Cancer Research KI PI-Retreat

DJURÖNÄSET

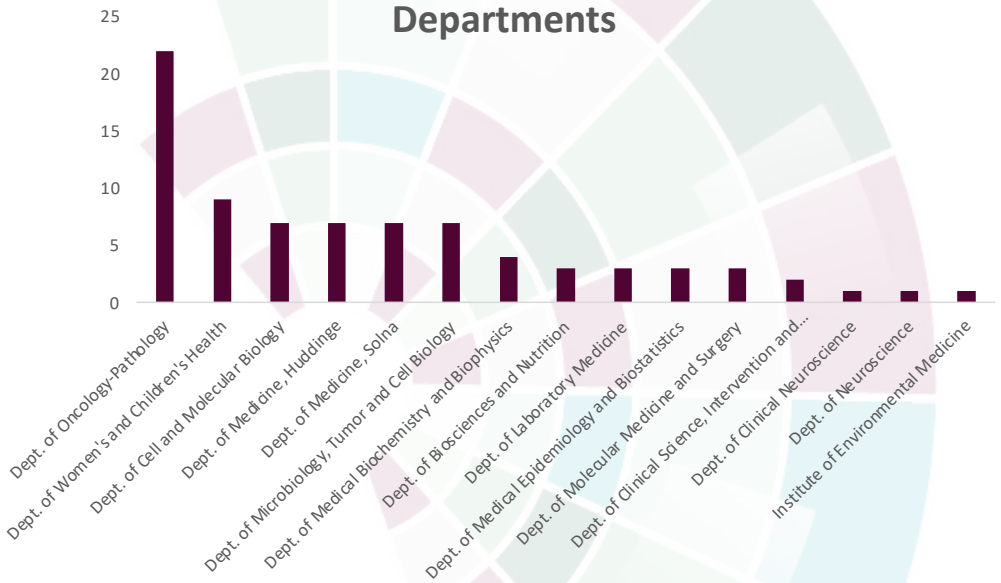
FEBRUARY 19-20, 2024

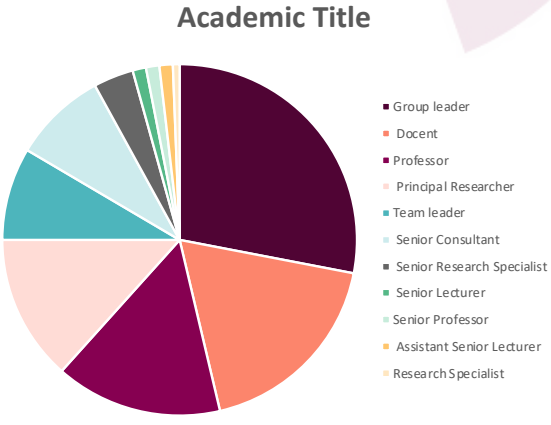
Welcome to the Cancer Research KI PI-Retreat

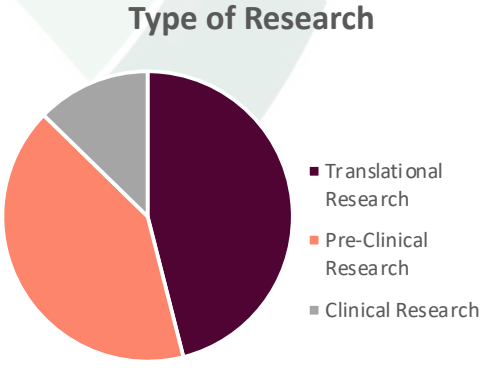
You are welcome to a 2-day meeting with research presentations and networking opportunities, which is only open for PI's that head research groups at Karolinska Insitutet within the field of Cancer Research. The meeting will provide high-level possibilities for networking within the cancer research field, opening your scientific horizons, and providing ample new possibilities for collaborations and funding initiatives.

During the meeting we will have oral presentation, elevator pitches, round table discussions and lots of possibilities for networking to strengthen and build new collaborations.

We are happy to share that we will have 15 departments represented during the retreat, from both Solna and Flemingsberg campus, with the attending researchers covering pre-clinical, translational, and clinical research areas.

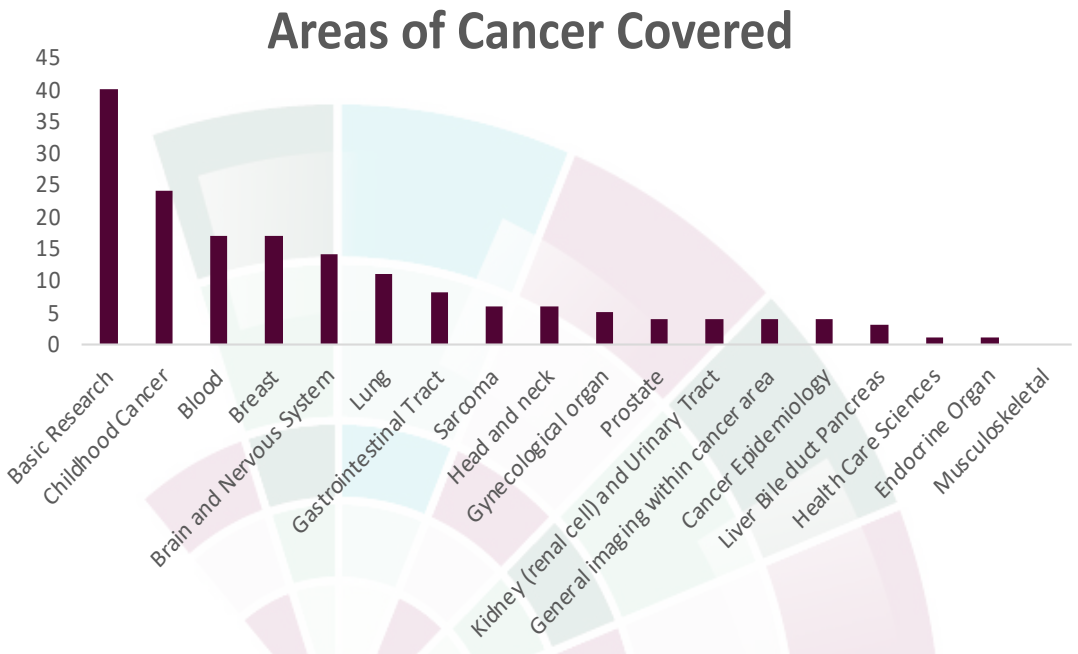






Welcome to the Cancer Research KI PI-Retreat

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



In the abstract booklet you will find information of the researchers attending including research area, expertise, and methodologies they can offer, short description of their research, top publications and what is the best way to reach them. Using the search function in the PDF version of the abstract booklet you can easily find people and topics of interest to you.

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

Johanna Ungerstedt
Elias Arnér
Ninib Baryawno
Linda Lindström
Claudia Kutter
Liselotte Bäckdahl
Dina Dabaghie

Cancer Research KI (CRKI) in a nutshell

Mission

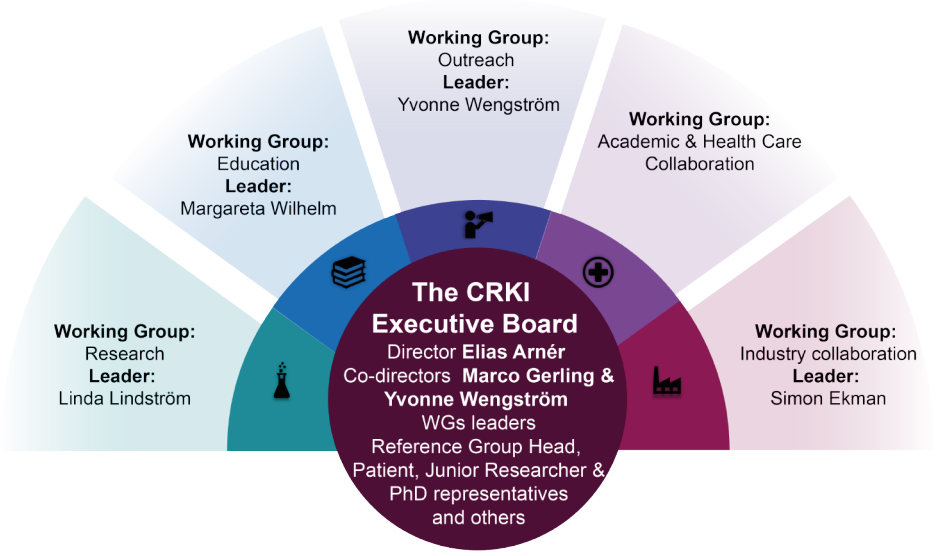
To aid in the generation of new scientific discoveries that can be rapidly translated into clinical practice for the benefit of patients and society.

An umbrella organisation for cancer research at Karolinska Institute

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

~400 PIs in cancer research at KI 22 Departments



The Executive Board

Elias Arner (Director), Yvonne Wengström(co-Director), Marco Gerling (co-Director), Margareta Wilhelm, Matthias Löhr, Simon Ekman, Linda Lindström, Päivi Östling, Renske Altena, Keith Humphreys, Ninib Baryawno (Junior Faculty), Jonas Fuxe (Reference Group Leader), Sara Abu Ajamieh (PhD Student Representative), Lise-lott Eriksson (Chair of the Blood Cancer Forum), Patrik Rossi (Acting Managing Director, Cancer Theme KUH), Lena Sharp (RCC Stockholm-Gotland), Eva Jolly (Karolinska Comprehensive Cancer Centre Coordinator), Liselott Bäckdahl (Research Coordinator), Dina Dabaghie (Research Administrator)

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 19th, 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 20th, app. 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 all through 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 earliest during the afternoon coffee break at 15.35.

MEETING

The meeting and coffee breaks through out the day will be held in House 7. All presentations are given 10 min each. Please stick to the allotted 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 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.

Monday, Februay 19

08:30 **Bus from Stockholm City**
09:15 **Arrival, coffee and registration**
09:45 - 10:10 **Welcome + Presentation of CRKI**
Johanna Ungerstedt + Elias Arnér

10:10 – 11:25 **Morning Session 1**
Chair: **Ninib Baryawno**

10:10 – 10:22 **Adamantia Fragkopoulou**, Dept. of Women's and Children's Health
Title: Antisense technology to ameliorate neuroinflammation and cognitive decline after cranial radiotherapy

10:25 – 10:37 **Ahmed Osman**, Dept. of Women's and Children's Health
Title: The Molecular Determinants of leptomeningeal Metastasis Growth and Response to Therapies

10:40 – 10:52 **Alexander Espinosa**, Dept. of Medicine, Solna
Title: The role of IL-8 in cancer and immunotherapy

10:55 – 11:07 **Arne Lindqvist**, Dept. of Cell and Molecular Biology
Title: CHK2 counteracts polyploidization after p53-dependent cell cycle exit from G2 phase.

11:10 – 11:22 **Arne Östman**, Dept. of Oncology-Pathology
Title: Basic and translational studies on CAFs and astrocytes

11:25 – 11:50 **Coffee Break**

11:50 – 12:50 **Morning Session 2**
Chair: **Johanna Ungerstedt**

11:50 – 12:02 **Brinton Seashore-Ludlow**, Dept. of Oncology-Pathology
Title: A translational platform to improve treatment options in gynecological cancers

12:05 – 12:17 **Caroline Palm Apergi**, Dept. of Laboratory Medicine
Title: RNAi therapeutics against childhood cancer

12:20 – 12:32 **Charlotte Rolny**, Dept. of Oncology-Pathology
Title: Reprogramming Immunosuppressive TAMs to Hinder Tumor Progression

12:35 – 12:47 **Dhifaf Sarhan**, Dept. of Laboratory Medicine
Title: Cancer immunotherapy- Tackle cancer from two directions! Exploiting innate memory in solid tumors and Reprogramming the TME (Genderized immunotherapies)

Monday, Februay 19

12:50 – 13:50 **Group Photo + Lunch**

13:50 – 15:05 **Afternoon Session 1**
Chair: **Ninib Baryawno**

13:50 – 14:02 **Emma Tham**, Dept. of Molecular Medicine and Surgery
Title: Multi-omics analyses in liquid biopsies

14:05 – 14:17 **Fredrik Wermeling**, Dept. of Medicine, Solna
Title: IL-4 suppresses tumor growth by inducing a Gcn1l1/Eif2ak4-regulated amino acid deprivation response

14:20 – 14:32 **Galina Selivanova**, Dept. of Microbiology, Tumor and Cell Biology
Title: p53, targeted therapy, anti-cancer immune response

14:35 – 14:47 **Hans Grönlund**, Dept. of Clinical Neuroscience
Title:First in human Phase I/II trial of personalized tumor-trained lymphocytes for treatment of colorectal cancer

14:50 – 15:02 **Hassan Abolhassani**, Dept. of Medical Biochemistry and Biophysics
Title: Etiologies of Pediatric Cancers Associated with Inborn Errors of Immunity

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

15:35 – 16:50 **Afternoon Session 2**
Chair: **Elias Arnér**

15:35 – 15:47 **Hildur Helgadottir**, Dept. of Oncology-Pathology
Title: Translational Melanoma Research

15:50 – 16:02 **Jana de Boniface**, Dept. of Molecular Medicine and Surgery
Title: Less is more: de-escalation of breast cancer surgery

16:05 – 16:17 **Joanna Zawacka-Pankau**, Dept. of Oncology-Pathology
Title: Reactivation of p53 protein family members for improved cancer therapy

16:20 – 16:32 **Thomas Helleday,**, Dept. of Oncology-Pathology
Title: Targeted DNA damage response inhibitors for a final attack on cancer

16:35 – 16:47 **Jonas Muhr,** Dept. of Cell and Molecular Biology
Title: SOX21 counteract glioblastoma growth by counteracting SOX2 activated gene expression

Monday, Februay 19

16:50 – 17:20 **Coffee Break**

17:20 – 18:00 **Elevator Pitches**
Chair: **Elias Arnér**

Elias Arnér
Hanna Brauner
Hong Qian
Ingemar Ernberg
Johanna Ungerstedt
Ning Xu Landén
Ninib Baryawno
Ola Hermanson
Ourania Kostopoulou
Sergio Martinez Hoyer
Simon Elsässer
Susanne Schlisio
Thuy Tran
Vanessa Lundin

18:00 – 19:00 **Mingle**

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

Tuesday, February 20

07:30 **Breakfast and Check-Out**

08:30 - 09:45 **Morning Session 1**
Chair: **Linda Lindström**

08:30 – 08:42 **Kasper Karlsson**, Dept. of Oncology-Pathology
Title: Precision strategies to overcome metastatic heterogeneity

08:45 – 08:57 **Klas Blomgren**, Dept. of Women's and Children's Health
Title: To prevent, or even reverse, cognitive late complications after cranial radiotherapy

09:00 – 09:12 **Lars Holmgren**, Dept. of Oncology-Pathology
Title: Targeting mechanotransduction in invasive cancer

09:15 – 09:27 **Laszlo Szekely**, Dept. of Laboratory Medicine
Title: The life of cancer inside and outside of the human body

09:30 – 09:42 **Magnus Tobiasson**, Dept. of Medicine, Huddinge
Title: Implementing genetic MRD assessment in the clinical care of patients with myelodysplastic syndrome

09:45 – 10:15 **Coffee Break**

10:15 – 11:30 **Morning Session 2**
Chair: **Johanna Ungerstedt**

10:15 – 10:27 **Maria Genander,** Dept. of Cell and Molecular Biology
Title: Functional fibroblast heterogeneity in the esophageal stem cell niche

10:30 – 10:42 **Maria Grazia Masucci,** Dept. of Cell and Molecular Biology
Title: Host cell remodeling by oncogenic herpes viruses

10:45 – 10:57 **Marianne Farnebo**, Dept. of Cell and Molecular Biology
Title: RNA-regulated DNA repair in cancer

11:00 – 11:12 **Marie Arsenian Henriksson**, Dept. of Microbiology, Tumor and Cell Biology
Title: Targeting MYC induces lipid droplet accumulation by upregulation of HILPDA in clear cell renal cell carcinoma

11:15 – 11:27 **Nick Tobin**, Dept. of Oncology-Pathology
Title: Translational 'Omics Oncology: Focus on the cell cycle and it's clinical applications

11:30 – 12:30 **Lunch**

Tuesday, February 20

12:30 – 14:00 **Afternoon Session 1**
Chair: **Linda Lindström**

12:30 – 12:42 **Nico Dantuma**, Dept. of Cell and Molecular Biology
Title: Targeting the ubiquitin-proteasome system in cancer

12:45 – 12:57 **Nicola Crosetto**, , Dept. of Microbiology, Tumor and Cell Biology
Title: Developing and applying single-cell DNA sequencing methods to study intratumor heterogeneity and evolution

13:00 – 13:12 **Nicole Marquardt**, Dept. of Medicine, Huddinge
Title: Tissue-resident Natural Killer cells comprise a potential future tool for immunotherapeutic approaches in lung cancer

13:15 – 13:27 **Nikolas Herold**, Dept. of Women's and Children's Health
Title: Overcoming therapy resistance in paediatric cancer

13:30 – 13:42 **Ola Larsson**, Dept. of Oncology-Pathology
Title: Epigenetic coordination of transcriptional and translational programs in hypoxia

13:45 – 13:57 **Olle Sangfelt**, Dept. of Cell and Molecular Biology
Title: Targeting Ubiquitin Ligases Maintaining Genome Stability for Cancer Therapy

14:00 – 14:30 **Coffee Break**

14:30 – 16:00 **Afternoon Session 2**
Chair: **Elias Arnér**

14:30 – 14:42 **Oscar Bedoya Reina**, Dept. of Microbiology, Tumor and Cell Biology
Title: Target genes of c-MYC and MYCN with prognostic power in neuroblastoma exhibit different expressions during sympathoadrenal development

14:45 – 14:57 **Rainer Heuchel**, Dept. of Clinical Science, Intervention and Technology
Title: Preclinical Pancreatic Cancer

15:00 – 15:12 **Richard Rosenquist Brandell**, Dept. of Molecular Medicine and Surgery
Title: Charting the complex molecular landscape in chronic lymphocytic leukemia: the path towards precision medicine

15:15 – 15:27 **Sean Rudd,** Dept. of Oncology-Pathology
Title: Towards precision cancer medicine with conventional chemotherapy – how can we better use the drugs we already have?

Tuesday, February 20

15:30 – 15:42 **Staffan Strömblad**, Dept. of Biosciences and Nutrition
Title: Role of Cell-ECM Interactions in Cancer

15:45 – 15:57 **Susanne Gabrielsson**, Dept. of Medicine, Solna
Title: Understanding immune responses to extracellular vesicles in the quest for novel immunotherapies, cancer therapeutic targets and biomarkers

16:00 – 16:30 **Coffee Break**

16:30 – 16:50 **Round Table Discussions**
Chair: **Johanna Ungerstedt**

16:50 -17:00 **Conclusion**
Johanna Ungerstedt + Elias Arnér

17:15 **Bus to Stockholm City**

Abstracts

Abstracts

Adamantia Fragkopoulou

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Cancer Research Area

- Basic Research
- Brain and Nervous System
- Childhood Cancer

Key research field interests

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

Unique instruments and methodologies used in the group

- Antisense technology
- RNAseq
- Stereotactic brain surgery in mice

Antisense technology to ameliorate neuroinflammation and cognitive decline after cranial radiotherapy

Adamantia Fragkopoulou

Approximately 100 children annually develop a brain tumor in Sweden. Radiotherapy (RT) can be life-saving, but leads to long-lasting side effects in cancer survivors. Our aim is to prevent and/or ameliorate the cognitive deficits after RT to the juvenile brain, without compromising the treatment effect on the disease. Using a mouse model of cranial irradiation (IR), and RNAseq analysis, our group has revealed a rapid inflammatory response 6h after IR (Osman et al., 2020), followed by a second peak 2w later (unpublished). Microglia seem to be the most dynamic cell population driving these responses. The second peak response is dominated by upregulation of type I interferon (IFN) pro-inflammatory genes. Our aim is to disrupt the neuroinflammation and the subsequent cognitive decline by using a novel therapeutic platform, the antisense oligonucleotides (ASOs) developed by Ionis Pharmaceuticals Inc. (Carlsbad, CA, USA). The ASOs have never been tested before in the context of paediatric oncology. We inject ASOs against different IFN stimulators intrathecally, before or after irradiation, and evaluate the neuroinflammatory responses and functional outcomes. The ASOs have a favorable safety profile and have been approved by FDA and EMA for use in humans.

A selection of publications from your group

Lithium treatment reverses irradiation-induced changes in rodent neural progenitors and rescues cognition. Zanni G#, Goto S#, Fragopoulou AF#, Gaudenzi G, Naidoo V, Di Martino E, Levy G, Dominguez CA, Dethlefsen O, Cedazo-Minguez A, Merino-Serrais P, Stamatakis A, Hermanson O, Blomgren K. Mol Psychiatry. 2021 Jan;26(1):322-340. doi: 10.1038/s41380-019-0584-0.
#Equal contribution

Ahmed Osman

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Cancer Research Area

- Leptomeningeal metastasis
- Brain metastasis
- CNS cancer recurrence after radiation
- CNS late complications after cancer treatment

Key research field interests

- Metastasis
- Radiation
- Cancer associated fibroblasts
- onco-immunology

Unique instruments and methodologies used in the group

- Iterative selection of metastatic cancer cells to the leptomeningeal compartment.
- Robust protocols for isolation of viable single cells from the brain and leptomeninges.
- Primary cultures of microglia and leptomeningeal fibroblasts
- Craniospinal irradiation
- Intrathecal drug delivery in mice

The Molecular Determinants of leptomeningeal Metastasis Growth and Response to Therapies

Ahmed Osman

Leptomeningeal metastasis (LM) is seeding of cancer cells to the pia and arachnoid mater covering the brain and the spinal cord. It causes fatal neurological complications, and it is associated with a poor prognosis. Without treatment, survival is 4-6 weeks, and with the currently available treatments median survival is 3–4 months. The only breakthrough efficacious intervention that was life-prolonging for LM patients was the application of proton craniospinal irradiation (pCSI) as demonstrated in two recent clinical trials at the MSKCC (NCT: NCT03520504 and NCT04343573). LM patients treated with pCSI had a median overall survival of 9 months, and those treated with the conventional photon involved-field radiotherapy had an median overall survival of 3 months. While a cohort of pCSI-treated patients survived over 18 months (responders), another cohort did not respond to pCSI and died within 1-3 months post-treatment (non-responders). We performed a prospective proteomic analysis on serially collected CSF samples from LM patients before treatment with pCSI (baseline) and at post treatment. Among the 92 analyzed proteins, we found that the chemokine CXCL1 levels were significantly decreased post pCSI. Moreover, CSF from LM patients had significant higher levels of CXCL1 compared to non-LM patients. In addition, patients with elevated CXCL1 at baseline had worse overall survival. To understand pCSI modulations of LM microenvironment and role of CXCL1 in the LM setting, we have established syngeneic mouse models of CSI that recapitulate these CXCL1 findings. We identified the sources of CXCL1 in the LM, and also established that CXCL1/CXCR2 axis is essential for LM growth in the leptomeningeal compartment that could be targeted pharmacologically to halt the disease progression.

We are currently establishing mouse models to study LM in pediatric sold brain tumors, prioritizing medulloblastoma, as it is the cancer type with the highest metastatic deposits to the leptomeningeal compartment.

A selection of publications from your group

1- Remsik J, Tong X, Kunes R, Li MJ, Osman AM, Chabot K, Sener UT, Wilcox JA, Isakov D, Snyder J, Bale T, Chaligné R, Pe'er D, Boire A. Leptomeningeal anti-tumor immunity follows unique signaling principles. 2023.03.17.533041 Preprint at https://doi.org/10.1101/2023.03.17.533041 (2023).

2- Wijetunga NA, Goglia AG, Weinhold N, Berger MF, Cislo M, Higginson DS, Chabot K, Osman AM, Schaff L, Pentsova E, Miller AM, Powell SN, Boire A, Yang JT. Dynamic mutational landscape of cerebrospinal fluid circulating tumor DNA and predictors of survival after proton craniospinal irradiation for leptomeningeal metastases. Clinical Cancer Research. 16;29(4):775-783. doi: 10.1158/1078-0432.CCR-22-2434.PMID: 36449664. 2023.

3- Osman AM, Sun Y, Burns TC, He L, Kee N, Oliva-Vilarnau N, Alevyzaki A, Zhou K, Louhivuori L, Uhlén P, Hedlund E, Betsholtz C, Lauschke VM, Kele J, and Blomgren K. Radiation triggers a dynamic sequence of transient microglial alterations in juvenile brain. 2020. Cell Reports. 2;31(9):107699.doi:10.1016/j.celrep.2020.107699. 2020.

Alexander Espinosa

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Cancer Research Area

- Basic cancer research

Key research field interests

- Bromodomain proteins
- The role of IL-8 in cancer
- Metastasis
- Melanoma

Unique instruments and methodologies used in the group

- We have generated a transgenic mouse strain (Hum-IL8) with physiological expression of IL-8 (CXCL8) and its receptors (CXCR1 and CXCR2). These mice contain two human bacterial artificial chromosomes with CXCL8, CXCR1 and CXCR2. To improve pharmacological studies of IL-8 we have also generated a unique Cxcl1-Cxcl2 double knockout mouse strain that can be crossed to the Hum-IL8 strain.
- We have developed an in vitro CRISPR screen system to identify genes regulating invasiveness of cancer cells

The role of IL-8 in cancer and immunotherapy

Alexander Espinosa

Our research currently focuses on three things. Firstly, we aim to understand the roles of IL-8 in cancer progression and resistance to immunotherapy. Mice lack IL-8 and there is therefore no good in vivo system to study the role of IL-8 in cancer. We have therefore generated a humanized mouse model with physiological expression of human IL-8 and its receptors. We are currently using this mouse model to investigate how IL-8 drives tumor progression and interferes with immunotherapy.

Secondly, we use a newly developed CRISPR screen system to identify genes that regulate invasiveness of cancer cells. We have recently identified a set of genes that seem necessary for cancer cell invasion, and we are currently investigating these genes further and testing small molecule inhibitors of the corresponding proteins.

Thirdly, we are developing new optogenetic CRISPR tools to be able to edit genes in a spatiotemporal manner in vivo. We have recently developed a blue-light inducible CRISPR system based that is able to knockout genes in mouse T cells in vivo. We aim to use this system to dissect T cell responses in vivo.

A selection of publications from your group

1. The bromodomain protein TRIM28 controls the balance between growth and invasiveness in melanoma. Nyberg WA, Velasquez-Pulgarin DA, He T, Sjöstrand M, Pellé L, Covacu R, Espinosa A. EMBO Rep. 2023 Jan 9;24(1).
2. TRIM21 controls Toll-like receptor 2 responses in bone-marrow-derived macrophages. Sjöstrand M, Carow B, Nyberg WA, Covacu R, Rottenberg ME, Espinosa A. Immunology. 2020 Mar;159(3):335-343.
3. miR-31 regulates energy metabolism and is suppressed in T cells from patients with Sjögren's syndrome. Johansson A, Nyberg WA, Sjöstrand M, Moruzzi N, Bergman P, Khademi M, Andersson M, Piehl F, Berggren PO, Covacu R, Jagodic M, Espinosa A. Eur J Immunol. 2019 Feb;49(2):313-322

Andreas Lundqvist

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Cancer Research Area

- Tumor Immunology

Key research field interests

- Immunology
- Biomarkers
- Translational

Unique instruments and methodologies used in the group

- Ex vivo immune assays

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. In order 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 the 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

1. Cancer Commun (Lond). 2023 Jul;43(7):855-859., Oncoimmunology. 2023 Mar 22;12(1):2175517., J Immunother Cancer. 2022 Oct;10(10):e005308.

Andreas Lennartsson

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Cancer Research Area

- Blood
- Childhood Cancer

Key research field interests

- Epigenetics
- Leukemia
- Hematology
- Transcriptomics

Unique instruments and methodologies used in the group

Abstract

Andreas Lennartsson

A selection of publications from your group

Arne Lindqvist

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Cancer Research Area

- Basic preclinical research

Key research field interests

- Cell cycle
- DNA damage
- Cell fate
- Quantitative Microscopy, Modelling

Unique instruments and methodologies used in the group

- Quantitative immunofluorescence.
- Multiplexing immunofluorescence (developed new method – cumulative microscopy).
- Live cell imaging. FRET-based reporters. ODE-based modelling.

CHK2 counteracts polyploidization after p53-dependent cell cycle exit from G2 phase.

Arne Lindqvist

Cell cycle progression in the presence of damaged DNA pose a risk for tumour development. In response to DNA damage in G2 phase, human cells can be forced to exit the cell cycle in a p53- p21- and APC/CCdh1-dependent manner. Cells that exit the cell cycle in G2 phase frequently become senescent, but it is unclear what determines this commitment. We find that a subset of immortalised RPE-1 cells and primary human fibroblasts spontaneously initiate DNA re-replication several days after forced cell cycle exit in G2 phase. By combining single cell tracking using quantitative phase imaging for more than a week with quantitative immunofluorescence, we find that the resulting very large polyploid cells contain increased levels of damaged DNA and frequently exit the cell cycle again in the next G2 phase. Subsequently, these cells either enter senescence or commit to another round of DNA re-replication, further increasing both size and ploidy. We identify CHK2 as a main regulator of whether polyploidization occurs. Our findings suggest a mechanism by which p53-positive cells can evade senescence that risks genome integrity.

A selection of publications from your group

1. Silva Cascales H, Burdova K, Middleton A, Kuzin V, Erik Müllers, Stoy H, Baranello L, Macurek L, Lindqvist A. 2021. Cyclin A2 localises in the cytoplasm at the S/G2 transition to activate PLK1 Life Science Alliance 3(4): e202000980
2. Lemmens B And Lindqvist A. 2019. DNA replication and mitotic entry: a brake model for cell cycle progression. Journal of Cell Biology 218(12): 3892-3902
3. Lemmens B, Hegarat N, Akopyan K, Sala-Gaston J, Bartek J, Hochegger H, Lindqvist A. 2018. DNA replication determines timing of mitosis by restricting CDK1 and PLK1 activation. Molecular Cell. 71(1): 117-128

Arne Östman

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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

Unique instruments and methodologies used in the group

- Multiplex staining
- Digital image analyses
- Cell and mouse models for cancer cell/host cell interactions

Basic and translational studies on CAFs and astrocytes

Arne Östman

The research group has a longstanding interest in the tumour microenvironment. Defining study features are broad interactions with clinical researchers, SciLifeLab and companies. Recent achievements include discovery of fibroblasts as drivers in breast DCIS progression, identification of a stromal biomarker for radiotherapy benefit patented and tested with a US company, and identification of CAF subsets discussed with Roche as candidate immunotherapy biomarkers (see selected publications). Three ongoing studies are high-lighted below.

Beter definition of CAF subsets are needed to exploit them as drug targets and biomarkers. SciLifeLab-supported single-cell RNAseq and 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 sub-compartments, not detected in whole tumour stroma.

Interactions between malignant cells and host cells drive glioma growth, suggesting prognostic potential of tissue architecture and cell composition. Analyses of two clinically well-annotated mutIDH glioma collections determines abundance of malignant cells and 6-8 host cell types including astrocytes, microglia/TAMs and endothelial cells. Spatial enrichment of cell pairs is also quantified. Metrics will next few months be analysed regarding associations with outcome and radiology status.

Earlier studies suggest astrocyte-mediated support of glioblastoma (GBM) as a novel target for GBM. With SciLIfeLab and "AZ Open Innovation" we therefore performed an astrocyte/GBM co-culture high-through-put screen. The screen results, PISA analyses and knock -down studies, suggest astrocyte-expressed Faty Acid Synthase (FASN) as a novel GBM drug target. Ongoing studies include validation in mouse models, and multiplex-based analyses of FASN 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

1. Fibroblast subsets in non-small cell lung cancer: Associations with survival, mutations, and immune features. Pellinen T, Paavolainen L, Martin-Bernabé A, Papatella Araujo R, Strell C, Mezheyeuski A, Backman M, La Fleur L, Brück O, Sjölund J, Holmberg E, Välimäki K, Brunnström H, Botling J, Moreno-Ruiz P, Kallioniemi O, Micke P, Östman A. J Natl Cancer Inst. 2023 Jan 10;115(1):71-82.
2. High PDGFRb Expression Predicts Resistance to Radiotherapy in DCIS within the SweDCIS Randomized Trial. Strell C, Folkvaljon D, Holmberg E, Schiza A, Thurtiell V, Karlsson P, Bergh J, Bremer T, Akslen LA, Wärnberg F, Östman A. Clin Cancer Res. 2021 Jun 15;27(12):3469-3477.
3. Impact of Epithelial-Stromal Interactions on Peritumoral Fibroblasts in Ductal Carcinoma in Situ. Strell C, Paulsson J, Jin SB, Tobin NP, Mezheyeuski A, Roswall P, Mutgan C, Mitsios N, Johansson H, Wickberg SM, Svedlund J, Nilsson M, Hall P, Mulder J, Radisky DC, Pietras K, Bergh J, Lendahl U, Wärnberg F, Östman A. J Natl Cancer Inst. 2019 Sep 1;111(9):983-995.

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Cancer Research Area

- Molecular Cytopathology

Key research field interests

- Fine Needle Aspiration (FNA)
- Biomarker profiling
- Adaptive responses
- Tumor microenvironment
- Machine learning

Unique instruments and methodologies used in the group

- Tumor sampling by FNA
- Sample preparation of minimal material
- Proximity extension assay (PEA)
- Mutation profiling
- in-situ analysis of cytology material using various methods.

Fine needle aspiration-based molecular profiling of tumor microenvironments

Bo Franzén

Diagnostic tissue biopsies are required to select therapy for patients with solid tumors. However, core needle biopsies can cause complications and may be difficult to repeat longitudinally. Sampling via fine needle aspiration biopsy (FNA) is globally established, minimally traumatic and can be repeated during treatment. FNA-samples can be used for ultra-sensitive multiplex molecular profiling, allowing for early diagnosis and for monitoring during treatment.

We have developed a procedure for sample preparation of minimal FNA material, compatible with clinical routines and targeted analysis of mutations, as well as gene and protein expression. Expression levels of 150-170 proteins per sample (leftover material only) were profiled by proximity extension assays (PEA, olink.com). Data were analyzed with statistical tools provided by e.g. Qlucore Omics Explorer (qlucore.com). We also applied machine learning strategies to identify tentative predictive biomarker signatures.

Key results were: (1) Identification of a tentative signature (benign vs cancer) for early diagnosis of breast cancer and good correlation with established key biomarkers. (2) Profiling of immune markers such as PD-L1 and many other immune-related proteins (including tentative markers for resistance to immunotherapy) in breast and lung cancer FNA-samples [1, 2]. (3) Identification of a tentative signature related to tumor stage of primary lung adenocarcinomas [2]. (4) Identification of a tentative signature related to tumor grade in prostate FNA samples, as well as analysis of immune-related proteins that may guide treatment in advanced prostate cancer [3].

We describe here the development of FNA-based atraumatic molecular cytology for precision cancer medicine. We have identified tentative biomarker signatures, and we demonstrated profiling of proteins related to the immune microenvironment and to resistance to immunotherapy. The methodology is highly sensitive and reproducible and permits extensive protein, RNA and mutation profiling with assessment of biomarkers for diagnosis, therapy selection and monitoring of therapy.

A selection of publications from your group

1. Franzén B, Alexeyenko A, Kamali-Moghaddam M, Hatschek T, Kanter L, Ramqvist T, Kierkegaard J, Masucci G, Auer G, Landegren U, Lewensohn R. Protein profiling of fine-needle aspirates reveals subtype-associated immune signatures and involvement of chemokines in breast cancer. Mol Oncol. 2019 Feb;13(2):376-391.

2. 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 fine-needle 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.

3. Röbeck P, Franzén B, Cantera-Ahlman R, Dragomir A, Auer G, Jorulf H, Jacobsson SP, Viktorsson K, Lewensohn R, Häggman M, Ladjevardi S. Multiplex protein analysis and ensemble machine learning methods of fine needle-aspirates from prostate cancer patients reveal potential diagnostic signatures associated with tumor grade. Cytopathology. 2023 Feb 24.

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Cancer Research Area

- Basic Research
- Lung

Key research field interests

- Lung cancer
- Cell death

Unique instruments and methodologies used in the group

Abstract

A selection of publications from your group

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Cancer Research Area

- Ovarian cancer

Key research field interests

- Functional precision medicine
- Drug repurposing
- Drug discovery
- Patient-derived models
- Adipocyte-cancer interactions

Unique instruments and methodologies used in the group

- Drug testing
- High-content imaging
- Short-term patient derived cell culture

A translational platform to improve treatment options in gynecological cancers

Brinton Seashore-Ludlow

Together with clinicians at Karolinska Sjukhuset, we have established GeMoRe, a translational study with the overarching goals of 1) identifying new approaches to predict clinical response to treatment, 2) understanding the biological mechanisms of relapse and 3) identifying new treatments for rare gynecological diseases. We have established wellfunctioning sample logistics for this study and receive 1-2 samples a week from patients with ovarian cancer (all subtypes) and rare gynecological diseases for drug testing, molecular characterization and biobanking. To date we have collected, processed and biobanked material from over 140 consenting patients. This collection includes peripheral blood mononuclear cells, flash frozen and viably biobanked tumor tissue and dissociated cancer cells, acellular ascites fluid, flash frozen adipose tissue and conditioned media from adipose tissue or mature adipocytes. In addition, we track clinical parameters for each patient, including staging, treatment response and time to disease progression. To enable rapid evaluation of the sensitivity of individual patients' disease to clinically relevant drugs we have developed the Drug Efficacy Testing in 3D Cultures (DET3Ct) platform, which uses high content imaging to quantify drug sensitivity. This has shown potential in distinguishing between patients with short (≤12 months) or long (>12 months) progression free survival to the standard of care therapy, as well as identifying patientmatched combinations. We are currently validating the use of this platform in predicting patient response to carboplatin in a larger retrospective cohort. In addition, we are building on this platform to study how various aspects of the microenvironment including cancerassociated fibroblasts, adipocytes, and acellular components of ascites fluid impact cellular response to drugs. Finally, we have on-going studies in image analysis of complex disease models and artificial intelligence methods to improve our biological interpretation of these data.

A selection of publications from your group

1. Åkerlund E, Guidotyte, G, Moussaud-Lamodière E, Lind O, Bwanika HC, Lehti K, Saheli S,-Carlson J, Wallin E, Fernebro J, Ostling P, Kallioniemi O, Joneborg U, Seashore-Ludlow B.The Drug Efficacy Testing in 3D Cultures (DET3Ct) platform enables rapid identification ofeffective drugs and drug combinations for ovarian cancer patients. https://doi.org/ 10.21203/rs.3.rs-2742592/v1, (2023). Accepted Nature Precision Oncology.
2. Zaghmi A, Aybay E, Jiang L, Shang M, Steinmetz-Späh J, Wermeling F, Kogner P, Korotkova M, Östling P, Jakobsson PJ, Seashore-Ludlow B, Larsson K. High-content screening of drug combinations of an mPGES-1 inhibitor in multicellular tumor spheroids leads to mechanistic insights into neuroblastoma chemoresistance. Molecular oncology 2023

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Cancer Research Area

- Tumor immunology

Key research field interests

- B cells
- Cancer immunotherapy
- Technology development
- Breast cancer

Unique instruments and methodologies used in the group

- Spatial antigen receptor analysis (Spatial VDJ)
- Spatial transcriptomic
- Single-cell RNAseq
- Murine tumor models

Spatially resolving B cell clonal dynamics in tissues

Camilla Engblom

Despite the clinical success of immunotherapy, many cancer patients lack optimal treatment options. B lineage cells have recently emerged as promising, yet untapped, therapeutic targets. In my newly started lab, we use cutting-edge, inhouse developed, spatial transcriptomics-based approaches to systematically interrogate B cell clonal biology in tumor progression and immunotherapy responses.
B lineage cells are compelling anti-cancer targets because they: i) infiltrate tumors and associate with positive prognosis and immunotherapy outcome across cancers, ii) present antigen to T cells, and iii) express clonal heritable B cell receptors (BCR) that confer exquisite molecular specificity. B cell receptors can be defined by sequencing, but these methods require tissue dissociation, which loses the location, and surrounding environmental cues, of tumor-infiltrating B cell clones. Discovering the B cell 'clonal niche' could identify key factors that determine to what, where, and how B cell clones respond, and harness these to boost anti-tumor immunity. We recently developed a spatial transcriptomics-based technology (Spatial VDJ) and the associated computational pipelines to capture and reconstruct full-length BCRs directly in their native tissues. In my research program, we use Spatial VDJ, along with other state of the art methods, to link tumor-associated B cell clones to their molecular and cellular environment with the ultimate goal to provide new immunotherapy strategies.

A selection of publications from your group

1. Engblom/Thrane/Lin et al., Spatial transcriptomics of B cell and T cell receptors reveals lymphocyte clonal dynamics. Science 382, eadf8486 (2023)
2. Zilionis/Engblom/Pfirschke/Savova, et al. Single-Cell Transcriptomics of Human and Mouse Lung Cancers Reveals Conserved Myeloid Populations across Individuals and Species. Immunity. 50, 1317–1334.e10 (2019).
3. Engblom/Pfirschke et al. Osteoblasts remotely supply lung tumors with cancerpromoting SiglecFhigh neutrophils. Science. 358 (2017).

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Cancer Research Area

- Childhood leukemia
- Osteosarcoma

Key research field interests

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

Unique instruments and methodologies used in the group

- RNAi prodrugs
- siRNA and peptides synthesis and conjugation
- CETSA

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, four more siRNA-based drugs have been approved by the FDA/EMA. Importantly two 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

1. 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.
2. 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.
3. Goroshchuk O, Vidarsdottir L, Björklund AC, Hamil AS, Kolosenko I, Dowdy SF, Palm-Apergi C. Targeting Plk1 with siRNNs in primary cells from pediatric B-cell acute lymphoblastic leukemia patients. Sci Rep. Feb 14;10(1):2688, 2020.
4. Kolosenko I, Edsbäcker E, Björklund AC, Hamil AS, Goroshchuk O, Grandér D, Dowdy SF, Palm-Apergi C. RNAi prodrugs targeting Plk1 induce specific gene silencing in primary cells from pediatric T-acute lymphoblastic leukemia patients. Journal of Controlled Release. Sep 10;261:199-206, 2017.

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Cancer Research Area

- Onco-Immunology

Key research field interests

- Angiogenesis
- Metastatic Dissemination
- Tumor-Associated
- Macrophages

Unique instruments and methodologies used in the group

- Macrophages
- T cells
- Immune Therapy
- State-of-the-art mouse models
- In vivo co-mingling assays
- Crosstalk between T cells and other immune or stroma cells in vitro
- Vessel functionality in vivo,
- Metastatic dissemination in vivo.

Reprogramming Immunosuppressive TAMs to Hinder Tumor Progression

Charlotte Rolny

Translational Immuno-Oncology- targeting immuosupressive TAMs
Our research primarily focuses on tumor immunology, with a specific emphasis on understanding the underlying mechanisms that regulate the pro-tumoral phenotype of immune cells known as Tumor-Associated Macrophages (TAMs). We employ state-of-the-art mouse models, cutting-edge molecular biology techniques, and patient samples to elucidate the various mechanisms governing the regulation of pro-tumoral TAM phenotypes. By targeting these controlled pathways, we can reprogram pro-tumoral TAMs into an anti-tumoral phenotype, leading to the activation of cytotoxic immune cells and inhibiting tumor growth and metastatic spread. We maintain a close collaboration with clinicians to ensure a seamless bench-to-bedside connection. Our recent data has uncovered the crucial role of selective mRNA translation changes as a central hub regulating the immunosuppressive functions of macrophages mediated by eIF4E activity. Both MNK2 and MNK2 regulate eIF4E phosphorylation; however, our preliminary data demonstrates that targeting MNK2, as opposed to MNK1, effectively modulates eIF4E activity in TAMs. This targeted approach results in the reprogramming of immunosuppressive TAMs. The phenotypic transformations mediated by MNK2 silencing in TAMs have profound implications. Firstly, they induce tumor blood vessel normalization, facilitating the intratumoral recruitment of cytotoxic T and natural killer (NK) cells while impeding mammary metastatic spreading. Additionally, the blockade of MNK2, but not MNK1, skews immunosuppressive TAMs toward an immunostimulatory phenotype, thereby enhancing the activity of cytotoxic T and NK cells. The importance of TAMs in regulating the cancer cell metastatic fate was demonstrated in our latest publication, showing that TAMs, through the expression of the lymphangiogenic molecule VEGF-C, play a critical role in influencing the metastatic fate of cancer cells. They redirect these cells from disseminating to the lungs to migrating towards the lymph nodes, shedding light on a novel mechanism in cancer metastasis

A selection of publications from your group

1. Banjerjee K, Kerzel T*, Bekkhus T*, Ferreira SS*, Wallmann T*, Wallerius M, Landwehr LS, Agardy DA, Bergh J, Bartish B, Hartman J, Ostman A, Squadrito ML#, and Rolny C#. VEGF-C expression in TAMs rewires the metastatic fate of breast cancer cells. Cell Reports, accepted in principle 2023-10-27. (IF: 10).
2. Bartish M#, Tong D#, Pan Y, Wallerius M, Squadrito M, Liu H, Ristau J, Souza Ferreira S, Wallmann T, van Hoef V, Masvidal L, Kerzel T, Joly AL, Goncalves C, Preston S, Ebrahimian T, Seitz C, Bergh J, Pietras K, Lehoux S, Naldini L, Andersson J, Squadrito ML, Rincón S, Larsson L*, and Rolny C*. MNK2 governs the anti-inflammatory macrophage phenotype. Proc Natl Acad Sci 2020 Nov 3;117(44) (IF: 12.8).
3. Wallerius M, Wallmann T, Bartish M, Östling J, Mezheyeuski A, Tobin N, Nygren E, Pangigadde P, Pellegrini P, Squadrito M, Pontén F, Hartman K, Bergh J, De Milito A, De Palma M, Östman A, Andersson J, and Rolny C. Guidance molecule SEMA3A restricts tumor growth by differentially regulating the proliferation of tumor-associated macrophages. Cancer Research. 2016; 11 (78) 3166 (IF: 13.3).

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Cancer Research Area

- Mechanisms and roles for telomerase activation in oncogenesis

Key research field interests

- TERT
- Telomerase
- Transcriptional regulation
- Oncogenesion
- Cancer progression

Unique instruments and methodologies used in the group

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

1. 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.
2. 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.
3. 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
- "genderized" immunotherapies
- Immune memory
- NK cells

Unique instruments and methodologies used in the group

- FACS
- Multiparametric IF/confocal microscopy
- Multiplex IF/Vectra
- Incucyte live imaging
- Artificial 3D tumor microenvironment.

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 antigen-presenting 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 anti-inflammatory 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

1. Almazán NM, Sala BM, Sandalova T, Sun Y, Resink T, Cichocki F, Söderberg-Naucle´ r 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.
2. 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.
3. Sarhan D, Hippen KL, Lemire A, Hying S, Luo X, Lenvik T, Curtsinger J, Davis Z, Zhang B, Cooley S, Cichocki F, Blazar BR, Miller JS. Adaptive NK Cells Resist Regulatory T-cell Suppression Driven by IL37. Cancer Immunol Res 2018. PMID: 29784636

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Cancer Research Area

- Basic science in redox biology, with translational applications

Key research field interests

- Redox biology
- Selenoproteins
- Thioredoxin
- Glutathione
- Signalling

Unique instruments and methodologies used in the group

- Recombinant selenoprotein production and characterisation
- Redox biology expertise
- Thioredoxin and glutathione system assays
- Redox biology probes for cell culture use
- Chemical biology expertise
- Cancer models

Selenoproteins in Redox Signalling, Health and Disease

Elias S.J. 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, NF B, HIF, STAT3 and p53?
- How can receptor tyrosine kinases (RTKs) signalling cascades through tyrosine phosphorylation cascades be regulated through redox regulation of phosphotyrosine phosphatases (PTPs)?

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

1. 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.
2. Dagnell, M., Cheng, Q., Rizvi, S.H.M., Pace, P.E., Boivin, B., Winterbourn, C.C., Arnér, E.S.J. (2019) Bicarbonate is essential for protein-tyrosine phosphatase 1B (PTP1B) oxidation and cellular signaling through EGF-triggered phosphorylation cascades. J Biol Chem. 294:12330-12338.
3. W. C. Stafford, X. Peng, M. H. Olofsson, X. Zhang, D. K. Luci, L. Lu, Q. Cheng, L. Trésaugues, T. S. Dexheimer, N. P. Coussens, M. Augsten, H.-S. M. Ahlzén, O. Orwar, A. Östman, S. Stone-Elander, D. J. Maloney, A. Jadhav, A. Simeonov, S. Linder, E. S. J. Arnér (2018) Irreversible inhibition of cytosolic thioredoxin reductase 1 as a mechanistic basis for anticancer therapy. Sci. Transl. Med. 10: eaaf7444

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Cancer Research Area

- Liquid biopsies
- Hereditary cancer

Key research field interests

- Cell-free DNA
- Biomarkers
- Cancer genetics
- Hereditary cancer

Unique instruments and methodologies used in the group

- Whole genome sequencing
- Targeted gene panel sequencing
- Nanopore sequencing
- Multiplex droplet digital PCR
- Cell-free DNA extraction

Multi-omics analyses in liquid biopsies

Emma Tham

Liquid biopsies (LB) are minimally invasive samples that can be used for diagnosis, prognosis and monitoring in adults and children with cancer and other conditions. They contain proteins, vesicles and cell-free DNA (cfDNA). The latter is released by dying cells and has a short half-life. The small fraction of cfDNA that derives from the tumour cells carries all the genetic aberrations in the tumour and represents the current tumour burden (Barbany 2019). Analysis of cfDNA in LB at diagnosis can detect therapeutic targets and disease-specific aberrations that can improve diagnosis (Arthur, submitted). LBs can also be used for monitoring therapy response and measurable residual disease using rapid, ultrasensitive multiplex digital PCR, which can detect relapse weeks – months prior to clinical diagnosis (Haider 2023; Arthur 2022; Sivars submitted). Furthermore, the presence of detectable tumour-derived cell-free DNA in plasma after surgery or oncological treatment is a negative prognostic marker (Wallander 2023; Sivars 2022). By combining multi-omics techniques and advanced bioinformatic analysis of sequencing data, we hope to further improve the analysis of LBs with the aim of clinical implementation.

In families with hereditary cancer of unknown cause, novel analysis techniques on whole genome sequencing can detect causative aberrations (Wallander 2021; Bilgrav Saether 2023; Tesi submitted), while data from gene panel analysis of larger cohorts can provide important knowledge on the genotype and phenotype of hereditary cancer syndromes (Öfverholm 2023; Omran in preparation). Identifying the genetic cause of a cancer syndrome enables predictive testing of family members, and carriers can then be offered surveillance programs, to reduce the risk of advanced cancer. Furthermore, these syndromes are rare, thus characterisation of the clinical phenotype and evaluation of surveillance is crucial to improve patient outcomes (e.g. in hereditary TP53 cancer syndrome Omran 2023; Omran 2022).

A selection of publications from your group

1. Arthur C, Jylhä C, de Ståhl TD, Shamikh A, Sandgren J, Rosenquist R, Nordenskjöld M, Harila A, Barbany G, Sandvik U, Tham E. Simultaneous Ultra-Sensitive Detection of Structural and Single Nucleotide Variants Using Multiplex Droplet Digital PCR in Liquid Biopsies from Children with Medulloblastoma. Cancers (Basel). 2023 Mar 25;15(7):1972. doi: 10.3390/cancers15071972. PMID: 37046633
2. Wallander K, Haider Z, Jeggari A, Foroughi-Asl H, Gellerbring A, Lyander A, Chozhan A, Cuba Gyllensten O, Hägglund M, Wirta V, Nordenskjöld M, Lindblad M, Tham E. Sensitive Detection of Cell-Free Tumour DNA Using Optimised Targeted Sequencing Can Predict Prognosis in Gastro-Oesophageal Cancer. Cancers (Basel). 2023 Feb 11;15(4):1160. doi: 10.3390/cancers15041160. PMID: 36831507
3. Wallander K, Thonberg H, Nilsson D, Tham E. Massive parallel sequencing in individuals with multiple primary tumours reveals the benefit of re-analysis. Hered Cancer Clin Pract. 2021 Oct 28;19(1):46. doi: 10.1186/s13053-021-00203-z. PMID: 34711244

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Cancer Research Area

- Drug target discovery
- Drug resistance
- Cancer immunology
- Autoimmunity

Key research field interests

- Animal models
- Melanoma
- Leukemia
- Molecular biology
- Immunology.

Unique instruments and methodologies used in the group

- CRISPR-Cas9 screen
- Viral delivery
- Flow cytometry
- RNAseq
- Mass spec.

IL-4 suppresses tumor growth by inducing a Gcn1l1/Eif2ak4-regulated amino acid deprivation response.

Fredrik Wermeling

The pleiotropic cytokine interleukin 4 (IL-4) is linked to allergies, protective responses in helminth infection, and shown to suppress autoantibody-mediated effector functions. Examining how IL-4 affects the activity of therapeutic antibodies used in the cancer setting, we found that IL-4 administrations, both with a therapeutic antibody and alone, potently suppressed the growth of several cancer cell lines in vivo. The activity of IL-4 was not dependent on IL-4 induced signaling in the cancer cells, instead depending on activity induced in cells of the hematopoietic lineage. The growth suppression was seen in both prophylactic and therapeutic settings, and gene expression analysis of the tumor mass identified an amino acid deprivation phenotype. This phenotype was further validated by mass spectrometry-based amino acid quantification, identifying an almost complete depletion of arginine and argininosuccinate in the tumor mass, in concordance with the distinct Arginase1 (Arg1) upregulation seen. An in vivo CRISPR screen further identified that B16-F10 cells lacking Gcn1l1 (Gcn1) and Eif2ak4 (Gcn2), activated by uncharged tRNAs, were more sensitive to IL-4 administrations in vivo. In conclusion, the study links a potent therapeutic activity of IL-4 to ARG1-mediated arginine depletion and identifies GCN1L1 and EIF2AK4 as potential synergistic treatment targets. IL-4 administrations could thus represent an alternative therapeutic approach in immunologically cold tumors often characterized by high ARG1 expression.

A selection of publications from your group

1. 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 SV, Iyer VS, Kasza Z, Sedimbi S, Lane DP, WERMELING F. Cancer Res. 2022 Jan 1;82(1):36-45. PMID: 34750099
2. 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. PMID: 34745454
3. IL-4 controls activated neutrophil FcyR2b expression and migration into inflamed joints. Panda SK, Wigerblad G, Jiang L, Jiménez-Andrade Y, Iyer VS, Shen Y, Boddul SV, Guerreiro-Cacais AO, Raposo B, Kasza Z, WERMELING F. Proc Natl Acad Sci U S A. 2020 Feb 11;117(6):3103-3113. PMID: 31980518

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Cancer Research Area

- Tumor biology
- Targeted therapies
- Inflammation and cancer

Key research field interests

- p53
- Targeted therapy
- Anti-cancer immune response

Unique instruments and methodologies used in the group

Pharmacologic activation of p53 triggers viral mimicry response thereby abolishing mutant p53- Gain-of-Function and immune evasion thus promoting anti-tumor immunity

Galina Selivanova

Immune escape is one of the important factors in the development and evolution of tumours. We found that p53 activated by three different MDM2 inhibitors induces the expression of repetitive sequences, endogenous retroviruses (ERV) in particular, via increased occupancy on ERV promoters and inhibition of two major ERV repressors, histone demethylase LSD1 and DNA methyltransferase DNMT1. ERVs expression produces double-stranded RNA, which causes dsRNA stress triggering viral mimicry response - type I/III interferon (IFN) expression. Pharmacologic activation of p53 in vivo unleashes the IFN program, promotes T-cell infiltration in colon carcinoma tumor model in mice and significantly enhances the efficacy of checkpoint therapy in an allograft melanoma mouse model.

Furthermore, in patients with melanoma, MDM2 inhibitor ALRN-6924 induces a viral mimicry pathway and tumor inflammation signature genes, the same that we found in human cancer cell lines and in mice. Moreover, we found that mutant p53-reactivating compound APR-246 counteracted mutant p53-mediiated cancer immune escape. APR-246 activated IFN signalling or repressed negative immune checkpoints in mutp53 cells. Moreover, Apr-246 promoted CD4+ T cells infiltration and prevented CD8+ T cells exhaustion within TME in vivo.

In conclusion, we discovered a novel biological mechanism of potentiating anti-cancer immune response upon p53 reactivation by small molecules via induction of interferon response. This leads to the recruitment of active immune cells to tumors. Therefore, tumors are killed both by activated p53 and by immune cells which produce efficient tumor suppression. Moreover, induction of interferon upon p53-targeting therapies may provide a mean to overcome resistance to immune checkpoint blockade.

The synergy between p53-targeting drugs and modern immunotherapies can be particularly important for patients who do not respond to immunotherapy.

A selection of publications from your group

1. Translating p53-based therapies for cancer into the clinic. Peuget S, Zhou X, Selivanova G.Nat Rev Cancer. 2024 Jan 29. doi: 10.1038/s41568-023-00658-3
2. Mutant p53 gain of function mediates cancer immune escape that is counteracted by APR-246. Zhou X, Santos GS, Zhan Y, Oliveira MMS, Rezaei S, Singh M, Peuget S, Westerberg LS, Johnsen JI, Selivanova G.Br J Cancer. 2022 Nov;127(11):2060-2071
3. Pharmacologic Activation of p53 Triggers Viral Mimicry Response Thereby Abolishing Tumor Immune Evasion and Promoting Antitumor Immunity. Zhou X, Singh M, Sanz Santos G, Guerlavais V, Carvajal LA, Aivado M, Zhan Y, Oliveira MMS, Westerberg LS, Annis DA, Johnsen JI, Selivanova G.Cancer Discov. 2021 Dec 1;11(12):3090-3105.

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Cancer Research Area

- Glioma

Key research field interests

- Glioma
- Oligodendroglia

Unique instruments and methodologies used in the group

- Single cell transcriptomics
- Single cell epigenomics
- Spatial transcriptomics
- Spatial epigenomics

Spatial transcriptomics and epigenomics to investigate the role of oligodendrocyte precursor cells

Gonçalo Castelo Branco

Gliomas are an heterogenous group of tumours that can infiltrate throughout the brain. While less frequent than in adults, pediatric high-grade gliomas, and in particular glioblastoma, are very aggressive and respond poorly to therapy. It has been shown recently that high-grade glioma can be originated from oligodendrocyte precursor cells (OPCs), with mutations at specific histone amino acid residues involved in epigenomic regulation being implicated in the etiology of a subset of gliomas. Moreover, OPCs have also been recently shown to transition to immune -like states in the context of disease. We are investigating how oligodendrocyte precursor cells (OPCs) transition to glioma initiating cells (GICs) and the role of immunocompetent GICs in the context of high-grade gliomas. We are also currently mapping the cellular dynamics in tumours in a mouse model of glioma and in human pediatric and adult glioblastomas (GBM), using single-cell epigenomics and spatial multiomics. By providing insights on how gliomas are transcriptionally and epigenetically regulated, we aim to uncover novel targets for epigenetic-based therapy for gliomas, that can be used in a clinical setting.

A selection of publications from your group

1. Di Zhang, Yanxiang Deng, Petra Kukanja, Eneritz Agirre, Marek Bartosovic, Mingze Dong, Cong Ma, Sai Ma, Graham Su, Shuozhen Bao, Yang Liu, Yang Xiao, Gorazd B. Rosoklija, Andrew J. Dwork, J. John Mann, Kam W. Leong, Maura Boldrini, Liya Wang, Maximilian Haeussler, Benjamin J. Raphael, Yuval Kluger, Gonçalo Castelo-Branco,*, Rong Fan,* Spatially resolved epigenome-transcriptome co-profiling of mammalian tissues at the cellular level NATURE 2023 616, pages 113–122. https://doi.org/10.1038/s41586-023-05795-1
2. Bartosovic M*, Castelo-Branco G*. Multimodal chromatin profiling using nanobody-based single-cell CUT&Tag. NATURE BIOTECHNOLOGY 2022 doi:10.1038/s41587-022-01535-4
3. Jäkel S, Agirre E, Mendanha Falcão A, van Bruggen D, Lee KW, Knuesel I, Malhotra D, Ffrench-Constant C*, Williams A*, Castelo-Branco G*. Altered human oligodendrocyte heterogeneity in multiple sclerosis. NATURE 2019 566;7745 543-547 doi:10.1038/s41586-019-0903-2

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Cancer Research Area

- Cutaneous lymphoma

Key research field interests

- Cutaneous lymphoma
- Skin cancer
- Immunology
- NK cells

Unique instruments and methodologies used in the group

- Isolation of human skin cells and analysis by flow cytometry
- Nanostring digital spatial profiling
- Clinical cohorts and material cutaneous lymphoma (register data, outcome measures, clinical data, biopsies, blood)

Cutaneous lymphoma – clinical and experimental studies on disease mechanisms, prognostic factors and effects of treatment

Hanna Brauner

Lymphomas located to the skin are rare and less studied than other forms of lymphoma. We aim 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

1. 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.
2. Wickström SL, Wagner AK, Fuchs S, Elemans M, Kritikou J, Mehr R, Kärre K, Johansson MH*, Brauner H*. MHC Class I-Dependent Shaping of the NK Cell Ly49 Receptor Repertoire Takes Place Early during Maturation in the Bone Marrow. J Immunol. 2022 Aug 15;209(4):751-759. *shared last author
3. Nenonen J, Winther A, Leijonhufvud E, Belfrage E, Ekström-Smedby K, Brauner H. Overall survival and registration of cutaneous T-cell lymphoma patients in Sweden: a multi-center cohort and validation study Acta Oncol. 2022 Mar 25:1-5.

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Cancer Research Area

- Neoantigen targeted T cell responses

Key research field interests

- Translational
- Adoptive
- Personalized
- Vaccination

Unique instruments and methodologies used in the group

- Tumor ranking software
- Antigen presentation
- T cell specificity
- Vaccine

First in human Phase I/II trial of personalized tumor-trained lymphocytes for treatment of colorectal cancer.

Hans Grönlund

The new generation of adoptive T cell therapy utilizing high-precision neoantigen targeting is gaining interest, particularly so in solid tumors. Personalized tumor trained lymphocytes is a novel autologous adoptive T cell therapy targeting patient-specific neoantigens. A phase I/II clinical trial of pTTL in Stage IV colorectal cancer (CRC) patients is ongoing.
pTTL are manufactured with a high rate of success and consists mainly of T cells, with small proportions of NK and B cells. The CD4/CD8 T cell ratio varies between patients and contains a significant proportion of memory T cells expressing markers indicating functionality, with limited levels of late-stage T cells. TCR sequencing has demonstrated increased clonality compared to the original resident T cells, indicating antigen-specific expansion. The ongoing FIH trial will include up to 16 patients with Stage IV CRC and limited remaining standard of care therapies. pTTL is administered as a single-dose monotherapy after chemotherapy-based preconditioning with cyclophosphamide and fludarabine. A doseescalation design is applied.
The trial is divided into three parts. Part I: Collection of materials for sequencing and pTTL production (tumour biopsy, surgical collection of lymph nodes), and manufacturing of EpiTCer beads and pTTL.
Part II: pre-conditioning, administration of pTTL and follow-up for 6 months.
Part III: Long-term follow-up to 5 years after pTTL administration.
The primary endpoint is safety. Secondary outcomes include response, overall survival, and progression-free survival. Biomarkers for pTTL persistence, pTTL characteristics, and response will be evaluated.

Trial Registration EUDRA CT #2022-000394-96.
Clinicaltrials.gov Identifier #NCT05908643

A selection of publications from your group

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Cancer Research Area

- Tumor immunology
- Immune surveillance
- Immunotherapy

Key research field interests

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

Unique instruments and methodologies used in the group

- NGS
- Single cell multi omics organoid
- Models gen me editing
- Drug monitoring

Etiologies of Pediatric Cancers A ssociated 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 tumor s 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 hypoth esis 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, prot eomics 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 , CTLA 4 , FOXP3 mutations), evadin g growth suppressors (DOCK8 , CXCR4 mutations), phenotypic plasticity (NFKB1 , NFKB2 mutations), epigenetic reprogramming (DNMT3B, ZBTB24, A ID 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

1. Clinical and Immunologic Characteristics of Non Hematologic Cancers in Patients with Inborn Errors of Immunity. Cancers (Basel). 2023 Jan 26;15(3):764.
2. Diversity of malignancies in patients with different types of inborn errors of immunity. Allergy Asthma Clin Immunol. 2022 Dec 12;18(1):106.
3. Updates of cancer hallmarks in patients with inborn errors of immunity. Curr Opin Allergy Clin Immunol. 2022 Dec 1;22(6):352 363.
4. Full list of publication s: https://scholar.google.com/citatio ns?user=fMy4pqMAAAAJ&hl=en

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Cancer Research Area

- Melanoma

Key research field interests

- Melanoma
- Immunotherapy
- BRAF/MEK
- Familial melanoma
- CDKN2A

Unique instruments and methodologies used in the group

- Clinical trials
- Biomarker studies
- Registry studies
- Germline genetics
- Real world data

Translational Melanoma Research — Hildur Helgadottir

Our research is on melanoma incidence, biology, genetics and different aspects related to prevention and treatment of the disease. Our main research projects are:

PROMMEL-Precision Radiotherapy in Immunotherapy resistant melanoma

Ellen Backlund, Muyi Yang, Hildur Helgadottir

PROMMEL is an ongoing clinical trial, including patients that are resistant to immune checkpoint inhibitors (ICI). Stereotactic radiotherapy (RT) is combined with ICI where we study synergic effects between the treatments, assessing responses and biomarkers. https://classic.clinicaltrials.gov/ct2/show/NCT04793737

BIO-MELANOM

Suzanne Egyhazi Brage, Fernanda Costa Svedman, Muyi Yang, Cissi Liu, Hildur Helgadottir

Biomarker study with sequential blood and tumor biopsies collected from patients undergoing ICI or targeted therapy. Current focus is on inflammation markers in plasma. We are collaborating with other groups applying single cell and in situ sequencing of tumor cells

MELCAYA-Melanoma in Children, Adolescents and Young Adults

Karina Schultz, Francesca Portelli, Hildur Helgadottir

We are studying melanoma occurrence in the young and through the Swedish Melanoma Registry (SweMR) we have observed an significant trend deviation in the young. We are studying the dermatoscopic, pathologic and molecular aspects of melanocytic lesions in young individuals including Spitz tumors and BAP1 inactivated melanocytic tumors.

BRAF mutation and Ulceration in Primary Melanoma

Johan Falkenius, Francesca Portelli, Hildur Helgadottir

Primary melanoma ulceration is after the Breslow thickness the most significant prognostic marker. Ulceration is also positively associated with tumor BRAF mutations. This project is focused on assessing ulceration as a continuous variable (in contrast to the usual yes/no) and the association with BRAF status (proportion of BRAF mutated alleles) and survival.

Melanoma germline genetics

Veronica Höiom, Hildur Helgadottir

We study hereditary melanoma and underlying genetics. We are particularly interested in germline mutations in CDKN2A and BAP1. We study risk spectrum, survival, and response to current melanoma treatments in high-risk individuals. There is also a focus on melanoma families with no known high-risk mutations where we are assessing polygenic risk scores and different features of families that can predict the melanoma risk and need for surveillance.

Hong Qian

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Cancer Research Area

- Leukemia

Key research field interests

- Leukemia
- Microenvironment
- Mesenchymal
- Stem cells
- Leukemic stem cells
- Hematopoietic stem cells

Unique instruments and methodologies used in the group

- Flow cytometry
- RNA-sequencing
- Mouse modeling
- Experimental transplantation
- Co-culture
- Confocal imaging

Hong Qian group has been working on hematopoietic microenvironment/niche with a focus of mesenchymal cell niche in myeloid leukemia using both mouse models and patient materials (https://ki.se/en/medh/hong-qian-group-leukemia-niche). The goal is to identify the niche factors that are altered in acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) and have therapeutic potential or prognostic values. The group has identified a set of dysregulated niche factors in AML or CML. The recent work from her group has demonstrated the critical role of Lama4 in AML progression and relapse (Cai, et al., Blood, 2022) and identified a chemokine CXCL14 as A new therapeutic option for patients with CML (Dolinska et al., Blood, 2023). In addition, the group has for the first time reported that the AML cells infiltrated in the skin tissue are leukemogenic and they are maintained by skin mesenchymal cell niches (Sandhow et al., JEM, 2023). These findings lay an important foundation for further understanding of microenvironmental contribution to the treatment responses of myeloid leukemia and other hematological malignancies.

A selection of publications from your group

1. Lakshmi Sandhow, Huan Cai#, Elory Leonard#, Pingnan Xiao, Luana Tomaipitinca, Alma Månsson, Makoto Kondo, Xiaoyan Sun, Anne-Sofie Johansson, Karl Tryggvason, Maria Kasper, Marcus Järås, Hong Qian. Skin mesenchymal niches maintain and protect AMLinitiating stem cells, Journal of Experimental Medicine, 2023, DOI:10.1084/jem.20220953
2. Dolinska M #, Cai, H #, Månsson, A #, Shen J, Xiao P, Bouderlique, T, Li, X, Leonard, E, Chang, M., Gao, Y., Medina Giménez, PJ., Kondo,M., Sandhow, L., Johansson, AS., Deneberg,S., Söderlund,S., Jädersten, M., Ungerstedt, J., Tobiasson, M., Östman, A., Mustjoki, S., Stenke, L., Le Blanc,K., Hellström-Lindberg, E., Lehmann,S., Ekblom,M., Olsson-Strömberg, U., Sigvardsson M.and Qian H. Characterization of Bone Marrow Niche in Patients with Chronic Myeloid Leukemia Patients Identifies CXCL14 as a New Therapeutic Option, 2023, Blood. 2023;142(1):73-89.
3. Cai H#, Kondo M#, Sandhow L, Xiao P, Johansson AS, Sasaki T, Zawacka-Pankau J, Tryggvason K, Ungerstedt J, Walfridsson J, Ekblom M, Qian H. Critical role of Lama4 for hematopoiesis regeneration and acute myeloid leukemia progression. Blood 2022 139;20 3040-3057.

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Cancer Research Area

- Infections and Cancer

Key research field interests

- Invasion
- Metastasis
- EBV-infectio
- Cell Plasticity
- Epigentics

Unique instruments and methodologies used in the group

- Cell metabolism (SeaHorse)
- Lipid droplet detection
- Migration assays
- Gene modification
- Immune histochemistry

The role of MTSS1 downregulation in metastasis of nasopharyngeal carcinoma

Ingemar Ernberg

Undifferentiated nasopharyngeal carcinoma (NPC) is an epithelial cancer that arises from the cells iutlining the surface of the nasopharynx. The pathogenesis depends on a challenging complex of risk factors, including polygenic genetic susceptibility, Epstein–Barr virus (EBV) infection, and other environmental factors.

Metastasis suppressor 1 (MTSS1) was identified in 2002 as a metastasis suppressor gene, and was named 'missing in metastasis' (MIM) because it was not expressed in invasive, metastatic bladder cancer cell lines20. Wild-type MTSS1 is 759 amino acids long, with a C-terminal 'Wiskott–Aldrich syndrome protein homology 2' (WH2) domain and an N-terminal 'inverse Bin–Amphiphysin–Rvs (I-BAR) domain21.

The C-terminal WH2 domain can bind to actin, and the I-BAR domain can bind to phosphoinositide-rich lipid bilayers. The I-BAR domain introduces a curvature into lipid bilayers, such as at the plasma membrane. In this way, I-BAR domains can induce the formation of protrusions at the cell surface.

MTSS1 can be detected in all human tissues. It is now well documented that loss of MTSS1 is related to metastasis and tumor progression in many different cancers. The anti-metastatic mechanism of MTSS1 is not yet well understood.

Here, we show that MTSS1 is down-regulated in nasopharyngeal carcinoma (NPC) tissue, which predicts poor patient prognosis. MTSS1 suppresses NPC cell migrationand invasion, in vitro through cytoskeletal remodeling at cell–cell borders and assembly of E-cadherin/B-catenin in adhesion complexes. Moreover, we show that the I-BAR domain of MTSS1 is both necessary and sufficient to promote formation of E-cadherin/B-catenin/F-actin–mediated cell adherens junctions. Thus, MTSS1 suppresses metastasis by controlling the integrity of the adherens junctions. This has clinical and therapeutic implications in all cancer types with decreased expression of MTSS1.

A selection of publications from your group

- Zhou X, Matskova L, Rathje LS, Xiao X, Gish G, Werner M, Ignatyev I, Yu N, Zhao W, Tian F, Hou B, Zhang Z, Pawson T, Chen F, Ernberg I. SYK interaction with ITG´ 4 suppressed by Epstein-Barr virus LMP2A modulates migration and invasion of nasopharyngeal carcinoma cells. Oncogene. 2015 Aug 20;34(34):4491-9. doi: 10.1038/onc.2014.380. Epub 2014 Dec 22.
- Li Q, Wennborg A, Aurell E, Dekel E, Zou JZ, Xu Y, Huang S, Ernberg I. Dynamics inside the cancer cell attractor reveal cell heterogeneity, limits of stability, and escape. Proc Natl Acad Sci U S A. 2016 Mar 8;113(10):2672-7. doi: 10.1073/pnas.1519210113. Epub 2016 Feb 29.
- Zheng S, Matskova L, Zhou X, Xiao X, Huang G, Zhang Z, Ernberg I. Downregulation of adipose triglyceride lipase by EB viral-encoded LMP2A links lipid accumulation to increased migration in nasopharyngeal carcinoma. Mol Oncol. 2020 Dec;14(12):3234-3252. doi: 10.1002/1878-0261.12824. Epub 2020 Nov 8. PMID: 33064888

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Cancer Research Area

- Lung cancer

Key research field interests

- Human Natural Killer cells and T cells
- Clonal heritability

Unique instruments and methodologies used in the group

- Advanced flow cytometry (28+ parameters, BD Symphony and Aurora spectral cytometry) combined with scRNAseq (10X, smartSeq3xprss)
- Using clonally expanded NK cells and T cells.

Determining NK cell tumor infiltration at the clonal level

Jakob Michaëlsson

As NK cells develop from CD34+ hematopoietic precursors they differentiate and form a highly diverse population based on variegated expression of a large number of different proteins, e.g. NKG2A, NKG2C, KIRs, CD57 and CD62L. To what extent the gene and protein expression in a given mature NK cell is stable over several cell generations remains largely unexplored. To investigate to what extent conventional human NK cells maintain clonally heritable gene expression patterns we analyzed in vitro expanded NK cell clones derived from single CD56bright CD16- or CD56dim CD16+ founder NK cells by combining flow cytometry and single cell RNA sequencing. Our results demonstrate marked clonally heritable patterns of gene and protein expression in NK cells, where each founder NK cell gave rise to highly homogenous, but clonally distinct progeny. The distinct clonal patterns of gene and protein expression included both activating and inhibitory receptors, chemokine and cytokine receptors, as well as effector molecules, and as such opens up for clone specific functions, including migration, infiltration and function. In the next phase of this project we will investigate clone-specific differences in tumor infiltration using in vitro spheroid models of both tumor cell lines and lung tumor-derived primary epithelial cells, and aim at linking gene and protein expression in individual clones with the capacity to infiltrate and kill tumor cells.

A selection of publications from your group

1. Accumulation of tissue-resident natural killer cells, innate lymphoid cells, and CD8+ T cells towards the center of human lung tumors. Brownlie D, von Kries A, Valenzano G, Wild N, Yilmaz E, Säfholm J, Al-Ameri M, Alici E, Ljunggren HG, Schliemann I, Aricak O, Haglund de Flon F, Michaëlsson J, Marquardt N. Oncoimmunology. 2023 12(1):2233402
2. Expansions of adaptive-like NK cells with a tissue-resident phenotype in human lung and blood. Brownlie D, Scharenberg M, Mold JE, Hård J, Kekäläinen E, Buggert M, Nguyen S, Wilson JN, Al-Ameri M, Ljunggren HG, Marquardt N, Michaëlsson J. Proc Natl Acad Sci U S A. 2021 118(11):e2016580118.
3. Divergent clonal differentiation trajectories establish CD8+ memory T cell heterogeneity during acute viral infections in humans. Mold JE, Modolo L, Hård J, Zamboni M, Larsson AJM, Stenudd M, Eriksson CJ, Durif G, Ståhl PL, Borgström E, Picelli S, Reinius B, Sandberg R, Réu P, Talavera-Lopez C, Andersson B, Blom K, Sandberg JK, Picard F, Michaëlsson J, Frisén J. Cell Rep. 2021 35(8):109174.

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Cancer Research Area

- Solid tumors and metastasis in children

Key research field interests

- Metastatic disease
- Molecular targets
- Alpha-emitting
- Radionuclides
- Radiopharmaceutical therapy
- Clinical trials

Unique instruments and methodologies used in the group

- Systematic target identification using cellular barcoding
- In vivo models of metastasis
- In-house radionuclide labelling and purification
- Ongoing phase 2 multicenter clinical trial

Development of radiopharmaceutical therapy for metastatic neuroblastoma

Jakob Stenman

Problem description

Neuroblastoma is the most common and deadly of childhood cancers. Despite multimodal therapy, survival in high-risk disease is only 50%. The most common cause of death is a metastatic relapse. We currently lead a European multicenter, phase 2 clinical trial, where the efficacy of radiopharmaceutical therapy (RPT) with Lutetium-177-DOTATATE is assessed in the treatment of relapsed or refractory high-risk neuroblastoma in children (LuDO-N Trial, EudraCT:2020-004445-36, PMID:35359899). The following opportunities for further development have been identified:

Alpha particle therapy

Currently used beta-emitters cannot deliver a sufficient radiation dose to small clusters of metastatic cells. High-energy alfa-emission from Astatine-211 or Actinium-225 releases a lethal radiation dose in a confined space, creating a possibility to deplete even single metastatic cells. We collaborate with pharma industry to develop alpha-RPT for neuroblastoma. In vitro development is performed at KI/SciLifeLab, Stockholm, in vivo validation at the Pre-clinical Cancer Treatment Center, SciLifeLab, Uppsala.

Novel targets

The short path length of alfa-radiation requires new molecular targets that are expressed in a high proportion of cancer cells. By single cell sequencing of metastatic cells, we have identified and validated targets with a uniform expression across tumor sub-clones. New targets are screened for monoclonal antibodies and peptide binders in collaboration with the SciLifeLab Drug Discovery and Development program. Radio-labelling is performed at the Karolinska University Hospital Radiopharmacy.

Radio-sensitization and protection

The therapeutic index of RPT can be improved by protecting the kidneys from dose-limiting toxicity during excretion of unbound radioligands. By subsequently applying tumor-specific radio-sensitizers, the therapeutic efficacy can be improved without added myelotoxicity. High-throughput drug re-purposing screens are performed to identify radio-sensitizers and protectors in collaboration with SciLifeLab Chemical Biology Consortium, Sweden. Using a precision lethality approach, based on cellular barcoding (Karlsson K, Nature 2023) we can identify radio-complementing drugs that target radiation resistant metastatic tumor subclones.

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Cancer Research Area

- Breast cancer surgery

Key research field interests

- Axillary surgery
- Neoadjuvant chemotherapy
- Physical exercise
- Tumour immunology
- Oncoplastic and reconstructive surgery

Unique instruments and methodologies used in the group

- International randomized phase 3 trials
- Prospective international cohort studies
- Patient-reported outcomes (surveys)
- Population-based cohort studies

Less is more: de-escalation of breast cancer surgery

Jana de Boniface

In the field of breast cancer research, much attention is on de-escalation and individualisation. Our research has a strong focus on rapid implementation in clinical guidelines and pushing for change. We run large randomized international clinical trials evaluating e.g., whether axillary clearance can be omitted in node-positive breast cancer (SENOMAC) and whether nodal radiotherapy can be omitted in node-positive hormonesensitive breast cancer (T-REX). Through collaboration with international academic groups such as EUBREAST and OPBC, we are instrumental to large prospective cohort studies assessing variations of clinical routines and their outcomes, such as AXSANA (evaluating axillary clearance versus targeted axillary dissection versus sentinel lymph node biopsy in clinically node-positive breast cancer patients receiving neoadjuvant chemotherapy; my group is responsible for patient-reported outcomes) and MELODY (evaluating methods for the marking of non-palpable breast lesions) and the randomized breast reconstruction trial OPBC-02/PREPEC (I am responsible for the report on early complications). In Sweden, we have set up population-based cohorts such as the Stockholm Breast Reconstruction Database (over 2000 patients) and the Stockholm DCIS database (under construction) and take advantage of the National Quality Register for Breast Cancer in evaluating surgical strategies. Most recently, we have started a randomized clinical trial testing whether a physical exercise intervention during neoadjuvant chemotherapy can improve the primary outcome, pathological complete response. Here, we are collaborating with several international sites both within and outside Europe and plan to enrol 790 patients until the end of 2025. In this trial, several translational collaborators work on explorative analyses studying the mechanism behind the anti-tumoral effect of physical exercise using blood and tumor samples as well as faeces. A yet unexplored interest is the potential of the perioperative period as a window for breast cancer treatment.

A selection of publications from your group

1. De Boniface J, Altena R, Haddad Ringborg C, Bolam KA, Wengström Y. Physical exercise during neoadjuvant chemotherapy for breast cancer as a mean to increase pathological complete response rates: trial protocol of the randomized Neo-ACT trial. PlosOne 2022. October 13. hBps://doi.org/10.1371/journal.pone.0274804
2. de Boniface J, Szulkin R, Johansson ALV. Survival aBer breast conservaCon versus mastectomy adjusted for comorbidity and socioeconomic status: naConal 6-year
3. ollow-up on 48986 women. JAMA Surg. 2021, 5:e211438.
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Cancer Research Area

Key research field interests

- p53
- p73
- Allosterism
- Cell death
- Cancer therapy, lung cancer, myeloid malignancies

Unique instruments and methodologies used in the group

- Circular dichroism
- Mass spectrometry
- Fluorescence polarisation
- Molecular docking
- FCS/FCCS

Reactivation of p53 protein family members for improved cancer therapy.

Joanna E Zawacka

p53 tumor suppressor belongs to the p53 protein family, which includes p53, p63, and p73 proteins. All family members regulate the same set of genes involved in apoptosis, cell cycle, senescence, or DNA damage repair and are inactivated in cancers. Current therapeutic efforts focus on the reactivation of p53 for improved cancer therapy at large.

APR-246 (eprenetapopt), a drug tested in several clinical trials both in solid and in hematological cancers, is converted to active molecule methylene quinuclidinone (MQ). MQ refolds mutant p53 to wild-type conformation through binding to cysteine residues in the p53 core domain. By applying a range of biophysical and cell-based assays, we have identified two cysteine residues targeted by MQ, which are critical for mutant p53 thermostabilization and death induction in cancer cells[1].

Unlike TP53, TP73 gene is rarely mutated in cancers, the protein is expressed and can be reactivated pharmacologically. The strategy aiming at the restoration of p73 in tumors lacking p53 is emerging as a novel approach for improved cancer therapy. Through the drug repurposing approach, we have recently found that heme analogs reactivate p73 tumor suppressor in cancer cells in a manner similar to wild-type p53. The drugs reinstate p53 through binding to p53 N-terminus and inhibiting the p53/MDM2 and p53/MDM4 interactions [2]. The mechanism of inhibition of protein-protein interactions is converging on the allosteric shift in the p53 N-terminus [3]. Our studies using fluorescent polarisation and yeast reporter assays revealed that molecules binding to p73 N-terminus, reactivate this tumor suppressor protein by inhibiting p73/MDM2/MDM4/ITCH axis. Further studies are on-going to fully comprehend the mechanism of reactivation of p53 and p73 by repurposed drugs.

A selection of publications from your group

1. 1. Zhang, Q.; Bykov, V. J. N.; Wiman, K. G.; Zawacka-Pankau, J. APR-246 reactivates mutant p53 by targeting cysteines 124 and 277. Cell Death Dis. 2018, 9, 439.
2. Jiang, L.; Malik, N.; Acedo, P.; Zawacka-Pankau, J. Protoporphyrin IX is a dual inhibitor of p53/MDM2 and p53/MDM4 interactions and induces apoptosis in B-cell chronic lymphocytic leukemia cells. Cell Death Discov. 2019, 5, 77.
3. Grinkevich, V. V.; Vema, A.; Fawkner, K.; Issaeva, N.; Andreotti, V.; Dickinson, E. R.; Hedström, E.; Spinnler, C.; Inga, A.; Larsson, L.-G.; Karlén, A.; Wilhelm, M.; Barran, P. E.; Okorokov, A. L.; Selivanova, G.; Zawacka-Pankau, J. E. Novel Allosteric Mechanism of Dual p53/MDM2 and p53/MDM4 Inhibition by a Small Molecule. Front. Mol. Biosci. 2022, 9, 823195.

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Cancer Research Area

- Cancer genomics and clinical trials

Key research field interests

- Prostate cancer
- Cancer genomics
- Trials

Unique instruments and methodologies used in the group

- Liquid biopsy assays
- Bioinformatic pipelines

AR pathway inhibitors versus taxanes in metastatic prostate cancer

Johan Lindberg

Background: The Prostate Biomarker (ProBio) trial is an international biomarker-driven, randomized, outcome-adaptive platform trial in men with metastatic castrate resistant prostate cancer (mCRPC) evaluating multiple agents.
Methods: We used outcome-adaptive randomization to compare biomarker-driven treatment selection (experimental arms) against physician's choice standard-of-care (SOC; control arm), and to compare agents against each other within the experimental treatment arms. Men with mCRPC were randomized based on genomic alterations in circulating tumor DNA in five biomarker signatures. Androgen receptor pathway inhibitors (ARPi; abiraterone and enzalutamide) and taxanes (docetaxel and cabazitaxel) were evaluated, using progression-free survival per PCWG3 criteria (PFS), as primary endpoint. Enrollment in the experimental group was stopped when the Bayesian probability of superiority reached prespecified thresholds ("graduation").
Results: In total, 219 men were randomized: 92 to SOC, vs. 76 and 51 to taxanes and ARPi, respectively, in the biomarker-driven arms. ARPi graduated in the "signature all", i.e. a signature encompassing all biomarkers. The median estimated PFS was 11.3 months (90% Bayesian credible interval [CI], 9.8 to 13.1) for ARPi compared with 7.2 months (90% CI, 6.5 to 8.1) in the SOC arm, for a hazard ratio (HR) of 0.52 (90% CI 0.37 to 0.72). ARPi demonstrated superiority to taxanes within the experimental arms (HR 0.54; 90% CI 0.38 to 0.76). We observed suggestive differential treatment effects for patients with TP53 mut and TMPRSS2:ERG fusion disease. The median estimated overall survival (OS) was 37.3 months (CI, 27.7 to NA) for ARPi compared with 20.2 months (90% CI, 18.4 to 23.0) taxanes within the experimental arms.
Conclusions: ARPi increases PFS and OS both compared to SOC and taxanes in patients with mCRPC. These are directly randomized data for ARPi and taxanes, showing the first evidence of a difference in PFS and OS for these agents in the mCRPC setting.

A selection of publications from your group

1. AR and PI3K Genomic Profiling of Cell-free DNA Can Identify Poor Responders to Lutetium-177- PSMA Among Patients with Metastatic Castration-resistant Prostate Cancer. European urology open science 2023 53; 63-66
2. Prognostic Value of Low-Pass Whole Genome Sequencing of Circulating Tumor DNA in Metastatic Castration-Resistant Prostate Cancer. CLINICAL CHEMISTRY 2023 69;4 386-398
3. Androgen Receptor Burden and Poor Response to Abiraterone or Enzalutamide in TP53 Wild-Type Metastatic Castration-Resistant Prostate Cancer. JAMA oncology 2019 5;7 1060-1062

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Cancer Research Area

- Translational hematology

Key research field interests

- Chronic myeloid malignancies
- Inflammation
- DNA methylation
- Genomics

Unique instruments and methodologies used in the group

- DNA methylation
- Transcriptomics
- Somatic mutations
- Epidemiology

Genotype, phenotype characterization of Chronic Myelomonocytic Leukemia (CMML) ; disease onset mechanisms and risk factors for aggressive disease

Johanna Ungerstedt

CMML is a clonal hematological stem cell disease with poor prognosis. CMML is clinically heterogenous with autoimmune manifestations in 30% of patients The relation between mutations, phenotype and outcome is not well understood . Loss of function TET 2 mutation is seen in 60 % of patient . For long it was considered that TET2 mutation did not impact prognosis, however a large metaanalysis recently showed that TET2 mutation was associated with a slig ht survival advantage.
Our recent population based data (Kjellander and Westerberg , manuscript) clearly demonstrates a higher hemoglobin , lower LDH, and a significant survival advantage in the TET2 mutated patients despite being 7 years older at diagnosis compared to TET2 wildtype patients We noted that 20% of the cohort had bone marrow examinations 5 20 years before diagnosis, and we are currently indepth analyzing the differences in the microenvironment between the pre CMML and diagnostic sample as well as assessing with sensitive methods if any/some/ all mutations present at diagnosis were present already long before overt diagnosis . This will increase our knowledge on disease onset mechanisms and the importance of the microenviroment .
In a separate study, we explored the transcriptome, methylome and s creened for novel potential driver mutations by exome sequencing in tumor and germline samples from 145 CMML patients (Kjellander, Nannya manuscript. Exome sequencing rendered two distinct clusters b y unsupervised clustering strongly driven by TET2 mutation . Unsupervised c lustering of DNA methylation data also gave two distinct clusters, and there was an almost 100 % overlap between the mutation and methylation clusters . Patients in the mutated TET2 associated cluster had a strong survival advantage. Methylation differences were mostly in genes associated with enhancer regions and repressed polycomb. We are now exploring how this associates with transcriptome output with the hope to find potential therapeutic targets for this disease where we have no specif ic treatment options today.

A selection of publications from your group

1. A proteomic and transcriptomic screening demonstrates increased mast cell derived CCL23 in systemic mastocytosis. Söderlund S, Boey D, van Midden W, Kjellander M, Axe K, Qian H, Dahlin JS, Ungerstedt J . J Allergy Clin Immunol 2023 Jul;152(1):205 213
2. Clinical Outcomes of Adults with Systemic Mastocytosis: A 15 Year Multidisciplinary Experience. Ungerstedt J, Ljung C, Klimkowska M, Gülen T. Cancers (Basel). 2022 Aug 16;14(16):3942 53
3. Prognostic scoring systems and comorbidities in Chronic Myelomonocytic Leukemia: a nationwide population based study. Moreno Berggren D, Kjellander M, Backlund E, Engvall M, Garelius H, Lorenz F, Nilsson L, Rasmussen B, Lehmann S, Hellström Lindberg E, Jädersten M Ungerstedt J, Ejerblad E. Br J Haematol. 2021 Feb;192(3):474 483

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Cancer Research Area

- Pediatric cancer

Key research field interests

- Neuroblastoma
- Medulloblastoma
- in vivo modelling
- Translational research

Unique instruments and methodologies used in the group

- Genetical engineered mouse and zebrafish model of cancer
- Organoids

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. Currently we are investigating the effects of Chr17q gain and candidate genes on Chr17q using zebrafish, HESC and iPS-derived neural crest cells in different phases of maturation as model systems.

A selection of publications from your group

1. 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.
2. Songbai Z, Miyakawa A, Vara-Godoy M, Kanatani S, Wickström M, Elfman LMH, Dyberg C, Kronqvist P, Repo H, Sahlgren C, Mikoshiba K, Lendahl U, Johnsen JI, Uhlén P. GIT1 guards against breast cancer growth through negative regulation of Notch. Nat Commun. 2022 Mar 22;13(1):1537. doi: 10.1038/s41467-022-28631-y.
3. 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

- Breast Cancer

Key research field interests

- Breast cancer
- Clinical studies
- Prognostic biomarkers
- Individual based treatments

Unique instruments and methodologies used in the group

Abstract

A selection of publications from your group

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Cancer Research Area

- Glioma

Key research field interests

- Stem cells
- SOX transcription factors
- Glioma
- Tumor suppressors

Unique instruments and methodologies used in the group

SOX21 counteract glioblastoma growth by counteracting SOX2 activated gene expression.

Jonas Muhr

High-grade glioma is the most frequent primary tumour of the brain. One reason why the standard of care of this tumour type unavoidably fails can be explained by the fact that rarely dividing glioma stem cells (GSCs), which have the capacity initiate and drive tumour recurrence, are resistant to current therapies. Members of the SOX family of transcription factors (TFs) are multifaceted regulators of various stem cell populations. For instance, the TF SOX2 has well recognized roles in maintaining healthy and cancerous stem cells in an undifferentiated, self-renewing state. Another member of the SOX TF family, termed SOX21, shares more than 95% sequence identity of its DNA binding domain with that of SOX2, but has the opposite function compared with SOX2.

Using a mouse glioma model, we have demonstrated that the removal of SOX21 strongly increases the capacity of the activated oncogenes, H-RAS and AKT, to induce the formation of high-grade glioma like tumours. In human SOX21 is a prognostic marker, where increased levels of SOX21 expression are associated with significant longer survival of high-grade glioma patients. Consistently, bioluminescent measurements and mouse survival data show that doxycycline-activated SOX21 expression in pre-established, orthotopic glioma significantly can decrease tumour growth. RNA-seq, ChIP-seq and ATAC-seq analyses of GSCs show that SOX21, achieve these functions by repressing active chromatin and the expression of cancer promoting genes, which are activated by SOX2. Together these findings reveal novel insights into the molecular machinery that sustain the maintenance and selfrenewal of GSCs.

A selection of publications from your group

1. Daniel W. Hagey, D., Topcic, D., Kee, N., Reynaud, F., Perlmann, T., Muhr, J. (2020) CYCLIN-B1/2 and -D1 act in opposition to coordinate cortical progenitor self-renewal and lineage commitment. Nature Commun. 2898 (11), doi.org/10.1038/s41467-020-16597-8
2. Kurtsdotter, I.,Topcic, D., Alexandra, K., Hagey, D., Singla, B., Bergsland, M., Nister, M., Carlson, J., Lefebvre, V., Persson, O., Holmberg, J., and Muhr, J. (2017). SOX5/6/21 prevent oncogene-driven transformation of brain stem cells. Cancer Research, 77, 4985-4997.
3. Sandberg, M., Källström, M. and Muhr, J. (2005). Sox21 promotes the progression of vertebrate neurogenesis. Nature Neuroscience 8, 995-1001.

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Cancer Research Area

- Cancer Epidemiology

Key research field interests

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

Unique instruments and methodologies used in the group

- Advanced statistical analyses
- Molecular epidemiology
- AI
- Registries
- Biobanking

Use of genetics and mammography features to improve survival in breast cancer patients

Kamila Czene

In Sweden, breast cancer diagnoses occur every hour, with one woman succumbing to the disease every sixth hour. Prognostic factors for breast cancer encompass both tumor characteristics and patient attributes. Our prior findings underscore the pivotal influence of a patient's inherited genetic background on the disease's aggressiveness. Additionally, an essential patient attribute is the mammographic density of the breast, which plays a critical role in both accurate diagnosis and prognosis.

The primary objective of our research is to gain a comprehensive understanding of the genetic and mammographic factors that impact breast cancer prognosis. We have outlined specific goals as follows:
Family Studies on Genetic Prognostic Factors
Molecular Studies on Genetic Prognostic Factors
Mammographic Factors Influencing Prognosis

In addition to examining breast cancer recurrence and mortality as a model for fatal breast cancer, we are utilizing two additional models - interval cancer and molecular subtypes of breast cancer.
A profound comprehension of the role of inherited genetics stands as a paramount necessity in the development of personalized screening strategies, particularly for women at high risk of aggressive breast cancer, including interval cancers. Moreover, insights into an individual's inherited genetic makeup will provide clinicians with invaluable guidance in optimizing hormonal therapy, ultimately bolstering the chances of an improved prognosis. Meanwhile, the clinical application of mammographic breast density will not only elevate diagnostic accuracy but also serve as a pertinent indicator of an early response to hormonal treatment.

A selection of publications from your group

1. Rodriguez J, Grassmann F, Xiao Q, Eriksson M, Mao X, Bajalica-Lagercrantz S, Hall P and Czene, K. Investigation of Genetic Alterations Associated with Interval Breast Cancer. JAMA Oncology. 2023; in press.
2. He W, Grassmann F, Eriksson M, Eliasson E, Margolin S, Thoren L, Hall P and Czene K. CYP2D6 Genotype Predicts Tamoxifen Discontinuation and Prognosis in Patients With Breast Cancer. Journal of Clinical Oncology. 2020;38(6):548-557.
3. Holm J, Humphreys K, Li J, Ploner A, Cheddad A, Eriksson M, Tornberg S, Hall P and Czene K. Risk Factors and Tumor Characteristics of Interval Cancers by Mammographic Density. Journal of Clinical Oncology. 2015;33(9):1030-7.

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Cancer Research Area

- Mainly pediatric cancer (neuroblastoma and rhabdomyosarcoma)

Key research field interests

- Tumor evolution
- Drug resistance
- Drug combinations
- Radiopharmaceutical Therapy
- Functional Precision Medicine

Unique instruments and methodologies used in the group

- Expressed cell barcodes
- High-throughput drug screening
- Organoids
- Microwells
- Single cell sequencing

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 subpopulations that enrich under standard of care treatment, and to systematically search for targeted therapies 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.

A selection of publications from your group

1. 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
2. Sockell A, Wong W, Longwell S, Vu T, Karlsson K, Mokhtari D, Schaepe J, Lo YH, Cornelius V, Kuo C, Valen DV, Curtis C, Fordyce P, A microwell platform for high-throughput longitudinal phenotyping and selective retrieval of organoids, Cell Systems, Volume 14, issue 9, pages 764-778(2023)
3. 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

Unique instruments and methodologies used in the group

- Natural history modelling
- Mathematical biology
- Tools for evaluating early detection
- Risk prediction

Tumour growth, random effects models for breast cancer screening data – studies of aggressive breast cancer and screening performance

Keith Humphreys

We develop and use biologically motivated statistical 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.

A selection of publications from your group

1. 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.
2. 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.
3. 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

- Late complications after cancer therapy, primarily cognitive deficits

Key research field interests

- Late complications
- Radiotherapy
- Paediatric brain tumours

Unique instruments and methodologies used in the group

- Animal models of cranial radiotherapy
- Advanced bioinformatics for single cell sequencing
- Experience from clinical trials

To prevent, or even reverse, cognitive late complications after cranial radiotherapy

Klas Blomgren

Lithium has been found to protect brain tissue from IR-induced injury and promote regeneration, without protecting tumour cells. Lithium has even been shown to have anti-tumour effects. There are currently no therapies available to prevent or ameliorate the effects of cranial radiotherapy, but there are 3 hubs where clinical trials for children have been initiated, Stockholm (lithium), St Jude, Memphis, USA (metformin), and Sick Kids, Toronto, Canada (memantine). We envision that in the coming decades, we will combine preventive measures and active treatments, just like how we combine anti-tumour treatments, to improve not only survival, but also the quality of survival.

LiBRA (Lithium treatment to prevent cognitive impairment after brain radiotherapy), EuCT Number: 2022-500175-32-00, is a phase 2, multi-centre, double blind, placebo-controlled, randomised clinical trial. It was approved by the ethics review board and the Swedish medical products agency on May 2nd, 2023. We aim to include 84 children after their tumour therapy and treat them with lithium or placebo for 6 months, followed by neuropsychological assessments, MRI and QoL questionnaires up to 5 years. Patients from Nordic countries and France will be included.

A selection of publications from your group

1. 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 and Blomgren K (2021) Lithium reverses irradiation-induced changes in rodent neural progenitors and rescues cognition. Molecular Psychiatry. 26(1):322-340. Epub 2019 Nov 14.
2. Yuan J, Song J, Zhu D, Sun E, Xia L, Zhang X, Gao C, Agam G, Wang X, Blomgren K and Zhu C (2018) Lithium treatment is safe in children with intellectual disability. Front Mol Neurosci. 11:425, 1-9.
3. Zhou K, Xie C, Wickström M, DolgaAM, Zhang Y, Li T, Culmsee C, Kogner P, Zhu C and Blomgren K (2017) Lithium protects hippocampal progenitors, cognitive performance and hypothalamus-pituitary function after irradiation to the juvenile rat brain. Oncotarget. 8(21):34111-34127.

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Cancer Research Area

- Molecular- and translational lung cancer research

Key research field interests

- Lung cancer
- Precision cancer medicin
- Radiotherapy
- Extracellular vesicles
- Eph signaling cascade

Unique instruments and methodologies used in the group

- Isolation/characterization of extracellular vesicles from plasma/serum
- Fine needle aspiration and biomarker discovery
- Characterization of radiotherapy signaling

Molecular- and translational research in non-small cell lung cancer- identification of precision cancer medicine and radiotherapy sensitizing targets

Kristina Viktorsson

Our team focus on non-small cell lung cancer (NSCLC) patients and their response to precision cancer medicine (PCM) treatment including small tyrosine kinase inhibitors (TKIs) and immune check point blockade. We are working in preclinical models of NSCLC but are also focusing on primary NSCLC cells as well as tumor- and liquid biopsies of NSCLC patients in relation to above mentioned therapies in national-and international collaborative efforts. We have a specific interest in integrating PCM with radiotherapy, in particular with stereotactic body radiotherapy (SBRT), where our work span from preclinical characterization into biomarker (BM) discovery in liquid biopsies.

We have a focus on extracellular vesicles (EVs) in plasma/serum as a source of BMs for prediction of treatment response but also on understanding their role as signaling drivers in context of PCM therapies and metastasis. Thus, we are currently studying the potential of using EV protein cargo to predict metastatic spread of early-stage NSCLC patients, a joint effort with Sheba Medical Center and Tel Aviv University. In another collaboration t with Uppsala University and Royal Institute of Technology, we are developing nanosensors for rapid and sensitive characterization of EV surface proteins.

We have identified the Ephrin- and Eph signaling to be important in NSCLC controlling survival, migration/invasion, and response to radiotherapy. Our unpublished data support a role for the Ephrin B3 and EphA2 receptor cascade in influencing response to EGFR-TKIs, constituting a possible next PCM target. We are in this context deciphering the role of EVs in transmitting such Ephrin- and Eph driving signaling circuits and their effect on treatment response. In summary, our team has know-how on BM discovery and novel treatment target identification in NSCLC spanning from preclinical characterization to biomarker discovery with a focus on PCM and/or its integration with SBRT.

A selection of publications from your group

1. 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.
2. 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 fine-needle 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.
3. 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.

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Cancer Research Area

- Tumor biology
- Metastasis
- Drug screening

Key research field interests

- Mechanotransduction
- Gene regulation
- Cancer therapy

Unique instruments and methodologies used in the group

- Proximity-dependent Biotin Identification (BioID)
- Chromatin-IP
- Atac-seq
- Proximity ligation Assay

Targeting mechanotransduction in invasive cancer

Lars Holmgren

Tumor cells possess the ability to infiltrate healthy tissues, forming small clusters at the tumor periphery, which is often associated with a dismal prognosis and presents a formidable challenge for conventional therapies. Our previous research pinpointed the significance of p60AmotL2 expression in invasive colon and breast cancer cells, revealing its pivotal role as part of the Hippo pathway. In vitro investigations unveiled that p60AmotL2 promotes the invasion of epithelial cells by negatively impacting E-cadherin binding affinity. In this study, we introduce an innovative strategy for combatting invasive cancer cells. We employed a library of compounds known for their anti-tumor activities and applied them to epithelial cells transfected with inducible p60AmotL2 in a phenotypic screening assay. This approach led us to the identification of 60 compounds exhibiting selective targeting of the expressing cells. Intriguingly, these compounds fell into two distinct categories: Epidermal Growth Factor (EGF) tyrosine kinase inhibitors and inhibitors of Bromodomain and Extra-Terminal motif (BET) proteins. Of particular note, the BET protein inhibitors consistently demonstrated potent anti-tumor activity not only in human cancer cell lines but also in organoids derived from colon cancer patients. These compelling findings underscore the efficacy of our phenotypic screening strategy in uncovering novel compounds specifically tailored to target invasive cancer cells. This research not only offers promising avenues for the development of new therapies aimed at combatting the relentless progression of invasive tumors but also highlights the critical role of p60AmotL2 in the Hippo pathway, providing valuable insights into the molecular mechanisms underlying tumor invasion and progression.

A selection of publications from your group

1. Mojallal, M., Zheng, Y., Hultin, S., Audebert, S., Van Harn, T., Johnsson, P., Lenander, C.,-Fritz, N., Mieth, C., and Corcoran, M. (2014). AmotL2 disrupts apical–basal cell polarity and promotes tumour invasion. Nature communications 5, 4557.
2. Subramani, A., Cui, W., Zhang, Y., Friman, T., Zhao, Z., Huang, W., Fonseca, P., Lui, W.O., Narayanan, V., Bobrowska, J., et al. (2023). Modulation of E-Cadherin Function through the AmotL2 Isoforms Promotes Ameboid Cell Invasion. Cells 12. 10.3390/cells12131682.
3. Zhang, Y., Zhang, Y., Hutterer, E., Hultin, S., Bergman, O., Kolbeinsdottir, S., Jin, H., Forteza, M.J., Ketelhuth, D.F.J., Roy, J., et al. (2023). The VE-cadherin/AmotL2 mechanosensory pathway suppresses aortic inflammation and the formation of abdominal aortic aneurysms. Nature Cardiovascular Research 2, 629-644. 10.1038/s44161-023-00298-8.

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Cancer Research Area

- Cancer pathology

Key research field interests

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

Unique instruments and methodologies used in the group

- Rapid autopsies
- Automated high-throughput ex-vivo assays
- Digital image analysis
- Multicolor immunohistochemistry

The life of cancer inside and outside of the human body

Laszlo Szekely

The vast majority of cancer research takes a reductionist approach to study cancer on model organisms, cell lines or surgically excised tumor samples. It is a rare opportunity to study cancer in the context of the entire human body, to follow the genetic/epigenetic evolution of a disseminating tumor, to study the various interactions with the host tissues and to dissect the response to various therapeutic interventions. During the Covid-19 pandemic we have developed procedures to carry out rapid autopsies (less than 24 hours post mortem) combined with very detailed sampling for subsequent scientific analysis. These routines are now in place and constitute a very valuable resource to obtain both fresh (living) and adequately fixed material also for basic cancer research as well as for the evaluation of the efficacy of novel therapies. Postmortem examination also helps to dispel frequent misconceptions about the cause of death of cancer patients. As overall and cancer specific mortality are important endpoints of clinical trials, precise determination of the reason and mechanism of death is paramount for correct evaluation of the therapy effect of new agents.

Studying the proper environment for cancer growth and survival in the body helped us to create ex vivo conditions that permit primary cancer cells not only to survive but also to thrive outside of the body. Combining these ex vivo systems with high throughput fluid handling and automated single cell imaging techniques allowed us to test large numbers of therapeutic agents to assist individualized therapy.

A selection of publications from your group

1. Pulmonary stromal expansion and intra-alveolar coagulation are primary causes of COVID-19 death. Heliyon 7: Szekely L, Bozoky B, Bendek M, Ostad M, Lavignasse P, Haag L, Wu J, Jing X, Gupta S, Saccon E, Sönnerborg B A, Cao Y, Björnstedt M & Szakos A (2021)
2. Cellular-resolution 3D virtual histology of human coronary arteries using x-ray phase tomography. Nature Portfolio Scientific reports 8: 1–7 Vågberg W, Persson J, Szekely L & Hertz HM (2018) Sensitivity of chronic lymphocytic leukemia cells to small targeted therapeutic molecules: An in vitro comparative study Sylvan Se, Skribek H, Norin S, Muhari O, Österborg A, Szekely L
3. Experimental hematology 2016;44(1):38-49.

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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

Unique instruments and methodologies used in the group

- Broad expertise in biostatistics/bioinformatics and epidemiology applied to cancer research
- Clinical trial annotation, i.e. collection and annotation of tumor tissue in the large STO-trials
- Currently running several projects with interest in intra-tumor heterogeneity using:
    - » Deep-learning (AI) to analyse IHC images stained with the clinically used markers
    - » Imaging mass cytometry (IMC) simultaneously imaging around 40 proteins at subcellular resolution

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

Linda Sofie 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

1. 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.
2. 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.
3. Lindström LS, Yau C, Czene K, Thompson CK, Hoadley KA, Van't Veer LJ, Balassanian R, Bishop JW, Carpenter PM, Chen YY, Datnow B, Hasteh F, Krings G, Lin F, Zhang Y, Nordenskjöld B, Stål O, Benz CC, Fornander T, Borowsky AD, Esserman LJ; STO Trialists Group. Intra-tumor heterogeneity of the estrogen receptor and the long-term risk of fatal breast Cancer. J Natl of Cancer Inst, (JNCI). 2018. PMID: 29361175.

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Cancer Research Area

- Hematology

Key research field interests

- Myelodysplastic syndrome
- Myeloid malignancies
- Allogeneic stem cell transplantation
- Next-generation sequencing
- Targeted therapy

Unique instruments and methodologies used in the group

- NGS
- Digital droplet PCR
- Super rolling circle amplification
- FACS

Implementing genetic MRD assessment in the clinical care of patients with myelodysplastic syndrome

Magnus Tobiasson

Clinical studies on transplantation in MDS

We performed a prospective observational study, NMDSG14B Part 1 between 2016-2021, in which we enrolled 266 Nordic MDS patients undergoing transplantation (HSCT). We developed a digital droplet PCR method to trace patient-specific mutations post-HSCT to be used as markers of measurable residual disease (MRD). MRD was strongly associated with relapse-free survival (HR 7.9, p<0.001) where pos MRD preceded clinical relapse by a median of 71 days. This opens a window where patients can be treated pre-emptively before a manifest clinical relapse. In the subsequent NMDSG14B Part 2, 2023-2027 200 consecutive patients will be enrolled in a prospective, multicenter, single-armed phase II study involving all transplantation centers in the Nordic countries. MRD will be analyzed in real time during the first 2 years post HSCT and used to advice clinical intervention where MRD-pos patients will receive treatment with Azacitidine and donor lymphocytes. MRD-pos patients who are still treated with immune suppressive drugs will first undergo tapering of the immune suppression. The NMDSG14B Part 2 study will use the same MRD methodology as NMDSG14B Part 1 and we will be able to compare outcome between Part 2 (intervention) and Part 1 (non-intervention), the latter serving as a control group.

Enhanced sensitivity of methods for detecting measurable residual disease

By using the biobank material from the NMDSG14B-project, we working on protocols for enhancing sensitivity of the MRD methodologies. In the first protocol we are using, digital droplet PCR on sorted CD34+ cells. In a second protocol, we are using the super rolling circle amplification.

Evaluation of the importance of achieving clone reduction before transplantation.

By using a large cohort (n=350) of transplanted MDS patients, we are investigating the importance of clone reduction before transplantation.

A selection of publications from your group

1. Nannya Y*, Tobiasson M*, Sato S, Bernard E, Ohtake S, Takeda J, Creignou M, Zhao L, Kusakabe M, Shibata Y, Nakamura N, Watanabe M, Hiramoto N, Shiozawa Y, Shiraishi Y, Tanaka H, Yoshida K, Kakiuchi N, Makishima H, Nakagawa MM, Usuki K, Watanabe M, Imada K, Handa H, Taguchi M, Kiguchi T, Ohyashiki K, Ishikawa T, Takaori-Kondo A, Tsurumi H, Kasahara S, Chiba S, Naoe T, Miyano S, Papaemmanuil E, Miyazaki Y, Hellstrom Lindberg E, Ogawa S. Post-azacitidine clone size predicts outcome of patients with myelodysplastic syndromes and related myeloid neoplasms. Blood Adv. 2023. * shared first author
2. Lindholm C, Olofsson E, Jädersten M, Ljungman P, Ejerblad E, Tobiasson M. Failure to reach hematopoietic allogenic stem cell transplantation in patients with myelodysplastic syndromes planned for transplantation: a population-based study. Bone Marrow Transplant. 2022;57(4):598-60
3. Magnus Tobiasson, Tatjana Pandzic, Johanna Illman, Lars Nilsson, Simone Weström, Karin Sollander, Elisabeth Ejerblad, Astrid Olsnes Kittang, Gitte Olesen, Olle Werlenius, Andreas Björklund, Joel Wiggh, carolin lindholm, Fryderyk Lorentz, Bengt Rasmussen, Jörg Cammenga, Duruta Weber, David Grönnås, Marios Dimitriou, Soili Kytölä, Gunilla Walldin, Per Ljungman, Kirsten Groenbeck, Stephan Mielke, Sten Eirik Jacobsen, Freja Ebeling, Lucia Cavelier, Lone Smidstrup Friis, Ingunn Dybedal, Eva Hellström-Lindberg, Patient-specific measurable residual disease markers predict outcome in patients with myelodysplastic syndrome and related diseases after allogeneic stem cell transplantation, Accepted for publication in Journal of Clinical Oncology, 2023

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Cancer Research Area

- Pediatric cancer
- Neuroblastoma
- Medulloblastoma

Key research field interests

- Neuroblastoma
- Differentiation
- Pharmacology
- Precision medicine

Unique instruments and methodologies used in the group

- In vitro and in vivo models for neuroblastoma

Novel approaches for neuroblastoma therapy

Malin Wickström Näsman

The research is focused on identifying and characterizing novel therapeutic approaches for pediatric cancers, mainly neuroblastoma. Neuroblastoma is a childhood cancer of the sympathetic nervous system and differentiation arrest of neural crest-derived cells is considered to contribute to neuroblastoma formation. We are evaluating novel targeted therapies including combinational treatments, with the aim to identify novel therapies to treat refractory and metastatic disease to improve patient survival and reduce side effects. We have a specific interest in drugs targeting differentiation and genes associated to neurogenesis such as Rho kinase and tenuerins. The lab is using screenings, in vitro models including 3D models, as well as in vivo models as patient derived xenograft and transgenic mouse models.

A selection of publications from your group

1. Ljungblad L, Bergqvist F, Tümmler C, Madawala S, Olsen TK, Andonova T, Jakobsson PJ,Johnsen JI, Pickova J, Strandvik B, Kogner P, Gleissman H, Wickström M. Omega-3 fatty acids decrease CRYAB, production of oncogenic prostaglandin E2 and suppress tumor growth in medulloblastoma. Life sciences 295:120394-, 2022
2. Dyberg C, Andonova T, Olsen TK, Brodin B, Kool M, Kogner P, Johnsen JI, Wickström M. Inhibition of Rho-associated kinase suppresses medulloblastoma growth. Cancers 12(1). pii: E73, 2019.
3. Dyberg C, Fransson S, Andonova T, Sveinbjornsson B, Lännerholm-Palm J, Olsen TK, Forsberg D, Herlenius E, Martinsson T, Brodin B, Kogner P, Johnsen JI, Wickström M. Rho-associated kinase is a therapeutic target in neuroblastoma. Proc Natl Acad Sci U S A 114(32):E6603-E6612, 2017

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Cancer Research Area

- Gastrointestinal Cancers (Liver Metastases and Pancreatic Cancer)

Key research field interests

- Digital pathology
- Cancer cell invasion strategies
- Cell competition
- ctDNA

Unique instruments and methodologies used in the group

- Clinical cohorts of liver metastases (several hundred patients)
- Multiplex ISH and IF
- Digital quantitative analyses of ISH and IF
- Mouse models of metastases and in vivo imaging

Cancer Cell Invasion

Marco Gerling

We study clinical and mechanistic aspects of how cancer cells invade non-malignant epithelial structures. Our focus is on colorectal cancer liver metastases and pancreatic cancer, for both of which we have built patient cohorts comprising clinical data and histopathological images, collected into a digital image database and linked to both paraffin-embedded and fresh tissue samples. With an international consortium, we have developed histological scoring guidelines for liver metastases, by which we systematize our approach to the histological image data.

Together with Martin Enge's group, we have used a novel computational method to identify direct cellcell interactions in intact tissue with RNA sequencing. Our unpublished data show that invading cancer cells reshape directly adjacent epithelial cells, such that they induce a chronic-injury-like response leading to dedifferentiation of the surrounding epithelial cells at the leading edge of tumor invasion. The extent of this reaction is associated with prognosis.

Single-cell based identification and in situ remapping of the interaction partners at the tumor leading edge have identified intercellular signaling pathways that potentially facilitate tumor cell invasion, including IL-6/p-stat3 and Jag1/Notch2, which we study in ongoing experiments in vivo in mice and with organoid models. Our mechanistic studies approach tumor invasion from the angle of cell competition, an evolutionary conserved mechanism that can either restrain or facilitate tumor cell invasion into healthy tissue. Based on our data on the involved cell types, we ask whether tumor cells and dedifferentiated non-malignant epithelial cells engage in cell competition, and how their interactions can be used to inhibit tumor invasion.

Clinically, we are part of an EU-funded study, GUIDE-MRD, which investigates the value of circulating tumor DNA to detect minimal residual disease (MRD) after surgical removal of liver metastases or pancreatic cancer. Through GUIDE.MRD, we prospectively collect data on somatic mutations, histology, and blood markers, aiming for improved diagnostics of relapse connected to tumor biological characteristics. We hope to be able to connect tumor invasion phenotypes with tumor genetics and clinical outcome, for which these prospective studies provide the necessary infrastructure

A selection of publications from your group

1. 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.
2. Histopathological growth patterns of liver metastasis: updated consensus guidelines for pattern scoring, perspectives and recent mechanistic insights. Latacz E, Höppener D, Bohlok A, Leduc S, Tabariès S, Fernández Moro C, Lugassy C, Nyström H, Bozóky B, Floris G, Geyer N, Brodt P, Llado L, Van Mileghem L, De Schepper M, Majeed AW, Lazaris A, Dirix P, Zhang Q, Petrillo SK, Vankerckhove S, Joye I, Meyer Y, Gregorieff A, Roig NR, Vidal-Vanaclocha F, Denis L, Oliveira RC, Metrakos P, Grünhagen DJ, Nagtegaal ID, Mollevi DG, Jarnagin WR, D'Angelica MI, Reynolds AR, Doukas M, Desmedt C, Dirix L, Donckier V, Siegel PM, Barnhill R, Gerling M*, Verhoef C*, Vermeulen PB*. British Journal of Cancer. 2022 Oct;127(6):988-1013. doi: 10.1038/s41416-022-01859-7.

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Cancer Research Area

- Pediatric neural tumors
- Cancer models
- PCM

Key research field interests

- Tumor initiation mechanisms
- Tumor microenvironment
- Targeted Therapy

Unique instruments and methodologies used in the group

- iPS reprogramming and neural differentiation
- Mouse models of cancer
- CNS organoids
- Zebrafish models
- High throughput drug screening platforms

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.

A selection of publications from your group

1. 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;
2. Susanto E., Marin Navarro A., Zhou, L., Sundström A, van Bree, N., Stantic, M., Moslem, M., Tailor J, Rietdijk J, Zubillaga, V., Hübner J, Weishaupt, H., Wolfsberger, J., Alafuzoff I, Nordgren A, Magnaldo T, Siesjö P., Johnsen J, Kool M, Darabi A, Swartling F., Falk A., and Wilhelm M. (2020) Modelling SHH-driven medulloblastoma with patient iPS cellderived neural stem cells. Proc Natl Acad Sci U S A 117(33):20127-20138, doi.org/10.1073/pnas.1920521117
3. Marin Navarro, A., Pronk, R.J., Tjitske van der Geest, A., Oliynyk, G., Nordgren, A., Arsenian-Henriksson, M., Falk, A., and Wilhelm, M. (2020) p53 controls genomic stability and temporal differenNaNon of human neural stem cells and affects neuralorganization in human brain organoids. Cell Death & Dis 11(52):1-15, doi.org/10.1038/s41419-019-2208-7

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Cancer Research Area

- Preclinical cancer research

Key research field interests

- Epithelial stem cells
- Niche signaling
- Cell heterogeneity

Unique instruments and methodologies used in the group

Functional fibroblast heterogeneity in the esophageal stem cell niche

Maria Genander

Fibroblasts are a key component of the healthy stem and tumor cell niche. Here, we identify and functionally characterize fibroblast heterogeneity in the esophagus during homeostasis and tumor development. We find that TROYPOS fibroblasts are differentially distributed from proximal to distal and are in direct contact with the esophageal epithelium. Transcriptional profiling suggests that TROYPOS fibroblasts are different from TROYNEG fibroblast regarding extracellular matrix organization, WNT and IGF signaling factors. However, organoidfibroblast cocultures show that both populations can support organoid formation and growth. Ablating TROYPOS fibroblasts, using the TroyiDTR mouse model, results in reduced epithelial proliferation and increase in organoid growth, establishing an important role for TROYPOS fibroblast in maintaining epithelial homeostasis of the esophagus.
To understand the dynamics and role of TROYPOS fibroblasts in cancer initiation, we treated mice with the carcinogen 4NQO. We find a spatial reorganization of the stromal niche, where TROYPOS fibroblasts loose contact with the epithelium and down regulate Troy expression. Xenografting demonstrate that TROYPOS fibroblasts from the untransformed esophagus inhibit tumor esophageal tumor growth and organoid co-cultures reveal functional alterations in TROYPOS cell states during transformation. Ablation of TROYPOS fibroblasts during 4-NQO treatment promotes remodeling of the esophageal epithelium and leads to an increase in intraepithelial immune cells. We identify an esophageal fibroblast niche cell dynamically regulated during tumor initiation.

A selection of publications from your group

1. Grommisch D, Wang M, Eenjes E, Svetlicic M, Deng Q, Giselsson P and Genander M Symmetrically fated progenitors dynamically accommodate tissue maintenance in the esophagus In Revision
2. Eenjes E, Grommisch D and Genander M Functional characterization and visualization of esophageal fibroblasts using organoid cocultures. J Vis Exp. (2023) Jan 6;191. doi: 10.3791/64905. PMID: 36688545
3. Kantzer CG, Yang W, Grommisch D, Vikhe Patil K, Mak KH and Genander M. ID1 and CEBPA coordinate epidermal progenitor cell differentiation. Development (2022) Nov 15;149(22):dev201262.PMID: 36330928

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Cancer Research Area

- Viral oncogenesis

Key research field interests

- Tumor viruses
- Ubiquitin-proteasome system
- mRNA translation
- Ribosome quality control
- Autophagy

Unique instruments and methodologies used in the group

Host cell remodeling by oncogenic herpes viruses

Maria Grazia Masucci

The post-translational modification of proteins by covalent conjugation of ubiquitin (Ub) or ubiquitin-like (UBL) polypeptides regulates numerous cellular processes. The effect of the modification is reversed by deconjugases that hydrolyze the covalent bond and recycle ubiquitin and the UBLs. The importance of protein ubiquitination for the control of viral infections is underscored by the finding that many DNA and RNA viruses encode Ub/UbL deconjugases (vDUBs) that interfere with cellular processes captured by viruses to promote infection and suppress antiviral responses. The herpesvirus's large tegument proteins' N-terminal domains encode a conserved vDUB with Ub- and NEDD8-specific deconjugase activity. The protein is expressed during productive infection and is incorporated into virus particles, suggesting possible roles during both the early and late phases of infection. Our research aims to elucidate how the vDUB encoded by the human oncogenic herpesvirus Epstein-Barr virus (EBV) contributes to the host-cell remodeling that accompanies acute and latent infection and promotes malignant transformation. We found the EBV vDUB interacts with numerous cellular proteins and protein complexes required for viral genome replication and the release of virus particles. The viral enzyme counteracts antiviral responses by regulating the activity of telomerase, mRNA translation, ribosome quality control, type I IFN response and autophagy. The conserved nature of the viral enzymes and their double role in the regulation of the virus life cycle and the host antiviral response makes them attractive targets for the development of new antiviral drugs.

A selection of publications from your group

1. Gastaldello S, Hildebrand S, Faridani O, Callegari S, Palmkvist M, Di Guglielmo C, Masucci MG. (2010) A deneddylase encoded by Epstein Barr virus promotes viral DNA replication by regulating the activity of cullin-RING-ligases. Nature Cell Biol. 12:351-361
2. Gupta S, Ylä-Anttila P, Callegari S, Tsai MH, Delecluse HJ, Masucci MG. (2018) Herpesvirus deconjugases inhibit the IFN response by promoting TRIM25 autoubiquitination and functional inactivation of the RIG-I signalosome. PLoS Pathog. 22;14(1):e1006852. doi: 10.1371/journal.ppat.1006852.
3. Ylä-Anttila P, Gupta S, Masucci MG. (2021). The Epstein-Barr virus deubiquitinase BPLF1 targets SQSTM1/p62 to inhibit selective autophagy. Autophagy. 2021 Jan 28:1-15. Doi 10.1080/15548627.2021.1874660.
4. Li J, Nagy N, Gupta S, Frisan T., Hennig T, Cameron DP, Baranello L, Masucci MG. (2021) The Epstein-Barr virus deubiquitinating enzyme BPLF1 regulates the activity of topoisomerase II during productive infection. PLoS Pathog. Sep 20;17(9):e1009954. doi: 10.1371/journal.ppat.1009954.
5. Liu J, Nagy N, Ayala-Torres C, Auilar-Alonso F, Esteves, F, Xu S, Masucci MG. (2023) Remodelind of Ribosomal Quality Control and Integrated Stress responses by viral ubiquitina deconjugases. Research Square Research Square https://doi.org/10.21203/rs.3.rs-2648447/v1 in review Nature Comm

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Cancer Research Area

- DNA repair

Key research field interests

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

Unique instruments and methodologies used in the group

- Cell biology techniques
- Microscopy, sequencing
- DNA repair and cell
- Survival assays
- RNA and chromatin immunoprecipitation

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. Evidence that RNA participates in DNA repair is accumulating, but the extent of this involvement, underlying mechanism(s) and therapeutic implications remain largely unclear. Our laboratory recently demonstrated that the small Cajal body-specific RNA 2 (scaRNA2) can regulate DNA repair by binding to and inhibiting the catalytic subunit of the DNA-PK repair enzyme. 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.
As a second part of my talk, I will present data that protein synthesis is controlled by mRNA pseudouridylation, the most abundant and widespread type of modification in RNA. We show that pseudouridine is incorporated into mRNAs during their transcription and that the pseudouridine synthase dyskerin plays a key role in this process. Moreover, we find that this modification reduces the rate of mRNA translation and that loss of dyskerin-mediated pseudouridylation results in global elevation of protein synthesis. Notably, this process is disrupted in patients with dyskeratosis congenita, caused by inherited mutations in dyskerin and suggesting that pseudouridylation of mRNA plays a role in the underlying pathogenesis. We propose that co-transcriptional pseudouridylation of mRNA enables coordination of transcription and translation, with important implications for both normal development and disease

A selection of publications from your group

1. 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/
2. 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

- Childhood cancer
- Neuroblastoma
- Neural differentiation
- Metabolism
- Lipid metabolism
- Clear cell renal cell carcinoma
- Cervical carcinoma

Key research field interests

Unique instruments and methodologies used in the group

- Aligent Seahorse XF analyzer
- Image Stream
- Live cell imaging;
- hiPS cells
- Nanoparticles (in collaboration)

Targeting MYC induces lipid droplet accumulation by upregulation of HILPDA in clear cell renal cell carcinoma

Marie Arsenan-Henriksson

Metabolic reprogramming is crucial during clear cell renal cell carcinoma (ccRCC) development, manifested by accumulation of lipid droplets (LDs). This process is mainly governed by the constitutive activation of the hypoxia inducible factors (HIFs) due to loss of the von Hippel-Lindau (VHL) gene, and upregulation of MYC signaling. Lipid droplets are specialized organelles composed of a core rich in triglycerides and sterol esters, surrounded by a phospholipid monolayer. For long, they have been considered as inert vesicles for fat deposit, product of altered metabolism. But, in recent years, they have gained recognition as emerging regulators of tumorigenesis. Yet, the mechanisms and factors regulating their biogenesis are still poorly described.

Here, we studied the molecular mechanism underlying lipid droplet accumulation in ccRCC after MYC inhibition. Using a combination of lipidomics and metabolic tracing, we found that constitutive HIF expression combined with MYC inhibition induces reprogramming of glutamine metabolism, which was directed towards accumulation of triglycerides, the main component of LDs. However, combined VHL expression with MYC inhibition resulted in an increase in inositol-related lipid species, and thus, no LD formation was observed. Importantly, concomitant inhibition of both MYC and glutamine metabolism using OMOMYC and BPTES resulted in reduced tumor burden and impaired LD accumulation in vivo. Using bulk RNAseq analysis, we identified the hypoxia inducible lipid droplet associated protein (HILPDA) as the key driver for LD accumulation upon MYC inhibition. We further demonstrated that this protein impairs proliferation as well as LD formation upon downregulation both in vitro and in vivo. Finally, by single-cell RNAseq analysis of ccRCC tumors and renal samples from healthy individuals, we showed that HILPDA is a specific biomarker for ccRCC.

Together, our study characterizes the molecular interplay between hypoxia and MYC signaling resulting in LD accumulation and the identification of HILPDA as a novel target for precision medicine. These discoveries provide an attractive approach for development of new therapeutic interventions for ccRCC.

A selection of publications from your group

1. Sainero-Alcolado L, Mushtaq M*, Liaño-Pons J*, Rodriguez-García A, Yuan Y, Liu T, Ruiz-Pérez MV, Schlisio S, Bedoya Reina O, and Arsenian-Henriksson M**. Expression and activation of nucelar hormone receptors result in neuronal differentiation and favorable prognosis in neuroblastoma. Journal of Experimental & Clinical Cancer Research 41(1):226 (2022). *Equal contribution. **Corresponding author.
2. Ruiz-Pérez MV*, Sainero-Alcolado L, Oliynyk G, Matuschek I, Balboni N, Ubhayasekera SJKA, Snaebjornsson MT, Makowski K, Aaltonen K, Bexell D, Serra D, Nilsson R, Bergquist J, Schulze A, and Arsenian Henriksson M*. Induction of neural differentiation in neuroblastoma upon inhibition of de novo fatty acid synthesis. iScience 24(2):102128 (2021). *Co-corresponding

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Cancer Research Area

- Pancreatic cancer & pre-stages and individuals at risk

Key research field interests

- Pancreatic cancer
- Liquid biopsy
- Intraductal pancreatic neoplasia (IPMN)
- Individuals at risk (IAR)
- Molecular profiling
- Artificial intelligence imaging

Unique instruments and methodologies used in the group

- The asset are the well described patient cohort that we are following prospectively. In addition, the AI supported analysis of imaging (CAT scan, MRI) developed by a joint PhD for the detection of pancreatic masses is unique.

Translational Pancreatic Cancer

Matthias Löhr

We are focusing on early pancreatic cancer and patients at risk for developing pancreatic cancer, especially those with pancreatic cystic lesions, intraductal pancreatic neoplasia (IPMN) and individuals at risk (IAR). Other groups with a risk of developing pancreatic malignancies are patients with chronic and autoimmune pancreatitis. We are following these prospectively and have >3'000 and >400 in our database, respectively. Besides the clinical work-up and characterization, we have now started to apply AI-based image analysis to identify malignant lesions (within the EU project PANCAIM). Two other EU projects focus on liquid biopsy, both prior to the diagnosis of pancreatic cancer (in IPMN, IAR and other risk groups: PANCAID) as well as after therapy (surgery) investigating the recurrence by monitoring the blood to detect minimal residual disease (GUIDE.MRD). Beside contributing patients we also investigate CTC and EV.

A selection of publications from your group

1. Klatte DCF, Wallace MB, Löhr M, Bruno MJ, van Leerdam ME. Hereditary pancreatic cancer. Best Pract Res Clin Gastroenterol. 2022 Jun-Aug;58-59:101783. doi: 10.1016/j.bpg.2021.101783. Epub 2022 Jan 3. PMID: 35988957
2. Pozzi Mucelli RM, Moro CF, Del Chiaro M, Valente R, Blomqvist L, Papanikolaou N, Löhr JM, Kartalis N. Branch-duct intraductal papillary mucinous neoplasm (IPMN): Are cyst volumetry and other novel imaging features able to improve malignancy prediction compared to well-established resection criteria? Eur Radiol. 2022 Aug;32(8):5144-5155. doi: 10.1007/s00330-022-08650-5. Epub 2022 Mar 11. PMID: 35275259
3. 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. J Extracell Vesicles. 2021 Oct;10(12):e12142. doi: 10.1002/jev2.12142.PMID: 34595842
4. El-Heliebi A, Hille C, Laxman N, Svedlund J, Haudum C, Ercan E, Kroneis T, Chen S, Smolle M, Rossmann C, Krzywkowski T, Ahlford A, Darai E, von Amsberg G, Alsdorf W, König F, Löhr M, de Kruijff I, Riethdorf S, Gorges TM, Pantel K, Bauernhofer T, Nilsson M, Sedlmayr P. In Situ Detection and Quantification of AR-V7, AR-FL, PSA, and KRAS Point Mutations in Circulating Tumor Cells. Clin Chem. 2018 Mar;64(3):536-546. doi: 10.1373/clinchem.2017.281295. PubMed PMID: 29301749.
5. All publications at http://bibliometrics.ki.se/public/publicProfile/231

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Cancer Research Area

- Bioinformatics, primarily breast cancer but with pan-cancer projects too

Key research field interests

- Cancer bioinformatics
- Cell cycle
- Gene expression signatures
- Breast Cancer
- Translational research

Unique instruments and methodologies used in the group

- Broad experienced with the analysis of publicly available large-scale genomic datasets in breast and pan-cancer studies
- Applying genomic classifiers in patient cohorts
- Assessing the additional prognostic capacity of biomarkers beyond routine clinical immunohistochemical biomarkers
- Currently running single-cell RNA-seq data projects, have previously run microarray, RNA-seq, DNA-seq, DNA-copy number and IHC-based projects, often integrating multiple 'omics data types

Translational Omics Oncology: Focus on the cell cycle and its clinical applications

Nick Tobin

The past two decades have heralded the arrival of 'omic data technologies including next generation genomics, transcriptomics and proteomics platforms. We are generating data from biological samples at a scale never before seen in history and it is estimated that by 2025, we will require over 5 exabytes of storage space for human genomes alone. This is enough space to house a written log of every word ever spoken by humans to this point in time! In this flood of data, the new bottleneck has become expertise in biological interpretation and the need to hypothesize, theorize and test rather than just generate data has become critical. Nobel prize winner Sir Paul Nurse recently highlighted these shortcomings, lamenting that "Researchers seem reluctant to come to biological conclusions or present new ideas". We place this need at the core of our research team, where the primary objective is to provide definitive answers to novel hypothesis driven questions focused on the cell cycle in cancer.

Specifically, we are currently focused on (i) understanding the differences in oncogenic signalling between cell cycle phases in breast cancer subtypes using single-cell RNA-seq data, and (ii) determining if a gene signature representing the cell cycle can provide prognostic information in older breast cancer patients[1]. Finally, we have also recently examined how the starting or baseline level of cell cycle activity/cell proliferation in normal tissue influences the level of tumour cell cycle activity and found that we can reclassify tumour cell cycle activity by placing it in terms of its normal tissue of origin[2,3].

A selection of publications from your group

1. Castresana-Aguirre M, Johansson A, Matikas A, Foukakis T, Lindström LS, Tobin NP. Clinically relevant gene signatures provide independent prognostic information in older breast cancer patients. medRxiv; 2023. p. 2023.02.14.23285920. Available from: https://www.medrxiv.org/content/10.1101/2023.02.14.23285920v1
2. Lundberg A, Yi JJJ, Lindström LS, Tobin NP. Reclassifying tumour cell cycle activity in terms of its tissue of origin. npj Precis Onc. 2022 Aug 20;6(1):1–10.
3. Lundberg A, Lindström LS, Parker JS, Löverli E, Perou CM, Bergh J, Tobin NP. A pancancer analysis of the frequency of DNA alterations across cell cycle activity levels. Oncogene. 2020 Aug;39(32):5430–40.

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Cancer Research Area

- Various cancers. Among others melanoma and pancreatic ductal adenocarcinoma (PDAC)

Key research field interests

- Ubiquitin-proteasome system
- Autophagy
- Cell-based reporter assays
- Screening
- Advanced microscopy

Unique instruments and methodologies used in the group

- Fluorescent reporter systems for intracellular protein degradation

Targeting the ubiquitin-proteasome system in cancer

Nico Dantuma

The removal of misfolded or otherwise damaged proteins from the intracellular environment is of critical importance for all cells as these aberrant proteins can give rise to toxic protein aggregates. The ubiquitin-proteasome system (UPS) is a central player in the cellular protein quality control as this is the primary proteolytic system responsible for the destruction of misfolded and dysfunctional intracellular proteins. Inhibition of the UPS has gained credit as a means for therapeutic intervention in cancer patients as malignant cells typically produce elevated levels of misfolded proteins, which makes these cells heavily dependent on a fully operative UPS. Consequently, malignant cells are more sensitive to curtailing the activity of the UPS than healthy, non-transformed cells, providing a therapeutic window for drugs that inhibit the activity of the UPS. Our research has been dedicated to understanding the role of the UPS in cancer and exploring its potential as a therapeutic target. Our long-term objective is to gain insight in the molecular interactions that regulate the activity of the UPS in malignant cells and identify new regulatory pathways that may be amenable to therapeutic intervention.

A selection of publications from your group

1. Giovannucci, T.A., F.A. Salomons, M. Haraldsson, L.H.M. Elfman, M. Wickström, P. Young, T. Lundbäck, J. Eirich, M. Altun. R. Jafari, A.-L. Gustavsson, John I. Johnsen and N.P. Dantuma*. 2021. Inhibition of the ubiquitin-proteasome system by an NQO1-activatable compound. Cell Death Dis.12:914. https://doi.org/10.1038/s41419-021-04191-9
2. 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.
3. 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

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Cancer Research Area

- Pre-clinical and translational cancer research
- Breast cancer
- Prostate cancer

Key research field interests

- 3D genome organization
- DNA double-strand breaks
- DNA copy number alterations and structural variants
- Intratumor heterogeneity
- Single-cell DNA sequencing

Unique instruments and methodologies used in the group

- Instruments: I.DOT nanodispensing device for single-cell assays.
- Methods:
- Single-cell DNA sequencing
- Single-cell extrachromosomal circular DNA sequencing
- Single-cell Hi-C
- Breaks Labeling In Situ and Sequencing (BLISS)

Developing and applying single-cell DNA sequencing methods to study intratumor heterogeneity and evolution

Nicola Crosetto

My main research interest is understanding how DNA double-strand breaks (DSBs) arising in cancer cells contribute to the formation of DNA somatic copy number alterations (SCNAs) and structural variants (SVs), and how SCNAs and SVs rewire the three-dimentional (3D) structure of the genome, in turn dysregulating gene expression programs and contributing to cancer phenotypes. Towards this goal, in my lab at KI-SciLifeLab we develop cutting-edge methods to map the location of DSBs genome-wide as well as to profile SCNAs/SVs, extrachromosomal circular DNAs (eccDNAs) and the 3D genome in single cells. We then apply these methods to patient-derived tumor samples (biopsies) with the ultimate goal of deriving clinically useful predictive and/or prognostic biomarkers based on DSBs, SCNAs/SVs and 3D genome. For the latter, we closely collaborate with the group of Assoc Prof Theodoros Foukakis at Karolinska University Hospital, applying our tools to breast cancer specimens obtained in the frame of state-of-the-art clinical trials.

A selection of publications from your group

1. Yan WX, Mirzazadeh R, Garnerone S, Scott D, Schneider MW, Kallas T, Custodio J, Wernersson E, Li Y, Gao L, Federova Y, Zetsche B, Zhang F*, Bienko M*, Crosetto N*. BLISS is a versatile and quantitative method for genome-wide profiling of DNA double-strand breaks. Nat Commun. 2017 May 12; 8:15058. doi: 10.1038/ncomms15058. PMID: 28497783. *Co-corresponding authors
2. Zhang X, Garnerone S, Simonetti M, Harbers L, Nico* M, Mirzazadeh R, Venesio T, Sapino A, Hartman J, Marchiò C, Bienko M * , Crosetto N * . CUTseq is a versatile method for preparing multiplexed DNA sequencing libraries from low-input samples. Nat Commun. 2019 Oct 18;10(1):4732. doi: 10.1038/s41467-019-12570-2. PMID: 31628304. *Co-corresponding authors
3. Girelli G, Custodio J, Kallas T, Agostini F, Spanjaard B, Wernersson E, Mota A, Gelali E, Crosetto N * , Bienko M* GPSeq reveals the radial landscape of chromatin and genomic alterations in the human cell nucleus. Nat Biotechnol. 2020 May 25. doi: 10.1038/s41587-020-0519-y. PMID: 32451505. *Co-corresponding authors

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Cancer Research Area

- Lung cancer

Key research field interests

- NK cells
- Lung tissue
- Lung cancer
- Respiratory viral infections

Unique instruments and methodologies used in the group

- 29-colour flow cytometry
- 45-colour spectral cytometry.
- RNAsequencing
- Live-cell imaging.

Tissue-resident Natural Killer cells comprise a potential future tool for immunotherapeutic approaches in lung cancer

Nicole Marquardt

We have a longstanding interest in Natural Killer (NK) cells in human tissues with a particular focus in human lung tissue. In collaboration with physicians and scientists at Karolinska University Hospitals Huddinge/Solna we collect lung tumor tissue and tumor-free lung tissue from patients undergoing surgery for suspected lung cancer as well as healthy lungs from human organ donors. Importantly, most of our current knowledge about NK cells is derived from studies in peripheral blood while comparatively little is known about NK cells in human tissues. We particularly focus on NK cell lung-homing, tumor-infiltration, tissue-residency, and cytotoxicity.
Our previous studies revealed that human lung NK cells are predominantly comprised of circulating hyporesponsive NK cells (Marquardt et al., JACI 2016). NK cells frequencies and function were further reduced in active cigarette smokers.
In addition to circulating NK cells, a subset of tissue-resident NK cells displaying a transcriptional signature specific for the lung could be identified in all donors (Marquardt et al, Nat.Communications 2019). In 20% of the donors, expansions of hyperresponsive adaptive-like tissue-resident NK cells could be identified in the lung (Brownlie et al., PNAS 2021), and preliminary data suggest uneven distribution of this NK cell subset at different sites of the lungs (Wild et al., in preparation). Finally, we recently found accumulations of functional tissue-resident NK cells in the center of human lung tumors (Brownlie et al., Oncoimmunology 2023), despite previous reports demonstrating a lack of NK cell infiltration into solid tumors. Together, our findings suggest a role for tissue-resident NK cells in human lung tumors, and we believe that tissue-resident NK cells represent a potential alternative for future immunotherapeutic applications for patients with solid tumors.

A selection of publications from your group

1. Brownlie D, von Kries A, Valenzano G, Wild N, Yilmaz E, Säfholm J, Al- Ameri M, Alici E, Ljunggren H-G, Schliemann I, Aricak O, Haglund de Flon F, Michaëlsson J, Marquardt N. Accumulation of tissue-resident natural killer cells, innate lymphoid cells, and CD8+ T cells towards the center of human lung tumors. Oncoimmunology Jul 11;12(1):2233402. 2023. PMID: 37448786
2. Brownlie D, Scharenberg M, Mold JE, Hård J, Kekäläinen E, Buggert M, Nguyen S, Wilson JN, Al-Ameri M, Ljunggren HG, Marquardt N*, Michaëlsson J*. Expansions of adaptive-like NK cells with a tissue-resident phenotype in human lung and blood. Proceedings of the National Academy of Sciences Mar;118: e2016580118. 2021. PMID: 33836578. *Shared senior authorship.
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Cancer Research Area

- Translational paediatric oncology

Key research field interests

- Therapy resistance
- Leukaemia
- Sarcoma
- Immunotherapy
- Nucleotide metabolism

Unique instruments and methodologies used in the group

- Liquid dispensing for drug-drug interaction matrices

Overcoming therapy resistance in paediatric 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 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. 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

1. 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
2. Rudd SG, Tsesmetzis N, Sanjiv K, Paulin CB, Sandhow L, Kutzner J, Hed Myrberg I, Bunten SS, Axelsson H, Zhang SM, Rasti A, Mäkelä P, Coggins SA, Tao S, Suman S, Branca RM, Mermelekas G, Wiita E, Lee S, Walfridsson J, Schinazi RF, Kim B, Lehtiö J, Rassidakis GZ, Pokrovskaja Tamm K, Warpman-Berglund U, Heyman M, Grandér D, Lehmann S, Lundbäck T, Qian H, Henter JI, Schaller T, Helleday T, Herold N. Ribonucleotide reductase inhibitors suppress SAMHD1 ara-CTPase activity enhancing cytarabine efficacy. EMBO Mol Med. 2020 Jan 17:e10419. doi: 10.15252/emmm.201910419. PMID: 31950591

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Cancer Research Area

- Complications of radiotherapy on the skin of cancer patients

Key research field interests

- Radiation biology
- Epigenetics
- Regulatory RNAs
- Wound healing and cancer

Unique instruments and methodologies used in the group

- Advanced bioinformatics for single cell sequencing
- Animal models of radiation and wound healing
- RNA biology

Erasure radiation memory of skin cells to treat adverse skin reactions of radiotherapy

Ning Xu Landén

With the improvement in cancer survival, the long-term toxicities of radiotherapy (RT) have become a significant problem in cancer survivorship. Our recent study has revealed that dermal fibroblasts in cancer patients' skin carry a long-term epigenetic memory of previous RT that impairs skin wound healing capacity, suggesting that the erasure of such maladaptive radiation memory may be used to treat the late on-set adverse effects (LAE) of RT. With the goal of developing innovative approaches to the prevention and reversal of RT toxicity, we further drill down the molecular mechanisms of the radiation memory by landscaping and functionally interrogating temporal, dynamic changes to gene expression, epigenome, and the chromatin features across the process of memory establishment, maintenance, and recall. Moreover, with advanced single-cell multi-omics analysis, we aim to obtain an overview of how radiation memory affects tissue fitness. With this new knowledge, we will explore the therapeutic potential of targeting radiation memory to promote wound repair of previously irradiated skin. This study will revolute our current understanding of the pathogenesis of LAEs and develop a conceptually innovative radiation memory targeting treatment that may lead to a therapeutic breakthrough in treating adverse skin reactions of radiotherapy.

A selection of publications from your group

1. Zhang L, Piipponen M, Liu Z, Li D, Bian X, Toma M, Sommar P, Xu Landén N. Human skin specific long noncoding RNA HOXC13-AS regulates epidermal differentiation by interfering with Golgi-ER retrograde transport. Cell Death and Differentiation, 2023 May;30(5):1334-1348. PMID: 36869179
2. Li D, Kular L, Vij M, Herter EK, Li X, Wang A, Chu T, Toma MA, Zhang L, Liapi E, Blomqvist L, Serezal IG, Rollman O, Wikstrom JD, Berglund D, Ståhle M, Sommar P, Jagodic M, Xu Landén N. Human skin long non-coding RNA WAKMAR1 regulates wound healing by enhancing keratinocyte migration PNAS 2019 May 7; 116(19):9443-9452. PMID: 31019085
3. Li, D., Wang, A., Liu, X., Meisgen, F., Grunler, J., Botusan, I.R., Narayanan, S., Erikci, E., Li, X., Blomqvist, L., Du, L., Pivarcsi, A., Sonkoly, E., Chowdhury, K., Catrina, S., Ståhle, M., Landén, N.X. (2015) MicroRNA-132 enhances transition from inflammation to proliferation during wound healing. Journal of Clinical Investigation 3;125(8):3008-26. PMID: 26121747

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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

Unique instruments and methodologies used in the group

- Single-cell RNA-seq
- Animal modeling
- Organoid modeling

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

1. 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.
2. 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.
3. 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

- Cancer-associated alterations in mRNA translation

Key research field interests

- mRNA translation
- Breast cancer
- Gene expression
- Personalized cancer medicine

Unique instruments and methodologies used in the group

- Polysome-profiling
- Transcriptome-wide analysis of mRNA translation
- Quantification and analysis of 5' untranslated regions
- Modeling of factors underlying alterations in mRNA translation

Epigenetic coordination of transcriptional and translational programs in hypoxia

Ola Larsson

Emerging data suggest that adaptation of cancer cells to hypoxia enhances malignancy and negatively impacts patient outcomes. Reprogramming of mRNA translation represents an essential component of the hypoxia-adaptive response. During hypoxia, cells undergo a global decrease in protein synthesis while translation of subsets of transcripts encoding stress-response, survival and stemness factors is increased. This selective regulation is thought to be governed largely via the interactions between specific mRNA features and remodeling of the translational apparatus. However, our understanding of the regulatory mechanisms that govern translational perturbations under hypoxia remains incomplete. To address this, we interrogated the effects of hypoxia on global changes in histone methylation and transcription site selection, coupled with monitoring corresponding alterations in total mRNA levels and translation efficiencies on a transcriptome-wide scale in T47D breast cancer cells and H9 human embryonic stem cells. This allowed us to map the impact of specific 5'UTR features on translation efficiency under hypoxia and revealed widespread hypoxia-induced epigenetic alterations leading to extensive remodeling of 5'UTRs. As a consequence of 5'UTR switching, numerous transcripts gain or lose specific mRNA features, allowing preferential translation under hypoxia. Among the genes that underwent hypoxia-induced 5'UTR remodeling was Pyruvate Dehydrogenase Kinase 1 (PDK1), an enzyme that is key in orchestrating metabolic adaption to hypoxia wherein cells shift from oxidative phosphorylation towards glycolysis. PDK1 undergoes a switch in TSS usage allowing for increased availability of 5'UTR isoforms that are efficiently translated under hypoxia, and we show that this effect is coordinated at an epigenetic level. Therefore, our findings provide a previously unappreciated mechanism driving translational reprogramming under hypoxia, whereby alterations in translational apparatus are orchestrated with epigenetic perturbations that result in 5'UTR remodeling of the transcriptome.

A selection of publications from your group

1. Watt et al. Epigenetic coordination of transcriptional and translational programs in hypoxia. 2023 bioRxiv doi: https://doi.org/10.1101/2023.09.16.558067 Sandri et al. Distinct Cancer-Promoting Stromal Gene Expression Depending on Lung Function. 2019 Am J Respir Crit Care Med 200(3): 348-58
2. Lorent et al. Translational offsetting as a mode of estrogen receptor alpha-dependent regulation of gene expression. 2019 EMBO J e101323

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Cancer Research Area

- Brain tumors

Key research field interests

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

Unique instruments and methodologies used in the group

- 3D bioprinting of neural glioma cells, generating tumoroids
- 3D bioprinting of neural stem and progenitor cells, used in studies of late complications
- Biomaterials development and validation, e.g. spider silk and algy-derived materials
- Bioelectronics, using polymers (oligothiophenes) to detect glioma stem cells during surgery

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 dev eloping numerous technologies as well as biomedical engineering approaches, including 2D/3D bioprinting, bioelectronics, and biomaterials, for improved studies of epigenetics and stem cell biology, and applications in precision medicine.

A selection of publications from your group

1. 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 Psychiatry, 13:258.
2. 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 (2023) Live detection of neural progenitors and glioblastoma cells by an oligothiophene derivative. ACS Appl Bio Mate Mater, 6:3790 3797. *Corresponding author.
3. 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

- Cancer biology and targeted therapies

Key research field interests

- Ubiquitin ligase
- Genome Instability
- Replication Stress
- Targeted therapy
- Immunotherapy

Unique instruments and methodologies used in the group

- We employ a multidisciplinary approach that combines cellular and molecular biology techniques with an emphasis on biochemistry. Methodologies include ubiquitination and protein degradation, replication fork dynamics, DNA damage and omics analysis.

Targeting Ubiquitin Ligases Maintaining Genome Stability for Cancer Therapy

Olle Sangfelt

While significant progress has been achieved in cancer treatment, a notable proportion of patients still confront relapse or unresponsiveness, even when subjected to aggressive multimodal therapies. To enhance treatment efficacy and sustainability of anti-tumor agents, it is essential to gain a deeper understanding of the complex mechanisms orchestrated by oncogenic drivers and uncover new targets and vulnerabilities within cancer.

Replication stress (RS), the stalling or slowing of replication forks, caused by activation of oncogenes is a common phenomenon in cancer and pre-malignant cells which sets them apart from healthy tissues. To counteract this stress, cancer cells hyperactivate an array of pathways collectively termed the RS response (RSR). Since healthy non-transformed cells do not depend on such pathways, RSR factors represent a pool of potential therapeutic targets.

Moreover, in recent years intriguing links between RS and the innate immune response has started to emerge. Certain components of the RSR have been found to mitigate the release of cytosolic DNA, which otherwise triggers cytosolic DNA sensors, including cGAS-STING, resulting in immune activation.

We have uncovered an unexpected molecular mechanism for the removal of FANCD2, a central regulator of the Fanconi Anemia (FA)/homologous recombination (HR) pathway, in cancer cells overexpressing CYCLIN E. This involves polyubiquitination and subsequent degradation of FANCD2 by the SCF-FBXL12 ubiquitin ligase, a mechanism essential for replication recovery and survival of cells facing CDK-driven RS. Currently, our efforts are focused on exploring strategies to disrupt the RSR by targeting the FBXL12-FANCD2 signaling axis, thereby rendering cancers more susceptible to immune detection.

A selection of publications from your group

1. 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, October 19, 2023.
2. Suryo Rahmanto A, et al. FBW7 suppression leads to SOX9 stabilization and increased malignancy in medulloblastoma. EMBO J. 2016 17;35(20):2192-2212.
3. Arabi A, et al. A proteomic screen for SCFFbw7 ubiquitin-ligase substrates reveals Fbw7 as a modulator of the NF-kB pathway. Nat Commun. 2012 31;3:976.

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Cancer Research Area

- Neuroblastoma
- Metastasis

Key research field interests

- Neuroblastoma
- Metastasis
- Evolution
- Bioinformatics
- Cross-species comparisons

Unique instruments and methodologies used in the group

- Single cell sequencing
- Cross-species comparison
- Mutation analysis
- Mathematical modeling
- AI

Target genes of c-MYC and MYCN with prognostic power in neuroblastoma exhibit different expressions during sympathoadrenal development

Oscar C. Bedoya-Reina

The deregulation of the MYC family of transcription factors, including c-MYC (encoded by MYC), MYCN, and MYCL, is of common occurrence in many human cancers. This deregulation significantly affects tumor initiation and progression, as well as the response to treatment. In the case of neuroblastoma (NB), approximately 40% of high-risk NB cases involve the amplification of the MYCN oncogene, while about 10% exhibit over-expression of c-MYC. However, we still lack a comprehensive understanding of the exact mechanism and stage of neural crest development at which MYCN and c-MYC contribute to the onset and progression of NB.

In our work we hypothesized that subtle differences in the expression of MYCN and/or c-MYC targets could more accurately stratify NB patients in different risk groups, as opposed to relying solely on the expression of each MYC gene individually. We employed an integrative approach using the transcriptome of 498 NB patients from the SEQC cohort and previously defined c-MYC and MYCN target genes to model a multigene transcriptional risk score.

Our findings demonstrate that defined sets of c-MYC and MYCN targets with significant prognostic value, effectively stratify NB patients into different groups with varying overall survival probabilities. In particular, patients exhibiting a high-risk signature score present unfavorable clinical parameters, including increased clinical risk, higher INSS stage, MYCN amplification, and disease progression. Notably, target genes with prognostic value differ between c-MYC and MYCN, exhibiting distinct expression patterns in the developing sympathoadrenal system. Genes associated with poor outcomes are mainly found in sympathoblasts rather than in chromaffin cells during the sympathoadrenal development.

A selection of publications from your group

1. 1. Yuan, Y., Alzrigat, M., Rodriguez-Garcia, A., Wang, X., Bexelius, T.S., Johnsen, J.I., Arsenian- Henriksson, M., Liaño-Pons, J. and Bedoya-Reina, O.C., 2023. Target Genes of c-MYC and MYCN with Prognostic Power in Neuroblastoma Exhibit Different Expressions during Sympathoadrenal Development. Cancers, 15(18), p.4599.
2. Bedoya-Reina, O. C., Li, W., Arceo, M., Plescher, M., Bullova, P., Pui, H., Kaucka, M., Kharchenko, P., Martinsson, T., Holmberg, J., Adameyko, I., Deng, Q., Larsson, C., Juhlin, C. C., Kogner, P. and Schlisio, S. Single-nuclei transcriptomes from human adrenal gland reveal distinct cellular identities of low and high-risk neuroblastoma tumors. Nature Communications, 12(1), p.5309.
3. Bedoya-Reina, O.C. and Schlisio, S., 2021. Chromaffin cells with sympathoblast signature: too similar to keep apart?. Cancer Cell, 39(2), pp.134-135.

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Cancer Research Area

- Childhood cancer and targeted therapy

Key research field interests

- Neuroblastoma
- Medulloblastoma
- Targeted therapy
- Combination treatments

Unique instruments and methodologies used in the group

- Apoptosis
- Cytotoxicity assays
- FACS
- Barcoding in collaboration with K.Karlsson

Studies on combined targeted therapies on neuroblastoma and medulloblastoma

Ourania Kostopoulou

Medulloblastoma (MB) and neuroblastoma (NB) are still not cured with today's therapies which come with severe side effects so new therapies are needed. Phosphoinositide 3-kinase (PI3K) is linked to pathological cell growth and oncogenesis and somatic mutations in the PIK3CA gene have been reported frequent in adult cancers. Therapies with PI3K inhibitors in adult cancer (with/without PI3K mutations) have been attempted. PIK3CA mutations are rare in NBs, but PI3K inhibitors together with other drugs have been tested experimentally in NB/MB, and initial reports were promising. The objectives of our studies are to: 1) Identify whether various combinations of targeted therapy with or without CT/RT could be useful for NB or MB patients, especially in cases where there is resistance to conventional therapies.2) Examine if combinational treatments could decrease drug concentrations and along with the possibility to increase survival also be able to decrease side effects. 3) In addition, by using barcoding and single cell RNA sequencing in more detail identify subclonal evolution and resistance patterns, according to specific NB/MB tumor molecular profile. Recently, we have very promising results using PI3K and FGFR inhibitors on NB and MB cell lines on 2D and 3D cultures. We found dose dependent responses to both PI3K and FGFR inhibitors and when we combined the two inhibitors, synergistic effects were obtained. We are presently exploring these data further by barcoding the cell lines and testing additional inhibitors alone and in combination with the above and according to tumor molecular profile.

A selection of publications from your group

1. 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.
2. Lukoseviciute M, Maier H, Poulou-Sidiropoulou E, Rosendahl E, Holzhauser S, Dalianis T, Kostopoulou ON. Targeting PI3K, FGFR, CDK4/6 signaling pathways together with cytostatics and radiotherapy in medulloblastoma cell lines. Frontiers in Oncology. 11, 748657, 2021.
3. Holzhauser S, Lukoseviciute M, Papachristofi C, Vasilopoulou C, Herold N, Wickström M, Kostopoulou ON*, Dalianis T*. Effects of PI3K and FGFR inhibitors alone and in combination, and with/without cytostatics in childhood neuroblastoma cell lines. International journal of Oncology. 58(2), 211-25, 2021. (*equal contribution)

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Cancer Research Area

- Translational Research
- Neuroblastoma
- Precision medicine

Key research field interests

- Pediatric Oncology
- Neuroblastoma
- Precision medicine
- Novel therapy

Unique instruments and methodologies used in the group

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Title

Name

A selection of publications from your group

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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.

Unique instruments and methodologies used in the group

- 3D-cell culture
- Inhouse developed imaging application to subclassify tumor-stroma heterospheroids as a reporter tool for high throughput drug screening.

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 is to uncover metabolic vulnerabilities of the cancer cells by modulating the mouse pancreatic stellate cells (CAFs) in their nutritional support of the cancer cells.

A selection of publications from your group

1. 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.
2. 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 co-culture spheroid model. BMC Cancer 2020, 20(1):475.
3. Longati P, Jia X, Eimer J, Wagman A, Witt MR, Rehnmark S, Verbeke C, Toftgard R, Löhr M, Heuchel RL: 3D pancreatic carcinoma spheroids induce a matrix-rich, chemoresistant phenotype offering a better model for drug testing. BMC Cancer 2013, 13:95.
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Cancer Research Area

- Theranostics
- Clinical trials with new molecular imaging agents

Key research field interests

- Molecular imaging
- Radiopharmaceuticals
- Theranostics
- Solid tumors

Unique instruments and methodologies used in the group

- We are performing clinical trials with new radiopharmaceuticals in patients with solid malignanies. We have a multidisciplinary group with radiopharmacists, medical physicists, nuclear medicine specialists and oncologists.

Molecular imaging of treatment targets in patients with solid tumors

Renske Altena

The overarching aim of our research activities is to better characterize, understand and manage metastatic cancer through precision imaging with contemporary radioisotopes. This is done in multidisciplinary collaborations at the local and national level.

There is an urgent need for more effective therapy-predictive biomarkers that identify the patients that optimally benefit from targeted cancer therapies. Usually pathological analyses on a tumor biopsy are used, but these can be non-representative of the whole burden of disease, can be technically difficult to obtain and are burdensome for patients.

Molecular imaging of treatment targets with positron emission tomography provides the possibility to visualize the presence of the target of treatment in real time in the whole body in a minimal invasive way. This concept of 'theranostics' provides not only diagnostic but also therapeutic options with modern radiopharmaceutical. We are conducting several clinical trials aimed to visualize and target different cancer features, such as the Human Epidermal growth factor Receptor 2 (HER2), Programmed Death Ligand 1 (PD-L1), Gastrin Releasing Peptide Receptors, Poly–(Adenosine Diphosphate–Ribose) Polymerase (PARP) and Trophoblast Receptor type 2 (TROP2).

A selection of publications from your group

1. Altena R, Af Burén S, Tran T, Axelsson R. HER2-low breast cancer can be visualized by HER2-PET. Letter to the editor J Nucl Med August 2023 online ahead of publication.
2. Altena R, Tzortzakakis A, Af Burén S et al. Current status of contemporary diagnostic radiotracers in the management of breast cancer: first steps toward theranostic applications. EJNMMI Res. 2023 May 17;13(1):43.
3. Altena R, Af Buren s, Karlsson A et al. HER2-low metastatic breast cancer can be visualized by positron emission tomography (PET) with [68Ga]Ga-ABY-025: results from a HER2-PET pilot study. poster presentation annual conference European Society of Medical Oncology, manuscript submitted

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Cancer Research Area

- Hematological malignancies

Key research field interests

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

Unique instruments and methodologies used in the group

- Immunogenetics
- NGS-based/omics technologies
- Single-cell analysis
- Tumor microenvironment
- Drug sensitivity profiling

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 (>30,000 cases), 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 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 proteogenomic 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 pladorm 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

1. Sufon LA, Ljungström V, Enjuanes A, Cortese D, Skajason A, Tausch E, Stano Kozubik K, Nadeu F, Armand M, Malcikova J, Pandzic T, Forster J, Davis Z, Oscier D, Rossi D, Ghia P, Strefford JC, Pospisilova S, SXlgenbauer S, Davi F, Campo E, Stamatopoulos K, Rosenquist R. ComparaXve analysis of targeted next-generaXon sequencing panels for the detecXon of gene mutaXons in chronic lymphocyXc leukemia: an ERIC mulX-center study. Haematologica 2021;106(3):682-691.
2. Mansouri L, Thorvaldsdonr B, Sufon LA, Karakatsoulis G, Meggendorfer M, Parker H, Nadeu F, Brieghel C, Laidou S, Moia R, Rossi D, Catherwood M, Kotaskova J, Delgado J, Rodríguez-Vicente AE, Benito R, Rigolin GM, Bonfiglio S, Scarfo L, Mafsson M, Davis Z, Gogia A, Rani L, Baliakas P, Foroughi-Asl H, Jylhä C, Skajason A, Rapado I, Miras F, MarXnez-Lopez J, de la Serna J, Rivas JMH, Thornton P, Larráyoz MJ, Calasanz MJ, Fésüs V, Mátrai Z, Bödör C, Smedby KE, Espinet B, Puiggros A, Gupta R, Bullinger L, Bosch F, Tazón-Vega B, Baran-Marszak F, Oscier D, Nguyen-Khac F, Zenz T, Terol MJ, Cuneo A, Hernández-Sánchez M, Pospisilova S, Mills K, Gaidano G, Niemann CU, Campo E, Strefford JC, Ghia P, Stamatopoulos K, Rosenquist R. Different prognosXc impact of recurrent gene mutaXons in chronic lymphocyXc leukemia depending on IGHV gene somaXc hypermutaXon status: a study by ERIC in HARMONY. Leukemia. 2023 Feb;37(2):339-347.

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Cancer Research Area

- Basic research
- Blood cancer

Key research field interests

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

Unique instruments and methodologies used in the group

- 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.

Towards precision cancer medicine with conventional chemotherapy – how can we better use the drugs we already have?

Sean Rudd

Our research centres upon understanding the molecular underpinnings of why some patients respond to cancer therapies – in particular standard-of-care chemotherapeutic agents – whilst others do not, and using this knowledge as the basis for refining treatment strategies.

The ultimate goal of our research is to provide cancer patients with better informed treatment options. We believe one way this can be achieved in a timely manner is by focusing research efforts upon commonly used chemotherapeutic agents. These therapies, which form standard-of-care for many cancers, typically kill tumour cells by targeting pan-essential pathways, principally metabolism of the DNA molecule or its 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 commonly used chemotherapeutic nucleoside analogue, 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.

A selection of publications from your group

1. Rudd SG. Targeting pan-essential pathways in cancer with cytotoxic chemotherapy: Challenges & opportunities. Cancer Chemotherapy & Pharmacology 2023 92(4):241-251
2. Zhang SM, Paulin CBJ, Michel M, Marttila P, Yagüe-Capilla M, Bwanika HC, Shu H, Papagudi Venkatram R, Wiita E, Jemth AS, Almlöf I, Loseva O, Ortis F, Dirk C, Koolmeister T, Linde E, Lee S, Llona -Minguez S, Haraldsson M, 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. bioRxiv 2023 doi.org/10.1101/2023.01.17.524275
3. Rudd SG, Tsesmetzis N, Sanjiv K, Paulin CB, Sandhow L, Kutzner J, Hed Myrberg I, Bunten SS, Axelsson H, Zhang SM, Rasti A, Mäkelä P, Coggins SA, Tao S, Suman S, Branca RM, Mermelekas G, Wiita E, Lee S, Walfridsson J, Schinazi RF, Kim B, Lehtiö J, Rassidakis GZ, Pokrovskaja Tamm K, Warpman-Berglund U, Heyman M, Grandér D, Lehmann S, Lundbäck T, Qian H, Henter JI, Schaller T, Helleday T, Herold N. Ribonucleotide reductase inhibitors suppress SAMHD1 ara-CTPase activity enhancing cytarabine efficacy. EMBO Molecular Medicine 2020 12;3 e10419

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Cancer Research Area

- Hematology

Key research field interests

- Immune Microenvironment
- ILC2s
- Bone marrow
- Fibrosis

Unique instruments and methodologies used in the group

- Bone marrow transplant
- Hematopoietic Stem Cell culture
- CRISPR editing
- Spectral Flow Cytometry

Role of ILC2s in the pathogenesis of hematological cancer

Sergio Martinez Høyer

Myeloproliferative neoplasms (MPNs) are hematological malignancies characterized by the excessive proliferation of hematopoietic stem and progenitor cells (HSPCs) and progressive bone marrow fibrosis. Type 2 immune signaling has been recently implicated in the pathogenesis of bone marrow fibrosis, but the cellular source for the initiation and maintenance of the type 2 response remains poorly defined. Group 2 innate lymphoid cells (ILC2s) are well-known regulators of Type 2 responses, which have been primarily characterized in the context of allergic responses and parasite expulsion. ILC2s also play an essential role in tissue repair responses to restore homeostasis after the inflammation is resolved. In the bone marrow, ILC2 functions remain unexplored. Emerging data is starting to postulate ILC2s as important contributors to cancer development. Our work aims to unravel the cellular and molecular mechanisms underlying the contribution of type 2 immunity to bone marrow fibrosis and identify a novel role for ILC2s in the progression of MPNs to bone marrow fibrosis. Our hypothesis is that bone marrow ILC2s are activated in the context of myeloproliferative bone marrow and subsequently orchestrate the type 2 immune response that contributes to the fibrosis observed in this disease. By identifying a role for ILC2s in the progression of bone marrow fibrosis, we may identify alternative therapeutic targets to help slow or halt the progression of this otherwise incurable disease.

A selection of publications from your group

1. Ma J, Urgard E, Runge S, Classon CH, Mathä L, Stark JM, Cheng L, Álvarez JA, von Zedtwitz S, Baleviciute A, Martinez Hoyer S, Li M, Gernand AM, Osbelt L, Bielecka AA, Lesker TR, Huang HJ, Vrtala S, Boon L, Beyaert R, Adner M, Martinez Gonzalez I, Strowig T, Du J, Nylén S, Rosshart SP, Coquet JM. Laboratory mice with a wild microbiota generate strong allergic immune responses. Sci Immunol. 2023 Sep 29;8(87):eadf7702.
2. Martinez-Høyer S, Deng Y, Parker J, Jiang J, Mo A, Docking TR, Gharaee N, Li J, Umlandt P, Fuller M, Jädersten M, Kulasekararaj A, Malcovati L, List AF, Hellström-Lindberg E, Platzbecker U, Karsan A. Loss of lenalidomide-induced megakaryocytic differentiation leads to therapy resistance in del(5q) myelodysplastic syndrome. Nat Cell Biol. 2020 May;22(5):526-533.

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Cancer Research Area

- Cancer Epigenomics

Key research field interests

- Epigenetics
- Drug Development
- Precision Medicine
- Circulating nucleosomes
- Biomarkers

Unique instruments and methodologies used in the group

- Quantitative epigenome profiling techniques (MINUTE-ChIP, ATAC-seq, CUT&Tag, ...)
- CRISPR/Cas9
- Quantitative proteomics (ProteinSimple JESS, Thermo Exploris LC-MS/MS)

Highly multiplexed quantitative Epigenome Profiling for Drug Screening and Biomarker Discovery

Simon Elsässer

My laboratory aims to understand epigenetic mechanisms that govern gene expression during development and tumorigenesis. An emerging class of drugs - epigenetic modifiers, or 'epidrugs' - hold great promise in oncology. Designing epidrugs with high efficacy, while excluding potential side effects on the epigenome, remains a challenge. We have developed a highly multiplexed, quantitative method for systematically profiling the interaction of drugs with the epigenome in human cell lines, primary cells, as well as fixed material, and are exploring applications of the technology in drug development and precision medicine.

A selection of publications from your group

1. Weigert R*, Hetzel S*, Bailly N*, Haggerty C, Yung PYK, Ilik IA, Navarro C, Bolondi A, Kumar AS, Anania C, Brändl B, Meierhofer D, Lupianez DG, Mueller FJ, Aktas T, Elsässer SJ, Kretzmer H, Smith ZD, Meissner A, "Dynamic antagonism between key repressive pathways in the placental epigenome", Nature Cell Biology (2023)
2. Kumar B*, Navarro C*, Winblad N*, Schell JP, Zhao C, Weltner J, Baqué-Vidal L, Mantero AS, Petropoulos S, Lanner F, Elsässer SJ, "Polycomb Repressive Complex 2 shields naïve human pluripotent cells from trophectoderm and mesoderm differentiation", Nature Cell Biology (2022)
3. Larsen BD, Benada J, Yung PYK, Bell R, Pappas G, Urban V, Ahlskog JK, Kuo TT, Janscak P, Megeney LA, Elsässer SJ, Bartek J, Sørensen CS, "Cancer cells utilize self-inflicted DNA breaks to evade growth limits imposed by exogenous genotoxic stress", Science (2022)

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Cancer Research Area

- Cancer Cell Biology

Key research field interests

- Cell-matrix interactions
- Mechanotransduction
- Cellular signaling
- Cell migration
- Cellular senescence

Unique instruments and methodologies used in the group

- Functionalized hydrogels with tunable stiffness
- Advanced light microscopy
- Advanced image analysis
- Transgenic mouse cancer models.

Mechanical regulation of mevalonate pathway enzyme synthesis drives a malignant breast cancer cell phenotype

Staffan Strömblad

Mechanical cues control cell fate in physiology and disease. In breast cancer, mechanotransduction from a stiffened extracellular matrix (ECM) drives proliferation and invasion. Here, quantitative mass spectrometry identified enrichment of ECM stiffness upregulated mevalonate pathway enzymes in breast cancer cells, suggesting sterol /isoprenoid metabolism reprogramming. Importantly, the rate-limiting mevalonate enzyme Hydroxymethylglutaryl-CoA Synthase (HMGCS1) protein was strongly upregulated in human breast cancer specimens and correlated with cross-linked ECM. ECM stiffness promoted HMGCS1 protein synthesis, not reflected at the mRNA level, and HMGCS1-RNAi blocked the stiffness-driven breast cancer proliferative and invasive phenotype. Mechanistically, we define mechanotransduction signaling through integrin 1 and Rac1 to control HMGCS1 protein synthesis that drives the breast cancer malignant phenotype. Intriguingly, the Rac1-P29S cancer mutant promoted a malignant phenotype without stiff ECM in a mevalonate-dependent manner. In summary, we define a mechanotransduction pathway that regulates mevalonate pathway enzyme synthesis critical for breast cancer.

A selection of publications from your group

1. Hu, J., Gong, X. & Strömblad, S. Local Rac-GTP nadirs and peaks restrict cell protrusions and retractions. Sci. Adv. 8, eabl3667 (2022).
2. Göransson, S. Chen, S., Olofsson, H., Larsson, O., & Strömblad, S. An extracellular matrix stiffness-induced breast cancer cell transcriptome resembles the transition from ductal carcinoma in situ (DCIS) to invasive ductal carcinoma (IDC). Biochem Biophys Res Commun 654, 73-79 (2023).
3. Hu, J., Serra-Picamal X., Bakker, G-J., Van Troys, M., Winograd-Katz, Ege, S.N., Gong X., Didan, Y., Grosheva, I., Polansky, O., Bakkali, K., Van Hamme, E., van Erp, M., Vullings, M., Felix Weiss, F., Clucas, J., Dowbaj, A.M., Sahai, E., Ampe, C., Geiger, B., Peter Friedl, P., Bottai, M., & Strömblad, S. Multi-site assessment of reproducibility in high-content cell migration imaging data. Mol Systems Biol. e11490 (2023).

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Cancer Research Area

- Immunotherapy
- Biomarkers

Key research field interests

- Extracellular vesicles,
- Exosomes
- Urinary bladder cancer
- Melanoma
- Immunotherapy

Unique instruments and methodologies used in the group

- Extracellular vesicle isolation
- Nanoparticle tracking analysis
- Differential ultracentrifugation
- Extracellular vesicle phenotyping

Understanding immune responses to extracellular vesicles in the quest for novel immunotherapies, cancer therapeutic targets and biomarkers

Susanne Gabrielsson

Extracellular vesicles (EVs) from antigen presenting cells constitute a potential cancer immunotherapy due to their capacity to stimulate tumor-specific activity in mice. However, clinical trials using peptide-loaded autologous EVs only showed moderate T cell responses, suggesting a need for optimization. In mouse models, we have shown that EVs loaded with whole protein antigen induced better T cell responses than peptides, and that they also induced B cell activation with antibody production. Our recent work investigated the combination of bone marrow derived dendritic cell (BMDC) derived EVs with checkpoint blockade therapy (anti PD-1 or anti PD-L1 antibodies) and showed a synergistic effect with EVs, where EVs induced tumor T cell infiltration and responsiveness to checkpoint therapy in a checkpoint refractory model.

As the BMDC EVs contain both PD1 and PD-L1, we speculated that removal of these molecules would further enhance their immunogenicity. We have isolated EVs from OVA-loaded BMDC from PD1 or PD-L1 knock out (KO) mice, and tested their antigen-specific immune stimulation and potency as anti-tumor therapy. Interestingly, both PD-1 and PD-L1 KO EVs induced higher immune responses and more immune cell infiltration in the tumor, but had still lower effect on tumor growth in B16 murine melanoma compared to WT EVs. These results highlight the need to further investigate the PD-1/PD-L1 axis in cancer therapy.

In other studies we investigate the function of cancer derived EVs, using EVs from blood and urine from patients with urinary bladder cancer. Here, we study EVs both to find biomarkers for disease, as well as targets for treatment. We find that the protein profile of cancer derived EVs is different between patients who has muscle invasive cancer or not, as well as whether they respond to neoadjuvant chemotherapy, highlighting their potential as biomarkers in cancer patients.

A selection of publications from your group

1. Veerman, RE, Güclüler Akpinar G, Annemarijn Offens A, Steiner L, Larssen P, Lundqvist, A, Karlsson, MCI, Gabrielsson S. Antigen-Loaded Extracellular Vesicles Induce Responsiveness to Anti-PD-1 and Anti-PD-L1 Treatment in a Checkpoint Refractory Melanoma Model. Cancer Immunol. Res. 2023. 2023 Feb 3;11(2):217-227.
2. Veerman RE, Teeuwen L, Czarnewski P, Güclüler Akpinar G, Sandberg A, Cao X, Pernemalm M, Orre LM, Gabrielsson S, Eldh M. Molecular evaluation of five different isolation methods for extracellular vesicles reveals different clinical applicability and subcellular origin. J Extracell Vesicles. 2021. 10(9):e12128.
3. Wagner AK, Gehrmann U, Hiltbrunner S, Carannante V, Luu TT, Näslund TI, Brauner H, Kadri N, Kärre K, Gabrielsson S. Soluble and Exosome-Bound a-Galactosylceramide Mediate Preferential Proliferation of Educated NK Cells with Increased Anti-Tumor Capacity. Cancers 2021, 13, 298.

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Cancer Research Area

- Basic Research
- Brain and Nervous System
- Childhood Cancer

Key research field interests

- Neuroblastoma
- Paraganglioma
- Pheochromocytoma
- Hypoxia
- Sympatho-adrenal development

Unique instruments and methodologies used in the group

- Single-cell RNA-seq
- Space-resolved transcriptomics
- Transgenic neuroblastoma and paraganglioma mouse models
- Mutation analysis

Abstract

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 adn paraganglioma models, enabling comparative differentiation trajectory analysis and lineage tracing of tumor subpopulations

A selection of publications from your group

1. 1. 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.
2. 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
3. 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

- Breast Cancer
- Childhood Cancer
- General imaging within cancer area
- Sarcoma

Key research field interests

Unique instruments and methodologies used in the group

Abstract

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A selection of publications from your group

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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

Unique instruments and methodologies used in the group

- Medicinal chemistry lead optimization
- Protein purification and assay development
- High-throughput screening
- DDR techniques - DNA fiber technique, COMET assay, iPOND, Advanced microscopy (FRAP, FRET), etc
- Formulation and in vivo PK/PD

Targeted DNA damage response inhibitors for a final attack on cancer

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 collaboartors in the following areas: 1. Identify biomarkers to identify responders from patients' material and using novel techniques. 2. Identify combination treatments that are improving the 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

1. 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.
2. 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.
3. 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, antibodies for molecular radiotherapy and diagnostics with positron emission tomography (PET), i.e. theranostics. Research is spanning from 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 and peptide-drug conjugates

Unique instruments and methodologies used in the group

- Cyclotron,
- Synthesis modules
- Radioisotope production
- Radiolabelling, and radioactive cell labelling
- Small-animal imaging with PET
- Alpha and beta emitter for therapy

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

Thuy Tran

Our group's research interests are focused on the developments of radiopharmaceuticals, radioactive drugs, for targeted therapy and diagnostics 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 or astatine-211 or beta emitters using lutetium-177 or iodine-131), the molecular features of a cancer target can be noninvasively visualized respectively treated by molecular radiotherapy.

Through close collaborations with Scilifelab for drug development of targeting agents, and with access to state-of-the-art modern radiopharmacy facility for in-house cyclotron production of isotopes, and that we possess unique experience in in vitro, in vivo methodologies, GMP synthesis, regulatory aspects of tracer developments, we achieve rapid translation to clinical testing.

A selection of publications from your group

1. 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).
2. 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).
3. Strand J, Sjöström K, Lamminmaki UJ, Vilhelmsson Timmermand O, Strand SE, Tran TA. Humanization, radiolabelling and biodistribution studies of an IgG1-type antibody targeting uncomplexed PSA for theranostic applications. Pharmaceuticals 14, 1251 (2021).

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Cancer Research Area

- Tumor Virology especially Human Papillomavirus (HPV) in Head and neck Cancer, but also other tumor viruses and also childhood cancer.

Key research field interests

- Personalized therapy of HPV positive head and neck cancer
- Prognostication
- Targeted therapy
- HPV positive oropharyngeal cancer
- Childhood cancer

Unique instruments and methodologies used in the group

- Luminex-Multiplex
- In vitro targeted therapies
- Incucyte analysis
- FACs analyses
- HPV Digital droplet PCR

Application of human papillomavirus and other markers to monitor and specifically target head neck cancer, for improved follow-up and therapy, increased survival and quality of life

Tina Dalianis

Human papillomvirus positive tonsillar and base of tongue cancer (HPV+TSCC/BOTSCC) is rising epidemically in incidence since the 1970s. However, despite intensive chemoradiotherapy and severe side effects thereof and though most patients usually respond to primary treatment, 20% of the patients relapse and are still not cured.

Our research focuses on identifying biomarkers of prognostic value and useful for targeted therapy, in order to better personalize patient therapy by e.g. de-escalating therapy when possible; identifying which patients may or may not respond to immunecheckpoint inhibitors; and adding targeted therapy when adequate and needed.

To do so we have compared the molecular profiles of tumors from patients that respond to therapy to those in tumors from patients that have relapsed using several types of techniques (immunohistochemistry, DNA sequencing, protein expression/OLINK). This way we have identified both prognostic and targetable markers (PIK-3CA,FGFR3, CDC27, BCLAF1 and others) and are continuing to do so.

Currently, we are also investigating the effects of various targeted therapies and their combinations (PI3K, FGFR, CDK4/6 inhibitors etc.) in vitro on HPV+/HPV-TSCC/BOTSCC cell lines grow as monolayers. Upon identifying the best options depending on the molecular profile of the tumor (e.g. by barcoding of the cells), similar experiments will be done in 3D culture and in vivo and ultimately, we will also test patients tumors with various molecular profiles in a similar way.

In parallel, we want to follow and quantify cell free HPV DNA before and after treatment in order to identify relapse earlier and thereupon offer the best treatments possible depending on the molecular nature of the specific tumor that is involved in the relapse. We anticipate that our research will increase survival as well as quality of life of our patients.

A selection of publications from your group

1. Ährlund-Richter A, Holzhauser S, Dalianis T, Näsman A, Mints M. Whole-Exome Sequencing of HPV Positive Tonsillar and Base of Tongue Squamous Cell Carcinomas Reveals a Global Mutational Pattern along with Relapse-Specific Somatic Variants. Cancers (Basel). 2021 Dec 24;14(1):77.
2. 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.
3. 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 Precise-Classification of Oropharyngeal Cancer? Lancet Oncology, Lancet Oncol. 2023

Vanessa Lundin

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Cancer Research Area

- Blood Cancer

Key research field interests

- Blood Cancer: Myeloid Malignancies
- Hematopoietic Stem Cells
- Germline Variants
- MDS

Unique instruments and methodologies used in the group

- iPSCs
- Hematopoietic Differentiation
- CRISPR-Cas9
- 3D scaffolds

Molecular Mechanisms in Myeloid Malignancies

Vanessa Lundin

Myeloid malignancies are clonal disorders of the bone marrow characterized by ineffective hematopoiesis. Myelodysplastic syndromes (MDS), a heterogenous group of such malignancies, originates in the hematopoietic stem cells and results in disrupted blood production, anemia and an increased risk of developing acute myeloid leukemia (AML). Understanding the genetic predisposition and early development of these malignancies is crucial to prevent disease onset and leukemic progression. Moreover, advances in treatment strategies require deeper mechanistic understanding of the molecular pathogenesis, which is hindered by adequate models that recapitulate the disease phenotype or a lack of experimental amenability of primary cells. The overall goal of our work is thus to establish novel human in vitro disease models, and leveraged with CRISPR-Cas9 gene editing and multiomics technologies, reveal molecular mechanisms underlying blood cancer risk and development. Specifically, we aim to untangle gene networks and regulatory mechanisms utilizing unique patient-derived induced pluripotent stem cells (iPSCs) from individuals in the MDS Biobank with specific, commonly occurring mutations in MDS and AML. Our iPSC lines harbor gene variants associated with genetic predisposition, clonal hematopoiesis, low risk- and high risk disease, can be expanded unlimitedly and specified into various hematopoietic cell types in the lab, including hematopoietic stem and progenitor cells, and thus provide a versatile and tractable system to study disease mechanisms. This work will increase our knowledge on myeloid regulation and deficiencies, relevant for a range of hematological malignancies, to facilitate the identification of druggable targets that hinder oncogenesis at early stages in patients. Moreover, these cell lines could provide a test bed for screening and validation of new cancer therapies before translation into the clinic.

A selection of publications from your group

1. Cabrerizo Granados D, Barbosa I, Baliakas P, Hellström-Lindberg E, Lundin V. The clinical phenotype of germline RUNX1 mutations in relation to the accompanying somatic variants and RUNX1 isoform expression. Genes, Chromosomes and Cancer 2023; 62(11): 672-677.
2. Moura P, Mortera Blanco T, Hofman I, Todisco G, Kretzschmar W, Björklund AC, Creignou M, Hagemann-Jensen M, Ziegenhain C, Cabrerizo Granados D, Barbosa B, Walldin G, Jansson M, Ashley N, Mead A, Lundin V, Dimitriou M, Yoshizato T, Woll P, Ogawa S, Sandberg R, Jacobsen SE, Hellström- Lindberg E. Erythroid differentiation intensifies RNA mis-splicing in SF3B1-mutant myelodysplastic syndromes with ring sideroblasts. Cancer Research, in Press.
3. Lundin V#, Sugden WW#, Theodore LN#, Sousa PM, Han A, Chou S, Wrighton PJ, Cox AG, Ingber DE, Goessling W, Daley GQ, North TE. YAP Regulates Hematopoietic Stem Cell Formation in Response to the Biomechanical Forces of Blood Flow. Developmental Cell 2020: 52(4) 446-460.e5. #Equal contribution.

Yenan Bryceson

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Cancer Research Area

- Immunosurveillance of cancer
- Immunotherapy of cancer

Key research field interests

- Lymphocyte cytotoxicity
- Lymphocyte differentiation
- Immunosurveillance of cancer
- Solid tumor microenvironment
- Adoptive cell therapy

Unique instruments and methodologies used in the group

- Multiparameter flow cytometry
- Transcriptomics
- Epigenetic assays
- Genetic engineering of lymphocytes

Understanding and utilizing lymphocyte tissue-residency programs for improved targeting of solid tumors

Yenan Bryceson

Research in my group is focused on gaining molecular understanding of cytotoxic lymphocyte biology and finding ways of utilizing such effector cells more efficiently against cancer. Recent breakthroughs in cancer immunotherapy, e.g. immune checkpoint blockade (ICB) and chimeric antigen receptor (CAR) T cells, highlight the potency of the immune system in controlling and eradicating cancer. However, most solid tumors do not respond to ICB and CAR T cells only work efficiently against some B cell malignancies. We have previously shown that the integrin CD49a marks epidermal-tissue-resident memory (TRM) cells with high cytotoxic potential. This subset also expresses the highest frequencies of ICB receptors. More recently, we demonstrated enrichment of RUNT family transcription-factor-binding motifs in human epidermal CD8+CD103+CD49a+ TRM cells, paralleled by high RUNX2 and RUNX3 protein expression. Sequencing of paired skin and blood samples revealed clonal overlap between epidermal CD8+CD103+CD49a+ TRM cells and circulating memory CD8+CD45RA-CD62L+ T cells. In vitro stimulation of circulating CD8+CD45RA-CD62L+ T cells with IL-15 and TGF-B induced CD49a expression and cytotoxic transcriptional profiles in a RUNX2- and RUNX3-dependent manner. Thus, we identified a reservoir of circulating cells with cytotoxic TRM cell potential. In melanoma patients, high RUNX2, but not RUNX3, transcription correlated with a cytotoxic CD8+CD103+CD49a+ TRM cell signature and improved patient survival. Together, our results indicate that combined RUNX2 and RUNX3 activity promotes the differentiation of cytotoxic CD8+CD103+CD49a+ TRM cells, providing immunosurveillance of infected and malignant cells. Based on these as well as other insights into the processes that govern the differentiation of cytotoxic tissue-resident lymphocytes, we hypothesize that genetic engineering of T cells for increased tissue homing, persistence and cytotoxic activity can provide new avenues for therapy in immunosuppressive tumor microenvironments. A primary aim is to develop novel strategies for transcriptional rewiring of T cells for improved adoptive cell therapy of solid tumors.

A selection of publications from your group

1. Zitti B, Hoffer E, Zheng W, Pandey RV, PerinettiSchlums H, Perinetti-Casoni G, Fusi I, Nguyen TLK, Kärner J, Kokkinou E, Carrasco A, Gahm J, Ehrström M, Haapaniemi S, Keita ÅV, Hedin C, Mjösberg J, Eidsmo L*, Bryceson YT*: CD49a expression and induction of cytotoxicity on human tissue-resident CD8+ T cells is controlled by RUNX2 and RUNX3 transcription factor activity. Immunity (2023) 56: 1285-1302.e7. PMID: 37269830. [Impact factor: 43.4] *Shared senior authorship. Demonstrating our proficiency in advanced scRNA-seq and epigenetic analyses, we identify critical roles for RUNX transcription factor co-operation in programming of tissue-resident, cytotoxic CD8+ T cell subsets. Our investigations uncover a new system for functional interrogation and reveal factors of interest for cytotoxic cell immunotherapy.

The Cancer Research KI PI-Retreat Organizing committee

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Thank you!