Kakhniashvili D, Sun L, Landry MP, **Saei AA*,** Mahmoudi M*. Deep plasma proteome profiling by modulating single nanoparticle protein corona with small molecules. BioRxiv Under final review in Nature Communications 2024.
- **Saei AA***, Lundin A, Lyu H, Gharibi H, Luo H, Teppo J, Zhang X, Gaetani M, Végvári Á, Holmdahl R, Gygi SP*, Zubarev RA*. Multifaceted proteome analysis at solubility, redox, and expression dimensions for target identification. Advanced Science. 2401502. 2024
- **Saei AA**, Beusch CM, Chernobrovkin A, Sabatier P, Zhang B, Tokat ÜG, Gaetani M, Végvári Á, Zubarev RA. ProTargetMiner as a proteome signature library of anticancer molecules for functional discovery. Nature Communications. 10: 5715. 2019.

Andrea Ponzetta

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Cancer Research Area

- Unconventional antitumor immunity in gastroesophageal adenocarcinoma patients

Key research field interests

- Gastroesophageal Adenocarcinoma
- Tissue immunology
- Unconventional T cells
- Chemo-immunotherapy
- Spatial immune mapping

Needs for collaborations

- Tumor organoids to model immune-tumor interactions
- Experience in predicting tumor-associated TCR ligands from TCRseq data
- Experimental platforms to test myeloid cell function
- Research questions that can be answered using a large patient biobank (n>300)

Interrogating the immune landscape in gastroesophageal cancer to improve current patient classification

Andrea Ponzetta

Gastroesophageal adenocarcinoma (GEAC) is among the top-ranking tumor types worldwide in terms of prevalence and mortality. GEAC patients are characterized by high heterogeneity at a histological, anatomical and mutational levels, and the efficacy of the current treatments is modest, with a 5-year overall survival around 20%. Despite having a relatively high tumor mutational burden, neoadjuvant immunotherapy has shown promising results only in a portion of GEAC patients, while the majority still relies on chemotherapy and surgery.
In addition, a prominent fraction of GEAC patients presents up-front with peritoneal metastatic dissemination and undergoes palliative treatment with dismal prognosis.
Predictive biomarkers for therapy success are largely missing and the mechanisms dictating the endogenous and therapy-driven antitumor response are unclear.
Thus, our work aims at integrating the tumor immune landscape with other biological parameters including molecular, histological and clinical data, with the objective of improving current patient classification. In addition, we strive to introduce immunomonitoring as a step towards precision medicine in GEAC, to better predict patient outcome and treatment efficacy.
Finally, we aim to better understand the basic mechanisms driving innate antitumor responses during GEAC tumorigenesis and upon therapy (both conventional and targeted), with a particular focus on the role of unconventional T cells, a class of innate-like lymphocytes enriched in most human tissues, endowed with a prominent cytotoxic and immunomodulatory potential.

A selection of publications from your group

- Carnevale S, Ponzetta A, et al. Neutrophils Mediate Protection Against Colitis and Carcinogenesis by Controlling Bacterial Invasion and IL22 Production by γδ T Cells. Cancer Immunol Res. 2024
- Lourda M, et al. High-dimensional profiling reveals phenotypic heterogeneity and disease-specific alterations of granulocytes in COVID-19. PNAS 2021
- Ponzetta A et al. Neutrophils Driving Unconventional T Cells Mediate Resistance against Murine Sarcomas and Selected Human Tumors. Cell 2019

Andreas Lennartsson

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Cancer Research Area

- Blood
- Leukemia

Key research field interests

- Epigenetics
- Transcriptomics

Needs for collaboration

- Single cell technologies
- Metabolomics

Epigenetic regulation of leukemia and normal blood development

Andreas Lennartsson

Acute Myeloid Leukemia (AML) is the most common type of acute leukemia. The prognosis for the patients is poor, with a long-term survival of only 25%. Thus, there is a considerable need for new treatments. Several epigenetic regulators, such as IDH1/2, TET2 and DNMT3A, are frequently mutated early in AML development. Moreover, KMT2A is frequently re-arranged in pediatric and infant acute leukemia. Hence, disturbed epigenetic regulation is a central for development of AML. We aim to increase the prognosis in both pediatric and adult AML by exploiting epigenetic vulnerability therapeutically. We are using several different methodologies to identify how DNA methylation, histone modifications and lncRNA, are co-regulated during AML development and drug response. Clonal heterogeneity of AML, and differential drug response leading to sub-clonal selection and evolution after treatment, have been demonstrated to cause relapse2. Therefore, it is absolutely crucial to understand the mechanisms and cellular interactions behind the heterogenic drug response. Clonal heterogeneity is dissected by using different single-cell technologies. Recently, we have started to be interested in metabolism-epigenetics-leukemia interactions.

A selection of publications from your group

- Perturbed epigenetic transcriptional regulation in AML with IDH mutations causes increased susceptibility to NK cells Anna Palau, Filip Segerberg†, Michael Lidschreiber†, Katja Lidschreiber, Aonghus J. Naughton, Maria Needhamsen, Lisa Anna Jung, Maja Jagodic, Patrick Cramer, Sören Lehmann*, Mattias Carlsten*, Andreas Lennartsson*, Leukemia, 2023
- AML Displays Increased CTCF Occupancy Associated to Aberrant Gene Expression and Transcription Factor Binding , Huthayfa Mujahed, Sophia Miliara, Anne Neddermeyer, Sofia Bengtzén, Christer Nilsson, Stefan Deneberg, Lina Cordeddu, Karl Ekwall, Andreas Lennartsson*, Soren Lehmann* Blood. 2020 Mar 31:blood.2019002326
- A regulatory role for CHD2 in myelopoiesis, Shahin Varnoosfaderani F, Palau A, Dong W, Persson J, Durand-Dubief M, Svensson JP, Lennartsson A. Epigenetics. 2020 Jan 10:1-13.

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Cancer Research Area

- Tumor Immunology

Key research field interests

- Immunology
- Biomarkers
- Immunotherapy
- Sarcoma
- Lung cancer

Needs for collaborations

Tumor Immunology

Andreas Lundqvist

The immune system plays an important role to prevent local growth and dissemination of cancer. Therapies based on activating the immune system can result in beneficial responses in patients with cancer. To harness the full potential of the immune system T and NK cells need to colonize tumors as well as to display optimal tumor killing potential. We investigate the ability of T and NK cells to migrate towards tumors, to persist within the tumor microenvironment, and to maintain their ability to and recognize and kill tumor cells. We study how T and NK cells interact with cells within the tumor microenvironment and exploit cellular and molecular mechanisms of tumor-induced immunosuppression to develop improved immunotherapy regimens in patients with cancer.

A selection of publications from your group

- Tong L, Kremer V, Neo SY, Liu Y, Chen Y, Wagner AK, Yang Y, Chen Z, Seitz C, Tobin NP, Ligtenberg MA, Alici E, Chen X, Haglund F, Seliger B, Harmenberg U, Colón E, Plogell AS, Liu LL, Lundqvist A. Cancer Commun (Lond). 2023 Jul;43(7):855-859. Renal cell carcinoma escapes NK cell-mediated immune surveillance through the downregulation of DNAM-1.
- Neo SY, Oliveira MMS, Tong L, Chen Y, Chen Z, Cismas S, Burduli N, Malmerfelt A, Teo JKH, Lam KP, Alici E, Girnita L, Wagner AK, Westerberg LS, Lundqvist A. J Exp Clin Cancer Res. 2024 Jan 9;43(1):13. Natural killer cells drive 4-1BBL positive uveal melanoma towards EMT and metastatic disease.
- Neo SY, Tong L, Chong J, Liu Y, Jing X, Oliveira MMS, Chen Y, Chen Z, Lee K, Burduli N, Chen X, Gao J, Ma R, Lim JP, Huo J, Xu S, Alici E, Wickström SL, Haglund F, Hartman J, Wagner AK, Cao Y, Kiessling R, Lam KP, Westerberg LS, Lundqvist A. Sci Transl Med. 2024 May 15;16(747):eadi2952. Tumor-associated NK cells drive MDSC-mediated tumor immune tolerance through the IL-6/STAT3 axis.

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Cancer Research Area

- Cancer epidemiology
- Biostatistics

Key research field interests

- Cancer epidemiology
- Breast cancer subtypes
- Reproduction and cancer
- Nordic cancer comparisons
- Biostatistics

Needs for collaborations

- Clinical cancer researchers with interest in epidemiology and patient outcomes (especially breast cancer, melanoma, gynecological cancer, CNS tumours and colorectal cancer).

Identifying risk and prognostic factors for breast cancer in the population-based setting

Anna Johansson

Despite Sweden's universal healthcare system with equal access to cancer screening, modern treatments and care, differences in breast cancer risk and survival are still present. Population-based cancer data integrated with state-of-the-art statistical methods are essential to address questions related to risk and survival differences across the wide range of patients.

Using methods from observational cancer epidemiology, our goal is to describe and identify subgroups of patients at particular high risk of breast cancer and adverse outcomes. We also want to quantify the potential gain in targeting specific groups with prevention and intervention strategies to minimize inequalities in breast cancer risk and survival.

We use data on patient characteristics (e.g. age, comorbidities, socioeconomic variables, screening history), breast cancer tumour characteristics (e.g. hormone receptor status, HER2, grade, stage) and treatments (e.g. localized and systemic) from the clinical breast cancer registries, as well as cancer registers and patient registers, to create nationwide cohorts in Sweden and the Nordic countries. Incidence and survival models estimate effects of subgroups and risk factors, while adjusting for confounding and time-varying effects. Observational data are important to understand underlying mechanisms in the real-world population of patients. With use of causal inference and mediation analysis, we can disentangle direct and indirect causal effects of different factors on risk and survival. We can also quantify the gain in targeting different factors for prevention. Novel methods and approaches are needed to overcome limitations in register-based data, e.g. methods for missing data.

A special interest of our group is pre-menopausal cancer in relation to pregnancy and reproduction. For this purpose, cancer register data in combination with data from medical birth registers are important to identify risks of adverse maternal and pregnancy outcomes in women with cancer. Several ongoing international collaborations to pool data have been initiated.

A selection of publications from your group

- **Johansson ALV**, Kønig SM, Larønningen S, Engholm G, Kroman N, Seppä K, Malila N, Steig BÁ, Gudmundsdóttir EM, Ólafsdóttir EJ, Lundberg FE, Andersson TM, Lambert PC, Lambe M, Pettersson D, Aagnes B, Friis S, Storm H. Have the recent advancements in cancer therapy and survival benefitted patients of all age groups across the Nordic countries? NORDCAN survival analyses 2002-2021. Acta Oncologica 2024 63; 179-191.
- Gkekos L, Lundberg FE, Humphreys K, Fredriksson I, **Johansson ALV**. Worse histopathology and prognosis in women with breast cancer diagnosed during the second trimester of pregnancy. ESMO Open 2024 9;4 102972.
- **Johansson ALV**, Trewin CB, Fredriksson I, Reinertsen KV, Russnes H, Ursin G. In modern times, how important are breast cancer stage, grade and receptor subtype for survival: a population-based cohort study. Breast Cancer Research 2021 23;1 17

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Cancer Research Area

- Supportive care
- Infections

Key research field interests

- B cell memory
- Immunization
- Treatment toxicity
- Infection

Needs for collaborations

- Molecular expertise
- Biostatistical expertise
- Clinical samples from young adults with cancer (AYAS)

Infections and Immunity in the Immunocompromised Child

Anna Nilsson

The central benefit of vaccination is that it prevents disease by stimulating the formation of immune memory against administered immunogens. A robust immunity following vaccination is correlated with high levels of pathogen-specific protective antibodies produced by plasma cells, which originate from B-lymphocytes. Loss of protective antibodies against vaccine-preventable diseases is one of the usual side effects after chemotherapy treatment, and as a rule more common among paediatric compared to adult patients. However, not all patients regain protective antibody titres despite revaccination. This may put them at risk of infection, that in turn aggravates the risk of late complications following cancer treatment. Here we aim to examine the cellular and molecular mediators behind defective antibody-mediated immune memory (humoral immunity) after paediatric cancer treatment by using lymphoblastic leukaemia (ALL) as our disease model. Cell lines and primary bone-marrow stromal cells are used to study factors important for plasma cell homing and survival in vitro. In addition to this experimental setup, we use clinical material from patients under chemotherapy treatment to gain further insights to why defective humoral immunity emerges after cancer treatment in children.

A selection of publications from your group

- INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES. 2024;25(13):6960

Bone Marrow-Suppressive Treatment in Children Is Associated with Diminished IFN-γ Response from T Cells upon Polyclonal and Varicella Zoster Virus Peptide Stimulation
Tiselius E; Sundberg E; Andersson H; Hobinger A; Jahnmatz P; Harila A; Palle J; Nilsson A; SaghafianHedengren S

- CLINICAL & TRANSLATIONAL IMMUNOLOGY. 2020;9(7):e1150

Deficits in the IgG+ memory B-cell recovery after anthracycline treatment is confined to the spleen of rhesus macaques
Lasaviciute G; Bricaud AL; Hellgren F; Ingelman-Sundberg HM; Eksborg S; Jonker M; Haanstra KG; Hed Myrberg I; Sverremark-Ekstrom E; Lore K; Saghafian-Hedengren S; Nilsson A

- HAEMATOLOGICA. 2015;100(4):e158-e161

Selective loss of vaccine-specific memory B cells in a rhesus macaque model of chemotherapy: influence of doxorubicin on immunological memory
Ingelman-Sundberg HM; Saghafian-Hedengren S; Jahnmatz M; Eksborg S; Jonker M; Nilsson A

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Cancer Research Area

- Translational cancer research

Key research field interests

- Tumour microenvironment
- Cancer-associated fibroblasts
- Tissue profiling
- Biomarkers
- Drug target discovery

Needs for collaborations

- Data analyses

Basic and translational studies on CAFs and astrocytes

Arne Östman

The research group has a longstanding interest in the tumour microenvironment. Common study designs are collaborative efforts with clinical researchers and SciLifeLab. Findings include discovery of fibroblasts as drivers in breast DCIS progression, identification of PDGFRb as a patented biomarker for radiotherapy (RT) benefit, and identification of novel CAF subsets associated with immune features, driver mutations and outcome (see selected publications). Some selected ongoing studies are highlighted below.

Better definition of CAF subsets is needed to exploit them as drug targets and biomarkers. SciLifeLabsupported single-cell RNAseq together with multiplex staining of human colorectal cancer identified novel multi-marker-defined CAF subsets, consistent with findings in an ongoing consortium study. Spatial analyses indicate differential effects of subsets on T-cell proliferation and tumour infiltration, and on cancer cell proliferation. Prognostic significance of some subsets was detected in stromal subcompartments, not detected in whole tumour stroma.

Our earlier breast cancer biomarker studies on randomized-trial-derived tissue collection, which identified associations between stromal PDGFRbeta and sensitivity to RT and tamoxifen, are developed in mechanistic and target identification studies. A mouse breast cancer RT model with fibroblasts has been established and will be used for experimental therapy studies. Also, a highthrough-put-screen (HTS) compatible co-culture system of fibroblast-mediated reduction of tamoxifen sensitivity is being developed for an HTS with CBCS, SciLifeLab and "AZ Open Innovation".

Our previous studies suggest astrocyte-mediated support of glioblastoma (GBM) as a novel target for GBM. With SciLIfeLab and "AZ Open Innovation" we have performed an astrocyte/GBM co-culture HTS. The screen results, PISA analyses and knock -down studies, suggest astrocyte-expressed FASN as a novel GBM drug target. Associations between FASN astrocytes and proliferating GBM cells have been detected in clinical samples.

Collectively, these studies should contribute towards developing fibroblasts and astrocytes to cancer drug targets and biomarkers of clinical utility.

A selection of publications from your group

- Fibroblast subsets in non-small cell lung cancer: Associations with survival, mutations, and immune features. Pellinen T, Paavolainen L, Martín-Bernabé A, ...Kallioniemi O, Micke P, Östman A. J Natl Cancer Inst. 2023 Jan 10;115(1):71-82.
- High PDGFRb Expression Predicts Resistance to Radiotherapy in DCIS within the SweDCIS Randomized Trial. Strell C, Folkvaljon D, Holmberg E, ...Akslen LA, Wärnberg F, Östman A. Clin Cancer Res. 2021 Jun 15;27(12):3469-3477.
- Impact of Epithelial-Stromal Interactions on Peritumoral Fibroblasts in Ductal Carcinoma in Situ. Strell C, Paulsson J, Jin SB, Tobin NP, ...Lendahl U, Wärnberg F, Östman A. J Natl Cancer Inst. 2019 Sep 1;111(9):983-995.

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Cancer Research Area

- Pan-cancer
- Pancreatic cancer

Key research field interests

- Tumor microenvironment
- Drug resistance
- Cancer metabolism
- Omics data integration
- Molecular networks

Needs for collaborations

- Experimental validation and in vitro models, expertise in cancer biology, and clinically relevant problems.

Predicting cancer mechanisms with deep learning

Avlant Nilsson

Cancer is a highly heterogeneous disease shaped by the cell type of origin, genetic alterations, as well as interactions within the tumor microenvironment. Because cellular processes are tightly interconnected through the cell's molecular networks, it is difficult to predict how these factors will impact the cancer, however this is important for selecting effective treatments. To address this complexity, we develop deep learning models that integrate cellular networks with multiomics data. The purpose of our research is to uncover governing mechanisms in cancer cells and to predict responses to different perturbations, including drug treatments. Our models leverage the interactome—a comprehensive map of molecular interactions within cells, including metabolic, signal transduction, and gene regulatory pathways. Using recurrent neural networks (RNNs), we model the propagation of molecular effects across these networks. The models are trained on high-throughput omics datasets, such as transcriptomics, metabolomics, and proteomics, from different experimental conditions to capture systems-level mechanisms underlying cancer progression. By constraining the models with known biomolecular interactions, we ensure that they are interpretable by humans and that they align with established biological knowledge. Our work has so far demonstrated great potential. We have applied it to model viability in response to drug treatments in different cell lines, with prediction performance on par with stateof-the-art methods, while presenting a much more scalable approach. We have also extended the approach to predict off-target effects of drugs on transcriptional responses, using chemical similarity as a prior in the model. We have constructed models of immune responses to different ligand environments. In particular, we trained a model of macrophage responses to predictligand combinations with synergistic effects on gene expression, e.g. IFNB1 and TNF on CDKN1A expression, which we have experimentally validated. Our approach can be appliedto study cellcell interaction, and we have a particular interest in pancreatic cancer, where tumor and stromal cells engage to drive disease progression. Taken together, our work demonstrates the utility and potential of network based deep learning in cancer. The long-term goal is to enable the computer-aided design of personalized cancer therapies to advance precision medicine.

A selection of publications from your group

- Meimetis, N., Lauffenburger, D. A. & **Nilsson, A**. Inference of drug off-target effects on cellular signaling using interactome-based deep learning. iScience 27, 109509 (2024).
- **Nilsson, A.***, Peters, J. M.*, Meimetis, N., Bryson, B. & Lauffenburger, D. A. Artificial neural networks enable genome-scale simulations of intracellular signaling. Nature Communications 13, 3069 (2022). * Shared first authorship.
- **Nilsson, A.***, Haanstra, J. R.*, Engqvist, M., Gerding, A., Bakker, B. M., Klingmüller, U., Teusink, B. & Nielsen, J. Quantitative analysis of amino acid metabolism in liver cancer links glutamate excretion to nucleotide synthesis. Proceedings of the National Academy of Sciences 117, 10294–10304 (2020). * Shared first authorship

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Cancer Research Area

- fundamental cancer cell biology
- Human cell proliferation and genome replication
- Drug resistance mechanisms
- Preclinical drug discovery

Key research field interests

- Cancer genetics
- DNA replication
- Human cell cycle dynamics
- Super-resolution microscopy
- Drug innovation

Needs for collaborations

- Fundamental research: advanced DNA sequencing technologies that complement our 3D nanoscale imaging approaches
- Translational research: clinical expertise and access to HR+/HER2- breast cancer samples

Direct visualisation and control of DNA replication initiation in single human cells provides molecular insight into targeted cancer treatments

Bennie Lemmens

The fidelity and timing of DNA replication have been directly linked to chromosome instability in precancerous lesions and advanced cancers, and many chemotherapies obstruct DNA replication. The Lemmens laboratory combines rapid protein depletion with state-of-the art imaging and 3D tissue expansion techniques to study fundamental principles of human DNA replication across scales. These technologies allow us to abolish DNA replication initiation in a matter of hours and combine these unique cell models with versatile multi-colour nascent DNA labelling protocols to directly visualise and classify DNA replication nanostructures in their native chromatin context. We also quantify drug-induced replication kinetics changes in time and space and directly compare these insights to nascent DNA sequencing measurements in synchronized populations or single cells. I look forward to discussing our recent findings with the CRKI community and present practical tips and validated models to study human DNA replication.

A selection of publications from your group

- Lemmens B, et al. Molecular Cell 71.1 (2018): 117-128.
- Lemmens B, Lindqvist A Journal of Cell Biology 218.12 (2019): 3892-3902.
- de Souza Gama, et al. Journal of Medicinal Chemistry (2024)67 (11), 8609-8629

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Cancer Research Area

- Pediatric Neuro-oncology

Key research field interests

- Cranial Radiotherapy
- Lithium
- Cognitive Impairment
- Neurons
- Microglia

Needs for collaborations

- Bioinformatics Expertise
- Cell Metabolism Expertise
- Vascular Biology Expertise

Lithium treatment protects microglia and newly generated neuronal populations in a mouse model of cranial radiotherapy

Carlos Rodrigues

Radiotherapy is a key treatment for high-grade brain tumors, significantly improving survival rates, especially in pediatric patients. However, it leads to long-term complications, including cognitive deficits, in 50-96 % of patients. No treatments currently exist to prevent these deficits. Lithium (Li), known for treating bipolar affective disorder, has been shown to reduce radiation-induced cognitive impairments in rodents by protecting the neuronal stem and progenitor cells in the hippocampus from apoptosis and promoting their proliferation. This study aimed to explore further the mechanisms underlying the protective and regenerative effects of Li in the irradiated young brain. To this end, postnatal day (PD) 21 C57BL6/J mice were injected intraperitoneally with Li chloride (4 mmol/kg) and kept on a Li carbonate-containing diet for 4 weeks. Control animals were injected with saline and administered an equivalent control diet. On PD 25, the animals were administered a singledose whole-brain radiation of 8 Gy and were subsequently sacrificed at different time points, spanning from 2 weeks to 1 year. Hippocampi were collected for single-cell RNA sequencing using a novel protocol to capture viable cells, including neurons, and for electrophysiology analysis. The results showed that radiation induced the expression of the senescence genes in hippocampal microglia (e.g., Cdkn1a, Ccl12), which Li prevented. Additionally, Li also prevented the radiation-induced loss of hippocampal gamma oscillations and protected the newly generated hippocampal neurons, leading to the development of new neuronal subpopulations that prevailed in the hippocampus long after irradiation. Finally, a subpopulation of pruning microglia was shown to play a key role in Li-driven neuronal changes. This study advances our understanding of the effects of Li in the irradiated brain and supports its potential as the first pharmacological treatment for radiation-induced late complications.

A selection of publications from your group

- Zisiadis GA, Alevyzaki A, Nicola E, Rodrigues CFD, Blomgren K and Osman AM* (2023). Memantine increases the dendritic complexity of hippocampal young neurons in the juvenile brain after cranial irradiation. Front. Oncol. 13:1202200.
- Zhou K#, Zisiadis GA#, Havermans M, Fragkopoulou A, Dominguez C, Ohshima M, Osman AM, Rodrigues CFD, Blomgren K* (2024). Microglia depletion and repopulation do not alter the effects of cranial irradiation on hippocampal neurogenesis. Brain, Behavior, and Immunity 30:123:57-63. (#co-first authors)
- Lastra-Romero A#, Preka E#, Pizzirusso G, Arroyo-Garcia LE, Zisiadis G, OlivaVilarnau N, Seitz T, Zhou K, Isla AG, Friess L, Sun Y, Shamik A, Rodrigues CFD, Fisahn A, Joseph B, Carlson LM, Fragkopoulou A, Betsholtz C, Zhu C, Lauschke VM, Osman AM†, Blomgren K*†.) Microglia Adopt Temporally Specific Subtypes after Irradiation, Correlating with Neuronal Asynchrony. Under revision in Immunity. (# cofirst authors; † co-last authors)

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Cancer Research Area

- Childhood leukemia
- Osteosarcoma

Key research field interests

- Drug delivery
- RNAi therapeutics
- Small molecules
- Polo-like kinases
- Oligonucleotides

Needs for collaborations

RNAi therapeutics against childhood cancer

Caroline Palm Apergi

Pediatric leukemia survivors show an alarmingly high incidence of health issues such as cardiac toxicity and fertility issues several years after treatment and the overall survival for resistant and relapsed patients is poor. Thus, there is a need for targeted drugs. The Polo-like kinase (PLK) family plays an important role in cell cycle regulation, and we have found PLK1 to be upregulated in pediatric leukemia patients. Clinical trials with small molecule drugs against PLK1 in adult leukemia patients have shown that specificity is a major issue. RNA interference (RNAi) is known for its catalytic activity and target selectivity and the breakthrough for RNAi therapeutics came in 2018 when the FDA approved the first RNAi-based drug, patisiran. Since then, five more siRNA-based drugs have been approved by the FDA/EMA. Importantly three of them are approved for children. We are utilizing our unique RNAi prodrug technology to knockdown cancer therapy targets, selectively. RNAi prodrugs enter primary peripheral blood and bone marrow mononuclear cells collected from pediatric T- and B-ALL and AML patients and induce mRNA knockdown of an endogenous targets, PLK1, without the use of a transfection reagent. The mRNA knockdown and resulting depletion of the protein, induce cell cycle arrest and apoptosis. Moreover, PLK1 knockdown sensitizes pediatric leukemia cells to chemotherapeutics such as cytarabine, as a combination of RNAi prodrugs and a nontoxic dose of cytarabine increases the number apoptotic cells. We have found PLK1 to be upregulated in several pediatric cancers and that its knockdown results in tumor cell death. Our hope is that PLK1-targeted RNAi prodrugs can be used for treatment of both adult and pediatric cancers and that a combination treatment may lead to a decrease in the concentration of chemotherapeutics. Our goal is to develop a more selective and less toxic therapy against childhood cancer.

A selection of publications from your group

- Palm-Apergi C. PLK4, a potential target in AML. Blood. 2023 Dec 7;142(23):1941-1942.
- Kolosenko I Goroshchuk O, Vidarsdottir L, Björklund AC, Dowdy SF, Palm-Apergi C. RNAi prodrugs decrease elevated mRNA levels of Polo-like kinase 1 in ex vivo cultured primary cells from pediatric acute myeloid leukemia patients. FASEB J, 35(5), e21476, 2021.
- Goroshchuk O, Kolosenko I, Kunold E, Vidarsdottir L, Pirmoradian M, Azimi A, Jafari R, Palm-Apergi C. Thermal proteome profiling identifies PIP4K2A and ZADH2 as off-targets of Polo-like kinase 1 inhibitor volasertib. FASEB J, 35(7), e21741, 2021.

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Cancer Research Area

- Endocrine Organ

Key research field interests

Needs for collaborations

Medical genetics

Catharina Larsson

A selection of publications from your group

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Cancer Research Area

- Colorectal cancer
- Ovarian cancer
- Breast cancer

Key research field interests

- Transcriptomics
- Nuclear receptors
- Hormonal signaling
- Immune microenvironment
- Microbiome

Needs for collaborations

- Clinical material and expertise

How estrogens regulate sex differences of the colon, its cancer, microbiome, and the immune microenvironment

Cecilia Williams

Colorectal cancer exhibits clear sex differences in incidence, survival, tumor location, and molecular characteristics. The Women's Health Initiative demonstrated that combined or estrogen-only menopausal hormone therapy reduces colorectal tumor development. Our population-wide study (Sweden) showed that past use of estrogen-only therapy correlated particularly strongly with reduced incidences (e.g., OR 0.36 95%CI for rectal cancers). We have revealed that deletion of intestinal estrogen receptor beta (ERβ) in mouse colon tumor models enhances tumor development in both sexes and that ERβ can act as a tumor suppressor and impact cytokine signaling via NFkB in human colon cells. We now investigate how estrogen and ERβ regulate tissue immunity and the tumor microenvironment in murine models. We spatially profile the immune cell landscape (using COMET multiplex immunofluorescence, unsupervised clustering, and spatial image analysis of tissues (SPIAT) for interactions) and analyze the corresponding gut microbiota (whole genome sequencing) and transcriptome (RNA-seq) during tumor development. We denote clear sex differences and an impact of ERβ and corroborate differences using plasma cytokine assays (Ella Automated Immunoassay). In particular, tumors from ERβ intestinal knockout mice displayed significantly increased macrophage infiltration, decreased T cell infiltration, and impaired NK cell infiltration, indicating an immunosuppressive tumor microenvironment.

A selection of publications from your group

- Holm M, Stepanauskaitė L, Bäckström A, Birgersson M, Socciarelli F, Archer A, Stadler C, Williams C. Spatial profiling of the mouse colonic immune landscape associated with colitis and sex. Communications Biology, accepted (2024)
- Hases, L; Stepanauskaite, L; Birgersson, M; Brusselaers, N; Schuppe-Koistinen, I; Archer, A; Engstrand, L; Williams, C. High-fat diet and estrogen modulate the gut microbiota in a sex-dependent manner in mice. Communications Biology 6(1):20 (2023)
- 3. Hases L, Indukuri R, Birgersson M, Nguyen-Vu T, Lozano R, Saxena A, Hartman J, Frasor J, Gustafsson JÅ, Katajisto P, Archer A, Williams C. Intestinal estrogen receptor beta suppresses colon inflammation and tumorigenesis in both sexes. Cancer Letters 492:54-62 (2020)

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Cancer Research Area

- Early detection and liquid biopsy

Key research field interests

- Blood diagnostics
- RNA-sequencing
- Extracellular vesicles
- Machine learning
- Precancer

Needs for collaborations

- Patient blood
- Tumour biopsy
- Bioinformatics expertise

Dynamic size and association profiles of tumour-derived DNA during pancreatic cancer progression

Daniel Hagey

Despite advances in diagnostic technology, clinicians still primarily rely on imaging and pathology to inform diagnosis, treatment decisions and disease monitoring. However, advances in liquid biopsy may provide clinicians with the high-resolution molecular insight needed to target the unseen attributes that drive disease. While current strategies are limited by assessing single markers, RNA-sequencing produces unbiased multifactorial information on the genetic landscape. As extracellular vesicles are an early hallmark of cancer, this project seeks to simplify and develop RNA-sequencing on circulating vesicles to provide clinically relevant information. Importantly, by working from blood drops and exploiting affordable single-cell technologies, the tools developed here can be used to inform the diagnosis and monitoring of diverse malignancies.

A selection of publications from your group

- Hagey DW, Ojansivu M, Bostancioglu BR, Saher O, Bost JP, Gustafsson MO, Gramignoli R, Svahn M, Gupta D, Stevens MM, Görgens A, EL Andaloussi S. The cellular response to extracellular vesicles is dependent on their cell source and dose. Science Advances. 2023; 9(35):eadh1168. doi: 10.1126/sciadv.adh1168.
- Hagey DW*, Kvedaraite E, Akber M, Görgens A, Javadi J, von Bahr Greenwood, T, Björklund C, Åkefeldt SO, Hannegård-Hamrin T, Arnell H, Dobra K, Herold N, Svensson M, EL Andaloussi S, Henter J-I, Lourda M. Myeloid cells from Langerhans cell histiocytosis patients exhibit increased vesicle trafficking and an altered secretome capable of activating NK cells. Haematologica. 2023; 108(9):2422-34. doi: 10.3324/haematol.2022.282638.
- Hagey DW*, Kordes M, Görgens A, Mowoe MO, Nordin JZ, Moro CF, Löhr JM, EL Andaloussi S. Extracellular vesicles are the primary source of blood-borne tumour-derived mutant KRAS DNA early in pancreatic cancer. Journal of Extracellular Vesicles. 2021; 10(12):e12142. doi: 10.1002/jev2.12142.

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Cancer Research Area

- Mechanisms and roles for telomerase activation in oncogenesis

Key research field interests

- TERT
- Telomerase
- Transcriptional regulation
- Oncogenesis
- Cancer progression

Needs for collaborations

Telomerase activation in cancer development and progression

Dawei Xu

Human linear chromosomes terminate with TTAGGG repetitive sequences, so-called telomeres that become progressively shorter with cellular division or aging. Very short telomeres trigger cellular apoptosis or senescence, thereby functioning as a tumor suppressor. It has been well established that stabilizing telomere length is essential to malignant transformation, while telomerase, response for telomeric extension and silent in normal human cells, is widely activated for telomere maintenance in up to 90% of cancer. The key underlying mechanism is the transcriptional de-repression of the telomerase reverse transcriptase (TERT), a gene encoding the telomerase catalytic component. Our research is mainly focused on how TERT expression/telomerase is induced during malignant transformation, and which roles TERT has in cancer progression in addition to its canonical telomere-lengthening activity. Recent mechanistic explorations by us and others have shown that both genomic and epigenetic alterations and their cooperation contribute to transcriptional activation of the TERT gene in oncogenesis. Moreover, we further probe whether the TERT-featured genomic and epigenetic aberrations are clinically useful in cancer diagnostics, prognosis, progression monitoring and treatment response.

A selection of publications from your group

- Strååt K., Liu C., Rahbar A., Zhu Q., Liu L., Wolmer N., Lou F., Liu Z., Shen J., Jia J., Kyo S., Björkholm M., Sjöberg J., Söderberg-Nauclér C. and Xu D (2009). Activation of telomerase by human cytomegalovirus. J Nat Cancer Inst, 101, 480-489.
- Liu T, Wang N, Cao J, Sofiadis A, Dinets A, Zedenius J, Larsson C and Xu D. (2014) The age- and shorter telomere-dependent TERT promoter mutation in follicular thyroid cell-derived carcinomas Oncogene 33, 4978–4984.
- Yuan H, Qin X, Yang Q, Liu L, Fang Z, Fan Y, Xu D. (2023) Dyskerin and telomerase RNA component are sex-differentially associated with outcomes and Sunitinib response in patients with clear cell renal cell carcinoma. Biol Sex Differ 14:46. doi: 10.1186/s13293-023-00526-7.

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Cancer Research Area

- Tumor immunology
- Immunotherapy

Key research field interests

- Sex immune dimorphism
- Tumor microenvironment
- Immunotherapies
- Immune memory
- NK cells

Needs for collaborations

- Humanized mouse models
- Biological samples and RNAseq data from colorectal cancer patients
- Need for a pathologist
- Cancer registry data and biological samples from transgender

Cancer immunotherapy- Tackle cancer from two directions! Exploiting innate memory in solid tumors and Reprogramming the TME (Genderized immunotherapies)

Dhifaf Sarhan

Our mission is to develop novel immunotherapies for cancer. Our research focuses on understanding the mechanisms that contribute to an immune suppressive tumor microenvironment (TME) in treatment-resistant cancers biased by sex dimorphism and utilizing targeted therapies to reshape the immune regulatory TME and to equip Natural killer cells (NK cells) with immune memory features against solid tumors. Immunotherapy for cancer has revolutionized the clinical practice, however, it is inefficient in more than 60% of all cancers due to highly immune-suppressive tumor microenvironment (TME) orchestrated by immune suppressor cells, which limit the infiltration of tumor-targeting immune cells, alternatively inhibit antigen-presentation and cytotoxic cell anti-tumor activity in situ resulting in ineffective immunotherapies. Here is an overview of the main projects of my group:

Research line I: Adaptive NK cell immunological memory in solid tumors. For decades NK cells were believed to lack immunological memory, however recent groundbreaking research by us and others revealed the opposite. We discovered novel mechanisms used by a subset of NK cells with immunological memory, called adaptive (a)NK cells, to resist the suppressive tumor environment. In this project, we focus on investigating the molecular mechanisms behind NK cell memory in tumors and the crosstalk with antigenpresenting cells like dendritic cells and B cells in cancer. Such knowledge will facilitate aNK cell therapies in the form of cellular therapy and vaccines.

Research line II: Studies of sex immune dimorphism in the TME. We found that a g-coupled protein receptor has predictive value for female pancreatic cancer patients. Hormone regulation of this receptor function has been shown to induce antiinflammatory properties in macrophages. This receptor impacts the immune landscape in TME biased by sex dimorphism. Investigations of the bulk tumor transcriptome revealed differentially enriched pathways crucial for regulating innate and adaptive immunity, as well as for different metabolic pathways in male and female patients. Extensive examination of the signal integration is ongoing to further elucidate mechanisms of action and clinical impact.

A selection of publications from your group

- Sun Y, Rodgers-Furones A, Gultekin O, Khare S, Neo SY, Shi W, Moyano Galceran L, Lam KP, Dasgupta R, Fuxe J, Salehi S, Lehti K, Sarhan D. CXCR2-mediated recruitment of adaptive NK cells with NKG2C/HLA-E dependent antigen-specific memory enhances tumor killing in ovarian cancer. bioRxiv, 2024.2003.2028.585607 (2024).
- Almazán NM, Sala BM, Sandalova T, Sun Y, Resink T, Cichocki F, SöderbergNaucler C, Miller JS, Achour A, Sarhan D. Non-classical HLA-E restricted CMV 15- mer peptides are recognized by adaptive NK cells and induce memory responses. Front. Immunol. 14:1230718. 2023. doi: 10.3389/fimmu.2023.1230718.
- He F, Tay AHM, Calandigary A, Malki E, Suzuki S, Liu T, Wang Q, Fernández-Moro C, Kaisso M, Olofsson-Sahl P, Melssen M, Sze SK, Björnstedt M, Löhr MJ, Karlsson MCI, Heuchel R, Sarhan D. FPR2 shapes an immune-excluded pancreatic tumor microenvironment and drives T-cell exhaustion in a sex-dependent manner. Cancer Research 2023. PMID: 36919330

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Cancer Research Area

- Colorectal cancer
- Cancer immunology

Key research field interests

- Mucosal Immunology
- Systems Immunology

Needs for collaborations

- Clinical material

Liver X Receptor unlinks intestinal regeneration and tumorigenesis

Eduardo Villablanca

Promoting intestinal tissue regeneration holds significant therapeutic potential for treating intestinal disorders characterized by chronic tissue damage, such as inflammatory bowel disease (IBD). However, mechanism known to date that promote tissue regeneration concomitantly promote tumor growth, highlighting the need to better understand the distinct mechanisms of tissue repair and tumor development.

In our study, we identified liver X receptor (LXR) pathway as a dual-function regulator stimulating intestinal tissue regeneration while suppressing tumor growth. Using bulk and single-cell RNA sequencing, organoid models, and spatial transcriptomics, we demonstrated that LXR activation enhances the regeneration of intestinal epithelial cells via amphiregulin (Areg), while it simultaneously triggered an adaptive immune response limiting tumor development. Notably, B and T lymphocytes were shown to play critical roles in mediating the LXR-dependent tumor suppression in experimental CRC models. These findings underscore the importance of a comprehensive understanding of the tumor microenvironment (TME) in CRC, which is essential for controlling tumor development and progression. To gain a deeper characterization of the TME, we employed unbiased technologies, such as single-cell and spatial transcriptomics, to create an in-depth gene expression atlas of the murine colon undergoing tumorigenesis. Our analysis revealed a distinct tumor cell transcriptomic profile, denoting expanded malignant regions overlooked by conventional histopathology. Moreover, we uncovered a tumor-specific immune network involving IgA-plasma cells, B cells, and neutrophils that consistently localized within the TME across independent datasets, suggesting their coordinated involvement in tumor regulation.

Overall, our work highlights the dual role of LXR in promoting intestinal tissue repair while limiting tumorigenesis and provides new insights into the TME's cellular and molecular complexity. By identifying specific immune cell networks and key regulatory pathways, we identified potential therapeutic targets for CRC treatment aimed at modulating the TME and promoting controlled tissue regeneration while limiting cancer risk.

A selection of publications from your group

- Das S., Parigi SM, Luo, X, Fransson J., Kern, BC., Okhovat A., Diaz OE., Sorini C., Czarnewski P., Webb AT., Morales RA., Lebon S., Monasterio G., Castillo F., Tripathi KP., He N., Pelczar P., Schaltenberg N., De la Fuente M., Lopez-Köstner F., Nylen S., Larsen HL., Kuiper R., Antonson P., Hermoso MA., Huber S., Biton M., Scharaw a., Gustafsson JA., Katahisto P. & Villablanca EJ. Liver X receptor unlinks intestinal regeneration and tumorigenesis. Nature. 2024
- Monasterio G., Morales RA, Bejarano DA, Abalo XM, Fransson J., Larsson L., Schlitzer A., Lundeberg J., Das S. & Villablanca EJ. A versatile tissue rolling tecnique for spatial-omics analysies of the entire murine gastrointestinal tract. Nature Protocols. 2024 Jun 21
- Frede A., Czarnewski P., Monsaterio G., Tripathi KP., Bejarano, D., Ramirez Flores RO, Sorini C., Larsson L., Luo X., Geerlings L., Novella-Rausell C., Zagami C., Kuiper R., Morales RA., Castillo F., Hunt M., Lacerda-Mariano L., Hu YOO., Engblom C., Lennon-Dumenil AM., Mittenzwei R., Westendorf AM., Hövelmeyer N., Lundeberg J., Saez-Rodriguez J., Schlitzer A., Das S., & Villablanca EJ. B cell expansion hinders the stroma-epithelium regenerative crosstalk during mucosal healing. Immunity. 2022, Dec 13;55(12):2336-2351

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Cancer Research Area

- Basic Experimental Cancer Research

Key research field interests

- Selenoproteins
- Thioredoxin Reductase
- Glutathione Peroxidase
- Cancer
- Redox Signalling

Needs for collaborations

Selenoproteins in Redox Signalling, Health and Disease

Elias Arnér

Cellular reduction and oxidation (redox) processes are crucial in physiological as well as pathological processes. Selenoproteins, i.e., proteins containing the rare and highly reactive amino acid Selenocysteine (Sec, U), play important roles in this context. The human genome encodes for 25 selenoproteins, eg. thyroid hormone deiodinases that modulate and activate thyroid hormone, thioredoxin reductases that provide reducing power to a range of redox signalling and antioxidant defence systems, and glutathione peroxidases that protect cells from oxidative stress and cell death through ferroptosis. We address the following questions:
- How do cytosolic and mitochondrial thioredoxin (Trx)-fold proteins, being substrates of selenoprotein thioredoxin reductases (TrxR, TXNRD), compare side-by-side, with regards to activities with key substrates such as peroxiredoxins, ribonucleotide reductase, nitrosylated proteins, persulfidated proteins, disulfides and cystine?
- What specific roles do the selenoproteins thioredoxin reductase 1 (TrxR1, also named TXNRD1) and glutathione peroxidases 1 and 4 (GPX1 and GPX4) play in cancer, and how can drug targeting of these selenoproteins be utilized for development of new and more efficient anticancer therapy protocols?
- How do redox modulated transcription factors underpin the anticancer effects of selenoprotein targeting, including altered activities of Nrf2, NFκB, HIF, STAT3 and p53?

These questions are addressed with biochemical, cell biological, molecular biological, biotechnological and clinical approaches and techniques, aiming to improve our understanding of redox biology. We also aim to develop diagnostics and therapies in human disease, specifically in cancer, based upon our understanding of selenoprotein functions.

A selection of publications from your group

- Martí-Andrés, P., Finamor, I., Torres-Cuevas, I., Pérez, S., Rius-Pérez, S., Colino-Lage, H., Guerrero-Gómez, D., Morato, E., Marina, A., Michalska, P., León, R., Cheng, Q., Jurányi, E.P., Borbényi-Galambos, K., Millán, I., Nagy, N., Miranda-Vizuete, A., Schmidt, E.E., Martínez-Ruiz, A., **Arnér, E.S.J.**, Sastre, J. (2024) TRP14 is the rate limiting enzyme for intracellular cystine reduction and regulates proteome cysteinylation. EMBO J, 43:2789-2812
- Cheff, D.M., Huang, C., Scholzen, K.C., Gencheva, R., Ronzetti, M.H., Cheng, Q., Hall, M.D., **Arnér, E.S.J.** (2023) The ferroptosis inducing compounds RSL3 and ML162 are not direct inhibitors of GPX4 but of TXNRD1. Redox Biol. 62:102703
- Zeisel, L., Felber, J.G., Scholzen, K.C., Poczka, L., Cheff, D., Maier, M.S., Cheng, Q., Shen, M., Hall, M.D., **Arnér, E.S.J.,** Thorn-Seshold, J., Thorn-Seshold, O. (2022) Selective cellular probes for mammalian thioredoxin reductase TrxR1: rational design of RX1, a modular 1,2-thiaselenane redox probe. Chem. 8:1493-1517

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Cancer Research Area

- Blood

Key research field interests

Needs for collaborations

Evren Alici

A selection of publications from your group

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Cancer Research Area

- Cellular biology
- Basic mechanisms of cancer
- Oncoimmunology
- Lung cancer
- Murine models of cancer

Key research field interests

- Aging
- Lung cancer
- Senescence
- Therapy resistance
- Cancer vaccines

Needs for collaborations

- Clinical material
- PDXs
- Pathological assessment of tumor lesions
- Spatial transcriptomics

Senescence-based immunotherapy for cancer prevention and treatment

Federico Pietrocola

The process of cellular senescence has entered the limelight for its critical implication in key aspects of cancer biology, from tumor suppression to therapy to metastasis/relapse. The lab has recently pivoted the concept that the induction of senescence enhances the immunogenicity of tumor cells, promoting a strong CD8 T cell mediated immune response. Nonetheless, several pitfalls hinder the implementation of senescence-targeted therapy in cancer. These include phenomena of senescence induction slippage, emergence of immunosuppressive senescent variants and cell-intrinsic escape from senescence, which gives rise to more malignant tumor cell variants. We leverage these limitations to implement novel therapeutic approaches based on the induction of senescence in tumors followed by immunotherapy regimens aimed at targeting immune resistant and escaper senescent variants.

A selection of publications from your group

- Meta-hallmarks of aging and cancer. López-Otín C, Pietrocola F, Roiz-Valle D, Galluzzi L, Kroemer G. Cell Metab. 2023 Jan 3;35(1):12-35.
- Cellular senescence enhances adaptive anticancer immunosurveillance. Marin I, Serrano M, Pietrocola F. Oncoimmunology. 2022 Dec 15;12(1):2154115.
- Cellular Senescence Is Immunogenic and Promotes Antitumor Immunity. Marin I, Boix O, Garcia-Garijo A, Sirois I, Caballe A, Zarzuela E, Ruano I, Attolini CS, Prats N, LópezDomínguez JA, Kovatcheva M, Garralda E, Muñoz J, Caron E, Abad M, Gros A, Pietrocola F#, Serrano M#. Cancer Discov. 2023 Feb 6;13(2):410-431. #Corresponding authors.

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Cancer Research Area

- Breast cancer
- Radiology

Key research field interests

- Visual AI
- Early detection Image generated with DALL-E
- Treatment response and prognosis prediction
- Magnetic Resonance Imaging
- Breast biopsy and image-guided minimally invasive excision

Needs for collaborations

- Large data sets of breast cancer pathology or gene expression (molecular subtype)
- Applying our AI tools and skills to other cancers with large data sets of images and other rich data

Artificial Intelligence for Breast Cancer Radiology

Fredrik Strand

We evaluate and develop artificial intelligence models for detection and prediction of breast cancer based on radiology images (mammography, ultrasound and magnetic resonance imaging). We also explore the use of vaccuum-assisted excision for removal of B3 lesions and for small cancers.

A selection of publications from your group

- Salim et al, Nature Medicine, 2024 (10.1038/s41591-024-03093-5)
- Dembrower et al, Lancet Digital Health, 2023 (10.1016/S2589-7500(23)00153-X)
- Yala et al, JCO, 2022 (10.1200/JCO.21.01337

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Cancer Research Area

- Drug target discovery

Key research field interests

- Cancer
- Immunology
- Cytokine
- CRISPR
- Preclinical models

Needs for collaborations

- As a preclinical researcher, interactions with clinically active researchers are often very rewarding, giving perspectives and ideas.

CRISPR-based identification of combinatorial vulnerabilities and drug targets in chronic lymphocytic leukemia

Fredrik Wermeling

This project focuses on identifying novel drug targets and understanding mechanisms of drug resistance in chronic lymphocytic leukemia (CLL), particularly in high-risk patient subgroups. CLL is the most common adult leukemia in the Western world and is characterized by a wide array of genetic mutations, with TP53 mutations being a significant predictor of poor outcomes. In our collaborative project, we use CRISPR/Cas9 screening techniques to explore genetic vulnerabilities in CLL cells with mutations in key genes, including TP53, and how these affect responses to BTK and BCL2 inhibitors (BTKi and BCL2i). We aim to identify genes that either sensitize or confer resistance to these therapies, enabling the development of potent combination treatments for defined CLL subpopulations.

In parallel, we study the development of drug resistance by monitoring genetic and transcriptional changes as CLL cells acquire resistance to BTKi and BCL2i. Using multiomics approaches, we compare findings in cell lines with patient data to validate our results and identify clinically relevant mutations. The outcomes of this research will advance precision medicine approaches in CLL treatment, providing insights into how genetic alterations drive drug resistance and offering novel therapeutic strategies to overcome it. By integrating CRISPR screening with clinical multi-omics data, our work aims to improve treatment decisions for high-risk CLL patients and reduce the risk of treatment resistance.

Project with Richard Rosenquist Brandell.

A selection of publications from your group

- Modulating T-cell activation with antisense oligonucleotides targeting lymphocyte cytosolic protein 2. Iyer VS, Boddul SV, Johnsson AK, Raposo B, Sharma RK, Shen Y, Kasza Z, Lim KW, Chemin K, Nilsson G, Malmström V, Phan AT, Wermeling F. J Autoimmun. 2022 Jul;131:102857. doi: 10.1016/j.jaut.2022.102857
- CRISPR/Cas9-Induced DNA Damage Enriches for Mutations in a p53-Linked Interactome: Implications for CRISPR-Based Therapies. Jiang L, Ingelshed K, Shen Y, Boddul S, Iyer V, Kasza Z, Sedimbi S, Lane DP, Wermeling F. Cancer Res. 2022 Jan 1;82(1):36-45. doi: 10.1158/0008-5472.CAN-21-1692.
- A rapid CRISPR competitive assay for in vitro and in vivo discovery of potential drug targets affecting the hematopoietic system. Shen Y, Jiang L, Iyer VS, Raposo B, Dubnovitsky A, Boddul SV, Kasza Z, Wermeling F. Comput Struct Biotechnol J. 2021 Sep 20;19:5360-5370. doi: 10.1016/j.csbj.2021.09.020.

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Cancer Research Area

- Blood
- Breast
- Basic Research

Key research field interests

Needs for collaborations

Development of small molecules restoring the tumor suppression functions of p53

Galina Selivanova

A selection of publications from your group

Hanna Brauner

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Cancer Research Area

- Cutaneous lymphoma
- Experimental cancer immunology
- Spatial analysis of microenvironment
- Translational studies
- Epidemiology

Key research field interests

- Cutaneous T cell lymphoma (CTCL)
- Mycosis fungoides (MF)
- Tumor microenvironment
- NK cells
- Short- and long-term effects

Needs for collaborations

- Exciting scientific discussions, novel methods, expertise in cancer biology

Determining disease trajectories in cutaneous lymphoma

Hanna Brauner

Lymphomas located to the skin are rare and less studied than other forms of lymphoma. The Hanna Brauner research team aims to generate knowledge for increasing survival and health of cutaneous T cell lymphoma (CTCL) patients, by combining epidemiologic, clinical and experimental studies. We will perform the first national registry study on predictive factors, mortality and effect of treatments, utilizing the uniquely large and population-based national lymphoma registry of approximately 650 patients and link to other national registers. In addition, we will study new diagnostic tools, investigate quality of life and informational needs in different manifestations of CTCL. In an experimental approach we aim to determine if failed immune surveillance explain disease progression and search for new cells and molecules against which future therapies can be directed. To do this we will perform a detailed analysis of CTCL cells and anti-lymphoma NK cells, CD8+ T cells and macrophages in fresh and formalin fixed skin biopsies from early vs advanced stages of disease and correlate to clinical outcome. Functional phenotyping with flowcytometry will be performed in primary human skin cells and spatial distribution analyzed by immunofluorescence and spatial proteomics and transcriptomics in fixed biopsies. Lastly, the immune processes required for successful rejection of lymphoma will be investigated by analyses of molecular changes in CTCL skin before and during treatment with curative intention.

A selection of publications from your group

- Li R, Johanna Strobl J, Poyner EFM, Torabi ABF, Mazin PV, Chipampe N-J, Stephenson E, Ramírez-Suástegui C, Shanmugiah VBM, Olabi LGB, Coulthard R, Botting RA, Zila N, Prigmore N, Gopee N, Chroscik M, Kritikaki E, Engelbert J, Goh I, Chan H, Johnson HF, Ellis J, Rowe V, Tun W, Reynolds G, Yang D, Foster AR, Gambardella L, Winheim E, Admane C, Rumney B, Steele L, Jardine L, Nenonen J, Pickard K, Lumley J, Hampton P, Hu S, Liu F, Li X, Horsfall D, Basurto-Lozada D, Grimble L, Bacon CM Weatherhead SC, Brauner H, Wang Y, Bai F, Reynolds NY, Allen YE, Jonak C, Brunner PM, Teichmann SA, Haniffa M. Cutaneous T cell lymphoma atlas reveals malignant Th2 cells supported by a B cell-rich tumour microenvironment. Nature Immunology, accepted.
- Ivert LU, Winther AH, Jonsson P, Brauner H. Exploring the educational needs of patients with cutaneous lymphoma using an educational needs assessment tool. Front Oncol. 2024 Aug 7;14:1433821. doi: 10.3389/fonc.2024.1433821.
- Scheffschick A, Nenonen J, Xiang M, Winther AH, Ehrström M, Wahren-Herlenius M, Eidsmo L, Brauner H. Skin infiltrating NK cells in cutaneous T-cell lymphoma are increased in number and display phenotypic alterations partially driven by the tumor. Front Immunol. 2023 Aug 25;14:1168684.

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Cancer Research Area

- Neoantigen-based adoptive cell transfer (ACT)
- Therapeutic vaccination

Key research field interests

- T cell immunotherapy
- Neoantigen
- Particle antigen presentation
- NGS
- Personalized

Needs for collaborations

- Before and during treatment, help define which parameters should be included in a report relevant to further therapy.
- Linking mutation profiles to patient selection, immunotherapy and clinical outcome.
- Clinical collaboration, biomarker selection and efficacy evaluation in solid cancer suitable for our ACT technology

Personal neoantigen targeting T cells for treatment of metastasized colorectal cancer

Hans Grönlund

Cancer is a genetic disease, based on patient-unique sets of protein coding mutations, which are commonly occurring when cells proliferate. The mutations may cause dysfunctional proteins, neoantigens, which in turn are displayed at cell surfaces as targetable 8-9 amino acid peptides complexed with MHC class I. This exposes the cells to patrolling T cells for removal. In case this does not happen uncontrolled cell proliferation, cancer, may appear.

We have adopted a technique to train massive numbers of autologous T cells to attack tumor-derived neoantigens for treatment of solid tumors. With the technique developed at our laboratory we have developed an ATMP product called Personalized Tumor Trained Lymphocytes (pTTL) comprising expanded tumor-specific T cells originating from sentinel or regional lymph nodes (RLN) using personal bead-bound neoantigens. A phase I/II First in Human (FIH) clinical trial of pTTL in Stage IV colorectal cancer (CRC) patients is ongoing.

pTTL is produced through in vitro expansion of T cells stimulated with an array of the most immunogenic neoantigens utilizing the in house technology. The variants are identified by NGS obtained from tumor and normal tissue and ranked using the paramagnetic micro-particles for GMP production. pTTL is characterized by FluoroSpot and FACS phenotyping of differentiation and activation markers.. The manufacturing process generates a T cell product with individually varying CD4/CD8 ratios and a significant proportion of memory T cells with limited number of terminally differentiated T cells. TCR sequencing shows an oligoclonal nature, indicating antigen specificity, a notion is corroborated by the upregulation of T cell activation-markers.

In the ongoing dose escalating trial, up to 16 patients with Stage IV CRC will be treated with a single-dose pTTL after chemotherapy-based preconditioning with cyclophosphamide and fludarabine. The primary endpoint is safety. Secondary outcomes include objective response, overall survival, and progression-free survival. Biomarkers for pTTL persistence, pTTL characteristics, and response will be evaluated.

A selection of publications from your group

- Bronge M, Kaiser A, Carvalho-Queiroz C, Nilsson OB, Ruhrmann S, Holmgren E, Olsson T, Gafvelin G, Grönlund. Sensitive detection of antigen-specific T-cells using bead-bound antigen for in vitro re-stimulation. H MethodsX. 2019,8:1635-41. PMID: 31367530
- Facing the future: challenges and opportunities in adoptive T cell therapy in cancer. Magalhaes I, Carvalho-Queiroz C, Hartana CA, Kaiser A, Lukic A, Mints M, Nilsson O, Grönlund H, Mattsson J, Berglund S. Expert Opin Biol Ther. 2019,30:1-17. PMID: 30986360
- Kiessling A, Ramanathan K, Nilsson OB, Notari L, Renken S, Kiessling R, Grönlund H, Wickström S Generation of tumor-specific cytotoxic T cells from blood via in vitro expansion using autologous dendritic cells pulsed with neoantigen-coupled-microbeads, Frontiers in Oncology 2022,31:866763

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Cancer Research Area

- Tumor immunology
- Immune surveillance
- Immunotherapy

Key research field interests

- Immunodeficiency
- Genetic
- Clinical immunology
- Lymphoma
- Hematologic cancers

Needs for collaborations

- Clinical material on cancer patients with inborn errors of immunity or lymphoma or thymoma/ Other immune related cancers associated with oncoviruses.

Etiologies of Pediatric Cancers Associated with Inborn Errors of Immunity

Hassan Abolhassani

Inborn errors of immunity (IEI) are a heterogeneous group of inherited disorders, and almost 500 genes associated with these disorders have been identified. Defects in IEI genes lead to diverse clinical manifestations including increased susceptibility to malignancies. The overall risk for cancer in children with IEI ranges from 5-25% and the type of malignancy is highly dependent on the specific mutant gene underlying IEI. Although the majority of IEI patients present hematologic cancers, the rate of solid tumors is also significantly higher than the normal population in this group of patients. My research group has continuously been involved in the field of immune system disorders through the integration of standard functional assays of immune cell subsets using the identification of monogenic causes of tumor development and a single-cell multi-omics approach. We systematically evaluate the hypothesis that a large proportion of immunodeficient patients with cancers especially lymphoma can be characterized by abnormal molecular signatures, which can be determined by a combination of the genome, epigenome, transcriptome, proteomics and metagenomics profiling. Our main patients cohort are corresponding to the oncogenic hallmarks related to molecular defects avoiding immune destruction (PI3KCD, PI3KR1 mutations), genome instability/DNA repair defects (ATM, BLM, MRE11 mutations), and mutation enabling replicative immortality (Fanconi anemia mutations), tumor-promoting inflammation/chronic viral infections (CD27, CD70 mutations), resisting cell death (FAS, FASL mutations), sustaining proliferative signaling (LRBA, CTLA4, FOXP3 mutations), evading growth suppressors (DOCK8, CXCR4 mutations), phenotypic plasticity (NFKB1, NFKB2 mutations), epigenetic reprogramming (DNMT3B, ZBTB24, AID mutations), and polymorphic microbiomes (IL10, IL10R mutations). Our recent findings from these translational projects showed that different types of malignancy could be associated with specific entities of IEI and cancer hallmarks, which their identification is fundamental for personalized treatment and appropriate management of patients.

A selection of publications from your group

- Clinical and Immunologic Characteristics of Non-Hematologic Cancers in Patients with Inborn. Errors of Immunity. Cancers (Basel). 2023 Jan 26;15(3):764.
- Diversity of malignancies in patients with different types of inborn errors of immunity. Allergy Asthma Clin Immunol. 2022 Dec 12;18(1):106.
- Updates of cancer hallmarks in patients with inborn errors of immunity. Curr Opin Allergy Clin Immunol. 2022 Dec 1;22(6):352-363.

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Cancer Research Area

- Pan-cancer

Key research field interests

- Machine-learning
- Bioinformatics
- Single-cell and spatial transcriptomics
- Tumor microenvironment
- Target identification

Needs for collaborations

- Fresh tissue samples from tumors or pre-metastatic tissues (bone, liver, lung, brain)
- Clinical trials collecting paired single-cell and spatial transcriptomics data and follow-up
- Partners for funding applications at the interface of clinical/biological and computational omics projects

Machine-learning of cancer-host interactions to target in therapy from multi-omics

Jean Hausser

We are researching a quantitative framework of cancer-host interactions designed to maximize the utility of human tumor spatial and single-cell transcriptomics data for identifying new therapeutic targets in the tumor micro-environment. To do so, we take inspiration from physics-style mathematical modeling which we implement into new machine-learning and bioinformatics methods. We calibrate these methods through experiments in vitro and validate them through proofof-concept in vivo. The long-term vision is for our quantitative framework to accelerate therapeutic innovation, by identifying targets from patient material within months or even weeks, instead of the many years needed with current target identification approaches. If selected for an oral presentation, I will present our approach as well as preliminary results towards this goal.

A selection of publications from your group

- NIPMAP: niche-phenotype mapping of multiplex histology data by community ecology, Anissa El Marrahi, Fabio Lipreri, Ziqi Kang, Louise Gsell, Alper Eroglu, David Alber, Jean Hausser. Nature Communications 2023

John Inge Johnsen

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Cancer Research Area

- Pediatric cancer
- Neuroblastoma
- Medulloblastoma
- In vivo modelling
- Translational research

Key research field interests

- Genetical engineered mouse and zebrafish models of cancer
- Organoids

Needs for collaborations

- Fish pathologist
- Comparative bioinformatician
- Imaging

Decoding and targeting mechanisms of neuroblastoma evolution

John Inge Johnsen

The overall goal for the research group is to reveal the heterogeneities, plasticity, molecular landscapes and cellular interactions of malignant and corresponding non-malignant cells in neuroblastoma (NB) to identify the cellular origin, mechanisms of drug resistance and druggable targets that can be transferred into clinical trials and new treatment options. NB is a neural crest-derived tumor of the peripheral nervous system showing heterogeneous clinical behavior manifested through numerous segmental chromosomal aberrations in which gene amplification of MYCN, deletion of chromosome (Chr)1p or 11q and segmental gain of Chr17q are associated with poor prognosis. Among these, gain of Chr17 is the most frequent genetic alteration observed in 80% of the patients.

We used a combination of Omic techniques to characterize the molecular and cellular landscape of NB. This together with evolutionary trajectories dissecting the accumulation of chromosomal instabilities in NB show that gain of Chr17 is an early genetic abnormality in NB development and linked to the accumulation of additional chromosomal aberrations and poor prognosis. Increased segmental gains of Chr17q are observed during clonal evolution, relapse disease and metastasis. We show that the p53-inducible Ser/Thr phosphatase, PPM1D, located on chr17q22.3, which acts as a negative regulator of p53, is activated by frequent segmental 17q-gain, gene-fusion or gain-of-function somatic and germline mutations in NB and that PPM1D overexpression strongly correlates to poor patient survival. We recently showed that PPM1D is a de novo oncogene developing tumors when overexpressed in mice, including NB. We also show that NB are strictly dependent on high expression of PPM1D for survival and that genetically or pharmacological inhibition of PPM1D suppress the growth of NB mouse xenografts. The importance of Chr17q gain and candidate genes on Chr17q in NB are currently investigated using zebrafish, HESC and iPS-derived neural crest cells in different phases of maturation as model systems.

A selection of publications from your group

- Olsen TK, Otte J, Mei S, Embaie BT, Kameneva P, Cheng H, Gao T, Zachariadis V, Tsea I, Björklund Å, Kryukov E, Hou Z, Johansson A, Sundström E, Martinsson T, Fransson S, Stenman J, Fard SS, Johnsen JI, Kogner P, Adameyko I, Enge M, Kharchenko PV, Baryawno N. Joint single-cell genetic and transcriptomic analysis reveal pre-malignant SCP-like subclones in human neuroblastoma. Mol Cancer. 2024 Aug 31;23(1):180. doi: 10.1186/s12943-024-02091-y. PMID: 39217332; PMCID: PMC11365129.
- Verhoeven BM, Mei S, Olsen TK, Gustafsson KU, Valind A, Lindström A, Gisselsson Nord D, Fard SS, Kogner P, Karchenko PV Johnsen JI*, Baryawno N*. The immune cell atlas of human neuroblastoma. Cell Rep Med. 2022 Jun 21;3(6):100657. doi: 10.1016/j.xcrm.2022.100657. *Shared last authorship
- Milosevic J, Fransson S, Gulyas M, Olsen TK, Gallo-Oller G, Treis D, Elfman LHM, Wilhelm M, Martinsson T, Baryawno N, Kogner P*, Johnsen JI*. High Expression of PPM1D Induces Tumors Phenotypically Similar to TP53 Loss-of-Function Mutations in Mice. Cancers (Basel). 2021 Oct 31;13(21):5493. doi: 10.3390/cancers13215493. *Shared last authorship.

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Cancer Research Area

- Cancer Epidemiology

Key research field interests

- Breast cancer
- Prognosis
- Mammography features
- Inherited genetics
- Screening

Needs for collaborations

Breast cancer epidemiology

Kamila Czene

A selection of publications from your group

Kasper Karlsson

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Cancer Research Area

- Pediatric cancer
- Neuroblastoma
- Rhabdomyosarcoma

Key research field interests

- Tumor evolution
- Cell barcoding
- Radiopharmaceutical therapy
- Drug screening
- Single cell biology

Needs for collaborations

- People interested in AI/Deep Learning, Drug response prediction, Tumor Evolution/Cell barcoding, Metastatic seeding and engraftment

Precision strategies to overcome metastatic heterogeneity

Kasper Karlsson

Metastatic heterogeneity is the main challenge for cancer research today. Metastases have a high clonal heterogeneity due to genetic instability, ongoing selection, and variable microenvironments with local adaptation. Most patients that die of cancer, succumb to a metastatic relapse, typically in the bone marrow, liver or brain. Tumor recurrency often depends on outgrowth of rare, therapy resistant subclones, frequently of metastatic origin.

A common strategy to overcome this heterogeneity is to use combination therapies. Most efforts so far have been spent on finding synergistic interactions between drugs. Synergy measures overall cell killing effect of two or more drugs on bulk tumor cells and is usually applied on relatively homogenous cell line models exposed to a single environment. This is in sharp contrast to the metastatic setting where the primary obstacle to cure often is rare tumor clones that survive even very high drug concentrations. We are working on two orthogonal approaches to specifically target rare therapy resistant clones: Precision Lethality and radiopharmaceutical therapy.

In precision lethality, cell barcoding is used to tag thousands of distinct tumor subclones, which make it possible to quantify clonal heterogeneity. We apply precision lethality to identify sub-populations that enrich under standard of care treatment, and to systematically search for targeted therapies drugs that specifically eradicates those sub-populations.

In radiopharmaceutical therapy, a targeting molecule carries a radioisotope specifically to tumor cells, including at metastatic sites. Compared to cytotoxic and immunomodulating drugs, radiopharmaceutical therapy has a distinct advantage in eradicating heterogenous metastatic cell clusters, since not all cancer cells need to express the target antigen to receive a lethal radiation dose. We use multiple approaches to widen the therapeutic window for radiopharmaceutical therapy.

We are also involved in projects to establish both organoid and PDX models from bone marrow metastases that will be crucial for clinical translation.

A selection of publications from your group

- Karlsson K*, Przybilla MJ*, Kotler E, Khan A, Xu H, Karagyozova K, Sockell A, Wong WH, Liu K, Mah A, Lo YH, Lu B, Houlahan KE, Ma Z, Suarez CJ, Barnes CP, Kuo CJ, Curtis C. Deterministic evolution and stringent selection during pre-neoplasia. Nature, volume 618, pages 383–393 (2023). * Equal contribution
- Park SW, Fransson S, Sundquist F, Nilsson JN, Grybäck P, Wessman S, Strömgren J, Djos A, Fagman H, Sjögren H, Georgantzi K, Herold N, Kogner P, Granberg D, Gaze MN, Martinsson T, Karlsson K*, Stenman JJE*, Heterogeneous SSTR2 target expression and a novel KIAA1549::BRAF fusion clone in a progressive metastatic lesion following 177Lutetium-DOTATATE molecular radiotherapy in neuroblastoma: A Case Report. Front. Oncol. 14:1408729
- Lo YH, Karlsson K, Kuo CJ, Applications of Organoids for Cancer Biology and Precision Medicine, Nature Cancer. Aug;1(8):761-773 (2020)

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Cancer Research Area

- Breast cancer

Key research field interests

- Biostatistics
- Breast cancer
- Epidemiology
- Screening

Needs for collaborations

- Clinical experise

Statistical models for breast cancer screening data – studies of aggressive breast cancer and screening performance

Keith Humphreys

We develop and use biologically motivated staistical models of tumor progression to study the incidence and mortality and epidemiology of breast cancer. We also use these models to predict the risk of (in particular, aggressive) breast cancer. The models are estimated using data from detailed population-based studies of breast cancer and breast cancer screening, combining longitudinal register, questionnaire, image and molecular data. We try to shed light on the roles of different factors in screening and symptomatic detection of breast cancer, and in tumor onset, growth and spread. The information we create can be used for planning and evaluating approaches to (secondary) prevention of breast cancer. Our risk prediction models rigorously incorporate screening information. We also use the models for studying treatment effects.

A selection of publications from your group

- Strandberg R, Czene K, Hall P, Humphreys K. (2023) Novel predictions of breast cancer risk in mammography screening cohorts. Statistics in Medicine. 42: 3816-3837.
- Strandberg R, Abrahamsson L, Isheden G, Humphreys K. (2023) Tumour Growth Models of Breast Cancer for Evaluating Early Detection – a Summary and a Simulation Study. Cancers. 15, 912.
- Isheden G, Grassman F, Czene K, Humphreys K. (2021) Lymph node metastases in breast cancer: investigating associations with tumour characteristics, molecular subtypes and polygenic risk score using a continuous growth model. Int. J. Cancer. 149: 1348-1357

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Cancer Research Area

- Fat cells and cancer
- Focus area breast cancer

Key research field interests

- Obesity
- Hyperinsulinemia
- Breast cancer
- Metastasis
- EMT

Needs for collaborations

- Clinical material (including tumour tissue and adjacent adipose tissue; distal and/or ipsilateral adipose tissue; adipose tissue from patients who have received chemotherapy and/or irradiation)

The impact of adipocyte senescence in breast cancer progression

Kirsty Spalding

Many diseases strongly associate with obesity, making obesity one of the major health challenges facing the world today1. Obesity leads to increased cancer risk and poorer patient outcomes in several types of cancers, including breast cancer. Despite the strong association with obesity, most current cancer treatments do not take into consideration the ongoing obesity epidemic. As such, there is a need to develop specific drug targets that could be leveraged to address the obesity component of the disease.

In recent work, my group has shown that human fat cells senesce in association with obesity and hyperinsulinemia2,3. Senescent cells alter their phenotype and are highly metabolically active, releasing increased levels of proteases, pro-inflammatory cytokines and chemokines. This secretory profile, termed the senescence-associated secretory phenotype (SASP), is rapidly emerging as a pathological mechanism behind many chronic diseases. In unpublished work we identify a subpopulation of adipocytes, enrichened both senescent and SASP transcripts, increases in number in obesity and hyperinsulinemia. Our work aims to identify how adipocyte senescence impacts on tumour progression, using breast cancer as our model system.

Survivors of cancer also face an increased risk of developing secondary cancers and cardiometabolic disease (including type 2 diabetes) but the mechanism behind this is poorly understood. Cancer treatments (irradiation and chemotherapy) induce oxidative stress and DNA damage, which are driving factors promoting senescence. We also are investigating whether cancer treatment induces adipocyte senescence, potentially contributing to the development of cardiometabolic disease in cancer survivors.

A selection of publications from your group

- Hagberg CE, Spalding KL. White adipocyte dysfunction and obesity-associated pathologies in humans. Nat Rev Mol Cell Biol. 2024 Apr;25(4):270-289. doi: 10.1038/s41580-023-00680-1. Epub 2023 Dec 12. Erratum in: Nat Rev Mol Cell Biol. 2024 Apr;25(4):333. doi: 10.1038/s41580-024-00712-4. PMID: 38086922.
- Li Q, Hagberg CE, Silva Cascales H, Lang S, Hyvönen MT, Salehzadeh F, Chen P, Alexandersson I, Terezaki E, Harms MJ, Kutschke M, Arifen N, Krämer N, Aouadi M, Knibbe C, Boucher J, Thorell A, Spalding KL. Obesity and hyperinsulinemia drive adipocytes to activate a cell cycle program and senesce. Nat Med. 2021 Nov;27(11):1941-1953. doi: 10.1038/s41591-021-01501-8. Epub 2021 Oct 4. PMID: 34608330.
- Dedic B, Westerberg L, Mosqueda Solís A, Dumont KD, Ruas JL, Thorell A, Näslund E, Spalding KL. Senescence detection using reflected light. Aging Cell. 2024 Aug 5:e14295. doi: 10.1111/acel.14295. Epub ahead of print. PMID: 39102872.

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Cancer Research Area

- Paediatric neuro-oncology

Key research field interests

- Radiotherapy
- Late complications
- Medulloblastoma

Needs for collaborations

- Humanised models

Lithium and radiation reduce tumour growth in Group 3 medulloblastoma

Klas Blomgren

Medulloblastoma (MB) is the most common high-grade paediatric brain tumour, accounting for ~20 % of all childhood CNS tumours. It comprises 4 distinct molecular subtypes, with Group 3 MB having the worst prognosis with an overall survival of around 50 %. Additionally, current treatments, especially radiotherapy (RT), come at a very high cost for the developing brain and result in permanent complications, including lower IQ, slower processing speed, as well as social problems and lifelong dependency. Lithium has been shown to protect neurogenesis and cognitive functions from the negative effects of RT on the juvenile brain in vivo and can, therefore, be hypothesised as a preventive treatment strategy to ameliorate these side effects. However, lithium's effects and mechanisms of action on MB tumours remain largely unknown. In this study, we used GMYC GFP Group 3 MB cells (Mainwaring et al., 2023) to study the effects of lithium and RT in vitro and created an orthotopic model of Group 3 MB to study those effects in vivo. Using a whole brain immunostaining technique (iDISCO+) and light sheet microscopy, we created a 3D model of every tumour and quantified the tumour volume under different treatment conditions. Our results show that lithium – alone and combined with radiation –decreases Group 3 MB tumour growth by more than 50% in vivo. We studied the transcriptomic changes induced by lithium, validating them through protein analysis that identified Klf4 as a potential effector of its underlying mechanism of action, correlating with blocked cell cycle progression. In addition, lithium induces widespread changes in the methylation landscape, for example, reduced methylation of Klf4 enhancers.

If successful, lithium could be the first treatment with the dual purpose of preventing cognitive complications as well as improving the anti-cancer treatment outcomes in children with brain tumours.

A selection of publications from your group

- Lastra Romero A, Preka E, Pizzirusso G, Arroyo-García LE, Zisiadis GA, Oliva-Vilarnau N, Seitz T, Zhou K, Gonzalez Isla A, Friess L, Sun Y, Shamik A, Xu Y, Zhu C, Rodrigues CFD, Fisahn A, Joseph B, Carlson LM, Fragkopoulou A, Lauschke VM, Betsholtz C, Osman AM, **Blomgren K** (2024) Microglia Adopt Temporally Specific Subtypes after Irradiation, Correlating with Neuronal Asynchrony. Immunity. In revision.
- Zanni G, Goto S, Fragopoulou AF, Gaudenzi G, Naidoo V, Di Martino E, Levy G, Dominguez C, Dethlefsen O, Cedazo-Minguez A, Merino-Serrais P, Stamatakis A, Hermanson O, **Blomgren K** (2021) Lithium treatment reverses irradiation-induced changes in rodent neural progenitors and rescues cognition. Molecular Psychiatry. 26(1):322-340.
- Osman A, Sun Y, Burns TC, He L, Kee N, Oliva-Vilarnau N, Alevyzaki A, Zhou K, Louhivouri L, Uhlén P, Hedlund E, Betsholtz C, Lauschke VM, Kele J, **Blomgren K** (2020) Radiation triggers a dynamic sequence of transient microglial alterations in juvenile brain. Cell Reports. 31(9):107699.

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Cancer Research Area

- Cancer biology
- Novel therapy

Key research field interests

- Tumor suppressor genes
- TP53
- Cell death
- Cancer drug discovery

Needs for collaborations

- Mouse histopathology
- Chemical library screening
- Medicinal chemistry
- Preclinical development
- Clinical trials
- Patient samples
- Bioinformatics

Cancer precision medicine by targeting mutant TP53

Klas Wiman

The TP53 tumor suppressor gene is frequently mutated in a wide range of human cancer types. Loss of p53 function allows evasion of p53-induced cell death in response to oncogenic stress. Restoration of p53 function in the context of activated oncogenes can induce cancer cell death. Many TP53 mutations are missense mutations that disrupt p53 specific DNA binding and transactivation of target genes. Compounds that target missense mutant p53 have been identified and some have been tested in clinical trials. Around 10% of cancer-associated TP53 mutations are nonsense mutations that give rise to truncated inactive p53 protein. The most common TP53 nonsense mutation is R213X, which is also one of the 10 most common TP53 mutations overall. Aminoglycoside antibiotics can induce translational readthrough of nonsense mutant TP53 and expression of full-length active p53 protein. However, their use in the clinic is limited by severe side effects. We identified the 5-FU metabolite 5-fluorouridine as a readthrough inducer of R213X nonsense mutant TP53. To study the impact of TP53 nonsense mutation at the organismal level and evaluate novel readthrough compounds in vivo, we have generated Trp53 R210X nonsense mutant knock-in mice. Mouse Trp53 R210X corresponds to human TP53 R213X. Trp53 R210X mice develop spontaneous tumors at early age. Pharmacological induction of translational readthrough is a promising strategy for treatment of tumors with TP53 nonsense mutation. This strategy could potentially also be applied for tumors with nonsense mutations in other tumor suppressor genes, including PTEN, APC and RB1.

A selection of publications from your group

- Tuval A, Strandgren C, Heldin A, Palomar-Siles M, Wiman KG. Pharmacological reactivation of p53 in the era of precision anticancer medicine. Nature Rev Clin Oncol. 21(2):106-120, 2024
- Heldin A, Cancer M, Palomar-Siles M, Öhlin S, Zhang M, Sun-Zhang A, Mariani A, Liu J, Bykov VJN, Wiman KG. Novel compounds that synergize with aminoglycoside G418 or eRF3 degraders for translational readthrough of nonsense mutant TP53 and PTEN. RNA Biol 20(1):368-83, 2023
- Palomar-Siles M, Heldin A, Zhang M, Strandgren C, Yurevych V, van Dinter JT, Engels SAG, Hofman DA, Öhlin S, Meineke B, Bykov VJN, van Heesch S, Wiman KG. Translational readthrough of nonsense mutant TP53 by mRNA incorporation of 5-Fluorouridine. Cell Death Dis 13(11):997, 2022

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Cancer Research Area

- Molecular- and translational lung cancer research

Key research field interests

- Lung cancer
- Precision cancer medicine
- Immune therapy
- Radiotherapy
- Extracellular vesicles
- Metastasis
- Eph signaling

Needs for collaborations

- Bioinformatic competence to explore publicly available genomic/DNA sequencing data sets in relation to our research questions; mouse tumor models and in vivo imaging for exploring our candidate therapeutic targets.

Non-small cell lung cancer- exploring the Ephrin/Eph signaling axis and extracellular vesicle protein cargo in context of precision cancer medicine and immune checkpoint blockade

Kristina Viktorsson

In non-small cell lung cancer (NSCLC) precision cancer medicine (PCM) treatment e.g. EGFR TKIs or immune check point blockade are important clinical regimens but responses are heterogenous. As tumor biopsy procedures are challenging and metastatic lesions are heterogenous, there is a need for identifying therapy-guiding biomarkers (BMs). We focus on such BM analyses in extracellular vesicles (EVs) isolated from plasma or serum of NSCLC patients. Thus we identified a set of EVs proteins that can predict efficacy of EGFR-TKI osimertinib as well as an EVs protein signature related to immune checkpoint blockade response in advanced NSCLC patients. We are currently jointly with a team at Sheba Medical Center and Tel Aviv University, exploring the plasma EVs protein cargo with the aim to predict risk for metastatic spread in early-stage NSCLC disease. In another ongoing project we are focusing on plasma-isolated EVs as source of BMs in context of precision radiotherapy/stereotactic body radiotherapy regimens in national collaborative efforts in both early -and advanced NSCLC patients.
We earlier reported that the Ephrin- and Eph signaling circuit control NSCLC cell survival, migration/invasion, and response to radiotherapy. We are currently exploring a role for this signaling cascade in mutated EGFR- or EML4-ALK fusion driven NSCLC with the aim to understand and reveal possible EGFR-or ALK TKIs resistance sensitizing approaches. In particular, we are interested in understanding the role of EVs protein cargo as a signaling hub in this context and in metastatic spread.

A selection of publications from your group

- Kaminskyy VO*, Hååg P, Novak M, Végvári Á, Arapi V, Lewensohn R, **Viktorsson K***. EPHA2 Interacts with DNA-PKcs in Cell Nucleus and Controls Ionizing Radiation Responses in Non-Small Cell Lung Cancer Cells. Cancers (Basel). 2021 Feb 28;13(5):1010. doi: 10.3390/cancers13051010. PMID: 33671073; PMCID: PMC7957683. * corresponding authors.
- Cavallaro S, Hååg P, Sahu SS, Berisha L, Kaminskyy VO, Ekman S, Lewensohn R, Linnros J, **Viktorsson K**, Dev A. Multiplexed electrokinetic sensor for detection and therapy monitoring of extracellular vesicles from liquid biopsies of non-small-cell lung cancer patients. Biosens Bioelectron. 2021 Dec 1;193:113568. doi: 10.1016/j.bios.2021.113568. Epub 2021 Aug 17. PMID: 34428672.
- Franzén B*, **Viktorsson K***, Kamali C, Darai-Ramqvist E, Grozman V, Arapi V, Hååg P, Kaminskyy VO, Hydbring P, Kanter L, Nyrén S, Ekman S, De Petris L, Lewensohn R. Multiplex immune protein profiling of fineneedle aspirates from patients with non-small-cell lung cancer reveals signatures associated with PD-L1 expression and tumor stage. Mol Oncol. 2021 Nov;15(11):2941-2957. doi: 10.1002/1878-0261.12952. Epub 2021 May 1. PMID: 33768639; PMCID: PMC8564641.* corresponding authors

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Cancer Research Area

- Cancer pathology

Key research field interests

- Postmortem examination
- Cancer/host interactions
- Molecular pathology
- Drug sensitivity

Needs for collaborations

The life of cancer inside and outside of the human body

Laszlo Szekely

A selection of publications from your group

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Cancer Research Area

- Breast cancer

Key research field interests

- Intra-tumor heterogeneity
- Long-term risk of metastatic disease
- Estrogen receptor signalling
- Endocrine treatment benefit
- Translational research

Needs for collaborations

- Seeking collaboration for the current projects with interest in intra-tumor heterogeneity using:
- Deep-learning (AI) to analyse IHC images
- Imaging mass cytometry (IMC) simultaneously imaging ~40 proteins at subcellular resolution

Translational breast cancer research with focus on long-term risk of metastatic disease and endocrine treatment benefit

Linda Lindström

We focus on breast cancer research in my research group with a bioinformatic toolbox, an interdisciplinary perspective and a specific interest in understanding the reasons behind the longterm risk of distant metastatic disease as seen in majority of patients with breast cancer.

Breast cancer is a truly diverse disease with the main fundamental difference being whether the tumor is hormone-sensitive or not, i.e., estrogen receptor-positive (ER+) or negative (ER-). A unique feature of ER+ breast cancer is the long-term risk of fatal disease decades after initial diagnosis, and half or more of all breast cancer metastases will be diagnosed beyond 5 to 10 years after diagnosis as shown by us and others. The factors underlying long-term risk remain poorly understood and current research is mainly focused on early risk, partly due to the lack of tumor samples from patients with complete long-term follow-up.

We are currently investigating intra-tumor heterogeneity of the breast cancer markers (IHC) and the heterogeneous ER+ tumor microenvironment, to identify tumor characteristics influencing long-term risk and benefit from endocrine treatment. Using novel deep-learning methods and in depth spatial analysis will enable the understanding of tumor biology down to single-cell level. We are using unique and large clinical trials with patients randomized to endocrine treatment versus not with complete long-term follow-up.

The distinction of long-term risk is essential, since accurate risk prediction allows for individualized treatment, decreases anxiety, and supports aggressive treatment for patients at high long-term risk of fatal disease. Our studies has the potential to answer vital questions about the influence of the tumor microenvironment and intra-tumor heterogeneity for long-term risk in ER+ breast cancer, helped by the interdisciplinary expertise in our team. Driving large-scale interdisciplinary research initiatives gives us the opportunity for in-depth understanding of the factors by which breast cancer survival is determined.

A selection of publications from your group

- Johansson A, Dar H, Nordenskjöld A, Perez-Tenorio G, Tobin NP, Yau C, Benz CC, Esserman LJ, van 't Veer LJ, Nordenskjöld B, Stål O, Fornander T, Lindström LS. Differential long-term tamoxifen therapy benefit by menopausal status in breast cancer patients: secondary analysis of a controlled randomized clinical trial. J Natl of Cancer Inst, (JNCI). 2024. PMID: 39656627
- Johansson A, Dar H, van 't Veer LJ, Tobin NP, Perez-Tenorio G, Nordenskjöld A, Johansson U, Hartman J, Skoog L, Yau C, Benz CC, Esserman LJ, Stål O, Nordenskjöld B, Fornander T, Lindström LS. Twenty-Year Benefit From Adjuvant Goserelin and Tamoxifen in Premenopausal Patients With Breast Cancer in a Controlled Randomized Clinical Trial. J Clin Oncol. 2022. PMID: 35862873.
- Yu N, Iftimi A, Yau C, Tobin NP, van 't Veer L, Hoadley KA, Benz CC, Nordenskjöld B, Fornander T, Stål O, Czene K, Esserman LJ, Lindström LS. Assessment of long-term distant recurrencefree survival associated with tamoxifen therapy in postmenopausal patients with Luminal A or Luminal B breast cancer. JAMA Oncol. 2019. PMID: 31393518

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Cancer Research Area

- Research aiming to improve survival and quality of life in patients with gastric and oeosphageal cancer. This includes epidemiological studies, investigator initiated clinical trials and close collaboration with basic scientists with the aim of developing and implementing new therapies.

Key research field interests

- Gastro-oesophageal cancer
- Peritoneal metastases
- Tumour immune microenvironment
- Clinical trials
- Cell therapy

Needs for collaborations

- Expertise in organoids, especially stromal-organoid co-culture
- Expertise in animal models of peritoneal tumours

Clinical and translational studies on gastric and oesophageal cancer

Magnus Nilsson

The background of the group was initially clinical epidemiology and then gradually moved more into leading international academic clinical trials addressing neoadjuvant therapies and definitive (curative intent) chemoradiotherapy in oesophageal cancer.

In the last years our focus has widened, and we have intensified biobanking and collaboration with basic science groups. Together we are doing multi-omics in blood, primary tumour, metastases and healthy mucosa from patients with oesophageal and gastric cancer. Recently we have particularly focused on gastric cancer (GC) with peritoneal metastases (PM), where our preliminary data suggest a severely immunodepleted tumour immune microenvironment (TIME). We are shortly planning to start an international phase III trial on intraperitoneally (IP) administered paclitaxel in GC PM patients, in which we will follow the peritoneal TIME longitudinally. We are exploring the possibility of developing IP immunotherapies, including cell therapies.

A selection of publications from your group

- Nilsson K, Klevebro F, Sunde ,Rouvelas I, Lindblad M, Szabo E, Halldestam I, Smedh U, Wallner B, Johansson J, Johnsen G, Aahlin EK, Johannessen HO, Alexandersson von Döbeln G, Hjortland GO, Wang N, Shang Y, Borg D, Quaas A, Bartella I, Bruns C, Schröder W and Nilsson M. Oncological outcomes of standard versus prolonged time to surgery after neoadjuvant chemoradiotherapy for oesophageal cancer in the multicentre randomised controlled NeoRes II trial. Annals of Oncology 2023 Nov;34(11):1015-1024.
- Sunde B, Lindblad M, Malmström M, Hedberg J, Lagergren P, Nilsson M. Health-related quality of life one year after the diagnosis of oesophageal cancer: a population-based study from the Swedish National Registry for Oesophageal and gastric Cancer. BMC Cancer 2021, 21:1277. https://doi.org/10.1186/s12885-021-09007-9
- Smyth EC, Nilsson M, Grabsch HI, van Grieken NCT, Lordick F. Gastric Cancer Seminar. The Lancet 2020; 396(10251): 635-648. Review.

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Cancer Research Area

- Gastrointestinal cancers
- Metastases
- Cell-cell interactions

Key research field interests

- Cell competition
- Tumor cell invasion into parenchymatous organs

Needs for collaborations

- What we have/do: The KaroLiver cohort, >1000 patient with operated liver metastases, pathological samples, complete outcome data), pancreatic cancers (pathologistannotated, stained), expertise in multiplex microscopy, histopathology, mouse models.
- What we are interested: Novel angles to use our clinical material and metastases models, immune system/immunotherapy expertise, new Spatial multiomic techniques

Cancer invasion fronts: Tumor epithelial interactions and cell competition

Marco Gerling

When tumor cells invade parenchymatous organs like the liver, they replace the organ's native parenchymal cells, such as hepatocytes. Our group investigates the molecular and cellular basis of tumor invasion and tissue replacement using liver metastases from different primary tumors and pancreatic cancer as primary clinical models.

We have discovered that tumor invasion in both the liver and pancreas triggers regenerative changes in the adjacent, non-malignant parenchymal cells, i.e. hepatocytes and pancreatic acinar cells.

Invading tumors are surrounded by a "halo" of injured parenchymal cells, which dedifferentiate into progenitor-like cells with regenerative properties. When tumor invasion is impaired, such as by chemotherapy, this regenerative reaction around the tumor matures, forming an encapsulating, benign-like stroma. Conversely, aggressive tumors can exploit peritumoral injury by engaging in active cell competition with dedifferentiated, regenerative host cells.

In the liver, dedifferentiation is driven by Jag1/Notch2 signaling. Knocking out Jag1 in tumor cells disrupts this process, limiting hepatocyte dedifferentiation and halting tumor invasion into the liver cell plates. Our results reveal a novel, potentially actionable response by peritumoral tissue that supports tumor growth.

A selection of publications from your group

- A distinctive tumor compartment in pancreatic lobules defined by nascent stroma and classical tumor cell phenotype. Söderqvist S, Viljamaa A, Geyer N, Strell C, Hekmati N, Engstrand J, Sparrelid E, Salmén C, Heuchel RL, Zacharouli A, Ghorbani P, Harrizi S, Hamidi Y, Khorosjutina O, Milanova S, Schmierer B, Bozóky B, Fernández Moro C, Gerling M. BioRxiv, 04/2024, doi: https://doi.org/10.1101/2024.03.14.584614
- Cellular spartans at the pass: Emerging intricacies of cell competition in early and late tumorigenesis. Fernández Moro C, Geyer N, Gerling M. Current Opinion in Cell Biology. 2024 Feb;86:102315. doi: 10.1016/j.ceb.2023.102315.
- An idiosyncratic zonated stroma encapsulates desmoplastic liver metastases and originates from injured liver. Fernández Moro C*, Geyer N*, Harrizi S*, Hamidi Y*, Söderqvist S, Kuznyecov D, Tidholm Qvist E, Salmonson Schaad M, Hermann L, Lindberg A, Heuchel RL, Martín-Bernabé A, Dhanjal S, Navis AC, Villard C, Del Valle AC, Bozóky L, Sparrelid E, Dirix L, Strell C, Östman A, Schmierer B, Vermeulen PB, Engstrand J, Bozóky B, Gerling M. Nature Communications. 2023 Aug 18;14(1):5024 doi:10.1038/s41467-023-40688-x

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Cancer Research Area

- Pediatric neural tumors
- Cancer models
- PCM

Key research field interests

- Tumor initiation mechanisms
- Tumor microenvironment
- Targeted Therapy

Needs for collaborations

- Clinical samples
- Biostatistics

Identifying molecular mechanisms and therapeutic targets in childhood neural tumors

Margareta Wilhelm

The goal of our research is to identify molecular mechanisms that occur during tumor development and how our findings can be used for precision cancer medicine. My laboratory has many years of experience in the development and analysis of in vivo cancer models. Currently, we are focused on developing humanized in vitro and in vivo models for medulloblastoma and neuroblastoma. For this purpose, we derive iPS cells and subsequently disease-relevant cells from non-cancerous somatic cells of patients with germline mutations causing the disease. In this way, we obtain normal neural stem cells carrying a driver mutation. We use these stem cells and patient material to create cellular systems, in vivo models, and multilayer CNS organoids. We are studying all stages of tumor development, from early to late stages. In addition, we are particularly interested in understanding the communication between tumor cells and the microenvironment, and study this both in vivo and in organoid or co-culture systems. We are using our models to understand the mechanisms of tumorigenesis, to elucidate how the premalignant and promalignant niches influence tumor formation, and to identify new potential therapeutic targets and therapies.

Unique methodologies used in the group:
iPS reprogramming and neural differentiation, Mouse models of cancer, CNS organoids, Zebrafish models, High throughput drug screening platforms

A selection of publications from your group

- Zhou, L., van Bree, N., Boutin, L., Ryu, J., Moussaud, S., Liu, M., Otrocka, M., Olsson, M., Falk, A., and Wilhelm, M. (2024) High-throughput neural stem cell-based drug screening identifies S6K1 inhibition as a selective vulnerability in SHH-medulloblastoma. Neuro-Oncology noae104, https://doi.org/10.1093/neuonc/noae104
- van Bree,N., Oppelt, A., Lindström, S., Boutin, L., Zhou, L., Coyle, B., Swartling F., J., Johnsen, J., Bräutigam, L., Wilhelm, M. (2024) Development of an orthotopic medulloblastoma zebrafish model for rapid drug testing. Neuro-Oncology, noae210, https://doi.org/10.1093/neuonc/noae210
- Wolfsberger, J., Sakil, H., Zhou, L., van Bree, N., Baldisseri, E., de Souza Ferreira, S., Zubillaga, V., Stantic, M., Fritz, N., Hartman, J., Rolny, C., and Wilhelm, M. (2021) TAp73 represses NFkB-mediated recruitment of tumor-associated macrophages in breast cancer. Proc Natl Acad Sci U S A, 2021 118 (10) e2017089118

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Cancer Research Area

- Basic mechanisms and novel therapies based on DNA repair and ncRNA

Key research field interests

- RNA
- DNA repair
- Nuclear organelles
- RNA modification
- RNA therapeutics

Needs for collaborations

- Clinical material
- Sequencing
- Biostatistical expertise

RNA-regulated DNA repair in cancer

Marianne Farnebo

Genomic instability is a hallmark of virtually all human cancers, promoting carcinogenesis as well as offering a therapeutic opportunity. RNAs are emerging as key regulators of DNA repair, but the underlying mechanism(s) remain unclear. Our laboratory recently found that small Cajal body-specific RNA (scaRNA) can regulate DNA repair by inhibiting the enzymes involved. Moreover, scaRNAs are often dysregulated in cancer for unclear reasons. We postulate the existence of a network of scaRNAs that participate in DNA repair by regulating repair enzymes and whose dysfunction could contribute to the development of various diseases, including cancer.

Antisense oligonucleotides (ASOs) are widely used tools to modulate gene expression in basic research and therapy. We have discovered that ASOs exert strong effects on DNA damage signaling, causing suppression of DNA repair, sensitization to DNA damage and reduced cell viability. Briefly, we show that this is caused by ASOs binding to repair enzymes, and triggering formation of nuclear condensates, in which repair factors are enriched and dysregulated. This provides insight into the regulation of DNA repair by oligonucleotides and highlights that the effects of ASOs on DNA damage signaling must be considered for appropriate experimental and therapeutic use of these agents.

A selection of publications from your group

- Small Cajal body-associated RNA 2 (scaRNA2) regulates the choice of DNA repair pathway by inhibiting DNA-PK. Bergstrand S, O'Brien EM, Coucoravas C, Hrossova D, Peirasmaki D, Schmidli S, Dhanjal S, Pederiva C, Siggens L, Mortusewicz O, O'Rourke JJ and Farnebo M. https://pubmed.ncbi.nlm.nih.gov/35197472/
- Control of protein synthesis through mRNA pseudouridylation by dyskerin. Pederiva C, Trevisan D. M, Peirasmaki D, Chen S, Savage SA, Larsson O, Ule J, Baranello L, Agostini F and Farnebo M. https://www.science.org/doi/10.1126/sciadv.adg1805

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Cancer Research Area

- Targeting MYC and metabolism for precision medicine

Key research field interests

- Childhood cancer
- MYC
- Metabolism
- Neural differentiation
- Structural biology

Needs for collaborations

- Clinical expertise and patient samples, in vivo tracing of metabolism in mice

Modulation of c-MYC structure and activity by targeting a conformational switch

Marie Arsenian Henriksson

The structural heterogeneity of Intrinsically Disordered Proteins (IDP) facilitates interaction with multiple binding partners but presents a unique challenge to target them for therapeutics. In this regard, we have demonstrated a strategy using the disordered c-MYC oncoprotein, that can be employed to modulate the disorder-function relationship of IDPs. We initially designed peptide derivatives of c-MYC and subjected them to probe-based molecular dynamics simulations. This led to the identification of an epitope (termed coreMYC for COnformational REgulator of c-MYC) within the transactivation domain (TAD) of c-MYC, which undergoes a ligand-induced conformational shift from a predominantly extended state to a more compact configuration. AlphaFold modelling indicated that the high-energy extended structure of coreMYC represent an active module for protein recognition, while the low-energy compact conformation is the inactive state. These observations were then verified using Ion mobility mass spectrometry, where incubation of the recombinantly produced coreMYC with a small molecule epigallocatechin gallate (EGCG), propagated the compact conformation and impeded its interaction with c-MYC TAD binding partners such as TRRAP and TBP. Finally, employing in situ proximity ligation assay, we saw that treatment of cells with EGCG indeed inhibited interaction of c-MYC with both the endogenous co-factors. Characterization of EGCG interaction with coreMYC using NMR spectroscopy indicated that the largest chemical shift perturbation was observed around the MYC Box II (MBII) region of c-MYC. We have also subjected coreMYC to mixed-solvent simulations with diverse chemical probes that led to the identification of a small molecule that interacted with better specificity to coreMYC than EGCG, and that we are further characterizing. Together, the study presents a blueprint for the systemic identification and characterization of ligand binding interfaces in IDPs. It also opens new avenues towards the development of shape-shifting compounds that could be the hallmark of targeting disordered proteins like c-MYC regarded as undruggable.

A selection of publications from your group

- Lourdes Sainero-Alcolado, Elisa Garde-Lapido, María Victoria Ruiz-Pérez, Marteinn Thor Snaebjörnsson, Sarah Schoch, Irene Stevens, Maria Victoria Ruiz-Perez, Christine Dyrager, Vicent Pelechano, Axelson H, Almutz Schulze, and **Marie Arsenian-Henriksson#**. MYC inhibition during hypoxia results in accumulation of lipid droplets in clear cell renal cell carcinoma. Proc Natl Acad Sci USA 121(7) 2024. #Corresponding author.
- Lama D*#, Vosselman T*, Sahin C, Liaño-Pons J, Cerrato C, Teilum K, Lane D, Landreh M#, and **Arsenian Henriksson, M#**. Modulation of c-MYC structure and activity by targeting a conformational switch. Nature Communications 15(1):1865 (2024). *Equal contribution. #Co-corresponding authors.
- Mushtaq M*#, Liaño Pons J*, Yuan Y, Jiansheng Wang, Ruiz-Pérez MV, Yi Chen,Kashuba E, Felix Haglund de Flon, Bertha B, and **Arsenian-Henriksson M#**. EZH2 inhibition sensitizes retinoic aciddriven senescence in Synovial sarcoma. In press in Cell Death and Disease 2024. *Equal contribution. #Co-corresponding authors

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Cancer Research Area

- Pancreatic cancer
- IPMN

Key research field interests

- Individuals at risk
- Familiar pancreatic cancer
- Surveillance
- Molecular profiling
- Spheroid models
- Tumour micro environment
- Liquid biopsy

Needs for collaborations

Pancreatic tumours: prestages, prevention, preclinical models, biomarkers

Matthias Löhr

Clinically, we focus on conditions that may lead to pancreatic cancer, i.e. chronic and autoimmune pancreatitis as well as intraductal papillary mucinous tumours (IPMN). Another group are individuals at risk (IAR)/familiar pancreatic cancer, part of them with genetic mutations (e.g. BRCA2, CDKN2A) where we have >400 patients in surveillance. We are currently describing the natural course of our cohort, especially since we became part of International Cancer of the Pancreas Screening (CAPS) Consortium. Translationally, we work within two EU projects PANCAID, and GUIDE.MRD on liquid biopsy markers and in PancAIM on the early detection on imaging for early detection of pancreatic cancer, especially in the above mentioned risk groups (IAR, IPMN). The MSC program PRECODE relates to our unique heterospheroid model consisting of tumour cells and stromal cells (pancreatic stellate cells/PSC becoming cancer associated fibroblasts/CAF) where we are now in the process of identifying drugs able to work on these minitumours.

A selection of publications from your group

- **Löhr JM**, Vujasinovic M, Kartalis N, Osten P. Pancreatic incidentaloma:incidental findings from history towards the era of liquid biopsy. eGastroenterology 2024, 2(3): sep 9. https://doi.org/10.1136/egastro-2024-100082
- Kordes M*, Malgerud M*, Frödin JE, Yachnin J, Fernandez Moro C, Ghazi S, Pozzi Mucelli R, Kartalis N, Ghorbani P, Del Chiaro M, Wirta V, Björnstedt M, Gustafsson Liljefors M*, **Löhr JM***. Consistency of a clinical decision support system with molecular tumour board recommendations for tumour sequencing-guided treatment of pancreatic cancer. ESMO Gastrointestinal Oncology 2024; 5 (issue C). Epub Jun19. https://doi.org/10.1016/j.esmogo.2024.100070
- **Löhr JM**, Öhlund D, Söreskog E, Andersson E, Vujasinovic M, Zethraeus N, Sund M. Can our experience with surveillance for inherited pancreatic cancer help to identify early pancreatic cancer in the general population? Fam Cancer. 2024 Aug 23(3): 399-403. doi: 10.1007/s10689-024-00363-6. Online ahead of print.PMID: 38441833

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Cancer Research Area

- Breast cancer
- Prostate cancer
- Colorectal cancer

Key research field interests

- Precision diagnostics
- Artificial intelligence
- Histopathology
- Spatial biology
- Epidemiology

Needs for collaborations

AI-based precision pathology – scalable solutions for cancer patient stratification and phenotyping

Mattias Rantalainen

Precision medicine has the potential to substantially improve cancer patient outcomes, but it requires precision diagnostic solutions for patient stratification to be effective. However, molecular diagnostics remains expensive, limiting patient access and imposing a high economic burden on healthcare systems. To address these challenges we develop, validate, translate and implement AI-based histopathology image analysis solutions for image-based phenotyping and patient stratification, with applications both in the clinical setting and for cancer research.

We currently have one of the largest retrospective multi-site breast cancer cohort studies in the world, including over 300,000 gigapixel histopathology images from >15,000 patients linked with health registry data. We are currently developing both methodology, foundational AI models, and specific precision diagnostic solutions (prognostic, treatment response predictive).

In our recent work, we have demonstrated how deep learning-based models can provide improved risk stratification for breast cancer patients compared to routine pathology, and offer similar performance as established (gene expression-based) molecular diagnostics[1]. The findings has subsequently been developed into a CE-IVD marked solution for clinical use, that has been validated in >2,700 patients[2].

We have also shown how AI can enable prediction of molecular phenotypes (mRNA expression) across the full transcriptome direct from H&E histopathology images, and capture prognostic information related to intratumour variability[3]. Examples of currently on-going work, include development of the first disease-specific AI foundation models for breast cancer histopathology images trained on >100M image tiles from >50,000 whole slide images, and development of methodology for spatial biology research and characterisation of intra-tumour heterogeneity using AI together with routine histopathology images.

A selection of publications from your group

- Wang, Y. et al. Improved breast cancer histological grading using deep learning. Ann. Oncol. 33, 89–98 (2022).
- Sharma, A. et al. Validation of an AI-based solution for breast cancer risk stratification using routine digital histopathology images. Breast Cancer Res 26, 123 (2024).
- Wang, Y. et al. Transcriptional intra-tumour heterogeneity predicted by deep learning in routine breast histopathology slides provides independent prognostic information. Eur. J. Cancer 191, 112953 (2023)

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Cancer Research Area

- Preclinical drug development
- Cellular models
- Various cancers (among others melanoma and pancreatic ductal adenocarcinoma).

Key research field interests

- Ubiquitin-proteasome system
- Autophagy
- Cell-based reporter assays
- High content screening
- Advanced microscopy

Needs for collaborations

- Medicinal chemistry
- Animal models
- Clinical material

Characterization of the novel compound CBK79 that impairs the ubiquitin-proteasome system and autophagy

Nico Dantuma

Cells rely on the ubiquitin-proteasome system (UPS) to maintain protein homeostasis (proteostasis). Cancer cells have ever so demanding proteostasis requirements due to their hyperactive state. Drugs that can impair the UPS have emerged as a therapeutic strategy to target malignant cells by limiting their capacity to clear misfolded and dysfunctional proteins. We performed a high-content screening for inhibitors of the UPS, which led to the development of CBK79. Interestingly, CBK79 not only inhibits the UPS but also impairs macroautophagy through the induction of non-canonical lipidation of the autophagy marker LC3. To gain insights in the molecular mechanisms responsible for the dual inhibition of these proteolytic pathways and induction of cell death, we analysed the transcriptome of cancer cells exposed to CBK79. This revealed a profile that was like the transcriptional response to proteasome inhibitors with as striking exception that CBK79, but not proteasome inhibitors, induced of the expression of metallothioneins – a family of proteins involved in metal ion homeostasis. Subsequent analysis showed that CBK79 interacts with Cu(II) ions. Presence of Cu(II) ions was critical for inhibition of the UPS and induction of cell death. Moreover, preloading of CBK79 with Cu(II) strongly enhanced its ability to inhibit the UPS as well as its toxicity towards cancer cells, further consolidating an important role for copper in the mode-of-action of CBK79. Our preliminary data suggest that CBK79 behaves as a copper ionophore that kills cancer cells through induction of cuproptosis (i.e. copper-induced cell death).

A selection of publications from your group

- Giovannucci, T.A., F.A. Salomons, H. Stoy, L.K. Herzog, S. Xu, W. Qian, L.G. Merino, M.E. Gierisch, M. Haraldsson, A.H. Lystad, H. Uvell, A. Simonsen, A.-L. Gustavsson, M. Vallin and N.P. Dantuma*. 2022. Identification of a novel compound that simultaneously impairs the ubiquitin-proteasome system and autophagy. Autophagy 18:1486-1502. https://doi.org/10.1080/15548627.2021.1988359
- Xu, S., M.E. Gierisch, A.K. Schellhaus, I. Poser, S. Alberti, F.A. Salomons and N.P. Dantuma*. 2023. Cytosolic stress granules relieve the ubiquitin-proteasome system in the nuclear compartment. EMBO J. 42:e111802. https://doi.org/10.15252/embj.2022111802
- Xu, S., M.E. Gierisch, I. Poser, S. Alberti, F.A. Salomons and N.P. Dantuma*. 2024. Chemical inhibition of the integrated stress response impairs the ubiquitin-proteasome system. Commun. Biol. 7:1282. https://doi.org/10.1038/s42003-024-06974-0

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Cancer Research Area

- Pre-clinical and translational cancer research
- Breast cancer

Key research field interests

- Genomic rearrangements
- Genome instability
- 3D genome organization
- Intratumor heterogeneity
- Single-cell sequencing

Needs for collaborations

- Clinical samples

Delineating tumor evolution during neoadjuvant therapy in Luminal B breast cancer patients

Nicola Crosetto

One of the ongoing efforts in my lab at KI-SciLifeLab is harnessing single-cell sequencing technologies to chart genomic copy number alterations (CNAs) and structural variants (SVs) in patient-derived tumor samples, with the overarching goal of developing CNA/SV-based biomarkers of response/resistance to treatment. As part of this effort, in collaboration with the group of Assoc. Prof. Theodoros Foukakis at Karolinska University Hospital, we are currently applying Acoustic Cell Tagmentation (ACT)—a plate-based, single-cell, low-pass DNA sequencing method—to profile CNAs in thousands of nuclei extracted from core biopsies from breast cancer (BC) patients enrolled in the randomized, cross-over, neoadjuvant therapy clinical trial 'PREDIX Luminal B' (NCT: 02603679; N=181 patients). Preliminary analyses of 15 baseline (V0) biopsies from 15 patients, from which we obtained high-quality single-cell sequencing data, revealed marked inter- and intra-patient heterogeneity of CNA patterns, with individual tumors typically consisting of 2–4 large subclones displaying different CNA patterns. For 6 of these 15 patients, we also analyzed single-cell data from a biopsy collected after the first line of neoadjuvant therapy (V2) and found dramatic shifts in clonal composition between V0 and V2 in 4 patients, while the remaining 2 patients exhibited overall clonal stability. Notably, the latter group responded to the first line of neoadjuvant therapy, as assessed by ultrasonography, whereas nonresponsive patients were associated with extensive clonal remodeling in post-treatment samples, irrespective of treatment type (endocrine or chemotherapy). In my talk, I will highlight the results of these single-cell analyses as well as of our ongoing comprehensive genomic profiling at baseline, after the first line of neoadjuvant therapy, and at surgery, for all the patients that completed the PREDIX Luminal B trial.

A selection of publications from your group

- Chen JP§, Diekmann C, Wu H, Chen C, Della Chiara G, Berrino E, Georgiadis KL, Bouwman BAM, Virdi M, Harbers L, Bellomo SE, Marchiò C, Bienko M§, Crosetto N§. scCircle-seq unveils the diversity and complexity of extrachromosomal circular DNAs in single cells. Nat Commun. 2024 Feb 27;15(1):1768. doi: 10.1038/s41467-024-45972-y. PMID: 38409079. §Co-corresponding authors
- Zhang N, Harbers L, Simonetti M, Diekmann C, Verron Q, Berrino E, Bellomo SE, Longo GMC, Ratz M, Schultz N, Tarish F, Su P, Han B, Wang W, Onorato S, Grassini D, Ballarino R, Giordano S, Yang Q, Sapino A, Frisén J, Alkass K, Druid H, Roukos V, Helleday T, Marchiò C, Bienko M, Crosetto N. High clonal diversity and spatial genetic admixture in early prostate cancer and surrounding normal tissue. Nat Commun. 2024 Apr 24;15(1):3475. doi: 10.1038/s41467-024-47664-z. PMID: 38658552.
- Wernersson E, Gelali E, Girelli G, Wang S, Castillo D, Mattsson Langseth C, Verron Q, Nguyen HQ, Chattoraj S, Martinez Casals A, Blom H, Lundberg E, Nilsson M, MartiRenom MA, Wu CT, Crosetto N, Bienko M. Deconwolf enables high-performance deconvolution of widefield fluorescence microscopy images. Nat Methods. 2024 Jun 6. doi: 10.1038/s41592-024-02294-7. PMID: 38844629

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Cancer Research Area

- Tumor immunology
- Primary liver cancer

Key research field interests

- Tumor microenvironment
- Human immunology
- Cytotoxic lymphocytes
- Spatial methods

Needs for collaborations

- Strategies to study germline risk for cancer
- Bioinformatics with focus on complex spatial data as well as integration of spatial data with genetic data
- High-throughput microscopy techniques

Spatial organization of cytotoxic lymphocytes in the tumor microenvironment as a predictor for treatment response and prognosis in cancer with poor outcome

Niklas Björkström

Cancer treatment has advanced, but personalized therapies face challenges in achieving consistent success across various malignancies. While breakthroughs like immunotherapy have shown success in cancers such as melanoma and lung cancer, aggressive malignancies like cholangiocarcinoma and pancreatic ductal adenocarcinoma remain resistant. These cancers exhibit poor prognoses, underscoring the need for novel approaches. The molecular basis for treatment responses remains unclear, especially as clinical trials show positive responses in some patients without explaining why others fail. Cytotoxic lymphocytes, particularly T cells and NK cells, play a crucial role in attacking tumor cells, but their effectiveness is influenced by the tumor microenvironment (TME), which can impair their function. Our research aims to address this gap by exploring the spatial organization of the TME and the activity of cytotoxic lymphocytes as predictors of treatment response in cancers with poor outcomes. Recent research has shown that spatial information best predicts response to immunotherapy in cancer. We aim to study factors regulating TME composition including cytotoxic lymphocyte activity. Studies are performed in a human translational setting including the usage of novel spatial methods to map TME composition. Understanding of factors regulating cytotoxic lymphocyte presence in the TME will be important for future precision diagnostic approaches as well as for personalized therapy strategies.

A selection of publications from your group

- Bister, J., Filipovic, I., Sun, D., Crona-Gusterstam, Y., Cornillet, M., Ponzetta, A., Michaelsson, J., Brusell Gidlöf, S., Ivarsson, MA, Strunz, B., **Björkström, NK.** Tissuespecific non-heritable influences drive endometrial immune system variation. Science Immunology 2024 9:eadj7168
- Zimmer, CL., Filipovic, I., Cornillet, M., O'Rourke, CJ., Berglin, L., Jansson, H., Sun, D., Strauss, O., Hertwig, L., Johansson, H., von Seth E., Dias, J., Glaumann, H., Melum, E., Ellis, EC., Sandberg, JK., Andersen, JB., Bergquist, A., **Björkström, NK**. MAIT cell tumor infiltration predicts long-term survival in cholagiocarcinoma. Hepatology 2022 75:1154-1168.
- Zimmer, CL., von Seth, E., Buggert, M., Strauss, O., Hertwig, L., Nguyen, S., Wong, AYW., Zotter, C., Berglin, L., Michaëlsson, J., Reuterwall Hansson, M., Arnelo, U., Sparrelid, E., Ellis, ECS., Söderholm, JD., Keita, ÅV., Holm, K., Özenci, V., Hov, JR., Mold, JE., Cornillet, M., Ponzetta, A., Bergquist, A., and **Björkström, NK**. A biliary immune landscape map of primary sclerosing cholangitis reveals a dominant network of neutrophils and tissue-resident T cells. Science Translational Medicine 2021 13:eabb3107. IF 16.3

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Cancer Research Area

- Translational pediatric oncology

Key research field interests

- Therapy resistance
- Leukemia
- Sarcoma
- Immunotherapy
- Nucleotide metabolism

Needs for collaborations

Overcoming therapy resistant in pediatric cancer

Nikolas Herold

Despite the large success of combination chemotherapy for paediatric cancer, we still fail to cure a substantial proportion of paediatric cancer patients. The main reason for this is treatment resistance, why the key to improve survival is to identify and target resistance factors. We have identified the protein SAMHD1 to be a main resistance factor for nucleoside analogues that are used in the treatment of e.g. AML and T-ALL. A phenotypic screen allowed us to identify small molecular drugs that can inhibit the effect of SAMHD1. One of these is hydroxyurea, a drug already approved for treatment of cancer, why this could relatively fast be translated into a clinical study. We have recently published data from this phase I trial showing this treatment to be both safe and efficacious. The phase II trial with an additional 60 patients has recently concluded inclusion. Preliminary results regarding efficacy are promising. In parallel we investigate the role of SAMHD1 in different malignancies. Furthermore, we have a strong interest in bone sarcomas. For osteosarcoma, the most common type of malignant bone tumours in children, adolescents and young adults, survival has stagnated for four decades, why novel treatment strategies are urgently needed. We and others have found that immune infiltration correlates with response to chemotherapy in osterosarcoma. Therefore, we believe that adding immunotherapies to standard regimes could be a possible way to improve survival. We hypothesize the key to overcome this is to find the right combination of immunomodulating drugs. Thus, we are investigating novel immunotherapeutic combinations and how this can be combined with conventional chemotherapy to improve treatment outcome. We also work on Ewing's sarcoma, a type of tumor that can occur both in bone and soft tissue and disproportionately affects younger people. The majority of Ewing sarcoma cases express a chimeric fusion protein as our recent data suggest we have a found a new way to inhibit this oncogenic driver.

A selection of publications from your group

- Morsy MHA, Lilienthal I, Lord M, Merrien M, Wasik AM, Amador V, Sureda-Gómez M, Johansson HJ, Lehtiö J, García-Torre B, Martin-Subero JI, Tsesmetzis N, Tao S, Schinazi RF, Kim B, Sorteberg AL, Wickström M, Sheppard D, Rassidakis GZ, Taylor IA, Christensson B, Campo E, Herold N*, Sander B*.SOX11 is a novel binding partner and endogenous inhibitor of SAMHD1 ara-CTPase activity in mantle cell lymphoma. Blood. 2024 Jan 18:blood.2023022241. *: shared last authorship
- Jädersten M, Lilienthal I, Tsesmetzis N, Lourda M, Bengtzén S, Bohlin A, Arnroth C, Erkers T, Seashore-Ludlow B, Giraud G, Shah Barhordar G, Tao S, Fogelstrand L, Saft L, Östling P, Schinasi RF, Kim B, Schaller T, Juliusson G, Deneberg S, Lehman S, Rassidakis GZ, Höglund M, Henter J-I, Herold N. Targeting SAMHD1 with hydroxyurea in first-line cytarabine-based therapy of newly diagnosed acute myeloid leukaemia: Results from the HEAT-AML trial. J Intern Med 2022 Dec;292(6):925-940
- Herold N*#, Rudd SG*, Ljungblad L, Sanjiv K, Myrberg IH, Paulin CB, Heshmati Y, Hagenkort A, Kutzner J, Page BD, Calderón-Montaño JM, Loseva O, Jemth AS, Bulli L, Axelsson H, Tesi B, Valerie NC, Höglund A, Bladh J, Wiita E, Sundin M, Uhlin M, Rassidakis G, Heyman M, Tamm KP, Warpman-Berglund U, Walfridsson J, Lehmann S, Grandér D, Lundbäck T, Kogner P, Henter JI, Helleday T, Schaller T#. Targeting SAMHD1 with the Vpx protein to improve cytarabine therapy for hematological malignancies. Nat Med. 2017 Feb;23(2):256-263. doi: 10.1038/nm.4265. *: equal contribution #: corresponding author

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Cancer Research Area

- Childhood cancer and bone metastases

Key research field interests

- Bone metastases
- Tumor microenvironment
- Stem cells
- Neuroblastoma
- Urological cancers

Needs for collaborations

The role of the tumor microenvironment in solid malignancies of the bone marrow

Ninib Baryawno

My lab is combining the expertise of cancer, stem cell and niche biology that I acquired during my PhD and postdoctoral training. By using this combined expertise, the primary focus of my laboratory is to understand the role of the microenvironment (niche) in cancer development, cancer metastases and cancer resistance. We study cancers that are prone to spread to the bone marrow, specifically childhood cancers such as neuroblastoma and medulloblastoma, and adult cancers of the prostate and kidney. Our benchmark is to understand basic stem cell biology in normal tissue homeostasis and then apply cancer as a stress model to discover the changes that occur by a tumor in order to support cancer development, metastases and cancer resistance. We are also focusing our efforts into understand critical cellular and molecular interactions between cancer cells and the tumor microenvironment, including stroma cells and immune cells. The methodologies my lab is using are single-cell profiling, computational modeling and preclinical testing, such as patient derived xenografts, transgenic mouse models, and organoid modeling. We apply these tools to delineate the cell-origin of cancers, and why tumor cells metastasize to the bone marrow. All aspects of our work is focusing on using primary tumor material from patients. The pediatric cancer research is focused at Karolinska Institutet, while the adult cancer research is in collaboration with Harvard University and Massachusetts General Hospital.

A selection of publications from your group

- Olsen TK, Dyberg C, Embaie B, Alchahin AM, Milosevic J, Otte J, Tümmler C, Hed Myrberg I, Westerhout EM, Koster J, Versteeg R, Kogner P, Johnsen JI, Sykes DB*, Baryawno N*. DHODH is an independent prognostic marker and potent therapeutic target in neuroblastoma. JCI Insights, 2022, 7:e153836 . Co-senior, *Corresponding author.
- Alchahin AM, Mei S, Tsea I, Hirz T, Kfoury Y, Dahl D, Wu CL, Subtelny AO, Wu S, Scadden DT, Shin JH, Saylor PJ, Sykes DB, Kharchenko PV*, Baryawno N*. A new transcriptional metastatic signature predicts survival in clear cell renal cell carcinoma. Nature Communications, 2022, 13:5747. Co-senior, *Corresponding author.
- Verhoeven BM, Mei S, Olsen TK, Gustafsson KU, Valind A, Lindström A, Gisselsson D, Shirazi Fard S, Hagerling C, Kharchenko PV, Kogner P, Johnsen JI, Baryawno N*. The immune cell atlas of human neuroblastoma. Cell Reports Medicine, 2022, 3:100657. Co-senior, *Corresponding author.

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Cancer Research Area

- Brain tumors

Key research field interests

- Epigenetics
- Stem cells
- Biomedical engineering
- Late complications
- High grade gliomas

Needs for collaborations

Molecular Neurodevelopment and Neuro-Oncology

Ola Hermanson

My research is focused on the development of the brain and maturation of neural stem and progenitor cells, with implications for psychiatric and neurological disease as well as tumors in the nervous system. More specifically, the main focus of my lab is to understand transcriptional and epigenetic regulation of differentiation of neural progenitors, especially of the cortex and in CNS tumors such as glioblastoma, paediatric high-grade glioma, and medulloblastoma. My lab has developed and is continuously developing numerous technologies as well as biomedical engineering approaches, including 2D/3D bioprinting, bioelectronics, and biomaterials, for improved studies in epigenetics and stem cell research, as well as translational and clinical applications in brain tumor surgery, treatment of late complications, and applications in precision medicine.

A selection of publications from your group

- Neofytou C, Backlund A, Blomgren K, Hermanson O. (2023) Irradiation and lithium treatment alter the global DNA methylation pattern and gene expression underlying a shift from gliogenesis towards neurogenesis in human neural progenitors. Transl Psychiatry, 13:258.
- Ilkhanizadeh S, Gracias A, Åslund AKO, Bäck M, Simon R, Kavanagh E, Migliori B, Neofytou C, Nelander S, Westermark B, Uhrbom L, Forsberg-Nilsson K, Konradsson P, Teixeira AI, Uhlén P, Joseph B, Hermanson O*, Nilsson KPR. (2023) Live detection of neural progenitors and glioblastoma cells by an oligothiophene derivative. ACS Appl Bio Mater, 6:3790-3797. *Corresponding author.
- Lewicki J, Bergman J, Kerins C, Hermanson O. (2019) Optimization of 3D bioprinting of human neuroblastoma cells using sodium alginate hydrogel. Bioprinting, 16:e00053

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Cancer Research Area

- Ubiquitin research
- Replication stress
- Targeted therapies

Key research field interests

- Ubiquitin ligase
- Replication Stress
- DNA repair
- Targeted therapy

Needs for collaborations

- Immunotherapy expertise
- In vivo models
- Protein structure prediction
- Bioinformatics

Exploiting ubiquitin ligases for targeted therapies to counter oncogene-driven replication stress tolerance mechanisms

Olle Sangfelt

Cancer cells are characterized by unrestrained growth and continuous division, propelled by powerful oncogenes such as Cyclin E and Myc. This rapid proliferation generates replication stress and excess single-stranded DNA. How oncogene-driven cancers sustain this growth while simultaneously tolerating persistent transcription/replication stress, even when checkpoint kinases like ATR and CHK1 are activated, still remains poorly understood.

We recently uncovered a novel mechanism for removing a critical DNA repair protein, FANCD2, from stalled replication forks in the context of Cyclin E-induced replication stress. Elimination of FANCD2 is mediated by the SCF-FBXL12 ubiquitin ligase, enabling fork restart and replication stress tolerance, making FBXL12 a promising target for cancer treatment. Our recent findings suggest that FBXL12 may play a crucial role in cancer progression and that high FBXL12 expression is a predictor of poor patient outcomes. Research is ongoing to characterize the FBXL12-FANCD2 axis in diaerent cancer types.

Understanding the mechanisms that allow cancer cells to manage high replication-transcription stress could reveal new therapeutic targets. Our research focuses on targeting these tolerance pathways by leveraging ubiquitin ligases, developing methodologies to identify compounds and molecular glues that can stabilize or destabilize critical replication fork substrates.

A selection of publications from your group

- Yan WX, Mirzazadeh R, Garnerone S, Scott D, Schneider MW, Kallas T, Custodio J, WerPublications: Malyukova A et al. Sequential drug treatment targeting cell cycle and cell fate regulatory programs blocks non-genetic cancer evolution in acute lymphoblastic leukemia. Genome Biology (2024), 25;143.
- Brunner A, et al. FBXL12 degrades FANCD2 to regulate replication recovery and promote cancer cell survival under conditions of replication stress Molecular Cell, 83, 1–20, 2023. Suryo Rahmanto A, et al. FBW7 suppression leads to SOX9 stabilization and increased malignancy in medulloblastoma. EMBO J. 2016 17;35(20):2192-2212

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Cancer Research Area

- Preclinical / translational
- Solid tumors (extra interest in breast cancer)

Key research field interests

- Liquid biopsies
- Targeted therapies
- Extracellular vesicles
- Nanoparticles
- Solid tumors

Needs for collaborations

- Expertise in different omics
- Interest in analysis of tumor associated exosomes/extracellular vesicles

Extracellular vesicle-based liquid biopsy and targeted therapy

Oscar Wiklander

In oncology, precision medicine has gained tremendous attention in recent years with the hope to tailor treatments to specific disease driving alterations to improve treatment efficacy and reduce side effects. The need of improved diagnostic tools to identify these specific alterations has also spurred an intense development of various omics to pinpoint relevant biomarkers. Despite intense research, there is still a great need for improved tissue specific targeted drugs and improved diagnostics. The hypothesis of this proposal is that cell secreted extracellular vesicles (EVs) could be utilized as therapeutic targetable vectors and as improved cancer biomarkers. EVs are nanoscale, membrane enclosed particles ubiquitously present in bodily fluids and tissues. Their ability to transport a plethora of different cargo, including protein, DNA, RNA, lipids and metabolites, through complex tissue microenvironments and deliver this to recipient cells makes them attractive candidates as diagnostic and therapeutic agents in a wide range of diseases, including cancer. The aim of my research focus is to engineer EVs as tailored targeted therapy and to explore circulating tumor EVs (tEVs), acting as a fingerprint of the cancer and its current status, as improved biomarkers for 1) early detection of relapsing cancer, 2) identification of molecular traits to aid cancer treatment choice, and 3) individualized dosing of targeted cancer drugs.

A selection of publications from your group

- Wiklander OPB, Mamand D, Mohammad D, Zheng W, Jawad Wiklander R, Sych T, Zickler A, Liang X, Sharma H, Lavado A, Bost J, Roudi S, Corso G, Lennaárd A, Abedi-Valugerdi M, Mäger I, Alici E, Sezgin E, Nordin J, Gupta D, Görgens A, EL Andaloussi S. Targeted Therapy by Antibody Displaying Extracellular Vesicles. Nature Biomedical Engineering (2024).
- Lennaárd AJ, Mamand DR, Wiklander RJ, El Andaloussi S, Wiklander OPB. Optimised Electroporation for Loading of Extracellular Vesicles with Doxorubicin. Pharmaceutics (2021).
- Wiklander OPB, R. B. Bostancioglu, J. A. Welsh, A. M. Zickler, F. Murke, G. Corso, U. Felldin, D. W. Hagey, B. Evertsson, X.-M. Liang, M. O. Gustafsson, D. K. Mohammad, C. Wiek, H. Hanenberg, M. Bremer, D. Gupta, M. Björnstedt, B. Giebel, J. Z. Nordin, J. C. Jones, S. EL Andaloussi, A. Görgens. Systematic Methodological Evaluation of a Multiplex BeadBased Flow Cytometry Assay for Detection of Extracellular Vesicle Surface Signatures. Frontiers in Immunology (2018).

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Cancer Research Area

- Childhood cancer and targeted therapy

Key research field interests

- Neuroblastoma
- Medulloblastoma
- Targeted therapy
- Combination treatments

Needs for collaborations

- Patient material
- Collaboration on the in vivo experiments
- Support on bioinformatic analysis

Studies on combined targeted therapies on neuroblastoma and medulloblastoma

Ourania Kostopoulou

Medulloblastoma (MB) and Neuroblastoma (NB) are tumors of the central and peripheral nervous systems, respectively. MB primarily affects children and adults under 40 years old, while most but not all NBs are diagnosed in children. Despite initially effective therapies, high-risk NB and metastatic MB often develop resistance, leading to fatal outcomes, with survivors, especially those with MB, facing significant long-term side effects. Therefore, there is an urgent need for improved treatments. To overcome therapy resistance in MB and NB by systematically identifying and precisely targeting multiple key pathways based on the unique molecular profiles of these tumors.

Our group's main focus is to: 1) identify optimal combinations of novel drugs (Phosphatidylinositol 3-kinase (PI3K), fibroblast growth factor receptor (FGFR), Cyclin-dependent kinase (CDK) 4/6, and other novel inhibitors with/without cytostatics) on monolayer (2D) /spheroid (3D) cultures (the latter to better mimic the in vivo situation) in correlation to tumor molecular profile; 2) follow subclonal evolution after optimally selected combination treatments using barcoded NB/MB cell lines and identify gene expression alterations in resistant clones by single cell RNA sequencing; 3) validate the best in vitro drug combinations in vivo in zebrafish and mouse models.

Recent data have shown that combinations of PI3K-FGFR and PI3K-CDK4/6 inhibitors demonstrated synergistic effects in 2D NB/MB lines, allowing for reduced drug doses compared to single treatments. Preliminary results from 3D NB cultures are promising and align with the findings from the 2D models.

Therefore, this project aims to accelerate the development of optimized combination therapies for NB/MB, addressing resistance to conventional treatments and improving both patient survival and quality of life through more effective, lower-dose treatments.

My team is also working in close collaboration with Tina Dalianis group which is focused on targeted therapy in head and neck cancer

A selection of publications from your group

- Lukoseviciute M, Need E, Birgersson M, Dalianis T, Kostopoulou ON. Enhancing targeted therapy by combining PI3K and AKT inhibitors with or without cisplatin or vincristine in medulloblastoma cell lines in vitro. Biomedicine and Pharmacotherapy, 180, 117500, 2024.
- Lukoseviciute M, Need E, Holzhauser S, Dalianis T, Kostopoulou ON. Combined targeted therapy with PI3K and CDK4/6, or FGFR inhibitors show synergistic effects in a neuroblastoma spheroid culture model. Biomedicine and Pharmacotherapy, 177, 116993, 2024.
- Lukoseviciute M, Holzhauser S, Pappa E, Mandal T, Dalianis T, Kostopoulou ON. Efficacy of combined targeted therapy with PI3K and CDK4/6 or PARP and WEE1 inhibitors in neuroblastoma cell lines. Oncology Reports, 50, 3, 2023

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Cancer Research Area

- Lung Cancer

Key research field interests

- microRNAs
- mRNAs
- Liquid biopsies
- Whole exome sequencing
- Tissue biopsies

Needs for collaborations

- Bioinformatics expertise

Multi-omics uncovers signatures associated with resistance to osimertinib in EGFR-mutant non-small cell lung cancer patients

Per Hydbring

Introduction: Targeted therapy with tyrosine kinase inhibitors (TKIs) against Epidermal Growth Factor Receptor (EGFR) is part of clinical routine for around 10-15% of advanced non-small cell lung cancer (NSCLC) patients with tumors harboring activating mutations in the kinase domain of EGFR. Osimertinib is a third-generation EGFR TKI displaying potency to both activating kinase domain EGFR mutations and the T790M gatekeeper mutation. Osimertinib is approved by the FDA and EMA for usage in the first line setting to NSCLC patients with EGFR activating mutations regardless of presence of T790M. Despite improved clinical response following osimertinib treatment compared to treatment with first-generation EGFR TKIs, resistance is inevitable. Intriguingly, a significant fraction of resistant cases following osimertinib treatment cannot be linked to additional genetic aberrations. We have analyzed if circulating RNAs, including mRNAs and microRNAs, as well as circulating proteins could provide clues of molecular factors associated with acquired resistance to osimertinib.
Results and Conclusions: Systematic transcriptome profiling revealed hundreds of differentially expressed mRNA transcripts, adjusted p-value <0.05, while only 13 microRNAs and 21 proteins displayed differential expression using an identical statistical cutoff. Interestingly, 20 out of 21 differentially expressed proteins were upregulated at disease progression while 12 out of 13 differentially expressed microRNAs were downregulated at disease progression. Baseline samples clustered in a distinct manner compared to samples from disease progression when using mRNAs and lncRNAs as input. We are currently investigating the therapeutic impact of modulating the expression of top-candidate RNAs and proteins in model systems with acquired resistance to osimertinib. Our study demonstrates the usage of circulating RNAs and proteins from plasma to unveil resistance signatures to the third-generation TKI osimertinib. Furthermore, it highlights the involvement of multiple RNAs and proteins of potential functional impact in osimertinib-refractory NSCLC patients.

A selection of publications from your group

- Alexeyenko A, Brustugun OT, Eide IJZ, Gencheva R, Kosibaty Z, Lai Y, De Petris L, Tsakonas G, Grundberg O, Franzen B, Viktorsson K, Lewensohn R, Hydbring P#, Ekman S#. Plasma RNA profiling unveils transcriptional signatures associated with resistance to Osimertinib in EGFR T790M positive non- small cell lung cancer patients. Translational Lung Cancer Research, 11:10 2064-2078, 2022. #Shared last author. PMID: 36386450.
- Kazmierczak D, Eide IJZ, Gencheva R, Lai Y, Lewensohn R, Tsakonas G, Grundberg O, de Petris L, McGowan M, Brustugun OT, Ekman S, Hydbring P. Elevated expression of miR-494-3p is associated with resistance to osimertinib in EGFR T790M-positive non-small cell lung cancer. Translational Lung Cancer Research, 11:5 722-734, 2022. PMID: 35693293.
- Tsakonas G, Lewensohn R, Botling J, Ortiz-Villalon C, Micke P, Friesland S, Nord H, Lindskog M, Sandelin M, Hydbring P#, Ekman S#. An immune gene expression signature distinguishes central nervous system metastases from primary tumours in non-small-cell lung cancer. European journal of cancer (Oxford, England : 1990), 132: 24-34, 2020. #Shared last author. PMID: 32325417.

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Cancer Research Area

- Basic Research
- Breast
- Kidney (renal cell) and Urinary Tract

Key research field interests

Needs for collaborations

A selection of publications from your group

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Cancer Research Area

- Late-complications

Key research field interests

- Radiotherapy
- Chondrocyte
- Cartilage
- Childhood cancer
- Late-complication

Needs for collaborations

- Clinical material
- Shared concepts between tissues

Understanding and preventing radiation-induced skeletal late-complications

Phillip Newton

Radiotherapy during childhood and adolescence can severely damage the growing skeleton, with acute toxicity eventually leading to skeletal late-complications. Skeletal late-complications have varying severity including short stature, limb length-differences, irregular body proportions and spinal curvature. Unfortunately, when the skeleton stops growing at the end of puberty these changes become permanent. The impact of these skeletal malformations varies but can hamper routine activities and cause chronic pain. With improved survival rates, increasing life-expectancies and limited treatment options, affected individuals suffer from these side-effects throughout their adult lives. We aim to reveal the underlying mechanisms by which growth plates regenerate after irradiation damage, establish more clinically-relevant laboratory models to study skeletal late-complications, and attempt rescue experiments using preventative strategies with a clear route to the patient.

A selection of publications from your group

- A protocol to differentiate the chondrogenic ATDC5 cell-line for the collection of chondrocyte-derived extracellular vesicles. Marchan-Alvarez JG, Teeuwen L, Mamand DR, Gabrielsson S, Blomgren K, Wiklander OPB, Newton PT. J Extracell Biol. 2024 Sep 5;3(9):e70004.
- Spatially resolved transcriptomic profiling of degraded and challenging fresh frozen samples. Mirzazadeh R, Andrusivova Z, Larsson L, Newton PT, Galicia LA, Abalo XM, Avijgan M, Kvastad L, Denadai-Souza A, Stakenborg N, Firsova AB, Shamikh A, Jurek A, Schultz N, Nistér M, Samakovlis C, Boeckxstaens G, Lundeberg J. Nat Commun. 2023 Jan 31;14(1):509.
- Altered developmental programs and oriented cell divisions lead to bulky bones during salamander limb regeneration. Kaucka M, Joven Araus A, Tesarova M, Currie JD, Boström J, Kavkova M, Petersen J, Yao Z, Bouchnita A, Hellander A, Zikmund T, Elewa A, Newton PT, Fei JF, Chagin AS, Fried K, Tanaka EM, Kaiser J, Simon A, Adameyko I. Nat Commun. 2022 Nov 14;13(1):6949.

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Cancer Research Area

- Pancreatic cancer
- Preclinical

Key research field interests

- Pancreatic ductal adenocarcinoma
- Tumor-stroma crosstalk / interaction
- Therapy resistance
- Drug screening

Needs for collaborations

Preclinical Pancreatic Cancer

Rainer Heuchel

We are interested in the biology of pancreatic ductal adenocarcinoma with a main focus on the tumor-stroma interactions. To this end we have developed a 3D heterospheroid model including human pancreatic cancer cells and mouse pancreatic stellate cells (CAFs) allowing the direct investigation of their crosstalk by expression profiling without any prior manipulation such as single cell preparation. We have adapted this model (then human/human) for high throughput drug screening in collaboration with the Chemical Biology Consortium Sweden (CBCS) and developed an imaging application as an optical reporter assay for viability as well as phenotypical shift determination (CAF-like ⇆ cancer cell-like). A major aim of the drug screen was to uncover metabolic vulnerabilities of the cancer cells by modulating the mouse pancreatic stellate cells (CAFs) in their nutritional support of the cancer cells. One hit has e.g. the potential of greatly increasing the potency of Gemcitabine, a long established PDAC drug, allowing to significantly reduce the toxic side effects at the same time.

A selection of publications from your group

- The Crosstalk Analysis between mPSCs and Panc1 Cells Identifies CCN1 as a Positive Regulator of Gemcitabine Sensitivity in Pancreatic Cancer Cells. Gündel B, Liu X, Pfützenreuter A, Engelsberger V, Weiskirchen R, Löhr JM, Heuchel R.Int J Mol Sci. 2024 Aug 29;25(17):9369. PMID: 39273316
- Liu X, Gündel B, Li X, Liu J, Wright A, Löhr M, Arvidsson G, Heuchel R: 3D heterospecies spheroids of pancreatic stroma and cancer cells demonstrate key phenotypes of pancreatic ductal adenocarcinoma. Transl Oncol 2021, 14(7):101107. PMID: 33201660
- Norberg KJ, Liu X, Fernandez Moro C, Strell C, Nania S, Blumel M, Balboni A, Bozoky B, Heuchel RL, Löhr JM: A novel pancreatic tumour and stellate cell 3D coculture spheroid model. BMC Cancer 2020, 20(1):475. PMID: 32460715

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Cancer Research Area

- Basic Research

Key research field interests

Needs for collaborations

Effects of hypoxia in physiological and pathological contexts, Hypoxia Inducible Factors (HIF)

Randall Johnson

A selection of publications from your group

Richard Rosenquist Brandell

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Cancer Research Area

- Hematological malignancies

Key research field interests

- Chronic lymphocytic leukemia
- Genomics
- Therapy resistance
- Prognostic/predictive biomarkers
- Precision medicine

Needs for collaborations

Charting the complex molecular landscape in chronic lymphocytic leukemia: the path towards precision medicine

Richard Rosenquist Brandell

Chronic lymphocytic leukemia (CLL) is highly heterogeneous in terms of its biological background and clinical outcome. Although new targeted drugs have been approved in recent years (e.g. BTK and BCL2 inhibitors), CLL is still an incurable disease with an urgent need for novel therapies and predictive biomarkers for high-risk patients. To bridge this knowledge gap, we believe that the best strategy is to identify patient subgroups with distinct features that respond differently to therapy. Based on the concept of B cell receptor stereotypy, we have proposed a novel molecular classification of unique patient subsets that display remarkably similar clinical and biological features. Taking advantage of our large CLL cohort, we will apply an array of high-throughput technologies (HTPs), including single-cell sequencing, to investigate clinically relevant subsets and follow the disease evolution. Through integrative multi-omics analyses, we will map patient-specific alterations in the genome, transcriptome and methylome, thus gaining detailed insight into the spectrum and interconnection of molecular events occurring in patients belonging to CLL subsets. Additionally, we will apply proteo-genomic approaches to assess our findings in the context of dysregulated signaling pathways and other regulatory processes. This newly acquired knowledge will be translated into drug discovery where putative targets will be investigated using an HTP drug sensitivity screening approach. The availability of longitudinal samples enables us to determine whether molecular changes occur over time that will assist in identifying factors linked to the development of resistance to targeted therapy. Findings from this proposal will be implemented in routine diagnostics through the SciLifeLab Clinical Genomics platform and Genomic Medicine Sweden. In summary, this comprehensive molecular characterization will lead to significantly improved risk stratification, and the identification of new predictive biomarkers and treatment strategies, hence paving the way for precision medicine approaches in CLL.

A selection of publications from your group

- Mansouri L, Thorvaldsdottir B, Sutton LA, Karakatsoulis G, Meggendorfer M, Parker H,..., Rosenquist R. Different prognostic impact of recurrent gene mutations in chronic lymphocytic leukemia depending on IGHV gene somatic hypermutation status: a study by ERIC in HARMONY. Leukemia. 2023 Feb;37(2):339-347.
- Bonfiglio S, Sutton LA, Ljungström V, Capasso A, Pandzic T, Weström S, Foroughi-Asl H, S, ..., Rosenquist R#, Ghia P#. BTK and PLCG2 remain unmutated in one third of patients with CLL relapsing on ibrutinib. Blood Adv. 2023 Jun 27;7(12):2794-2806. #Contributed equally.
- Hägerstrand D, Oder B, Cortese D, Qu Y, Binzer-Panchal A, Österholm C, Del Peso Santos T, ..., Rosenquist R. The non-canonical BAF chromatin remodeling complex is a novel target of spliceosome dysregulation in SF3B1-mutated chronic lymphocytic leukemia. Leukemia. 2024 Nov;38(11):2429-2442.

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Cancer Research Area

- Lung

Key research field interests

Needs for collaborations

Precision cancer medicine and precision radiotherapy in lung cancer - from molecular mechanisms/biomarkers to clinical trials

Rolf Lewensohn

A selection of publications from your group

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Cancer Research Area

- Basic Research
- Childhood leukemias
- Blood Cancer

Key research field interests

- Mass spectrometry-based proteomics
- Multi-omic analysis of cancer
- Precision therapy of cancer
- Drug development
- Data-driven life science

Needs for collaborations

- Access to suitable clinical material
- Pre-clinical and translational models

Phenotype centered multi-omics analysis of childhood ALL for precision therapies

Rozbeh Jafari

Acute lymphoblastic leukemia, the most common childhood cancer, results from the accumulation of immature blasts in the bone marrow. Despite high survival rates, patients face poor long-term health outcomes due to standard treatments that often lack precision and compromise tolerability.

Our research aims to improve treatment options by identifying phenotypes linked to drug sensitivity. Using mass-spectrometry-based proteomics, we characterize leukemia biology and pair these insights with drug sensitivity profiling to uncover mechanisms for precision therapies.

Our comprehensive multi-omics profiling of childhood ALL cell lines (https://proteomics.se/forall/) allowed us to obtain unprecedented molecular dissection of leukemia phenotypes, which we have pursued to identify new precision therapy approaches. First, we identified lineage-dependent drug sensitivity correlations and the DAG-analog bryostatin-1 as a therapeutic candidate in MEF2D-rearranged high-risk subtype (1). Second, we identified that triciribine, an adenosine analog pro-drug, could potentially have a clinical applicability in leukemia subtypes overexpressing adenosine kinase (ADK), the enzyme responsible for activating triciribine. Third, using thermal proteome profiling for drug target identification we identified novel targets (e.g. TYMS and NSUN2/6) for widely used hypomethylating agents azacitidine and decitabine, shedding more light on their mechanism (2). Using thermal proteomics, we developed an approach to stratify the cellular proteome into functional proteoform groups. This method revealed differences in proteoform-proteoform interactions and associations between proteoform groups and specific drug responses in ALL cell lines (3). We applied this approach to resolve drug target landscapes at the proteoform level. For example, in analyzing ibrutinib, we uncovered novel protein interactions, such as with BRAF, and demonstrated that cancer drugs can interact differently with distinct forms of the same protein (e.g., WASHC2C) (4).

We are expanding our sample pool to include translational models and integrating whole-genome sequencing, epigenetic profiling, and post-translational modification analysis. These efforts, combined with our proteoform-level deconvolution of the ALL proteome, aim to provide a data-driven, comprehensive understanding of childhood ALL biology advancing precision medicine capabilities for childhood ALL patients.

A selection of publications from your group

- Leo IR, et al. Integrative multi-omics and drug response profiling of childhood acute lymphoblastic leukemia cell lines. Nat Commun 13, 1691 (2022).
- Cheung LC, et al. Preclinical efficacy of azacitidine and venetoclax for infant KMT2A-rearranged acute lymphoblastic leukemia reveals a new therapeutic strategy. Leukemia, (2022).
- Kurzawa N, et al. Deep thermal profiling for detection of functional proteoform groups. Nat Chem Biol 19, 962-971 (2023).
- Leo I, et al. Functional proteoform group deconvolution reveals a broader spectrum of ibrutinib offtargets. Nat Commun, 2025 (in press).

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Cancer Research Area

- Basic research
- Blood cancer

Key research field interests

- Cancer therapy
- Antimetabolites
- Genome Stability
- Nucleotide metabolism
- Drug resistance

Needs for collaborations

- Advanced/near-patient disease models
- Clinical material

Towards precision cancer medicine with conventional chemotherapy – a focus upon molecular mechanism

Sean Rudd

The Rudd lab is a curiosity-driven research group interested in nucleotide metabolism and molecular pharmacology, and we apply these interests to better understand how current cancer therapies work to inform optimal mechanism-based use.

Many commonly used cancer therapies kill tumour cells by targeting pan-essential pathways, principally metabolism of the DNA molecule or its deoxynucleoside triphosphate (dNTP)building blocks. In our research program we aim to define the molecular underpinnings of why some cancers respond to these therapies whilst others do not. This information can provide the basis for rational therapy improvements through the identification of biomarkers and therapeutic targets together with the design of mechanism-based drug combinations. We employ a multidisciplinary approach in our research – centred upon biochemical, biophysical, and cell-based methods – and use both hypothesis-driven and hypothesis-free approaches in our efforts to define and exploit the molecular mechanisms underpinning clinical efficacy of chemotherapeutic agents.

The utility of this approach was underscored by our work on chemoresistance in acute myeloid leukaemia. Following identification of a key regulator of dNTP metabolism as a chemoresistance factor, we have conducted biochemical and phenotypic screening campaigns to identify small molecules to inactive this enzyme in cancer cells, with one approach now under clinical testing. In a parallel project, to decipher the mode-of-action of a nucleoside analogue in leukaemia treatment, we have conducted a series of thermal proteome profiling experiments and whole-genome CRISPR screens working with the CBGE platform at SciLifeLab, to systematically map out the drug interactome together with sensitisation and resistance factors, and we are currently following up these data.

Methods in the group include biochemical & biophysical assays with recombinant enzymes, cell-based assays to monitor ligand-target binding, drug sensitivity assays in cell lines, dNTP pool measurements, many phenotypic assays related to dNTP metabolism and the DNA damage response.

A selection of publications from your group

- Wang J, Strauss R, Bartek J, Rudd SG. Glutamine-addiction in cisplatin resistant cancer cells is mediated by SLC7A11 and can be targeted with asparaginase therapy. 2024 bioRxiv doi: 10.1101/2024.07.19.604261
- Zhang SM, Paulin CBJ, Shu H, Yagüe-Capilla M, Michel M, Marttila P, Ortis F, Bwanika HC, Dirks C, Venkatram RP, Wiita E, Jemth AS, Almlöf I, Loseva O, Hormann FM, Koolmeister T, Linde E, Lee S, Llona-Minguez S, Haraldsson M, Axelsson H, Strömberg K, Homan EJ, Scobie M, Lundbäck T, Helleday T, Rudd SG. Identification and evaluation of small-molecule inhibitors against the dNTPase SAMHD1 via a comprehensive screening funnel. 2024. iScience, 27;2 108907.
- Rudd SG. Targeting pan-essential pathways in cancer with cytotoxic chemotherapy: Challenges & opportunities. Cancer Chemotherapy & Pharmacology 2023 92(4):241-251

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Cancer Research Area

- Hematology

Key research field interests

- Hematopoiesis
- Innate lymphoid cells
- Clonal hematopoiesis
- Myeloid malignancies

Needs for collaborations

- Seeking collaborations to study ILC2s in different cancer models

Regulation of normal and malignant hematopoiesis by Group 2 innate lymphoid cells

Sergio Martinez-Høyer

Group 2 innate lymphoid cells (ILC2s) are key regulators of Type 2 immune responses, which are commonly associated with allergic reactions and parasite defense. These cells are highly responsive to alarmins released from damaged epithelial cells, such as IL-33, and are found throughout the body, including in the bone marrow. However, the role of ILC2s in the bone marrow is not fully understood. Our observations suggest that, during Type 2 inflammation, ILC2s in the bone marrow become activated and influence hematopoiesis. We hypothesize that, in the context of clonal hematopoiesis, the activation of bone marrow ILC2s may promote the expansion of mutant hematopoietic stem cell (HSC) clones.

ILC2s are also known to play critical roles in tissue repair processes, including fibrosis. Type 2 immune signaling has recently been implicated in the development of bone marrow fibrosis, though the specific cellular sources driving the initiation and maintenance of this response remain unclear. Our preliminary data indicate that ILC2s are activated in the early stages of bone marrow fibrosis in various mouse models. We propose that, upon expansion of mutant HSCs, ILC2s in the bone marrow become activated and contribute to the Type 2 immune response, which may drive the onset of bone marrow fibrosis.

Emerging evidence suggests that ILC2s play important roles in cancer, where they can either promote or inhibit tumor progression depending on the context. Our research aims to better understand the functions of ILC2s in tumor biology, with the goal of exploring their potential as therapeutic targets.

A selection of publications from your group

- Mathä L*, Krabbendam L*, Martinez Høyer S*, et al. Human CD127 negative ILC2s show immunological memory. J Exp Med. 2024;221(8):e20231827. doi:10.1084/jem.20231827. *Equal contribution.
- Martinez-Høyer S, Deng Y, Parker J, et al. Loss of lenalidomide-induced megakaryocytic differentiation leads to therapy resistance in del(5q) myelodysplastic syndrome. Nat Cell Biol. 2020;22(5):526-533. doi:10.1038/s41556-020-0497-9

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Cancer Research Area

- Cancer Epidemiology
- Gastrointestinal Cancer

Key research field interests

- Oesophageal cancer
- Stomach cancer
- Liver cancer
- Cancer aetiology
- Precision prevention

Needs for collaborations

- Bio-samples
- Molecular expertise
- Omics data analysis

Risk-adapted prevention of upper gastrointestinal cancer

Shaohua Xie

Upper gastrointestinal cancer is common globally and carries a poor prognosis, stressing the great need for effective prevention strategies. We propose a risk-adapted concept for prevention of upper gastrointestinal cancer which is based on the best available scientific evidence and assigns the most appropriate preventive measures according to individualised risk assessment.

The overarching aim of our research is to provide evidence that will support tailored prevention of upper gastrointestinal cancer according to individuals' risk profile. Specifically, we aim to:

- Better understand the causes of upper gastrointestinal cancer;
- Develop and validate risk prediction models;
- Assess potential prevention approaches including chemoprevention; and
- Optimize surveillance of high-risk individuals.

We have found interesting associations between sex hormonal exposures and risk of esophageal and gastric cancer, and will further investigate whether such associations are causal and pinpoint the specific contributing hormones.

We have developed several prediction models for projecting individuals' future risk of esophageal cancer with good performance. We will further validate these models in external populations and assess whether including certain protein biomarkers can improve the predictiveness of these models.

The epidemiology of primary liver cancer in Nordic countries (particularly Sweden) differs from that in other populations such as the United States and Asian countries. We have started to work on the etiology and prevention of liver cancer in Nordic countries.

Our research has been mainly based on population-based cohort and case-control studies, and data from the unique health data registries in Nordic countries.

A selection of publications from your group

- Circulating Sex Hormone Levels and Risk of Esophageal Adenocarcinoma in a Prospective Study in Men. Am J Gastroenterol 115(2):216-223. (2020)
- Association Between Levels of Sex Hormones and Risk of Esophageal Adenocarcinoma and Barrett's Esophagus. Clin Gastroenterol Hepatol 18(12):2701-2709. (2020)
- Assessing the feasibility of targeted screening for oesophageal adenocarcinoma based on individual risk assessment in a population-based cohort study in Norway (The HUNT Study). Am J Gastroenterol 113(6):829-835. (2018)

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Cancer Research Area

- Lung
- Brain and Nervous System

Key research field interests

Needs for collaborations

Precision Cancer Medicine in Lung Cancer - Preclinical, Translational & Clinical Research

Simon Ekman

A selection of publications from your group

Simon Elsässer

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Cancer Research Area

- Cancer diagnostics

Key research field interests

- Cancer Epigenomics
- Biomarkers
- Non-canonical Translation

Needs for collaborations

- Liquid biopsies,
- Clinical Material

Profiling circulating nucleosomes as epigenetic biomarkers in health and disease: Method development, pilot studies and plans for cancer diagnostics

Simon Elsässer

Cell-free DNA and nucleosomes (cfDNA, cfNUC) circulate in the blood stream of animals due to normal tissue turnover. Accelerated growth and cell death in tumors leads to an overproportional contribution of molecules into the blood of patients. Circulating nucleosomes carry the same epigenetic modifications that the originating chromatin, hence providing a cross-section of the epigenetic state of the individual. Based on a multiplexed ChIP-seq protocol originally established in my laboratory and commercialized in a spin-off company, we have developed a multiplexed quantitative epigenome profiling platform for liquid biopsy material, validated on blood serum and plasma, as well as ascite fluid.

A selection of publications from your group

- Schlesinger S, Dirks C, Navarro C, Lafranchi L, Eirich J, Elsässer SJ, "A large-scale sORF screen identifies putative microproteins and provides insights into their interaction partners, localisation and function", bioRxiv (2023), iScience (accepted)
- Lafranchi L, Spinner A, Hornisch M, Schlesinger S, Navarro C, Brinkenstråhle L, Shao R, Piazza I, Elsässer SJ, "Pooled overexpression screen identifies PIPPI as a novel microprotein involved in the ER stress response", bioRxiv (2024)

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Cancer Research Area

- Primary brain cancers

Key research field interests

- Glioblastoma
- Gene therapy
- Lipid nanoparticles
- Single-cell omics

Needs for collaborations

- Nucleic-acid based medicines
- Delivery methods (especially to the brain, e.g. crossing BBB or convection-enhanced delivery)
- Advanced cancer immunotherapies

Towards curative reprogramming of human glioblastoma

Sten Linnarsson

Glioblastoma is the most common malignant primary brain tumor, and the most severe with less than 10% five-year survival (Girardi et al. 2023). The standard treatment of surgery, radiotherapy, and temozolomide chemotherapy (Stupp et al. 2005) fails to cure the disease. No effective targeted therapy exists, despite decades of genomic, transcriptomic and functional characterization, and despite numerous clinical trials of both small molecule and biological drugs that have been effective in other cancers (Weller et al. 2024). Immunotherapies show promise but have not yet yielded breakthroughs (Agosti et al. 2023).

In collaboration with Oscar Persson (KI), we have mapped human glioblastoma using single-cell RNA-seq, discovering that previously claimed 'mesenchymal' cell states instead represent a futile wound response affecting tumor and non-tumor cells alike. Next, we sampled glioblastoma tumors beyond the contrast-enhancing region and found drastic differences between core and periphery, involving both tumor cells (more proliferative, less differentiated, less wound reactive in the periphery) and immune cells (dominated by microglia in the periphery, macrophages in the core).

Based on this improved understanding of the tumor composition, my group is pursuing a novel approach of targeting the tumor using highly specific and active DNA vectors, delivered using lipid nanoparticles (LNPs). Specificity can be achieved using oncospecific enhancers or by exploiting tumor-specific properties such as proliferation. Once DNA is successfully delivered totumor cells, they can be directly killed e.g. using Gasdermin membrane channels, or reprogrammed to attract a potent immune response (e.g. by reprogramming to dendritic cells as in Ascic et al. 2024).

In preliminary findings, we have discovered more than a hundred oncospecific enhancers in glioblastoma, and developed fully synthetic DNA LNP formulations that efficiently transfect human glioblastoma in a xenotransplantation model. Using these and other tools, we will pursue tumor direct reprogramming as a therapeutic strategy in human glioblastoma.

A selection of publications from your group

- Alejandro Mossi Albiach, Jokubas Janusauskas, Ivana Kapustová, Egle Kvedaraite, Simone Codeluppi, Johannes B. Munting, Lars E. Borm, Jesper Kjaer Jacobsen, Alia Shamikh, Oscar Persson and Sten Linnarsson. Glioblastoma is spatially organized by neurodevelopmental programs and a glial-like wound healing response. bioRxiv 2023 10.1101/2023.09.01.555882
- Siletti K, Hodge R, Mossi Albiach A, Lee KW, Ding SL, Hu L, Lönnerberg P, Bakken T, Casper T, Clark M, Dee N, Gloe J, Hirschstein D, Shapovalova NV, Keene CD, Nyhus J, Tung H, Yanny AM, Arenas E, Lein ES, Linnarsson S. Transcriptomic diversity of cell types across the adult human brain. Science. 2023 Oct 13;382(6667):eadd7046. doi:10.1126/science.add7046.
- Braun E, Danan-Gotthold M, Borm LE, Lee KW, Vinsland E, Lönnerberg P, Hu L, Li X, He X, Andrusivová Ž, Lundeberg J, Barker RA, Arenas E, Sundström E, Linnarsson S. Comprehensive cell atlas of the first-trimester developing human brain. Science. 2023 Oct 13;382(6667):eadf1226. doi:10.1126/science.adf1226

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Cancer Research Area

- Neuroblastoma
- Paraganglioma

Key research field interests

- Neuroblastoma
- Paraganglioma
- Plasticity
- Heterogenety
- Oxygen sensing

Needs for collaborations

- Tumor material

Neuroblastoma and paraganglioma cell stage dynamics and plasticity in tumor formation and therapy resistance

Susanne Schlisio

Acquired cancer therapy resistance is the direct consequence of intratumor heterogeneity. Intratumor heterogeneity is a hallmark of high-risk pediatric neuroblastoma (NB) and malignant paraganglioma which underpins dismal prognosis and treatment outcomes. Apart from a well-recognized "genetic mosaicism", when tumors are comprised of several clones with distinct mutations, neuroblastomas have recently been shown to exhibit striking phenotypic drift upon treatment and changes in local microenvironment. Denoted as "tumor plasticity", the latter phenomenon does not appear to stem from de novo genetic mutations but is rather driven by complex transcriptional rearrangements in neuroblastoma cells triggered by still poorly understood signaling clues. Phenotypic plasticity thus comprises a new dimension of intratumor heterogeneity, mechanisms of which need to be properly understood to develop more efficient treatments. Here we introduce a analytic approach based on space-resolved single nuclei transcriptomics with integrated mass spectrometry on human and mouse neuroblastoma samples. Our work is supplemented by mechanistic studies in animal neuroblastoma and paraganglioma models, enabling comparative differentiation trajectory analysis and lineage tracing of tumor subpopulations.

Unique instruments and methodologies used in the group:
- Single-cell RNA-seq
- Space-resolved transcriptomics (Visum HD, ISS)
- Transgenic neuroblastoma and paraganglioma mouse models
- Mutation analysis

A selection of publications from your group

- Li S, Li W, Yuan J, Bullova P, Wu J, Zhang X, Liu Y, Plescher M, Rodriguez J, Bedoya-Reina OC, Jannig PR, Valente-Silva P, Yu M, Henriksson MA, Zubarev RA, Smed-Sörensen A, Suzuki CK, Ruas JL, Holmberg J, Larsson C, Christofer Juhlin C, von Kriegsheim A, Cao Y, S. SCHLISIO. Impaired oxygen-sensitive regulation of mitochondrial biogenesis within the von Hippel-Lindau syndrome. Nature Metabolism. 2022 Jun;4(6):739-758.
- O. C. Bedoya-Reina, W. Li, M. Arceo, M. Plescher, P. Bullova, H. Pui, M. Kaucka, P. Kharchenko, T. Martinsson, J. Holmberg, I. Adameyko, Q. Deng, C. Larsson, C. C. Juhlin, P. Kogner and S. SCHLISIO. Single-nuclei transcriptomes from human adrenal gland reveal distinct cellular identities of low and high-risk neuroblastoma tumors. Nature Communications. 2021 Sep 7;12(1):5309
- Bedoya-Reina OC, SCHLISIO S. Chromaffin Cells with Sympathoblast Signature: Too Similar to Keep Apart? Cancer Cell. 2020 Dec 28:S1535-6108(20)30657-7.

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Cancer Research Area

- Hereditary Cancer Risk Syndromes with focus on germline TP53 and germline CDH1

Key research field interests

- Li-Fraumeni Syndrome
- Germline TP53
- Genotype-phenotype
- Riskprediction and surveillance
- Polygenic risk score

Needs for collaborations

Previvors of hereditary cancer risk syndromes with focus on the Swedish gTP53 cohort

Svetlana Bajalica Lagercrantz

In Cancer care, the health care system is mainly focused on treatment and evaluate its success in terms of survival and survivors. The focus in the field of hereditary cancer and in families with inherited cancer risk is on cancer prevention in terms of surveillance and risk reducing measures. Such previvors, commonly healthy individuals but with extreme cancer risk, become consumer of health care prior to a cancer diagnose. This scope of my research is to improve the clinical handling of previvors with a germline TP53 (gTP53), with a 70-100% lifetime risk to develop a tumor. Also, to increase the understanding of genotype-phenotype presentations of hTP53rc and highlight differences and similarities between certain family phenotypes. We have collected a Swedish gTP53 cohort with a total of 82 families consisting of 175 variant carriers harboring 47 different gTP53 variants from all seven hereditary cancer units in Sweden tested during the period January 2000 - March 2022. A genotype-phenotype characterization has shown that 65% of the families have an increased risk for early onset breast cancer, sarcomas, brain tumors and adrenocortical carcinomas, commonly during childhood. The remaining 35% of the families appear to have an exclusive risk for breast cancer. We want to further explore genomic, epigenetic and proteomic factors to explain the vide variety of phenotypic presentations. A phenotypic prediction would add granularity to personalized risk modeling with potential implications for tailored screening regimes.
Moreover, we have since 2016 included Swedish TP53-carriers in surveillance and clinical follow-up within the national Swedish TP53 Study (SWEP53) with nearly 100 participants included, around 80 adults and 20 children. These are followed with intensive surveillance programs including yearly whole-body MRI in adulthood. Also a questionnaires for psychosocial evaluation of the surveillance program is continuously collected and analyzed.

A selection of publications from your group

- Omran M.*, Blomqvist L., Brandberg Y., Pal N., Kogner P., Stahlbom AK., Tham E., Bajalica-Lagercrantz S. Whole-body MRI within a surveillance program for carriers with clinically actionable germline TP53 variants - the Swedish constitutional TP53 study SWEP53. Hereditary cancer in clinical practice. 2020;18(1):1–1.
- Omran M.*, Tham E., Brandberg Y., Ahlström H., Lundgren C., Paulsson-Karlsson Y., Kuchinskaya E., Silander G., Rosén A., Persson F., Leonhardt H., Stenmark-Askmalm M., Berg J., van Westen D., Bajalica-Lagercrantz S. and Blomqvist L. Whole-Body MRI Surveillance-Baseline Findings in the Swedish Multicentre Hereditary TP53-related Cancer Syndrome Study (SWEP53). Cancers (Basel). 2022;14(2):380–.
- Omran M.*, Johansson H., Lundgren C., Silander G., Stenmark-Askmalm M., Loman N., Baan A., Adra J., Kuchinskaya E., Blomqvist L., Tham E., Bajalica-Lagercrantz S., and Brandberg Y. Whole-body MRI surveillance in TP53 carriers is perceived as beneficial with no increase in cancer worry regardless of previous cancer – data from the SWEP53 study. Cancer. 2023; 1-10

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Cancer Research Area

- Basic cancer research
- Gastrointestinal tract cancer

Key research field interests

- p53
- Tumor suppression
- Inflammation
- Microbiota
- Oncogenic bacteria

Needs for collaborations

- We always welcome collaborators that can provide precious clinical material or patient data, especially in the field of colorectal cancer, to complement our own expertise at the molecular level.

Deciphering the links between oncogenic bacteria and cancer for innovative therapies

Sylvain Peuget

Our lab aims to investigate the molecular interplay linking microbiota and cancer, with a focus on the regulation of the key tumor suppressor protein p53 by bacteria. Over the last decade, dysregulation of the microbiome has been recognized as an enabling characteristic of cancer. Moreover, growing evidence highlights that microbiota dysregulation can significantly influence various stages of cancer, from initiation to therapeutic response. However, the precise molecular mechanisms by which bacteria contribute to tumorigenesis are still largely unknown.
To address this gap, our lab investigates how certain bacteria modulate the p53 pathway and its consequence for carcinogenic processes. Notably, we examine how cancerassociated bacteria can disrupt p53 function either through inflammatory response or by secreting p53-targeting toxins. For instance, we have shown that inflammation induced by *Klebsiella pneumoniae*, a putative oncogenic bacterium, can impair p53 tumor suppressive function under genotoxic and oncogenic stress, effectively lowering the barrier against cancer progression in absence of p53 mutation. Additionally, we are identifying and characterizing specific bacterial systems responsible for p53 inhibition and analyzing their contribution to tumorigenic processes, both in vitro and in animal studies in mice. Ultimately, our research aims to identify novel molecular targets that account for microbiota-cancer interactions, either from the host or the microbiota, paving the way for innovative cancer therapies.

A selection of publications from your group

- Translating p53-based therapies for cancer into the clinic. Peuget S, Zhou X, Selivanova G. Nat Rev Cancer. 2024 Mar;24(3):192-215. PMID: 38287107
- Enterobacteria impair host p53 tumor suppressor activity through mRNA destabilization. Aschtgen MS, Fragkoulis K, Sanz G, Normark S, Selivanova G, Henriques-Normark B, Peuget S. Oncogene. 2022 Apr;41(15):2173-2186. PMID: 35197571
- Pifithrin-α alters p53 post-translational modifications pattern and differentially inhibits p53 target genes. Zhu J, Singh M, Selivanova G, Peuget S. Sci Rep. 2020 Jan 23;10(1):1049. PMID: 31974452

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Cancer Research Area

- Breast

Key research field interests

Needs for collaborations

Theodoros Foukakis

A selection of publications from your group

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Cancer Research Area

- Epidemiology and Biostatistics

Key research field interests

- Survival
- Register-based
- Statistical methods
- Epidemiology

Needs for collaborations

- Clinical expertise

Statistical Methods For Cancer Patient Survival

Therese Andersson

I am a biostatistician, working with statistical methods for cancer epidemiology. My main research interest is cancer patient survival and I have published studies on cancer patient survival for a range of cancer sites. I develop statistical methods as well as apply the methods to register-based data. I have also worked on international benchmarking of cancer patient survival, for example the International Cancer Benchmarking Partnership SURVMARK-2, run by the International Agency for Research on Cancer (IARC) and in Nordic collaborative projects.
I have developed methods for estimating the life expectancy and loss in life expectancy (LLE) for cancer patients, and further extend and evaluate the methodology to enable use of the measure in different contexts. Life expectancy is calculated by obtaining the area under a survival curve. Life expectancy is a well-established, easily understood concept that quantifies the expected number of life years remaining. In comparison to many other measures, it takes the whole time scale into account instead of at particular points during follow-up (such as the 1- or 5-year survival). Another statistic, closely related to the life expectancy, is the LLE, a measure of how much a patient's life expectancy is reduced due to a cancer diagnosis. The LLE can be used to address a wide range of research questions on both individual and population levels, and to quantify survival differences between groups. Another use of LLE is to quantify the burden of cancer on society as the total number of life years lost in the population in this way, it can be useful for measuring cancer control progress and to provide guidance for resource allocation.

A selection of publications from your group

- Andersson TM-L; Myklebust TA; Rutherford MJ; Moller B; Arnold M; Soerjomataram I; Bray F; Parkin DM; Lambert PC. Five ways to improve international comparisons of cancer survival: lessons learned from ICBP SURVMARK-2. BRITISH JOURNAL OF CANCER. 2022;126(8):1224-1228
- Lundberg FE; Birgisson H; Engholm G; Olafsdottir EJ; Morch LS; Johannesen TB; Pettersson D; Lambe M; Seppa K; Lambert PC; Johansson ALV; Holmichj LR; Andersson TM-L. Survival trends for patients diagnosed with cutaneous malignant melanoma in the Nordic countries 1990-2016: The NORDCAN survival studies. EUROPEAN JOURNAL OF CANCER. 2024;202:113980
- Syriopoulou E; Osterman E; Miething A; Nordenvall C; Andersson TM-L. Income disparities in loss in life expectancy after colon and rectal cancers: a Swedish register-based study. JOURNAL OF EPIDEMIOLOGY AND COMMUNITY HEALTH. 2024;78(6):402-408

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Cancer Research Area

- Translational research

Key research field interests

- DNA damage response and repair
- Small molecule inhibitor
- New anti-cancer treatments
- Cancer metabolism
- Translational medicine

Needs for collaborations

MTHFD1/2 inhibitors as a breakthrough anti-cancer treatment

Thomas Helleday

Previously, we pioneered targeting of the DNA damage respone (DDR) with PARP inhibitors in BRCAmut cancers (Bryant et al, 2005). These are now FDA and EMA approved in first-line treatment of breast, ovarian and pancreatic cancers and there are several other DDRi developed that exploit the synthetic lethal concept in treatment of cancer. The success of this treatment was owing to a therapeutic index of 200, which since then not have been achieved. Now, we have developed MTHFD1/2 inhibitors that we demonstrate have a therapeutic index of 100,000, which we nor anyone else have heard of. While this holds fanatsatic opportunity to make a real difference for cancer treatments there remain many challenges and we seek collaborators in the following areas: 1. Identify biomarkers to identify responders from patients' material and using novel techniques. 2. Identify combination treatments that are improving efficacy, targeting resistance mechanisms or expanding responding cancers. 3. Show proof-of-concept in cancer indications. 4. Design and initiate investigator sponsored clinical trials. 5. Identify novel targets that synergize with MTHFD/2i and develop targeted therapeis to those. 6. Identify how the immune response is altered following MTHFD1/2i. 7. Imaging of cancer and activity following treatments. 8. Uncover further detailed mechanisms of action of the compounds and context how they can be used. We truly believe interdisciplinary teams that combines expertise in cancer has the potential to yield groundbreaking insights into cancer biology, fundamental processes, and novel therapies.

A selection of publications from your group

- Bryant, H.E., Schultz, N, Thomas, H.D., Parker, K.M., Flower, D., Lopez, E., Kyle, S., Meuth, M., Curtin, N.J., Helleday, T#. (2005) Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose)polymerase Nature, 434, 913-7.
- Bonagas N, Gustafsson NMS, ... Warpman Berglund U, Homan EJ, Helleday T#. (2022). Targeting MTHFD2 kills cancer via thymineless-induced replication stress. Nature Cancer, 3(2):156-172.
- Green AC, Marttila P, Kiweler N, ..., Helleday T#, Henriksson M#, Meiser J#. (2023). Formate overflow drives toxic folate trapping in MTHFD1-inhibited cancer cells. Nature Metabolism. DOI: 10.1038/s42255-023-00771-5 (# co-correspondent authors)

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Cancer Research Area

- Radiotracers and radiopharmaceuticals developments based on small molecules, peptides, and antibodies for molecular radiotherapy and diagnostics with positron emission tomography (PET), i.e. theranostics. Research spans from cancer target identification, radiochemistry, cyclotron developments to biological evaluations (in vitro and in vivo in animal models) and translational studies with GMP manufacturing of pharmaceuticals for early clinical trials.

Key research field interests

- Targeted radiopharmaceutical therapy
- Molecular imaging with PET and SPECT
- Radiomolecular theranostics
- Targeted alpha therapy
- Antibody-drug conjugates
- Peptide-drug conjugates

Needs for collaborations

Radiopharmaceutical Developments for Translational Theranostics of Cancer Based on Small Ligands, High-affinity Peptides and Antibodies – From Bench to Bedside

Thuy Tran

Our group's research interests are focused on the developments of radiopharmaceuticals, radioactive drugs, for targeted **thera**py and diag**nostics** of cancer, so called theranostics. It refers to a cutting-edge approach "see what you treat and treat what you see" in cancer medicine that combines the therapeutic and diagnostic processes to tailor treatment to individual patients. This approach allows for personalized therapy by ensuring that the right drug is given to the right patient.

By radiolabel targeting agents (such as small molecules, peptides or antibodies) with a positron-emitting radionuclide (for example fluorine-18; gallium-68 or zirconium-89) or therapeutic radionuclides (alpha particles using actinium-225, astatine-211 or beta emitters using lutetium-177, iodine-131), the molecular features of a cancer target can be noninvasively visualized respectively treated by molecular radiotherapy.

A selection of publications from your group

- Friberger IH, Nilsson JN, Lu L, Siikanen J, Ardenfors O, Milton S, Samén E, Goos ACM, Carlsten M, Holmin S, Tran TA. Comparative in vivo biodistribution of cells labelled with [89Zr]Zr(oxinate)4 or [89Zr]Zr-DFO using PET. EJNMMI Res 13, 73 (2023). https://doi.org/10.1186/s13550-023-01021-1
- Jussing E, Milton S, Samén E, Moein M.M, Bylund L, Axelsson R, Siikanen J, Tran TA. Clinically Applicable Cyclotron-Produced Gallium-68 Gives High-Yield Radiolabeling of DOTA-Based Tracers. Biomolecules 11(8):1118 (2021). https://doi.org/10.3390/biom11081118
- Altena R, Burén SA, Blomgren A, Karlsson E, Tzortzakakis A, Brun N, Moein MM, Jussing E, Frejd FY, Bergh J, Tran TA, Hartman J, Axelsson R. Human Epidermal Growth Factor Receptor 2 (HER2) PET Imaging of HER2-Low Breast Cancer with [68Ga]Ga-ABY-025: Results from a Pilot Study. J Nucl Med. 2024. doi: 10.2967/jnumed.123.266847 doi: 10.2967/jnumed.123.266847.

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Cancer Research Area

- Tumor viruses
- Human papillomavirus positive head and neck cancer
- Childhood cancer

Key research field interests

- Human papillomavirus
- Oropharyngeal squamous cell carcinoma
- Targeted therapy
- Neuroblastoma
- Medulloblastoma

Needs for collaborations

- Primary tumor material from head and neck and childhood cancer
- Tumor cell lines
- Bioinformatic expertise
- Expertise in sc RNA seq

Improving follow-up, survival and quality of life in human papillomavirus positive head and neck cancer and childhood cancer

Tina Dalianis

BACKGROUND: Human papillomavirus positive tonsillar/base of tongue cancer (HPV+TSCC/BOTSCC) will increase for decades before present HPV vaccination abrogates this development. Present chemoradiotherapy cures 80% of all patients but presents acute/late side effects, hampering swallowing/eating/talking preventing normal social life. Thus new therapies are needed to increase survival and life quality.
PREVIOUS RESULTS: We have earlier detected a series of specific markers in HPV+TSCC/BOTSCC that seem useful as prognostic markers and as targets for new targeted therapies.
WORK PLAN: 1) The new prognostic markers will be validated for their value in identifying patients with high risk for recurrence; 2) To improve follow-up cell free tumor HPVDNA will be analyzed in blood at diagnosis/during/after treatment and at routine follow ups for 5-years-with the hypothesis that it disappears upon successful treatment and that if it re-occurs this is due to an early recurrence that is still treatable; 3) New targeted therapies and their combinations will be examined for growth inhibitory effects in non-barcoded and barcoded HPV+TSCC/BOTSCC cell lines grown as monolayers or as spheroids, with single cell RNA sequencing of resilient clones in order to later better modify and find the
best most dose-lenient optimized combination therapies.
SIGNIFICANCE: The aim of the project is to use tumor markers as tools for improved prognostication, follow up and as targets for individualized targeted therapy. Our research should improve patient survival and quality of life.
We also work with targeted therapy on childhood cancer together with Doc Ourania Kostopoulou.

A selection of publications from your group

- Zupancic M, Kostopoulou ON, Holzhauser S, Lukoseviciute M, Jylhä C, Marklund L, Näsman A, Sivars L, Dalianis T. Human papillomavirus (HPV) load is higher in HPVDNA/p16 positive than in HPVDNA positive/p16 negative oropharyngeal squamous cell carcinoma but does not differ significantly between various subsites or correlate to survival. Oral Oncol. 2024 Apr;151:106749. doi: 10.1016/j.oraloncology.2024.106749. Epub 2024 Mar 10.
- Mehanna H, Taberna M, Tous S, Brooks J, Von Buchwald C, Mena M, Morey F, C.Grønhøj G, Høygaard J, Bruni L, Batis N, Brakenhoff R Baatenburg De Jong R, Klussmann JP, Dalianis T, Mirghani H, Schache A, James JA, Sh.Huang S, Broglie MA, Hoffman M, Alemany L. On behalf of EPIC-OPC group. Is Dual p16 Immunostaining and HPV Supported for PreciseClassification of Oropharyngeal Cancer? Lancet Oncology, Lancet Oncol. 2023 Mar;24(3):239-251.
- Byskata K, Lukoseviciute M, Tuti F, Zupancic M, Kostopoulou ON, Holzhauser S, Dalianis T. Targeted Therapy with PI3K, PARP, and WEE1 Inhibitors and Radiotherapy in HPV Positive and Negative Tonsillar Squamous Cell Carcinoma Cell Lines Reveals Synergy while Effects with APR-246 Are Limited. Cancers (Basel). 2022 Dec 23;15(1):93.

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Cancer Research Area

- Drug data analysis
- Precision oncology
- Acute myeloid leukemia (AML)

Key research field interests

- Bioinformatics methodology development
- Cancer research
- Single-cell analysis
- Pharmacogenomics

Needs for collaborations

- We are seeking collaborations for accessing to diverse omics data and applying our developed methodologies to other diseases.

Statistical and bioinformatics methodologies for omics data analysis in precision oncology

Trung Nghia Vu

Our research group focuses on advancing bioinformatics methodologies to improve cancer research and treatment. We develop statistical and computational tools for analysis of different types of high-throughput omics data, for example, gene and isoform quantification from RNA sequencing, metagenomics, and abnormal RNA detection (gene fusions, circular RNAs). In single-cell sequencing, we focus on analyzing scRNA-seq data, developing methods for differential expression analysis, isoform expression discovery, and mutation detection to explore deeper insights into cellular heterogeneity. Our cancer research emphasizes identifying driver alterations and subtype-specific biomarkers, particularly in breast cancer and acute myeloid leukemia (AML), as well as investigating mutant-allele expression. We also focus on pharmacogenomics, developing predictive models for drug responses in both monotherapy and combination therapies, with application in AML. By integrating multi-omics data and advanced computational models, our goal is to enhance personalized cancer therapy and contribute to more effective, data-driven medical treatments.

Moving forward, we plan to expand our research by incorporating diverse omics data and utilizing modern AI methods to improve the models for personalized prediction and personalized drug repurposing. This will further advance precision oncology by providing tailored therapeutic strategies based on the molecular characteristics of individual tumors.

A selection of publications from your group

- Trac QT, Pawitan Y, Vu TN. Prediction model for drug response of acute myeloid leukemia patients. NPJ Precision Oncology, 2023.
- Trac QT, Zhou T, Pawitan Y, Vu TN. Discovery of druggable cancer-specific pathways with application in acute myeloid leukemia. GigaScience, 2022.
- Pan L, Dinh HQ, Pawitan Y, Vu TN. Isoform-level quantification for single-cell RNA sequencing. Bioinformatics, 2022.

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Cancer Research Area

- Cancer initiation and prevention

Key research field interests

- Cancer initiation
- 3D organoid models
- Tumor microenvironment
- Cancer prevention
- Prophylactic treatments

Needs for collaborations

- Open to all kinds of collaboration

Innovative ex-vivo models for unraveling early cancer initiation in women: Towards targeted prevention strategies

Twana Alkasalias

Cancer prevention strategies for women at elevated risk, such as those with pathogenic BRCA mutations, remain an urgent but challenging area of research. This is due to the multifactorial nature of cancer initiation and the limitations of current experimental models, as well as lack of non-surgical risk reducing alternatives. Our research focuses on developing innovative ex-vivo 3D culture models of breast, endometrial, and ovarian tissues to study early cancer initiation and identify potential preventive interventions.

We have developed a 3D organoid model using primary breast cells from BRCA mutation carriers. This model, currently being optimized to incorporate stromal components such as adipose, endothelial, and fibroblast cells, allows for the study of the crosstalk between stroma and epithelium during early carcinogenesis. Early findings reveal the mitogenic effects of progesterone on luminal progenitor and basal cells, particularly in BRCA mutation carriers. Surprisingly, approaches, such as utilizing RANKL inhibitors, have shown limited effects, emphasizing the need for further investigation of progesterone signaling pathways. Importantly, the model enables us to explore the potential of progesterone antagonists like mifepristone as a preventive strategy. Our results show that mifepristone induces differentiation of tumor precursor cells into mature luminal cells, a promising avenue for prophylaxis.

Parallel to the breast cancer model, we are developing an endometrial tissue culture system aimed at improve our understanding of the early events in endometrial carcinogenesis. Preliminary results highlight the importance of hormone-driven cell state transitions in the uterine epithelium. We also aim to extend this model to ovarian tissue, facilitating the study of early cancer initiation across hormonally responsive tissues.

Altogether, these projects aim to provide physiologically relevant models for investigating cancer initiation and developing novel non-invasive prevention strategies for women at high genetic risk, potentially allowing early cancer detection and prophylaxis for several reproductive cancers.

A selection of publications from your group

- D. Utjés, N. R. Boggavarapu, M. Rasul, I. Koberg, A. Zulliger, S. Ponandai-Srinivasan, C. von Grothusen, P. G. Lalitkumar, K. Papaikonomou, Twana Alkasalias*[1] and Gemzell K*. (2024). Transcriptomic profile of normal breast tissue post-mifepristone treatment: secondary outcomes of a randomized controlled trial. Int J Mol Sci. 2024 Jul 10;25(14):7590. doi: 10.3390/ijms25147590. * Equal contribution. [1] corresponding author. (https://www.mdpi.com/2865438)
- Shaun Haran, Kantaraja Chindera, May Sabry, Nafisa Wilkinson, Rupali Arora, Agnieszka Zubiak, Thomas E. Bartlett, Iona Evans, Allison Jones, Daniel Reisel, Chiara Herzog, Twana Alkasalias et al. (2024). Natural Killer Cell Dysfunction in Premenopausal BRCA1 Mutation Carriers: A Potential Mechanism for Ovarian Carcinogenesis. Cancers. 16(6):1186. (https://www.mdpi.com/2717730).

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Thank you!