The XXIth
Cancer Research KI Retreat

DJURÖNÄSET

SEPTEMBER 23-24, 2024

Welcome to the XXIst Annual Cancer Research KI Retreat

The retreat brings together PhD students, post-docs, and scientists from Karolinska Institutet, Karolinska University Hospital and other Stockholm hospitals for a two-day meeting to enhance interactions, promote interdisciplinary contacts, and discover new areas for collaboration.

The retreat is organized by Cancer Research KI (CRKI), a hub for all scientists that conduct research and care in the cancer field at KI. In its strategic planning, CRKI aims to be inclusive, highly collaborative, and transparent – and we invite all of you to not only discuss science, but to take an active part in shaping the future of cancer research in the Stockholm Region!

Cancer Research KI has remained active in a number of areas during the last year, and we here briefly describe some of the initiatives. We continue with our successful funding initiatives, including the BlueSky grants for visionary high risk/high reward research and the Translational Seed Grants that foster new collaborations between preclinical and clinical scientists. The international program with the Mayo Clinic (the Collaborative Mayo grant) continues to support collaborative cancer research between KI and Mayo, and further activities are in the pipeline. Our database mapping the cancer research landscape at KI has surpassed 390 principal investigators and team leaders across the KI campuses and at the major Stockholm hospitals. Moreover, this year marked our first Cancer Research KI - PI Retreat, where principal investigators and team leaders were invited to a 2-day retreat to network, exchange knowledge, and establish new collaborations. This year, Cancer Research KI, in collaboration with Karolinska Comprehensive Cancer Centre and Precision Cancer Medicine, participated in the political week Almedalen, discussing the importance of precision medicine in the future of health care – probably the most pressing aspect of medicine to gain visibility in public debate. Intensive work has been done in the re-accreditation process for the Karolinska Comprehensive Cancer Centre. CRKI and Karolinska Comprehensive Cancer Centre have actively represented Sweden in several ongoing EU-initiatives, such as Establishing of Cancer Mission Hubs: Networks and Synergies (ECHoS) and Comprehensive Cancer Infrastructures for Europe (CCI4EU). With future initiatives planned to launch by the end of the year including European Network on Comprehensive Cancer Centres (EUnetCCC) and the second phase of the Joint Action on Networks of Expertise (JANE 2). CRKI continues to be an important hub for communication of cancer research at KI towards the general public. We have ongoing digital meetings with patient organisation and our new edition of 'A day for cancer research' is planned to be broadcasted to the general public in November this year.

We now look forward to meeting all of you at Djurönäset, and to spending two days of exciting discussions on science; discussions, which we are convinced will inspire new ideas and collaborations to further accelerate cancer research at KI.

Finally, we would like to welcome our guests to this retreat, starting with our keynote speakers: Dr. Clare Isack, Institute of Cancer Research, London; Dr. Caroline Verbeke, Oslo University; Dr. Raza Ali, University of Cambridge. A warm welcome also to all invited speakers, resident physicians (ST-läkare), students, and all other participants. We would also like to thank the organizing committee, chaired by Linda Lindström, for their work to plan the event and Elekta for supporting the poster prizes.

On behalf of Cancer Research KI, a warm welcome to you all!
The directors of Cancer Research KI
Elias Arnér, Yvonne Wengström and Marco Gerling

#CRKIretreat2024

For the **extended version** of the XXIth CRKI retreat program, scan this QR code

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Elekta

The XXIth Cancer Research KI Retreat
September 23-24th 2024
GENERAL PROGRAM OUTLINE

Monday, September 23:

Bus from Stockholm City **8:30**

Arrival, coffee and registration **9:30**

Welcome and introduction **10:05**

Morning session **10:15**

Group photo **12:30**

Lunch **12:45**

Afternoon session **13:45**

Coffee break and check-in **15:25**

Breakout session **16:15**

Mingle and welcoming drink **17:45**

Dinner **18:15**

Poster session **20:15**

Tuesday, September 24:

Breakfast and check out **7:30**

Morning session **9:00**

Coffee break **10:00**

Lunch **11:30**

Afternoon session **12:30**

Coffee break **14:00**

Bus departure **16:00**

Arrival Stockholm City **17:00**

Keynote Speakers

Dr. Clare Isacke, Institute of Cancer Research, London

Dr. Caroline Verbeke, Oslo University

Dr. Raza Ali, University of Cambridge

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, September 23rd, 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, September 24th, app. 17.00.

ARRIVAL AT DJURÖNÄSET

You will get the program and a name badge when you arrive. Please, wear the name badge visible all through the conference. Coffee/tea and sandwiches are served prior to the conference that starts at 10:05. Our luggage will be stored temporarily until check-in time earliest during the afternoon coffee break at 15.25.

ACCOMMODATION

Students have to share rooms. We try, as far as possible, to meet your wishes regarding a roommate. Checking-out time is Tuesday, before the morning session at 9.00.

MEALS

Lunches are buffet meals. Those of you who have informed us of special food requests - contact the serving staff in the restaurant. They have received information beforehand.

POSTERS

The poster session will take place Monday evening at the main hall. Mounting of posters should be done 17.45-18.15. Check the digital abstract book for your poster number as the frames will be numbered.

INTERNET

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

LEISURE

At the conference center there is a 25 m swimming pool, a gym and sauna, open between 15.00-23.00. On the evening of 23rd, the sea-side wooden sauna will be opened 21.00-24.00.

THE RETREAT PROGRAM

The extended version of the program is available using the QR code on the page 2.

Monday, September 23

8:30 Departure by bus from the City Terminal, Klarabergsviadukten, Stockholm

9:30 Arrival conference center Djurönäset, coffee and registration

10.05 – 12:30 **Morning session**

10:05 – 10:15 Opening of meeting & Welcome Remarks
Elias Arnér

Chairs: **Ola Hermanson and Paula Camargo Romera**

10:15 – 11:00 Keynote speaker **Clare Isacke**, Institute of Cancer Research London
"Targeting the tumour stroma"

11:00 – 11:30 **Representative from Karolinska Comprehensive Cancer Center**
"Karolinska Comprehensive Cancer Center "

Chairs: **Staffan Strömblad** and **Sara Abu Ajamieh**

11:30 – 11:45 **Jakob Stenman**, Dept. of Women's and Children's Health
"Development of radiopharmaceutical therapy for neuroblastoma"

11:45 – 12:00 **Juan Du**, Dept. of Microbiology, Tumor and Cell Biology
"The microbiome and cancer "

12:00 – 12:15 **Zahra Haider,** Dept. of Molecular Medicine and Surgery
"Non-invasive circulating tumor DNA analyses for diagnosis and monitoring of treatment response in Hodgkin lymphoma"

12:15 – 12:30 **Oscar Bedoya Reina,** Dept. of Women's and Children's Health
"Single cell sequencing from paired samples reveal neuroblastoma transcriptional evolution from primary tumors to metastasis"

12:30 – 12:45 **Photo session** (Group photo of all taken outside)

12:45 – 13:45 **Lunch**

13:45 – 15:25 **Afternoon session**

Chairs: **Klas Blomgren** and **Radosveta Gencheva**

13:45 – 14:30 Keynote speaker **Caroline Verbeke**, Oslo University
"Intratumour heterogeneity in pancreatic cancer"

14:30 – 14:45 **Renske Altena**, Dept. of Oncology-Pathology
"Clinical cancer trials with radiopharmaceuticals for imaging and therapy"

14:45 – 15:00 **Yvonne Wengström**, Dept. of Neurobiology, Care Sciences and Society
"Effects of an exercise intervention for women with advanced breast cancer the EFFECT Trial"

15:00 – 15:25 **Selected posters pitching**
Moderator: **Dina Dabaghie**

15:25 – 16:15 **Coffee and check-in**

16:15 – 17:45 **Breakout sessions**

1. Patient Perspectives
    - A. Melanoma
    - B. Thyroid Cancer
    - C. Lung Cancer
    - D. Inherited Cancer
2. Scientific Presentations
3. Meet the scientist
    - Clare Isacke
    - Caroline Verbeke

For details on breakout sessions see the next page.

17:45 – 18:15 **Networking and hors d'oeuvre**
Mounting of posters (main hall)

18:15 – 20:15 **Dinner**

20:15 – 22:00 **Poster session (main hall)**

Breakout sessions
Monday, September 23 (16:15-17:45)

Breakout session 1: Patient Perspectives

In these breakout sessions you will be able to join one of our oncologists and their patients on a discussion about their journey and their perspective. The session will start with a short introduction on the topic, followed by a discussion led by the oncologist with the patient, with an opportunity for an open discussion with the audience afterwards.

Breakout session 1A: Patient Perspective on Melanoma
Chair: Hildur Helgadottir — Location: Conference room house 1 A

Breakout session 1B: Patient Perspective on Thyroid Cancer
Chair: Renske Altena — Location: Conference room house 2 A

Breakout session 1C: Patient Perspective on Lung Cancer
Chair: Luigi de Petris — Location: Conference room house 3 A

Breakout session 1D: Patient Perspective on Inherited Cancer
Chair: Svetlana Bajalica Lagercrantz — Location: Conference room house 4 A

Breakout session 2: Scientific Presentations, selected from abstracts
Chairs: Ingemar Ernberg and Laia Gorchs — Location: Conference room house 7

Breakout session 3: Meet the Scientist

Get the opportunity to have a conversation and network with one of our keynote speakers.

Breakout session 3A: Meet Clare Isacke, Institute of Cancer Research London
Chair: Ourania Kostopoulou — Location: Coffe lounge house 5

Breakout session 3B: Meet Caroline Verbeke, Oslo University
Chair: Matthias Löhr — Location: Coffee lounge house 6

Notes:

* **Pre-registration is required for the different sessions**, if you have not registered please talk to the organisers if there are spaces available.
* Abstracts and further information on speakers can be found in the extended abstract booklet online.

Tuesday, September 24

07:30 – 08:45 **Breakfast and check out**

09:00 – 12:00 **Morning session**

Chairs: **Marco Gerling** and **Julia Tutzauer**

09:00 – 09:45 Keynote speaker **Raza Ali**, Cambridge University
"Charting the intact breast tumour microenvironment"

09:45 – 10:00 Cancer Research KI + Doctoral Programme in Tumour Biology and Oncology (FoTO)

10:00 – 10:30 **Coffee break**

Chairs: **Tina Dalianis** and **Hala Habash**

10:30 – 10:45 **Daniel Hagey**, Dept. of Laboratory Medicine
"Dynamic size and association profiles of tumour-derived DNA during pancreatic cancer progression"

10:45 – 11:00 **Filip Christiansen**, Dept. of Clinical Science and Education, Södersjukhuset
"AI-driven ultrasound detection of ovarian cancer that generalizes: an international multicentre validation study"

11:00 – 11:15 **Natalie Geyer**, Dept. of Clinical Science, Intervention and Technology
"Liver metastases of gastrointestinal cancer induce a pro-invasive parenchymal niche through Jagged 1-dependent Notch signaling activation"

11:15 - 11:30 **Yajie Yang**, Dept. of Oncology-Pathology
"Insights into IGF2BP3 in metastasis of Merkel cell carcinoma"

11:30 – 12:30 **Lunch**

12:30 – 15:30 **Afternoon session**

Chairs: **Keith Humphreys** and **Lourdes Sainero Alcolado**

12:30 – 13:00 **Mef Nilbert**, National Board of Health and Welfare
Swedish Cancer Strategy

13:00– 13:15 **Jennie Engstrand**, Dept. of Clinical Science, Intervention and Technology
"From Resection to Research: Tackling Liver Metastases at Karolinska"

13:15 – 13:30 **Kristian Pietras**, Dept. of Translational Cancer Research, Lund University
"Pericytes orchestrate a tumor-suppressive microenvironment in glioblastoma"

13:30 – 13:45 **Johan Lindberg**, Dept. of Medical Epidemiology and Biostatistics
"Androgen receptor pathway inhibitors or taxanes for patients with metastatic castration-resistant prostate cancer: A direct comparison in ProBio, a randomized, outcome-adaptive, biomarker-driven platform trial"

13:45 – 14:00 **Klas Wiman**, Dept. of Oncology-Pathology
"Therapeutic targeting of nonsense mutant TP53 in cancer"

14:00 – 14:30 **Coffee break**

Chairs: **Magdalena Paolino** and **Dimitrios Salgkamis**

14:30 – 14:45 **Glancis Luzeena Raja**, Dept. of Medical Biochemistry and Biophysics
"Mining for function in the small proteome"

14:45 – 15:00 **Ioannis Zerdes**, Dept. of Oncology-Pathology
"Multidimensional characterization of immune micro- and macro-environment in neoadjuvant-treated early breast cancer patients"

15:00 – 15:15 **Ewelina Dratkiewicz**, Dept. of Medical Biochemistry and Biophysics
"Crosstalk between the FGF2-FGFR signalling pathway, p53, and ribosome biogenesis in glioma"

15:15 – 15:30 **Carlos Rodrigues**, Dept. of Women's and Children's Health
"Lithium treatment protects microglia and newly generated neuronal populations in a mouse model of cranial radiotherapy"

15:30 – 15:45 **Conclusions, final remarks and poster prizes**

16:00 **Bus departure (Arrival to Stockholm at 17:00)**

Abstracts
Keynote speakers

Clare Isacke, PhD
Institute of Cancer Research London
Keynote Speaker
Monday 23rd, 10:15

Targeting the tumour stroma

The tumour microenvironment is characterised by the infiltration and activation of stromal cells and establishment of both reinforcing tumour-stroma crosstalk pathways and crosstalk between different stromal cell populations. This seminar will focus on the role of the cancer-associated fibroblasts (CAFs) and pericytes in breast cancer progression, particularly in the context of dormant disseminated disease, and the therapeutic strategies we are developing, including CAR-T cells and antibody-drug conjugates, to target these activated stromal cell populations.

Biosketch:
Clare Isacke her PhD identifying growth factors in development at the University of Oxford. She then moved to Tony Hunter's laboratory at the Salk Institute in San Diego to work on cell signalling as a postdoctoral fellow. On returning to England, she started her own research at Imperial College London. In 2001, Clare moved to The Institute of Cancer Research in London to take up an appointment as Professor of Molecular Cell Biology in the Breast Cancer Now Research Centre where her laboratory focusses on breast cancer metastasis and the tumour microenvironment. Their goal is to identify pathways and processes that can be targeted for the prevention or suppression of secondary disease or which are responsible for treatment-resistant tumour progression. In 2013 she was appointed Academic Dean at the ICR.

Caroline Verbeke, PhD
Oslo University
Keynote Speaker
Monday 23rd, 13:45

Intratumour heterogeneity in pancreatic cancer

Intratumour heterogeneity is considered a major cause of treatment failure in pancreatic cancer, which is amongst the deadliest of al solid cancers. While for more than a decade the existence of intratumor heterogeneity has been acknowledged, especially morphologically, it was not until the advent of single-cell and single-nucleus RNA-sequencing analysis that the full extent of intratumor heterogeneity was revealed, both in the cancer cell population and all components the tumour microenvironment. Although insight into the complexity of pancreatic cancer has rapidly expanded, data are mainly limited to the primary, treatment-naïve tumour, which stands in stark contrast with the clinical reality of metastasis largely determining patient outcome and neoadjuvant/induction treatment being part of standard patient management. Hence, research has recently shifted focus to heterogeneity in metastatic disease and following neoadjuvant treatment, as well as to the spatial distribution of the heterogeneous neoplastic and nonneoplastic cell populations.

Biosketch:
Dr Caroline Verbeke trained in Histopathology at the University Hospital in Antwerp (Belgium) and Mannheim/Heidelberg (Germany). She worked as a research associate in Experimental Pathology at the Kovler Viral Oncology La-boratories (University of Chicago). She was a Consultant GI Histopathologist and Honorary Senior Lecturer with a special interest in endocrine and pancreatic pathology at St James's University Hospital Leeds (UK). She worked at Karolinska University Hospital, Stockholm (Sweden) as a Consultant Histopathologist and Associate Professor. Since 2014, she works as a Professor and Consultant Histopathologist at the University of Oslo and Oslo University Hospital. She leads the Norwegian Cancer Society's National Group of Expertise on Pancreatic Can-cer Research. She has more than 25 years of experience in the field of pancreat-ic pathology and is actively involved at a national and international level in the development of diagnostic data sets and guidelines for the reporting of pancre-atic disease. She is particularly interested in tumour heterogeneity and the characterisation of residual pancreatic cancer following neoadjuvant treatment.

Raza Ali, PhD
Cambridge University
Keynote Speaker
Tuesday 24th, 09:00

Charting the intact breast tumour microenvironment

The diagnosis and treatment of breast cancer continues to rely on decades-old techniques in traditional histopathology. Immunotherapy has proved effective among some patients but not others, and this variation is poorly explained by traditional assays. Using imaging mass cytometry – a technique that couples antibodies conjugated to rare earth metal reporters and time-of-flight mass spectrometry to infer epitope abundance at subcellular resolution – my group has shown that the complexity of the TME can be reliably enumerated in situ and used to predict response in a large randomised trial of neoadjuvant immunotherapy in triple-negative breast cancer. Moreover, we show how immunotherapy remodels the TME, and how resistant cancer cells endure treatment by analysing serial samples collected over the treatment course. I will share our results and offer some insights on the wider implications for spatial cancer biology.

Biosketch:
Dr H. Raza Ali is Leader of the Systems Cancer Pathology group, based at CRUK Cambridge Institute, University of Cambridge, Associate Director for Clinical Academic Training , and an Honorary Consultant Pathologist at Addenbrookes hospital. He read medicine in Cardiff and began his training as a pathologist there before moving to Cambridge to undertake a PhD in the quantitative pathology and genomics of breast cancer, under the supervision of Prof Carlos Caldas. He completed his specialist clinical training in Cambridge as an NIHR Clinical Lecturer before moving to University of Zurich. In Zurich, he worked under the supervision of Prof Bernd Bodenmiller, inventor of imaging mass cytometry. There, he conducted research using highly multiplexed epitope-based tissue imaging to understand the principles of spatial organisation that characterise breast tumour ecosystems. His group uses imaging mass cytometry to understand the spatial dynamics of breast cancer through disease progression and treatment, in order to identify adaptations and biomarkers associated with relapse and response.

Abstracts
Invited speakers

Representative from Karolinska Comprehensive Cancer Center Monday 23rd, 11:00

Karolinska Comprehensive Cancer Center

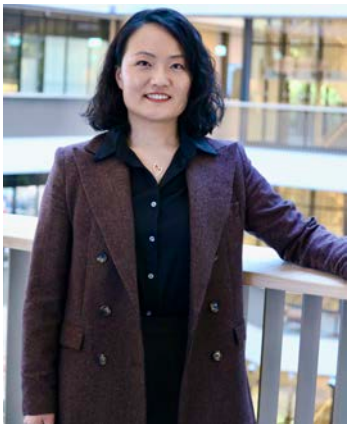
The Organization of European Cancer Institutes has during several decades developed a peer review based accreditation system, in order to promote excellence in cancer care and research. The importance of Comprehensive Cancer Centers has since the start of the European Cancer Mission initiated several programmes to enhance the development och cancer care and accelerating cancer research.
Karolinska university Hospital and Karolinska Institutet was jointly accreditades as a CCC in March 2020 and I due for reaccreditation in March 2025 and the reaccreditation process is now in progress and will involve everybody engaged in cancer research, education and care.

Jakob Stenman
Dept. of Women's and Children's Health
Monday 23rd, 11:30

Development of radiopharmaceutical therapy for neuroblastoma

Neuroblastoma is one of 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, EU CT No.: 2023-503684-42-00, PMID:35359899). While the treatment has been well tolerated and seems to be benefit some of the patients, we also have identified limitations and opportunities for further development. 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 Uppsala University and at the Pre-clinical Cancer Treatment Center, SciLifeLab, Uppsala. 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. One of the greatest challenges is that patients who experience a relapse are already severely weakened by their illness and by previous treatments, and optimally this type of treatment should be given at an earlier time point. For this purpose, we develop radio-pharmaceutical therapy based on the alpha-emitters to deplete single, or small clusters of metastatic cells and thus prevent relapses from occurring. The aim of the research project is to generate data to support a phase 1-2 clinical trial that utilizes targeted alpha-RPT as part of first line therapy for metastatic neuroblastoma. By controlling the systemic disease early, we believe that the cure rates in high-risk neuroblastoma can be significantly improved. We aim to translate our results into a new clinical trial in humans, within 5 years.

Juan Du
Dept. of Microbiology, Tumor and Cell Biology
Monday 23rd, 11:45



The microbiome and cancer

Our bodies are home to trillions of microbes, including those in the gastrointestinal, vaginal, and oral microbiomes. Recent research has highlighted the significant role that the microbiome plays in cancer development, progression, and response to treatment.

In our research, we studied the vaginal microbiota of 345 young Swedish women and found that non-Lactobacillus-dominant vaginal microbiota is strongly associated with HPV infection, particularly oncogenic types. We also conducted a meta-analysis study that found a significantly higher risk of cervical dysplasia with non-Lactobacillus-dominant vaginal microbiota than Lactobacillus-dominant vaginal microbiota, indicating the important role of vaginal microbiota in HPV infection and cervical cancer development.

Furthermore, we performed microRNA expression profiling on the same group of women and found that microRNAs were clustered into distinct groups according to vaginal microbiota composition. We also evaluated the salivary microbiota of participants with and without cervical dysplasia, finding that certain bacteria significantly increased in those with dysplasia, especially among smokers compared to never-smokers. Currently, we are exploring more immune response-related genes and investigating the mechanisms of vaginal microbiome-related inflammation using in vitro 2D and 3D models.

Additionally, we analyzed the whole-genome sequencing of gastric mucosa, which bolstered our knowledge on stomach physiology with respect to the gastric microbiome and microbial function. Moreover, we present a comprehensive immune cellular landscape of the human stomach, which will be a valuable resource to interrogate the pathology of gastric cancer.

Overall, our findings have significant implications for cancer development and surveillance with the microbiome in both research and clinical settings.

Renske Altena
Dept. of Oncology-Pathology
Monday 23rd, 14:30

Clinical cancer trials with radiopharmaceuticals for imaging and therapy

There is a clinical need for reliable and representative therapy-predictive biomarkers for targeted cancer therapies, where biopsy-based strategies are the current reference standard but have several limitations. Precision medicine approaches with positronemission tomography (PET)-imaging constitute a non-invasive, real-time assessment of the presence and accessibility of the target of treatment, and may be a more convenient alternative for patients and clinicians. Radiopharmaceuticals for PET-imaging can be based on small molecules or whole antibodies, and can be coupled to diagnostic radioisotopes but also to radiation-emitting isotopes for local delivery of radiation therapy. This field of diagnostic and therapeutic radiopharmaceuticals is rapidly expanding, and at Karolinska we are conducting several investigator-initiated and industry-sponsored clinical trials in different phases that aim to evaluate the applicability and use of new radiopharmaceuticals. In my presentation, I will discuss general principals of precision imaging strategies, ongoing and completed clinical trials and share future perspectives in the field of radiotheranostics.

Yvonne Wengström
Dept. of Neurobiology, Care Sciences and Society
Monday 23rd, 14:45

Effects of an exercise intervention for women with advanced breast cancer the EFFECT Trial

Physical exercise both during and after curative cancer treatment has been shown to reduce side effects. There is a paucity of evidence in the metastatic cancer setting.
The multinational RCT EFFECT assessed the effects of exercise on fatigue and HRQOL in patients with MBC. The trial included 357 patients with MBC and a life expectancy of ≥6 months but without unstable bone metastases were recruited at eight study centers across five European countries and Australia. Participants were randomly assigned to usual care or a 9-month supervised exercise program. Intervention effects on physical fatigue were determined by comparing the change from baseline to 3, 6 (primary timepoint) and 9 months between groups using mixed models for repeated measures, adjusted for baseline values of the outcome, line of treatment (first or second versus third or higher) and study center. Exercise resulted in significant positive effects on both primary outcomes. Physical fatigue was significantly lower (-5.3 (95% confidence interval (CI), -10.0 to -0.6), Bonferroni-Holm-adjusted P = 0.027; Cohen's effect size, 0.22) and HRQOL significantly higher (4.8 (95% CI, 2.2-7.4), Bonferroni-Holm-adjusted P = 0.0003; effect size, 0.33) in the exercise group than in the control group at 6 months.

Daniel Hagey
Dept. of Laboratory Medicine
Tusday 24th, 10:30

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

Circulating tumour-derived DNA (ctDNA) is an increasingly important marker of minimal residual disease. Although generally referring to histone-bound fragments of <200bp, the term ctDNA can describe any length of DNA in various potential macromolecule complexes. To uncover which of these is most enriched in tumour-derived material, we used differential centrifugation to separate blood into eight cellular, vesicular and soluble components. Furthermore, we segregated long (>400bp) and short DNA fragments using ligation and tagmentation-based library amplification. To judge these dynamics at different stages of disease, we collected 53 samples from pancreatic cancer patients and separated these into 7 without progressive disease, 23 with advanced cancer and 23 at terminal stages. Using digital PCR and shallow whole genome sequencing, we find most short ctDNA associated with apoptotic bodies, which are removed in standard protocols. In contrast, the greatest overall enrichment of ctDNA is found as long fragments associated with small vesicles at earlier stages and soluble proteins in terminal disease. We further characterize the macromolecular complexes associated with these fragments using gel electrophoresis and serial centrifugation. This work suggests that ctDNA can be enriched based on its biological associations and that this may improve diagnostic sensitivity and clinical disease monitoring.

Mef Nilbert
National Board of Health and Welfare
Tuesday 24th, 12:30

Swedish Cancer Strategy

Mef Nilbert is a professor of Oncology and a senior consultant at Lund University. She has been appointed by the government as an investigator for the updated Swedish Cancer Strategy, which will be presented in the end of November 2024.
Mef Nilbert will talk about the major areas of the new cancer strategy with a special focus on research needs.

Jennie Engstrand
Dept. of Clinical Science, Intervention and Technology
Tuesday 24th, 13:00

From Resection to Research: Tackling Liver Metastases at Karolinska

The liver is a common site for metastases. Partly owing to the liver's remarkable regenerative potential, surgical resection of liver metastases is frequently performed, particularly for patients with metastases from colorectal cancer. At Karolinska, over 130 liver resections for metastases are conducted annually, with most patients contributing to biobanked samples, providing exceptional translational research opportunities on metastases.

In this talk, I will address common clinical challenges associated with liver metastasis resections, such as post-hepatectomy liver failure and early relapse. I will also discuss our approaches to leveraging the extensive clinical data available to understand these issues and improve outcomes. Additionally, I will present recently started clinical trials for liver metastasis patients, including the NewComet trial, which compares liver metastasis resection to ablation, and the EU-funded GUIDE-MRD project, which explores the use of circulating tumor DNA measurements to detect early metastasis relapse—one of the most critical issues in liver metastasis surgery.

Finally, I will introduce KaroLiver, a retrospective cohort study of over 1000 liver metastasis operations, linked to a local biobank of fresh tissue and serum samples, invaluable for translational research. Through these studies and clinical resources, we aim to advance metastasis treatments and improve patient care by improving tailored patient selection and follow-up.

Kristian Pietras
Division of Translational
Cancer Research, Lund University
Tuesday 24th, 13:15

Pericytes orchestrate a tumor-suppressive microenvironment in glioblastoma

Glioblastoma (GBM) is characterized by fast progression, an infiltrative growth pattern, and a high rate of relapse. A defining feature of GBM is the existence of spatially and functionally distinct cellular niches, i.e. a hypoxic niche, a leading-edge niche, and a peri-vascular niche, in which malignant cells engage in paracrine crosstalk with cell types comprising the tumor microenvironment. Here, by analysis of single-cell transcriptomic data of human GBM and transgenic mouse models of GBM, we unexpectedly identified pericytes, intimately associated with the endothelium, as the most active paracrine signaling hub within the tumor parenchyma. Exclusive signaling axes emanating from pericytes were received by endothelial cells, malignant cells, astrocytes, and immune cells. Depletion of pericytes through genetic engineering in several different transgenic and orthotopic mouse models of GBM demonstrated accelerated tumor progression, a disrupted blood-brain-barrier, and premature death of pericyte-poor mice. Mechanistic studies revealed that pericyte deficiency altered the cellular composition of GBM, remodeled the endothelium, and impacted on the immune cell landscape, exacerbating tumor cell invasion and immune suppression. Specifically, endothelial cells deprived of pericyte association altered their signaling programs, which in turn attracted peri-vascular, tumor-associated macrophages polarized towards an immune-suppressive phenotype. The recruited macrophages expressed Hepatocyte Growth Factor (HGF), which reinforced activation of its receptor tyrosine kinase MET on a mesenchymal subtype compartment of GBM cells driven by the key phenotypic regulator Fosl1 within hypoxic regions. Indeed, orthotopic implantation of isolated, MET-expressing GBM cells corroborated their superior tumor-initiating capability and invasive phenotype, compared to cells negative for MET. Taken together, we infer that the pericyte represents a critical modulator of GBM development by orchestrating a tumor-suppressive microenvironment; our findings thus highlight the importance of pericyte preservation in the face of current and future GBM therapies.

Johan Lindberg
Dept. of Medical Epidemiology and Biostatistics
Tuesday 24th, 13:30

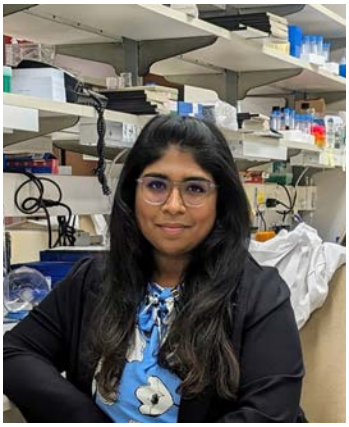
Androgen receptor pathway inhibitors or taxanes for patients with metastatic castration-resistant prostate cancer: A direct comparison in ProBio, a randomized, outcome-adaptive, biomarker-driven platform trial.

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. The primary endpoint was the time to no longer clinically benefitting (NLCB) as per PCWG3 criteria. Enrollment in the experimental group was stopped when the Bayesian probability of superiority reached prespecified thresholds ("graduation").
Results: In total, 218 randomizations were performed: 92 to SOC, vs. 75 and 51 to taxanes and ARPi, respectively, in the biomarker-driven experimental arms. ARPi graduated in the "signature all", i.e. a signature encompassing all biomarkers. The median estimated NLCB was 11.1 (90% Bayesian credible interval [CrI]: 9.6 to 13.3) months for ARPi compared with 7.4 (90% CrI: 6.7 to 8.4) months in the SOC arm, for a survival time ratio (STR) of 1.50 (90% CrI: 1.20 to 1.86). ARPi demonstrated superiority to taxanes within the experimental arms (STR of 1.60, 90% CrI: 1.28 to 2.01). In the experimental arms, the median NLCB was 11.1 (90% CrI: 9.6 to 13.3) months for ARPi vs. 6.9 (90% CrI: 6.2 to 8.0) months for taxanes.

Androgen receptor pathway inhibitors or taxanes for patients with metastatic castration-resistant prostate cancer: A direct comparison in ProBio, a randomized, outcome-adaptive, biomarker-driven platform trial.

Biomarker signature findings suggest that the largest increase in time to NLCB was observed in AR (single-nucleotide variant/ genomic structural rearrangement)-negative and TP53 wild-type patients and TMPRSS2–ERG fusion-positive patients, whereas no difference between ARPIs and taxanes was observed in TP53-altered patients. The median estimated overall survival (OS) was 38.7 (90% CrI: 31.1 to 54.1) months for ARPi compared to 21.7 (90% CrI: 19.0, 26.1) months for taxanes in the experimental arms. Conclusions: ARPIs outperform taxanes and physician's choice treatment in patients with metastatic castration-resistant prostate cancer with detectable circulating tumor DNA.

Glancis Luzeena Raja
Dept. of Medical Biochemistry and Biophysics
Tuesday 24th, 14:30



Mining for function in the small proteome

Microproteins are short open reading frames (sORFs) encoded proteins (SEPs) of less than 100 codons. In the human genome, sORFs outnumber annotated ORFs coding for canonical proteins, suggesting that microproteins could constitute a substantial fraction of the proteome. Emerging evidence anticipates that microproteins play a role in a variety of diseases: Deregulation of translation towards non-canonical protein products is frequently observed in tumorigenesis. To date, a small number of cancer-associated microproteins have been characterized. However, the functional relevance of a vast majority of sORF candidates is unknown. We curated a large sORF library from literature and database and performed high-throughput CRISPR/Cas9 knock-out and cDNA overexpression screens for ~11,000 sORFs in cancer cell lines. From our KO screens, we characterized six candidate sORFs that were affecting for cancer cell growth, finding several microprotein candidates with distinct subcellular localization compartments reproducible, specific protein interaction partners. Efforts to more precisely tie down the expression and function of each candidate in cancers are ongoing. From our overexpression screen, we identified two cytoprotective microproteins that counteracted cellular stress in response to chemotherapeutics, one of which has not been described in literature. Detailed mutational analysis revealed critical amino acids specific interaction partners of this novel microprotein. Besides providing mechanistic insights on a new microprotein, our studies highlight the power of using pooled KO and overexpression screens to identify functional microproteins.

Speakers selected from abstracts

Zahra Haider
Dept. of Molecular Medicine and Surgery
Monday 23rd, 12:00

Non-invasive circulating tumor DNA analyses for diagnosis and monitoring of treatment response in Hodgkin lymphoma.

Genetic profiling of Hodgkin lymphoma (HL) for improving diagnostics has been challenging owing to the rarity of malignant Hodgkin and Reed-Sternberg cells (0.1-3%) in tissue biopsies. Analyzing plasma circulating cell-free tumor DNA (ctDNA) has emerged as a promising non-invasive approach for characterizing somatic aberrations. Longitudinal ctDNA analyses can also enable dynamic monitoring of treatment response, allowing for immediate clinical interventions. Here, we aim to evaluate the clinical feasibility of analyzing ctDNA using deep panel sequencing for comprehensive and sensitive genomic profiling of HL. We further aim to study the potential of using targeted ctDNA analysis for monitoring treatment response and progression compared to FDG-PET/CT-based evaluations including metabolic tumor volume (MTV) and total lesion glycolysis (TLG).

This ongoing study comprises of 36 HL patients from the prospective BioLymph study at Karolinska University Hospital. After obtaining informed consent, plasma samples were collected before start of primary treatment, at interim evaluation, end of primary treatment, at follow-up and during relapse treatment for refractory patients (n=5). Baseline clinic-pathological data and longitudinal radiological evaluations were also collected. Comprehensive genomic profiling of HL i.e. single nucleotide variant (SNV), short insertion/deletion (indel) and copy-number variant (CNVs) detection, was performed by sequencing plasma ctDNA and matched normal genomic DNA from blood using the Genomic Medicine Sweden (GMS) Lymphoid Gene panel (Twist Bioscience, CA, US). Libraries with unique molecular identifiers (UMI) for error-correction and identification of variants with low variant allele frequency (VAF), were sequenced at a depth of 100 million read pairs using the NovaSeq 6000 instrument (Illumina CA, US). Bioinformatic analyses and somatic variant calling were performed using the BALSAMIC-UMI pipeline followed by variant filtering, interpretation, and classification.

Non-invasive circulating tumor DNA analyses for diagnosis and monitoring of treatment response in Hodgkin lymphoma.

Total cell-free DNA (cfDNA) burden at baseline correlated significantly with MTV (R=0.38, p<0.05) and TLG (R=0.37, p 0.05). Non-synonymous SNV/Indels (median VAF 1.3%, range 0.2-48%) were identified in all 36 patients (median of 18 variants/patient) in known genes implicated in HL including SOCS1, TNFAIP3, GNA13, B2M, ARID5B, and STAT6. We also performed CNV profiling, investigating clinically relevant gains in 9p and 2p arms. Paired tumor tissue and plasma analyses in 8 patients showed VAF was significantly higher in plasma than in tissue (p<0.001). For monitoring treatment response, a custom-designed targeted sequencing panel, following 7 to 107 targets in patients, will be compared with personalized multiplex droplet digital PCR analyses in serially collected plasma samples as well as PET/CT evaluations. We have preliminarily shown the potential and feasibility of targeted deep sequencing of ctDNA for tumor-naïve, comprehensive genomic profiling in HL.

Oscar Bedoya Reina
Dept. of Women's and Children's Health
Monday 23rd, 12:15

Single cell sequencing from paired samples reveal neuroblastoma transcriptional evolution from primary tumors to metastasis

Neuroblastoma (NB) is a highly heterogeneous disease with a broad range of outcomes and prognosis. In our study, we aimed to determine the cell of origin of metastasis in high-risk neuroblastoma and to reconstruct the molecular changes from cells in primary tumors to metastasis. To this end, we obtained and sequenced single cells from paired samples, including primary and metastatic tumors from three different patients. We sorted the cells with markers to ensure they were alive and further sequenced them using Smart-Seq3. We obtained approximately 7,000 cells with high-quality features, which were further clustered and analyzed.

We identified clusters of cells with transcriptional profiles resembling stromal cells (e.g., fibroblasts, endothelial cells, plasma cells, and immune cells), glial cells, and neuroendocrine cells. Our analysis revealed that different clusters resembled various fates of the developing sympathoadrenal system to different extents, and that they presented adrenergic- and mesenchymallike signatures to varying degrees. The neuroendocrine cells identified in our study most likely resembled noradrenergic neuroblastoma cells. Further analysis revealed significant downregulation of genes in segments of 11q, in a cluster enriched in metastatic cells. Our study provides, for the first time, an accurate glimpse into the evolution of cells from primary tumors to metastasis in neuroblastoma.

Filip Christiansen
Dept. of Clinical Science and Education, Södersjukhuset
Tuesday 24th, 10:45

AI-driven ultrasound detection of ovarian cancer that generalizes: an international multicentre validation study

Objectives: Ovarian lesions are common, and often incidentally detected. A critical shortage of expert ultrasound examiners has raised concerns of unnecessary interventions and delayed cancer diagnoses. Artificial intelligence (AI)-driven diagnostic support has the potential to alleviate this burden and improve patient outcomes. Deep learning has shown promising results in ovarian cancer detection in ultrasound images; however, external validation is lacking. We aimed to develop an AI model for ovarian cancer detection, evaluate its robustness and ability to generalize in a large multicentre setting, and assess an AI-assisted triage strategy.

Methods: In this international multicentre retrospective study, we developed and validated transformer-based neural network models using a comprehensive dataset of 17,119 ultrasound images from 3,652 women with an ovarian lesion (2,224 benign, 1,428 malignant) across 20 centres in eight countries. A total of 2,660 cases were assessed by a minimum of seven expert and six non-expert examiners. For each centre in turn, we trained a model using data from the remaining centres and compared the models' diagnostic performance with that of 33 expert and 33 non-expert examiners, considering sensitivity, specificity, F1 score, and area under the receiver operating characteristic curve (AUC). Furthermore, we retrospectively simulated and assessed how these models could be used in AI-assisted triage and compared it to current practice.

Results: The models demonstrated robust performance across centres, ultrasound systems, and histological diagnoses, with an AUC of 0.93 (95% CI 0.92–0.94) and F1 score of 83.5% (95% CI 82.1–84.9) on cases from unseen centres. They outperformed both expert and non-expert examiners (66 out of 66), with F1 scores of 79.4% (95% CI 77.9–80.9; $\Delta = 4.1$ [95% CI, 2.6–5.5, $p < 0.0001$]) and 74.1% (95% CI 72.4–75.8; $\Delta = 9.4$ [95% CI, 7.8–11.0, $p < 0.0001$]), respectively. The models were further shown to produce well-calibrated predictions. In a retrospective simulation, AI-assisted diagnostic support reduced the number of referrals to experts by 63%, while significantly surpassing the diagnostic performance of the current practice (F1 77.2% vs 82.7%; $\Delta = 5.5$ [95% CI, 4.3–6.7, $p < 0.0001$]).

AI-driven ultrasound detection of ovarian cancer that generalizes: an international multicentre validation study

Conclusions: The models exhibit strong generalization and outperform expert examiners in diagnostic accuracy. Introducing AI-driven diagnostic support for ovarian cancer detection has the potential to alleviate the shortage of expert ultrasound examiners and improve patient outcomes by increasing diagnostic accuracy and optimizing clinical workflow. The models' robust performance under comprehensive evaluation indicates that they are ready for prospective clinical implementation studies, bringing us closer to the adoption of AI-assisted diagnostics in clinical settings.

Natalie Geyer
Dept. of Clinical Science, Intervention and Technology
Tuseday 24th, 11:00

Liver metastases of gastrointestinal cancer induce a pro-invasive parenchymal niche through Jagged 1-dependent Notch signaling activation

Background
The diagnosis of gastrointestinal cancer liver metastases (LM) characterizes an advanced disease stage with a 5-year overall survival below 10 %. While it is known that the liver creates a pre-metastatic niche for disseminated tumor cells, the impact of the hepatic microenvironment on LM growth is poorly understood.
Results
Here, we used Cell Interaction by Multiplet sequencing (CIMseq, PMID: 34253926) to globally analyze the tumor microenvironment (TME) of murine LM. We show that the parenchyma within the TME shows a high degree of plasticity and we could characterize cell populations associated with an acute phase reaction as well as hepatocytes that adopt a progenitor-like status in LM.
We mapped the different phenotypes in situ to sections from human colorectal cancer LM that were collected at Karolinska Hospital (KaroLiver cohort) using a combination of multiplex RNA in situ hybridization, immunofluorescence, and immunohistochemistry. We uncovered a spatial gradient of hepatocytes with acute phase protein production in the perimetastatic liver, de-differentiation in the outer tumor region, and complete exhaustion in the tumor core. This phenotypic trajectory is a specific characteristic of aggressive LM invasion and is stalled in areas of tumor regression. CIMseq and ligand-receptor pair analysis indicated that juxtacrine Notch signaling regulates liver parenchyma plasticity in the TME. We used CRISPR/Cas9-based genetic editing of the ligand Jagged 1 to show that interference with tumor-hepatocyte interactions at the level of Notch reduces the capacity of murine LM to successfully invade into the liver. These findings highlight the functional importance of parenchymal plasticity and juxtacrine tumor-hepatocyte contact in the TME of LM.
Discoveries
We characterized the hepatic injury reaction that is triggered by LM invasion and could show that LM shape their surrounding parenchymal TME towards a pro-invasive phenotype through Notch signaling activation.

Yajie Yang
Dept. of Oncology-Pathology
Tuesday 24th, 11:15

Insights into IGF2BP3 in metastasis of Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a highly aggressive skin cancer that lacks biomarkers for early detection of metastatic disease and effective treatment options for advanced disease. In this study, we investigated the clinical significance and functional impact of the RNA binding protein Insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3) in MCC. Our results revealed that IGF2BP3 expression was significantly higher in MCC metastases compared to primary tumors, and its elevated expression was associated with shorter disease-specific survival, emphasizing its clinical relevance. In an MCC xenograft model, lung metastases exhibited increased IGF2BP3 expression. Notably, higher IGF2BP3 levels in xenografted tumors correlated with a greater propensity for lung metastasis. Our functional studies revealed that IGF2BP3 primarily regulates cell migration and invasion, rather than cell growth, in MCC; this functional role underscores its impact on metastatic processes. RNA immunoprecipitation sequencing analysis identified 281 RNA targets of IGF2BP3. Some of these targets are linked to biological processes involved in metastasis. Importantly, several IGF2BP3 targets overlapped with genes differentially expressed between MCC primary tumors and metastases, suggesting that IGF2BP3 and its targets contribute to tumor progression. Furthermore, pharmacological inhibition of BRD transcription regulators or silencing BRD4 reduced IGF2BP3 expression, suggesting BRD4 as a potential regulator of IGF2BP3. In summary, our study sheds light on the involvement of IGF2BP3 in MCC tumor metastasis, highlights its potential as a prognostic biomarker, and provides valuable insights into the molecular mechanism underlying MCC progression.

Klas Wiman
Dept. of Oncology-Pathology
Tuesday 24th, 13:45

Therapeutic targeting of nonsense mutant TP53 in cancer

The TP53 tumor suppressor gene is frequently mutated in human cancer. A large fraction of TP53 mutations are missense mutations that disrupt specific DNA binding and transactivation of target genes. Compounds that target missense mutant p53 and induce tumor cell death have been identified and some are being tested in clinical trials. Around 10% of cancer-associated TP53 mutations are nonsense mutations that give rise to truncated inactive p53 protein. The most common TP53 nonsense mutation is R213X which is also one of the 10 most common TP53 mutations overall. Aminoglycoside antibiotics such as G418 (Geneticin) can induce translational readthrough of nonsense mutant TP53 and expression of full-length active p53 protein. However, their use in the clinic is limited by severe side effects. A number of novel compounds have been shown to promote readthrough of nonsense mutant TP53. We have found that the 5-FU metabolite 5-fluorouridine has readthrough activity and triggers cell death in tumor cells carrying R213X nonsense mutant TP53. In a chemical library screen in collaboration with CBCS/SciLife lab, we have identified novel candidate readthrough-inducing compounds that will be characterized further. To study the impact of TP53 nonsense mutation and evaluate novel readthrough compounds in vivo, we have generated mice carrying the Trp53 nonsense mutation R210X, corresponding to human TP53 R213X. Trp53 R210X/R210X mice develop spontaneous tumors at early age. Induction of translational readthrough is a promising strategy for targeted therapy of tumors with TP53 nonsense mutation. This strategy could potentially also be applied for tumors with nonsense mutations in other tumor suppressor genes, such as APC, PTEN and RB1.

Ioannis Zerdes
Dept. of Oncology-Pathology
Tuesday 24th, 14:45

Multidimensional characterization of immune micro- and macro-environment in neoadjuvant-treated early breast cancer patients

Background: Increased anti-tumor immune responses correlate with improved rates of pathologic complete response (pCR) in early breast cancer (BC) patients treated with neoadjuvant therapy. However, given the complexity of breast tumor ecosystem and its drivers, the local and systemic immune landscape and temporal evolution during treatment require further investigation.

Methods: Patient material from two neoadjuvant randomized early breast cancer clinical trials: (1) The international EORTC 10994/BIG 1-00 phase III trial (neoadjuvant taxane/anthracycline vs FEC). FFPE tissue from pre-treatment samples was used for applying machine learning (ML)-based algorithms for digital tumor-infiltrating lymphocytes (dTIL, CNN11 classifier) quantification (n=587) and spatial multiplex immunofluorescence analysis (n=487); (2) The Swedish PREDIX HER2 phase II trial early HER2+ BC patients (trastuzumab + pertuzumab + docetaxel vs trastuzumab emtansine (T-DM1), n=197). Baseline and on-treatment biopsies (for TIL enumeration and/or genomic-transcriptomic data) and plasma samples (for multiplexed circulating protein immune profiling) were obtained. Correlations with patient clinicopathological characteristics and treatment outcomes were performed.

Results: In the EORTC trial, dTIL were higher in the triple-negative (TN) subtype and independently predicted pCR in the whole cohort (ORadj= 1.59, 95% CI 1.00–2.54, p=0.05). Expression of CD4+ (ORadj=1.79, 95% CI 1.07-2.97, p=0.026) and intra-tumoral CD8+ T-cells (ORadj=1.83, 95% CI 1.05-3.20, p=0.033) was associated with increased chemosensitivity. Higher colocalization between immune and tumor cells was observed in TN patients who achieved pCR versus those with residual disease (chi-squared p=0.01). In the PREDIX HER2 trial, the systemic proteomic landscape at baseline (n=87) revealed a number of markers (i.e. LAP TGF-beta-1, LAMP3, IL-7, IL-18, CXCL11, CRTAM), significantly enriched in non-pCR patients receiving the antibody-drug conjugate T-DM1. This systemic response was accompanied by lower baseline mean TILs levels in non-pCR patients. On-treatment plasma proteomic data (n=59) revealed systemic IL-33 upregulation in patients receiving pCR, which was accompanied by significantly increased TILs levels at cycle 2 (deltaTILs: non-pCR= 8.8% vs pCR=34.4%, p=0.018; n=32).

Conclusions: Our data indicate that both abundance and spatial distribution of immune markers using ML-based methods contain prognostic information. The integration of systemic immune component could provide further biological and prognostic insights when studying the immune infiltrate in early BC. Additional validation is warranted.

Ewelina Dratkiewicz
Dept. of Medical Biochemistry and Biophysics
Tuesday 24, 15:00

Crosstalk between the FGF2-FGFR signalling pathway, p53, and ribosome biogenesis in glioma

High-grade gliomas (HGGs) are characterised by their aggressive growth behaviour and resistance to therapies. While surgery, radiation, and chemotherapy with temozolomide are the standard of care, more specific molecular targets are emerging and may lead to better and more personalised treatment in the future. The fibroblast growth factor receptor (FGFR1-FGF2) axis is implicated in glioma cell proliferation, survival, invasion, autophagy, and stemness features, thereby contributing to glioma relapse and resistance to therapies. In contrast to several other cancer types, HGGs usually exhibit an increased expression of FGFR1, while levels of FGFR2 are low (since FGFR2 often is co-deleted with PTEN). From a large shRNA screen, FGFR signalling was found to be a potential therapeutic target in paediatric gliomas, and we have previously described synergistic inhibition of glioma growth following co-treatment with a transcription inhibitor and the FGFR inhibitor (FGFRi) erdafitinib in paediatric and adult HGGs. While a common side-effect of FGFRi is hyperphosphatemia, a better understanding of FGFR1-FGF2 functions in HGG may pave the way for improved combinatorial treatment options. One target of FGFR is ribosome biogenesis which is often increased in response to upregulated signalling downstream from receptor tyrosine kinases in cancer cells. Here we set out to better understand the regulation of FGFR1-FGF2 in response to chemotherapeutic agents and in relation to p53 and ribosome biogenesis.
We found that A172 and H4 glioma cells (wt p53) treated with known inducers of p53, namely BMH-21, CBL0137 (curaxin), and nutlin-3a, show a distinct pattern of FGFR1 downregulation. Knock-down of p53 was able to partially rescue this effect. When investigating potential mediators of p53-dependent regulation of FGFR1 expression, we observed a significant reduction of 4E-BP1 phosphorylation following incubation with BMH-21, which state suggests its inhibitory effect on translation. While erdafitinib as monotherapy had modest growth inhibitory effects, the combination of erdafitinib and nutlin-3a displayed potent anti-proliferative effects in wt p53 HGGs. Based on our findings, we evaluated combination therapies of erdafitinib with examined p53 inducers and noted synergistic effects for all of them, however, varying between tested cell lines. We also describe FGF2 enrichment in cell nucleoli in a subset of HGG cell lines and tissue samples. Overall, our ongoing studies support the design and further evaluation of FGFRi-based combination therapies in malignant brain tumours.

Carlos Rodrigues
Dept. of Women's and Children's Health
Tuesday 24th, 15:15

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

Radiotherapy remains a cornerstone of the treatment of high-grade brain tumors, and the refinement of its protocols resulted in a dramatic improvement in the survival rates of brain tumor patients, particularly among the pediatric population. However, while lifesaving, radiotherapy results in long-term complications in 50-96% of the treated individuals, where cognitive deficits are particularly debilitating. Currently, no treatments or preventive strategies are available to avert these deficits. Lithium (Li), used to treat bipolar affective disorder, has been shown to reduce radiation-induced cognitive deficits in rodent models by preventing apoptosis of the neuronal stem and progenitor cells in the hippocampus and stimulating their proliferation. This work aimed to further elucidate the mechanisms behind the protective and pro-regenerative actions of Li in the irradiated young brain. To this end, postnatal day (PD) 21 C57BL6/J mice were injected intraperitoneally with Li chloride (4 mmol/kg) and kept on a Li carbonate-containing diet for 4 weeks. Control animals were injected with saline and administered an equivalent control diet. On PD 25, the animals were administered a singledose whole-brain radiation of 8 Gy and were subsequently sacrificed at different time points, spanning from 2 weeks to 1 year. At sacrifice, the hippocampi were harvested for single-cell RNA sequencing using a novel, 2-step protocol to harvest viable cells of all types, including neurons. The attained results showed that radiation triggered the expression of senescencerelated genes in the hippocampal microglia (e.g., Cdkn1a, Ccl12), which Li has prevented through the activation of the Bcl2 family of genes. Moreover, they corroborate the protective effect of Li on the newly generated hippocampal neurons, which undergo remodeling over time, leading to the emergence of new subpopulations. This work represents another advancement towards understanding the action of Li in the irradiated brain and confirms its potential to become the first pharmacological treatment for radiation-induced complications.

The Cancer Research KI retreat Organizing committee

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Booklet design: Dina Dabaghie

Photo: 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 Institutet

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

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

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

>390 PIs in cancer research at KI 21 Departments

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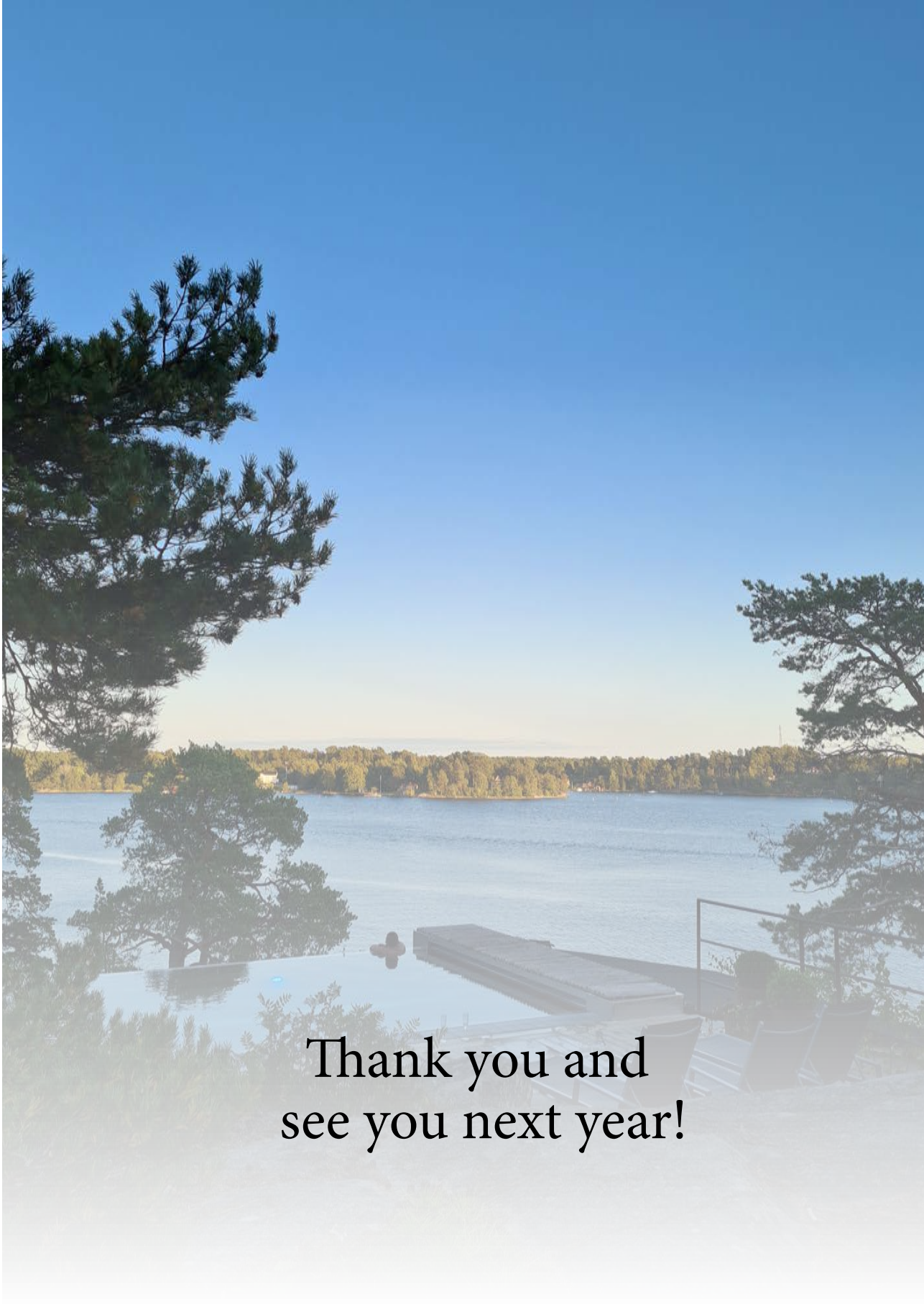
More information on the website

Notes



Thank you and
see you next year!