The XXth
Cancer Research KI Retreat

DJURÖNÄSET

SEPTEMBER 25-26, 2023

Welcome to the XXth Annual Cancer Research KI

The retreat will bring together students, post-docs, senior scientists, and healthcare professionals from Karolinska Institutet and Karolinska University Hospital convening for a two-day meeting to enhance interactions and interdisciplinary contacts and to learn more about our ongoing cancer research at KI. This year marks a milestone, and we are celebrating our 20- year anniversary of the annual Cancer retreat, with its roots in prior meetings and activities organized by the former KI Cancer and StratCan networks, bringing the Cancer Research community together!

The retreat is organized by Cancer Research KI, a hub for all scientists that conduct research and care in the cancer field at KI, and with the aim to be inclusive, collaborative, and transparent in all strategic planning. 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 Blue Sky 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) also continues and supports collaborative research between KI and Mayo broadly in the cancer field. This year marked the launch of new international collaboration with Cancer Research UK's innovation engine, Cancer Research Horizons. Another major initiative is our database that maps the cancer research landscape at KI. The database contains more than 350 principal investigators and team leaders across both KI campuses and at the major Stockholm hospitals with an aim to increase visibility of Cancer Research at KI and to facilitate new collaborations. Cancer Research KI furthermore continues its partnering with Karolinska Comprehensive Cancer Center, for example by having a common Scientific Advisory Board, working towards common missions spanning from basic research to patient care, and representing Sweden in different EU-initiatives including: The project Establishing of Cancer Mission Hubs: Networks and Synergies (ECHoS) and Comprehensive Cancer Infrastructures for Europe (CCI4EU). Cancer Research KI also continues to be an important hub for communication of cancer research at KI towards the general public. We have established digital biannual patient organisation meetings and 'A day for cancer' that was broadcasted to the general public and viewed thousands of times online.

After this brief vignette of some of the ongoing activities, 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. We are also looking forward to celebrating our Cancer Research community and look back to 20 years together.

Finally, we would like to welcome our guests to this retreat, starting with our keynote speakers: Dr. Matthew Goetz, Mayo Clinic; Dr. María A. Blasco, Spanish National Cancer Research Centre; Dr. Juha Klefström, University of Helsinki. A warm welcome also to all invited speakers, clinical fellows (ST-läkare), students, and all other participants. We would also like to thank the organizing committee, chaired by Johanna Ungerstedt, for their work to plan the event and Kancera AB for supporting the poster prizes.

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

Celebrating the Cancer Community, 20th anniversary of the annual Cancer Retreat at KI !

Cancer Research KI (previously: KI Cancer and StartCan)

#CRKIretreat2023

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

This is Kancera AB

Kancera is developing a new class of drugs targeting the fractalkine axis (small molecule CX3CR1 antagonists) for treatment of cancer and severe inflammatory diseases. In the field of cancer, Kancera focuses on the development of candidate drugs that block DNA repair and modify the tumor environment (Cancers 2021, 13 (6), 1442). The lead project is currently studied in a combined phase Ib/IIa study in ovarian cancer patient with relapse from platinum chemotherapy. The study is conducted in collaboration with the Nordic Society of Gynecological Oncology at the leading university hospitals in Sweden (including KS), Norway and Denmark.

Please visit our home-page for more information: www.kancera.com

The XXth Cancer Research KI Retreat
September 25-26th 2023
GENERAL PROGRAM OUTLINE

Monday, May 24:

Bus from Stockholm City **8:30**

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

Welcome and introduction **10:05**

Morning session **10:15**

Group photo **12:15**

Lunch **12:30**

Afternoon session **13:30**

Coffee break and check-in **15:35**

Breakout session **16:15**

Mingle and welcoming drink **17:45**

Dinner **18:30**

Poster session **20:00**

Tuesday, May 25:

Breakfast and check out **7:30**

Morning session **9:00**

Coffee break **10:00**

Lunch **11:30**

Afternoon session **12:30**

Coffee break **14:15**

Bus departure **16:00**

Arrival Stockholm City **17:00**

Keynote Speakers

María A. Blasco PhD, Spanish National Cancer Research Centre

Matthew Goetz PhD, Mayo Clinic

Juha Klefström PhD, University of Helsinki

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 25th, 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 26th, 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 15.35.

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 house 7. Mounting of posters should be done 17.45-18.30. 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 25th, 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 25

8:30	Departure by bus from the City Terminal, Klarabergs-viadukten, Stockholm
9:30	Arrival conference center Djurönäset and coffee
10.05 – 12:10	**Morning session**
10:05 – 10:15	Opening of meeting & Welcome Remarks **Jonas Bergh and Ingemar Ernberg** Chairs: **Klas Wiman** and **Judit Liano Pons**
10:15 – 11:00	Keynote speaker **Maria Blasco**, Spanish National Cancer Research Centre "Telomere-originated genomic instability at the origin of cancer and aging"
11:00 – 11:30	**Malin Sund**, Umeå University/University of Helsinki "Early detection of pancreatic cancer using pre-diagnostic plasma samples " Chairs: **Yvonne Wengström** and **Carolina Maya Gonzalez**
11:30 – 11:45	**Poya Ghorbani**, Dept. of Clinical Science, Intervention and Technology "Intraductal papillary mucinous neoplasm (IPMN)– a friend or a foe in the battle against pancreatic cancer?"
11:45 – 12:00	**Helen Kaipe**, Dept. of Laboratory Medicine "Cancer-associated fibroblasts and tumor-infiltrating T cells in human pancreatic cancer"
12:00 – 12:15	**Charlotte Rolny,** Dept. of Oncology-Pathology "Reprograming Tumor-Associated Macrophages into an immunostimulatory and anti-metastatic phenotype by targeting MNK2"
12:15 – 12:30	**Photo session** (Group photo of all taken outside)
12:30 – 13:30	**Lunch**
13:30 – 15:35	**Afternoon session**

Chair: **Jonas Bergh**

13:30 – 14:15 Keynote speaker **Matthew Goetz**, Mayo Clinic
"Selective estrogen receptor modulators for hormone receptor positive breast cancer. Back to the future?"

Chairs: **Johanna Ungerstedt** and **Niek Van Bree**

14:15 – 14:30 **Nikolas Herold**, Dept. of Women's and Children's Health
"Targeting drug resistance: a translational oncology approach"

14:30 – 14:45 **Camilla Engblom,** , Dept. of Cell and Molecular Biology
"Mapping B and T cell receptors using spatial transcriptomics"

14:45 – 15:00 **Blaz Oder,** , Dept. of Molecular Medicine and Surgery
"The BAF chromatin remodeling complex is a novel target of spliceosome dysregulation in SF3B1-mutated chronic lymphocytic leukemia"

15:00 – 15:15 **Award of Dan Granders Prize**
Karin Dembrower , Dept. of Oncology-Pathology
"Deep Learning in Breast Cancer Screening"

15:15 – 15:35 **Selected posters pitching**
Moderator: **Margareta Wilhelm**

15:35 – 16:15 **Coffee and check-in**

16:15 – 17:45 **Breakout sessions**

1. Spatial transcriptomics - methodology to study the tumor ecosystem.
2. From academia to industry and how to collaborate?
3. Artificial Intelligence in cancer research in KI
4. Meet the scientist

For details on breakout sessions see the next page.

17:45 – 18:30 **Networking and hors d'oeuvre**
Mounting of posters

18:30 – 20:00 **Dinner**

20:00 – 22:00 **Poster session**

Breakout sessions
Monday, September 25 (16:15-17:45)

Breakout session1:

Spatial transcriptomics - methodology to study the tumor ecosystem.

Chair: Jonas Fuxe. Location: Conference room 1A

- Joakim Lundeberg, SciLifeLab
- Per Uhlen, Dept. of Medical Biochemistry and Biophysics
- Alejandro Mossi Albiach, Dept. of Medical Biochemistry and Biophysics

Breakout session2:

From academia to industry and how to collaborate?

Chair: Elias Arner Location: Conference room 2A

- NeoGAP
- Xpress Genomics
- Cancer Research Horizons

Breakout session3:

Artificial Intelligence in cancer research in KI.

Chair: Benedek Bozoky Location: Conference room 5A

- StratiPath
- Fredrik Strand, Dept. of Oncology-Pathology
- Abhinav Sharma, Dept. of Medical Epidemiology and Biostatistics

Breakout session 4:

Meet the Scientist

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

Chairs: Kamilla Czene and Johanna Ungerstedt

Location: You will get informed of the location on the day

Matthew Goetz PhD, Mayo Clinic

Juha Klefström PhD, University of Helsinki

Notes:

* Limited spaces avaialble for breakout session 4, for detailed bio of the keynote speakers please check the extended abstract booklet online.
* Abstracts and further information on speakers can be found in the extended abstract booklet online.

Tuesday, September 26

07:30 – 08:50 **Breakfast and check out**

09:00 – 12:00 **Morning session**

Chairs: **Linda Lindström and Mireia Cruz De Los Santos**

09:00 – 09:15 Cancer Reseearch KI and Doctoral Programme in Tumour Biology and Oncology (FoTO)

09:15 – 09:45 **Patrik Rossi**, Managing Director, Cancer Theme Karolinska University Hospital
"Karolinska Comprehensive Cancer Center, -What's in it for us?"

09:45 – 10:00 **Olof Akre**, Dept. of Molecular Medicine and Surgery
"SPCG-15 – Primary radical prostatectomy versus radiotherapy for locally advanced prostate cancer: an open randomized clinical trial"

10:00 – 10:30 **Coffee break**

Chairs: **Ioannis Zerdes** and **Mark Zupancic**

10:30 – 10:45 **Dhifaf Sarhan,** Dept. of Laboratory Medicine
"Sex immune dimorphism in cancer – towards gender-optimized (Genderized) immunotherapy"

10:45 – 11:00 **Ning Xu Landén**, Dept. of Medicine Solna
"Radiation memory compromises skin wound repair capacity of dermal fibroblasts in cancer patients"

11:00 – 11:15 **Helene Rundqvist**, Dept. of Laboratory Medicine
KI External Engagement Office-Industry Collaboration
"Exercise induced immune modulation – consequences for tumor progression"

11:15 – 11:30 **Emma Tham**, Dept. of Molecular Medicine and Surgery
"Cell-free DNA as a biomarker in cancer"

11:30 – 12:30 **Lunch**

Afternoon session

Chairs: **Mikael Karlsson** and **Manouk Bronte Verhoeven**

12:30– 13:15 Keynote speaker **Juha Klefström**, University of Helsinki
"Activating resident tumor immunity through MYC-directed synthetic lethal strategies"

13:15 – 13:30 **Marco Gerling**, Dept. of Biosciences and Nutrition
"Tumor growth through efficient cell competition at tumor invasion fronts"

13:30 – 13:45 **Bethel Embaie**, Dept. of Women's and Children's Health
"Deciphering the transcriptomic landscape of a neuroblastoma transgenic mouse model"

13:45 – 14:00 **Meis Omran**, Dept. of Oncology-Pathology
"Whole-body MRI surveillance in TP53 carriers is perceived as beneficial with no increase in cancer worry regardless of previous cancer – data from the SWEP53 study"

14:00 – 14:15 **Hanna Brauner**, Dept. of Medicine, Solna
"Skin infiltrating NK cells in cutaneous T-cell lymphoma are increased in number and display phenotypic alterations partially driven by the tumor"

14:15 – 14:45 **Coffee break**

Chairs: **Simon Ekman** and **Paula Hahn**

14:45 – 15:00 **Maximilian Kordes**, Dept. of Clinical Science, Intervention and Technology
"Extracellular vesicles are the primary source of blood-borne tumor-derived mutant KRAS DNA early in pancreatic cancer"

15:00 – 15:15 **Klas Bratteby**, Dept. of Oncology-Pathology
"Preclinical evaluation of [Zr]Zr-DFO*-sacituzumab,a PET tracer for imaging of whole body TROP-2 expression as a potential selection tool for treatment with TROP-2 antibody drug conjugates (ADC)"

15:15 – 15:30 **Brinton Seashore-Ludlow**, Dept. of Oncology-Pathology
"The Drug Efficacy Testing in Ex Vivo 3D Cultures (DETECt) platform enables rapid identification of effective drugs and drug combinations for ovarian cancer patientsl"

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

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

Abstracts
Keynote speakers

María A. Blasco, PhD
Spanish National Cancer ResearchCentre
Keynote speaker
Monday 25th, 10:15

Telomere-originated genomic instability at the origin of cancer and aging

Telomeres are nucleoprotein complexes which protect the ends of linear chromosomes and which play a pivotal role in cellular and organismal ageing. Over the past two decades short telomeres have been associated with a large disease spectrum including degenerative diseases and cancer. In addition, a number of diseases known as telomeropathies or telomere sydromes, including some cases of aplastic anemia and pulmonary fibrosis, are linked to mutations in telomere maintenance genes. Our laboratory has made significant contributions to dissect the role of telomerase and telomere length as one of the key molecular pathways underlying cancer and aging. We previously demonstrated that telomerase activation by means of trans-genesis as well as vector-based gene therapy delays a variety of age-related pathologies and increases survival in wild-type mice. Here, I will discuss our more recent work validating the effectivity of telomerase gene therapy for the treatment of diseases related to the presence of short telomeres including models for myocardial infarction, aplastic anemia and pulmonary fibrosis.

Matthew Goetz, PhD
Mayo Clinic
Keynote speaker
Monday 25th, 13:30

Selective estrogen receptor modulators for hormone receptor positive breast cancer. Back to the future?

About 65-75% of breast cancer expresses estrogen receptors (ER) or progesterone receptors (PR). In this group of patients, endocrine therapy represents the most important treatment modality. Tamoxifen, the selective estrogen receptor modulator (SERM) has been studied and utilized in breast cancer for the last fifty years. When administered to women with ER-positive breast cancer for 5 years after surgery, tamoxifen almost halves the annual recurrence rate and reduces the breast cancer mortality rate by one-third in both pre- and post-menopausal women. Further, tamoxifen's continued importance is reflected by its status as the only hormonal agent approved by the FDA for the prevention of premenopausal breast cancer, the treatment of ductal carcinoma in situ, and the adjuvant treatment of pre-menopausal invasive breast cancer. However, 3rd generation aromatase inhibitors have supplanted tamoxifen in the pre and postmenopausal treatment of metastatic and early-stage ER+ early-stage breast cancer and in combination with targeted therapies in these settings. Furthermore, oral selective estrogen receptor degraders have demonstrated early efficacy in the metastatic setting, both as monotherapy in combination with targeted therapies, and are now being studied in the adjuvant setting. Amid this rapidly changing landscape, new SERMs including Z-endoxifen and lasofoxifene, are now being tested in the prevention, (neo) adjuvant and metastatic setting. This lecture will review the current landscape of hormonal therapies and focus on the new SERMs, their novel mechanisms of action, side effect profiles, and potential role in the treatment of HR+ breast cancer.

Juha Klefström, PhD
University of Helsinki
Keynote speaker
Tuesday 26th, 12:30

Activating resident tumor immunity through MYC-directed synthetic lethal strategies

Oncogenic MYC overexpression (MYChigh) in cancer reprograms cellular metabolism, cell cycle and cell death machineries, which enables cancerous incessant cell growth and propagation in tissues. These MYC-induced reprogramming events also generate cancer specific vulnerabilities, which can be targeted through synthetic lethal approaches. The MYChigh-dependent drug cytotoxicity would specifically target tumor cells while sparing healthy cells, which makes the MYC-dependent synthetic lethality as a lucrative therapeutic concept. We have shown that the induction of MYC augmented cell death with synthetic lethal (SL) drugs can be highly immunogenic in vivo, eliciting therapeutically targetable anticancer immune responses (Haikala et al Nat Commun 2019). However, MYC also establishes an immunosuppressive tumor immune microenvironment (TIME) (Lee et al Nat Commun, 2022) and for this reason optimal MYC SL acting drugs should trigger immunogenic cell death and simultaneously overcome the MYC-dependent immunosuppression. Our recent work has discovered that the biguanide metformin, an anti-hyperglycemic drug with pleiotropic effects, strongly augments MYC-dependent cell death and shows MYC-dependent antitumor effects in vivo. Our ongoing research suggest that this MYC-dependent pro-apoptotic mode of metformin action is coupled to inhibition of mitochondrial respiratory chain complex I. Furthermore, we have examined the metformin action in 3D cultures of breast cancer patient-derived primary tumor cultures (PDECs; Munne et al Nat Commun 2021), which preserve the resident immune cells of TIME. Interestingly, metformin shows specific immunometabolic effects that could counteract MYC's immunosuppressive effects and facilitate antitumor immunity in context of MYChigh cancer.

Abstracts
Invited speakers

Malin Sund
Umeå University/
University of Helsinki
Monday 25th, 11:00

Early detection of pancreatic cancer using pre-diagnostic plasma samples

Pancreatic ductal adenocarcinoma (PDAC) is a disease with a grim prognosis and a 5-year survival of 3-5%. This dismal prognosis has hardly improved during the last 30 years, and PDAC remains a disease where the incidence matches the mortality. Surgical resection remains the only curative treatment, but merely 25-30% can be offered surgery due to disseminated disease at diagnosis. Suboptimal clinical staging tools lead to most patients likely being understaged, explaining the poor long-term survival (5-year survival 10-20%) even in those who have undergone radical surgery. Early PDAC seldom gives clinical symptoms and once symptoms occur they are unspecific. The combination of late and unspecific symptoms, lack of efficient systemic therapies and suboptimal staging leads to the logical conclusion that early detection of pancreatic cancer would be the best way of improving survival. The Umeå PDAC early detection cohort is nested case-control study designed from the population-based Northern Sweden Health and Disease Study (NSHDS) and contains prediagnostic blood samples from individuals later diagnosed with PDAC (case; n=374). These individuals are matched to two controls (n=748) based on age, gender, time point of sample collection and no cancer in the control. For 274 of these individuals the blood sample is within 10 years from PDAC diagnosis. This cohort has been analysed with multiple different omic-based techniques with the aim to find early signs of the disease that could be used to set the diagnose earlier and cure more. In this presentation both data from the Umeå PDAC early detection cohort as well as other efforts to diagnose PDAC early are presented.

Poya Ghorbani
Dept. of Clinical Science, Intervention and Technology
Monday 25th, 11:30

Intraductal papillary mucinous neoplasm (IPMN) – a friend or a foe in the battle against pancreatic cancer?

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers. The majority (70%) of patients has at the time of diagnosis disseminated or unresectable tumor. Of the remaining 30%, only one in five survive five years after surgery and chemotherapy. The main reason is early and aggressive relapse and extensive tumour heterogeneity that evades current medical treatment.

Intraductal papillary mucinous neoplasm (IPMN) is a type of pancreatic cyst characterized by overproduction of mucin and dilatation of the pancreatic main duct and/or branch ducts. It was first scientifically reported in 1982. In 2004 it was endowed with its first criteria for definition, evaluation and management that have dictated the structure for contemporary guidelines. It is one of five precursors of PDAC and accounts for 10-15 % of all PDAC cases. With advances in radiology, increased awareness of its invasive potential, and a possible rise in incidence, the diagnosis and surgical resection of IPMN has increased dramatically in recent decades. The exact prevalence of IPMN is unknown but between 2-49% has been reported.

The risk for malignant transformation of IPMN is primarily influenced by where the pancreatic duct is affected. Main duct IPMN is associated with high risk and thus treated with surgery, while branch duct has low risk for malignancy and therefore treated conservatively with radiological surveillance.

Most patients with IPMN never reach the stage on which a surgery in needed. Of those a surgical resection is deemed a necessity, only 10-25 % have progressed to high-grade dysplasia (HGD) or invasive cancer (inv-IPMN). Thus, the majority is of low-grade dysplasia (LGD) and that may never have had progressed to inv-IPMN if left untreated.

Most common surgical options include partial or total pancreatoduodenectomy (PD) and distal pancreatectomy. Although mortality rates have decreased in recent years, the morbidity rates remain high (reaching 50%). High volume centres have 30-day mortality rates of 1-3%. Nevertheless, of patients resected for IPMN with LGD, 5% die within one year.

The pre-operative diagnostic accuracy and prediction of the level of dysplasia and tumour stage for IPMN, is seemingly low, increasing the risk of surgical mismanagement and exposing patients to unnecessary risks. To balance the risk of invasive transformation with surveillance with the inherent hazard pancreatic surgery is associated with, the histological optimum for pre-emptive resection of IPMN needs further attention. Our research is focusing on optimizing the timing for intervention in the malignant transformation of IPMN and finding predictors for those a surgery is needed and those with harmless cysts in which a discontinuation of surveillance is the best option.

Helen Kaipe
Dept. of Laboratory Medicine
Monday 25th, 11:45

Cancer-associated fibroblasts and tumor-infiltrating T cells in human pancreatic cancer

Despite advancements in therapeutic modalities, the 5-year overall survival rate for pancreatic cancer remains below 10%. Pancreatic tumors are characterized by a desmoplastic stroma, primarily consisting of activated cancer-associated fibroblasts (CAFs). While pancreatic CAFs have emerged as important regulators of the tumor microenvironment, their interaction with immune cells is still being explored. Infiltration of T cells in the tumor microenvironment is considered a predictor of a favorable prognosis, but pancreatic cancer has shown limited response to immunotherapy.

Our research has demonstrated that CAFs isolated from human pancreatic tumors have the ability to suppress T cell function and induce an upregulation of co-inhibitory markers on T cells in vitro. Additionally, CAFs impact the expression of chemokine receptors on T cells, impairing their migratory capacity. Immunohistochemistry stainings of pancreatic tumor tissues have revealed that the majority of CD8+ T cells are located within the stroma, distanced from the malignant cells, with little interactions with tumor nests. CD8+ T cells co-expressing CD39 and CD103, which recently has been described to display tumor reactivity in other types of solid cancers, could be detected in pancreatic tumors at high interpatient variability. These CD39+CD103+ CD8+ T cells were predominantly found in the center of the tumor compared to peripheral and non-tumor tissues and exhibited an exhausted phenotype expressing PD-1 and TIM-3. Moreover, CD39+CD103+ CD8+ T cells expressed higher levels of Ki67, suggesting recent encounters with their cognate antigen, and displayed a distinct chemokine receptor expression profile compared to CD8+ T cells lacking expressing of CD39. Importantly, a higher proportion of CD39+CD103+ CD8+ T cells among intratumoral CD8+ T cells was associated with an increased overall survival in pancreatic cancer patients.

In summary, T cells face a challenging microenvironment within pancreatic tumors, with CAFs playing a crucial role in suppressing their anti-tumor activity. However, CD39+CD103+ CD8+ T cells, which possess characteristics reminiscent of tumor-reactive T cells, can be identified in pancreatic tumors at interpatient variability and are correlated to an increased patient survival. Considering the abundance of CD39+CD103+ CD8+ T cells could potentially aid in the selection of patients suitable for immunotherapy trials in pancreatic cancer.

Nikolas Herold
Dept. of Women's and Children's Health
Monday 25th, 14:15

Targeting drug resistance: a translational oncology approach

Chemotherapy remains a cornerstone for systemic treatment of haematological and solid malignancies. While effective drugs and drug combinations for different cancer diagnoses have been established empirically during the last 60 years, we are still far from curing all patients with cancer. Our research is particularly intrigued by the question how tumours in patients that are cured are phenotypically different from tumours in patients that fail to respond to standard chemotherapy. Operationally, our aim is to identify drug resistance factors and characterise their mode of action. Using small-molecule drug screening is then used to find resistance factor inhibitors. Subsequently, clinical trials are essential to validate whether addition of a small-molecule inhibitor is able to restore drug sensitivity in patients with resistant cancer. Here, I summarise our findings on SAMHD1, an enzymatic resistance factor for various nucleoside analogues and how targeting SAMHD1 might improve survival for patients with both haematological and solid malignancies.

Camilla Engblom
Dept. of Cell and Molecular Biology
Monday 25th, 14:30

Mapping B and T cell receptors using spatial transcriptomics

The spatial distribution of lymphocyte clones within tissues is critical to their development, selection, and expansion. We have developed spatial transcriptomics of VDJ sequences (Spatial VDJ), which maps full-length B and T cell receptor sequences in human tissue sections. Our method is an extension of a commercially available and widely used spatial transcriptomics protocol from frozen tissue sections. Spatial VDJ generated clonal, whole transcriptome and anatomical distribution from the same tissue section. The B and T cell clonal spatial distribution captured by Spatial VDJ matched canonical B cell, T cell, and plasma cell distributions and amplified clonal sequences were confirmed by orthogonal methods. In breast tumor tissue, we found spatial congruency between paired receptor chains, develop a computational framework to predict receptor pairs, and linked the expansion of distinct B cell clones to different tumor-associated gene expression programs. Spatial VDJ captured putative class switching events that occurred in extra-follicular regions. Finally, we uncovered B cell clonal diversity and receptor evolution within and between germinal centers in human lymphoid tissue. Thus, Spatial VDJ captured lymphocyte spatial clonal architecture across tissues, providing a platform to harness clonal sequences for therapy, in cancer and beyond.

Patrik Rossi
Cancer Theme
Karolinska University Hospital
Tuesday 26th, 09:15

Karolinska Comprehensive Cancer Center, -What's in it for us?

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 has just started and will involve everybody engaged in cancer research, education and care.

Olof Akre
Dept. of Molecular Medicine and Surgery
Tuesday 26th, 09:45

SPCG-15 – Primary radical prostatectomy versus radiotherapy for locally advanced prostate cancer: an open randomized clinical trial

Despite that prostate cancer is the leading cause of cancer death among Nordic men, there is a striking lack of trials of multimodal treatments of those with advanced but potentially curable disease. We are therefore conducting the first randomized trial with the primary aim to assess whether radical prostatectomy with adjuvant radiotherapy if needed leads to better cancer-specific survival than primary radiotherapy plus neoadjuvant castration therapy. Secondary endpoints include metastasis-free survival and long-term quality-of-life outcomes assessed in repeated questionnaires during 20 years of follow up. The study has presently randomized 958 out of 1,200 men. No previous attempts to run similar trials have succeded. We present the rationale, the current status of the study, and describe how the study was launched.

Dhifaf Sarhan
Dept. of Laboratory Medicine
Tuesday 26th, 10:30

Sex immune dimorphism in cancer – towards gender-optimized (Genderized) immunotherapy

Background: Pancreatic cancer (PC) is a disease with increasing prevalence and high mortality rate. It is predicted to rank as the second cancer related deaths in the near future. Studies have shown that different components of the tumor microenvironment (TME), including cells of the immune system, the surrounding non-malignant stromal cells, and secreted factors, directly or indirectly involved in the development and progression of tumors. Several studies proposed, men in general have higher incidence rate and cancer related fatality in various cancer types compared to females. However, the roll of the TME underlying sex immune dimorphism in malignancies are poorly investigated. Our preliminary data investigating RNA sequencing of pancreatic tumors, highlights differentially expressed immune regulatory genes, hormones/hormone like molecules in the different sexes. Thus, we hypothesize that immune responses underlay sex dimorphism in cancer and result in progression and treatment response discrepancies in men and women.

Methods: To test our hypothesis, we first investigated PC transcriptomic data from publicly available resources like TCGA and ICGC. Further, we investigated the enriched signaling pathways based on the found differentially expressed genes in male and female PC patients. Ex-vivo, we sought to validate these differences in our cohort of PC plasma by mass spectrometry and tumor tissues by multiparametric immunofluorescence staining.

Results: We found at least 10000-16000 genes that were differentially expressed in male and female PC patients respectively compared to their normal counterpart. These differences highlighted differentially expressed immune regulatory genes, hormones/hormone like molecules in the different sexes. In addition, applying the top 200 genes from the different sexes we found that different metabolic pathways and invasion were enriched. Our ex-vivo validations could confirm that FPR2, TGFβ, IL17, IL-3, fatty acid oxidation, and glycolysis were higher in the TME of female patients compared to type I IFN, and the metabolic TCA cycle were highly enriched in male patients.

We also validated the therapeutic potential of antagonizing the G-protein coupled receptor FPR2 and found that it has a remarkable effect on restoring T cell anti-tumor activities and reversing immunosuppressive myeloid cell function exclusively in females.

Conclusions: In this study, we have shown that immune sex differences are involved in shaping the TME of PC and can be targeted for gender-specific immunotherapy. We also concluded that further validation targeting the enriched pathways is required to identify additional immunotherapy targets for both sexes that may already exist in the clinic.

Emma Tham
Dept. of Molecular Medicine and Surgery
Tuesday 26th, 11:15

Cell-free DNA as a biomarker in cancer

Liquid biopsies are minimally invasive samples of body fluids such as plasma or cerebrospinal fluid. They contain several different entities including short fragments of cell-free DNA (cfDNA) that are released when cells die. CfDNA carry the same genetic composition as the mother cells and have a short half-life, thus they provide a snapshot of the genetic make-up in the cells at that particular time. Therefore, cfDNA may be a good biomarker of the current cancer burden at diagnosis and during treatment and may also provide prognostic information. Most of the cfDNA in a plasma sample derives from the white blood cells, but a tiny proportion derives from cancer cells and very sensitive methods are needed for detection. Furthermore, it is important to understand the technical performance of the methods used and the biology of the cancer type studied in order to avoid false positives (for instance clonal haematopoiesis or technical artefacts) and to correctly interpret negative results.

In our studies, we have developed an amplitude multiplex droplet digital PCR (m-ddPCR) for ultra-sensitive detection of tumour-derived cfDNA (ctDNA) and have shown that m-ddPCR can be used to detect diagnostic markers and treatable targets. cfDNA is detectable at diagnosis and can be used to monitor therapy response and to detect early relapse. Individuals who are ctDNA-positive after treatment have a worse progression-free survival than those who are negative.

In addition, we have optimised a method for low-coverage whole genome sequencing and gene panel analysis of cfDNA in plasma. Using this method, we can detect 55% of the known copy number- and single nucleotide variants in primarily operable gastric cancer.

Marco Gerling
Dept. of Biosciences and Nutrition
Tuesday 26th, 13:15

Tumor growth through efficient cell competition at tumor invasion fronts

Interactions with tumor cells and non-malignant epithelial cells characterize the leading edge of solid cancers. A key mode of solid tumor growth relies on the replacement of adjacent healthy cells. However, the mechanisms of this cellular replacement are largely unknown.
To chart tumor-epithelial cell interactions in gastrointestinal malignancies, we have - together with the surgeons and pathologists at Karolinska University Hospital in Huddinge - built KaroLiver, a cohort of more than 700 liver metastases patients. With KaroLiver, we studied histological invasion patterns in liver metastases. We found that efficient replacement of the healthy liver parenchyma is the standard pattern of tumor invasion, demonstrated by strong effects on prognosis. When replacement fails, a benign-like reparative injury response encapsulates the metastasis, which is clinically reflected by a favorable prognosis. Single-cell sequencing of murine liver metastases identified a highly confined perimetastatic injury response, specific to areas of active tumor invasion, which has prognostic potential in human liver metastases. In addition, we discovered a highly similar mode of invasion in primary pancreatic cancer, where tumor cell invasion into healthy pancreatic acini induced reshaping of the tumor-adjacent pancreas, preceding the development of desmoplasia.
Our data identify how healthy, tumor-adjacent parenchyma is reshaped during successful and failed tumor invasion, and they suggest novel targets to inhibit replacement-type tumor growth.

Maximilian Kordes
Dept. of Clinical Science, Intervention and Technology
Tuesday 26th, 14:45

Extracellular vesicles are the primary source of blood-borne tumor-derived mutant KRAS DNA early in pancreatic cancer

Liquid biopsies are a non-invasive diagnostic tool for cancer detection and monitoring. Among the various blood components that have been analyzed, circulating tumor DNA (ctDNA) and circulating tumor cells have been extensively studied. Recently, extracellular vesicles (EVs) have also attracted increasing interest as potential carriers of tumor-derived material in the bloodstream. Apart from these sources, leukocytes, platelets, and apoptotic bodies (ABs), which are subcellular fragments from apoptotic cells, have been identified as possible carriers of tumor-related genomic material. However, the detection of tumor-derived nucleic acids in liquid biopsies can be limited by their variable abundance. In some cases, the levels of ctDNA may be too low for accurate detection, leading to false-negative results or reduced sensitivity in identifying cancer-related mutations. Focusing liquid biopsy assays on a specific blood fraction with a higher tumor DNA content could lead to more reliable and informative results. However, a systematic comparison of different blood components is lacking. To address this issue, we collected twenty-three blood samples from seventeen patients with pancreatic cancers with known variants in KRAS codon 12. Following sampling, we divided them into two groups based on the time of patient survival. We then used differential centrifugation to stepwise isolate red cells and buffy coat, platelets, ABs, large extracellular vesicles (LEVs), small extracellular vesicles (SEVs), and soluble proteins (SP). The enrichment of the specific blood component in each fraction was assessed with electron microscopy, Western blotting, nanoparticle tracking analysis, and a bead-based multiplex flow cytometry assay. Using digital PCR to target wild-type and tumor-specific mutant KRAS alleles, we measured the levels of tumor DNA associated with the different blood fractions at earlier and later stages of the course of disease. The results indicated that early in disease progression, mutant KRAS DNA was mostly associated with LEVs and SEVs. As the disease advanced, the levels of mutant KRAS DNA were highest in association with SEVs and SP, the fraction typically associated with ctDNA. Significantly, throughout disease progression, SEVs consistently exhibited the highest ratio of tumor-derived mutant to wild-type DNA.

These findings support an increased focus on EVs, especially SEVs, as reliable sources of tumor-derived DNA to develop more sensitive and accurate liquid biopsy assays, enabling early cancer detection and monitoring of treatment response.

Speakers selected from abstracts

Charlotte Rolny
Dept. of Oncology-Pathology
Monday 25th, 12:00

Reprograming Tumor-Associated Macrophages into an immunostimulatory and anti-metastatic phenotype by targeting MNK2

Tumor-associated macrophages (TAMs) exhibit remarkable cellular plasticity, ranging from anti-tumor to pro-tumor phenotypes. These versatile cells possess the unique ability to influence both the adaptive immune system and regulate vessel functionality, acting as gateways for hematogenous dissemination. Within TAMs, the intricate interplay between mitogen-activated protein kinase (MAPK) interacting protein kinase (MNK) 1 and MNK2 plays a pivotal role. These kinases selectively modulate mRNA translation by impacting eIF4E phosphorylation, thereby facilitating reshaping of the proteome without altering the abundance of corresponding mRNAs.

Our recent research has uncovered the crucial role of selective mRNA translation changes as a central hub regulating the immunosuppressive functions of macrophages. Building upon this knowledge, our latest study demonstrates that targeting MNK2, rather than MNK1, effectively modulates eIF4E activity in TAMs. This targeted approach results in the reprogramming of immunosuppressive TAMs, effectively impeding the growth of mammary tumors. Moreover, we have observed that these reprogrammed TAMs adopt an angiostatic/anti-metastatic phenotype.

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 towards an immunostimulatory phenotype, thereby enhancing the activity of cytotoxic T and NK cells.

Based on our findings, we propose that targeting MNK2 represents a highly efficient strategy to reprogram TAMs into an anti-tumoral phenotype. This novel therapeutic approach holds tremendous potential in combating cancer, offering new avenues for intervention and treatment.

Blaz Oder
Dept. of Molecular Medicine and Surgery
Monday 25th, 14:45

The BAF chromatin remodeling complex is a novel target of spliceosome dysregulation in SF3B1-mutated chronic lymphocytic leukemia

Spliceosome dysregulation due to SF3B1 mutations is a recurring event in chronic lymphocytic leukemia (CLL), predominantly observed in the clinically aggressive stereotyped subset #2. To investigate the impact of SF3B1 mutations on splicing, we conducted RNA sequencing analysis of 17 SF3B1MUT and 18 SF3B1WT subset #2 cases. Our investigation revealed 61 alternatively spliced transcripts, with notable events concerning exon inclusion in the non-canonical BAF (ncBAF) chromatin remodeling complex component, BRD9, and alternative splicing of five additional BAF complex interactors, including ZEB1, PLSCR1, TENT4B, DCAF16, and DLST. Long-read RNA sequencing confirmed the presence of the splice variants, and expanded analyses encompassing 65 other subset cases (including 6 SF3B1MUT cases), 74 non-subset cases (including 8 SF3B1MUT cases), and CLL cell lines further supported the association between these splicing events and SF3B1 mutations.

Overexpression of mutated SF3B1 in CLL cell lines induced alternative splicing of BRD9, resulting in the generation of a novel protein isoform with an alternative C-terminus. Comparative protein interactome analysis of the regular and alternative BRD9 isoforms revealed an enhanced interaction of the alternative isoform with the ncBAF complex. However, diminished interactions were observed with previously described BAF complex interacting proteins, including SPEN, BRCA2, and CHD9. Integrative analysis of gene expression and chromatin accessibility identified a BRD9-bound gene quartet on chromosome 1 (NOL9, TAS1R1, KLHL21, and ZBTB48) to be higher expressed and display more accessible chromatin in SF3B1MUT CLL.

Analysis of CRISPR/RNAi-perturbed cell line data showed that an SF3B1-mutated CLL cell line (CII) exhibited a high sensitivity to BRD9 knockout, suggesting BRD9 dependency in CLL. The level of BRD9 isoform dependency is currently being examined in a cell line panel by isoform-specific RNAi targeting. Furthermore, treatment with BRD9 inhibitors indicated selective potency in SF3B1-mutated cell lines. Thus, patient-derived samples are currently being assessed to solidify the therapeutic significance of targeting BRD9.

In conclusion, our findings elucidate the multifaceted impact of SF3B1 mutations on splicing and the multiple alterations of the BAF interactome, unveiling a novel pathobiological mechanism in SF3B1-mutated CLL. This study provides valuable insights into the molecular consequences of SF3B1 mutations, paving the way for potential therapeutic interventions targeting the BAF complex in CLL.

Ning Xu Landén
Dept. of Medicine Solna
Tuesday 26th, 10:45

Radiation memory compromises skin wound repair capacity of dermal fibroblasts in cancer patients

Radiotherapy (RT) is a common cancer treatment, but often results in an unintended injury to overlying skin and contributes to poor wound healing that can occur even months to years after RT. Our study aimed to understand the pathological mechanisms underlying the late onset of adverse effects (LAEs) caused by RT on the skin. By comparing matched skin biopsies from previously irradiated (RT+) and non-irradiated (RT-) sites of breast cancer patients who received RT years ago, we found that the wound healing capacity and fibroblast functions were compromised in the RT+ skin. Using the assay of transposase accessible chromatin sequencing (ATAC-seq), we unravelled an altered chromatin landscape in the RT+ fibroblasts. By intersecting the ATAC-seq results with the gene signature of human skin wound healing, we identified THBS1 as a wound repair-related gene epigenetically primed in the RT+ fibroblasts. Analysis of single-cell RNA-sequencing (scRNA-seq) and spatial transcriptomic (ST) data of human wounds further underscored the important role of THBS1 in fibroblasts during wound repair. However, we found more potent and persistent THBS1 expression in the RT+ fibroblasts in both the mouse in vivo and human ex vivo radiation wound models, which impaired fibroblast motility and contractibility. Importantly, the functional knockdown of THBS1 enhanced wound contraction and re-epithelialization of the RT+ skin. Together, our study suggests that dermal fibroblasts carry a long-term radiation memory recorded in the form of epigenetic changes and the erasure of the maladaptive epigenetic memory holds great promise for treating the LAEs.

Helene Rundqvist
Dept. of Laboratory Medicine
Tuesday 26th, 11:00

Exercise induced immune modulation – consequences for tumor progression

BACKGROUND
Maintaining a physically active lifestyle after a cancer diagnosis is associated with a reduced risk of recurrence and mortality. How exercise exerts its beneficial effects is currently unknown. Using pre-clinical models of breast cancer, we have showed that the immune system, and especially CD8+ T-cells, are instrumental for the anti-neoplastic effects of exercise.
AIM
The overarching aim was to explore how exercise enhances immune function, through altering the metabolic landscape, and thereby promotes anti-tumoral immune surveillance.
METHODS
Twenty moderately active healthy men and women between the age of 18-35 year performed a 3x30 sec all-out sprint exercise. Blood samples were collected before, 3 min after and 1 hour after exercise. CD8+ T-cells were analysed for gene expression, functional markers, metabolism, and cytotoxicity. Functional consequences of exposing CD8+ T-cells to exercise induced metabolites was investigated using mass spectrometry, expression analysis and real time metabolic flux monitoring.
RESULTS
The high intensity exercise induced a substantial change in blood metabolites such as lactate, and led to a significant increase in circulating T-cells (CD3+). The number of circulating CD8+ T-cells increased three-fold after exercise compared to baseline. Subpopulation analyses showed that exercise primarily recruited effector cells, with an enhanced IFNγ response to viral antigen and ex vivo tumor cell cytotoxicity. Furthermore, ex vivo experiments showed that lactate can be taken up by activated CD8+ T cells and displace glucose as a primary source of carbon. Activation in the presence of lactate significantly alters the CD8+ T cell transcriptome, including the expression of key effector differentiation markers such as granzyme B and IFNγ.
CONCLUSION
The obtained results suggest that the CD8+ fraction of the immune cell populations recruited during exercise have a more pronounced effector function - which can be mediated by exercise induced metabolites - and is in line with an enhanced anti-tumoral activity.

Bethel Embaie
Dept. of Women's and Children's Health
Tuesday 26th, 13:30

Deciphering the transcriptomic landscape of a neuroblastoma transgenic mouse model

MYCN amplification is found in approximately 20% of neuroblastoma (NB), representing a critical stratifying prognostic marker. Given that MYCN plays a key role in NB tumorigenesis and aggressiveness, the TH-MYCN transgenic mouse model is widely used. This model is characterized by the overexpression of MYCN, driven by tyrosine hydroxylase (TH) promoter, giving rise to tumors exclusively in the sympathoadrenal system, reflecting human NB.
Here we aim to explore the transcriptional landscape of TH-MYCN tumors and bone marrow samples by scRNA-seq, and provide comparative analysis with murine fetal adrenal gland and human NB, to decipher the cellular identity, heterogeneity, interactive network, and clinical relevance. Harnessing the bioinformatically predicted essential interactions, we establish organoids (tumoroids).
Tumors and bone marrow from three homozygous and two hemizygous (and bone marrow from three WT) TH-MYCN mice were dissociated into single cells, profiled by scRNA-seq (10x Genomics), sequenced with Illumina NextSeq, and analyzed using Seurat. TH-MYCN transcriptomes were further aligned with previously published transcriptomes from three murine fetal adrenal glands and 19 NB patient tumors. Intercellular communication networks were inferred by CellChat. Tumoroids were established and expanded for immunofluorescence staining.
scRNA-seq of TH-MYCN tumors revealed 16 clusters, spanning stromal, immune and tumor compartments. MYCN+ tumor cells predominantly resembled sympathoblasts, while MYCN+ chromaffin cells were rare. Alignment with fetal adrenal samples confirmed that TH-MYCN tumor cells resembled normal embryonic chromaffin cells and sympathoblasts. Comprehensive comparison of tumors from NB patients and TH-MYCN mice showed resemblance in adrenergic tumor cell composition. CellChat analysis showed diverse cellular communication networks. Twelve signaling pathways were common to human and mouse tumors and receptor-ligand analysis of conserved pathways unraveled targetable vulnerabilities. Notably, high expression of ITGB2-ICAM2 and NCAM1-FGFR1 were significantly correlated with poor survival in human NB. Subsequent analysis of bone marrow from matched tumor-bearing and wild type (WT) mice, revealed compositional and transcriptional shifts in the bone marrow microenvironment. Moreover, ex vivo tumoroid cultures were robust, highly proliferative and exhibited histological resemblance with the originating tumor.
We provide a comprehensive tumor cell atlas, which is fundamental for the therapeutic application of NB models in preclinical research.

Meis Omran
Dept. of Oncology-Pathology
Tuesday 26th, 13:45

Whole-body MRI surveillance in TP53 carriers is perceived as beneficial with no increase in cancer worry regardless of previous cancer – data from the SWEP53 study

Current guidelines in Sweden regarding individuals with a pathogenic or likely pathogenic germline TP53 variant recommend patients to take part of the national Swedish P53 Study (SWEP53). All known adult eligible carriers, regardless of age, are offered to take part in a surveillance program, offering yearly whole-body, breast, brain MRIs and breast ultrasound. A special surveillance program for individuals <18 years old with a 50% risk of being a mutation carrier or with a verified TP53 variation, includes ultrasound of the abdomen and urine corticosteroid profiles. Further clinically motivated examinations are performed when needed. In a submitted publication, we present the surveillance program within the SWEP53 including further work-up by describing two case reports – one patient with prior malignancies and a healthy carrier with a common benign finding. So far, 25 adults and 9 children have been included in SWEP53 and 24 adults have performed their baseline MRI. In seven of the 24 adults (29%), imaging findings needing further work-up were identified on whole-body MRI at baseline.
In Europe, there are surveillance programs within studies such as SIGNIFY (UK) and LIFSCREEN (France), but the SWEP53 is the first structured surveillance program including radiological and clinical routines for TP53 mutation carriers in the Scandinavian setting.

Hanna Brauner
Dept. of Medicine, Solna
Tuesday 26th, 14:00

Skin infiltrating NK cells in cutaneous T-cell lymphoma are increased in number and display phenotypic alterations partially driven by the tumor

Cutaneous T cell lymphomas (CTCL) are characterized by focal infiltration of malignant T cell clones in solitary skin lesions. Many CTCL patients experience an indolent disease, but some progress to advanced disease with high fatality. We hypothesized that natural killer (NK) cells participate in local control of tumor growth in CTCL skin. Immunohistochemistry and flow cytometry analysis of the density, localization, phenotype and function of NK cells in twenty-nine fresh or formalin fixed skin biopsies from twenty-four CTCL patients and twenty-three biopsies from twenty healthy controls highlighted higher numbers of CD56+CD3- NK cells in CTCL skin. A reduced fraction of CTCL skin NK cells expressed the maturation marker CD57, the cytotoxic protein granzyme B and the activation marker CD69, indicating reduced tumor killing abilities of NK cells. Retained expression of immune checkpoint proteins or inhibitory proteins including PD1, TIM3, LAG3, CD73 and NKG2A and the activating receptors CD16 and NKp46 indicated maintained effector functions. Indeed, the capacity of NK cells to produce anti tumor acting IFNγ upon PMA+ionomycin stimulation was similar in CTCL and healthy skin. Co-cultures of primary human NK cells or the NK cell line NKL with CTCL cells resulted in reduced levels of granzyme B and CD69, indicating that close cellular interactions with CTCL cells induced the impaired functional NK cell phenotype. Conclusively, increased numbers of NK cells in CTCL skin exhibit a partially activity impaired phenotype. Enhancing NK cell activity with NK cell activating cytokines such as IL-15 or immune checkpoint blockade therefore represents a potential immunotherapeutic approach in CTCL.

Klas Bratteby
Dept. of Oncology-Pathology
Tuesday 26th, 15:00

Preclinical evaluation of [Zr]Zr-DFO-sacituzumab, a PET tracer for imaging of whole body TROP-2 expression as a potential selection tool for treatment with TROP-2 antibody drug conjugates (ADC)*

Objectives Trophoblast cell-surface antigen 2 (TROP-2) is a transmembrane glycoprotein with an extracellular domain which is upregulated in most cancer cells. Metastatic triple negative breast cancer (mTNBC) is an aggressive cancer type with more limited treatment options compared to other breast cancer subtypes. About 80% of mTNBC patients show moderate to strong expression of TROP-2 in the tumors.1 This has been utilized in the development of the TROP-2 targeting antibody drug conjugate (ADC) Sacituzumab govitecan which recently gained FDA/EMA approval for patients with mTNBC with disease progression after at least one line of palliative systemic therapy, based on data from the ASCENT clinical trial.2 Warranting results were even noted in patients with estrogen receptor positive breast cancer.3 Currently, no therapy-predictive biomarkers have been identified enabling patient selection for this treatment. The objective of this project is to develop an antibody-based PET-tracer to quantify the expression of TROP-2 in order to select the patients who will benefit from the TROP-2 targeted treatments and gain more knowledge about this novel treatment.
Methods The clinically approved Sacituzumab govitecan (Trodelvy), was hydrolyzed in to remove the cytotoxic payload (SN-38) and analyzed by LCMS. The hydrolyzed antibody (Sacituzumab) as well as the intact ADC was conjugated with DFO*-NCS and radiolabeled with 89Zr. The resulting PET tracer [89Zr]Zr-DFO*-sacituzumab/ADC was analyzed in vitro by cell binding assays and LigandTracer using TROP-2 high/low expressing cell lines. The 89Zr-labeled antibodies were then evaluated in vivo in nude mice carrying a TROP-2 (+/-) xenograft. The tumor uptake and biodistribution was evaluated day 1-9 using μPET/CT and day 6 using ex vivo biodistribution.
Results and conclusions The radiolabeled 89Zr-Sacituzumab/ADC showed a significantly higher binding in vitro and increased tumor uptake in vivo compared to blocked cells or xenografts respectively as well as TROP-2 (-) cells/xenografts. The binding specificity and affinity was retained for both the modified TROP-2 binding antibodies compared to the original ADC warranting that these both these 89Zr-labeled mAbs could be used as an imaging tool to analyze the whole-body TROP-2 expression in patients and aid in the treatment plan and selection.

Brinton Seashore-Ludlow
Dept. of Oncology-Pathology
Tuesday 26th, 15:15

The Drug Efficacy Testing in Ex Vivo 3D Cultures (DETECt) platform enables rapid identification of effective drugs and drug combinations for ovarian cancer patients

Most patients with advanced ovarian cancer (OC) relapse and progress despite systemic therapy, pointing to the need for improved and tailored therapy options. Functional precision medicine can help to identify effective therapies for individual patients in a clinically relevant timeframe. Here, we present a scalable functional precision medicine platform: DETECt (Drug Efficacy Testing in Ex vivo 3D Cultures), where the responses of primary patient cells to drugs and drug combinations are tested with live-cell imaging. We demonstrate the delivery of individual drug sensitivity profiles in 20 samples from 16 patients with ovarian cancer in both 2D and 3D culture formats, achieving over 90% success rate in providing actionable data six days after operation. All patients in this cohort received carboplatin as treatment and the ex vivo carboplatin drug response scores were significantly different between patients with a complete clinical response and those with a partial response or progression ($p<0.05$). In addition, carboplatin ex vivo response also predicted progression free interval (PFI) of patients ($p<0.05$). We find that the 3D culture format better retains proliferation and characteristics of the in vivo setting. Using the DETECt platform we evaluate 27 tailored combinations with results ready 10 days after operation. Notably, carboplatin and A-1331852 (Bcl-xL inhibitor) showed an additive effect in four of eight OC samples tested. Interestingly, afatinib treatment led to an increase of BIM and Bcl-xL expression in OC cells, which could be reversed by Bcl-xL inhibition, leading to increased cell death and synergy in 5/7 OC models. In conclusion, our 3D DETECt platform can rapidly define potential, clinically relevant data on efficacy of existing drugs in OC for precision medicine purposes, as well as provide insights on emerging drugs and drug combinations that warrant testing in clinical trials.

The Cancer Research KI retreat Organizing committee

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Booklet design: Dina Dabaghie

Photo: Djurönäset, Johanna Furuhjelm

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

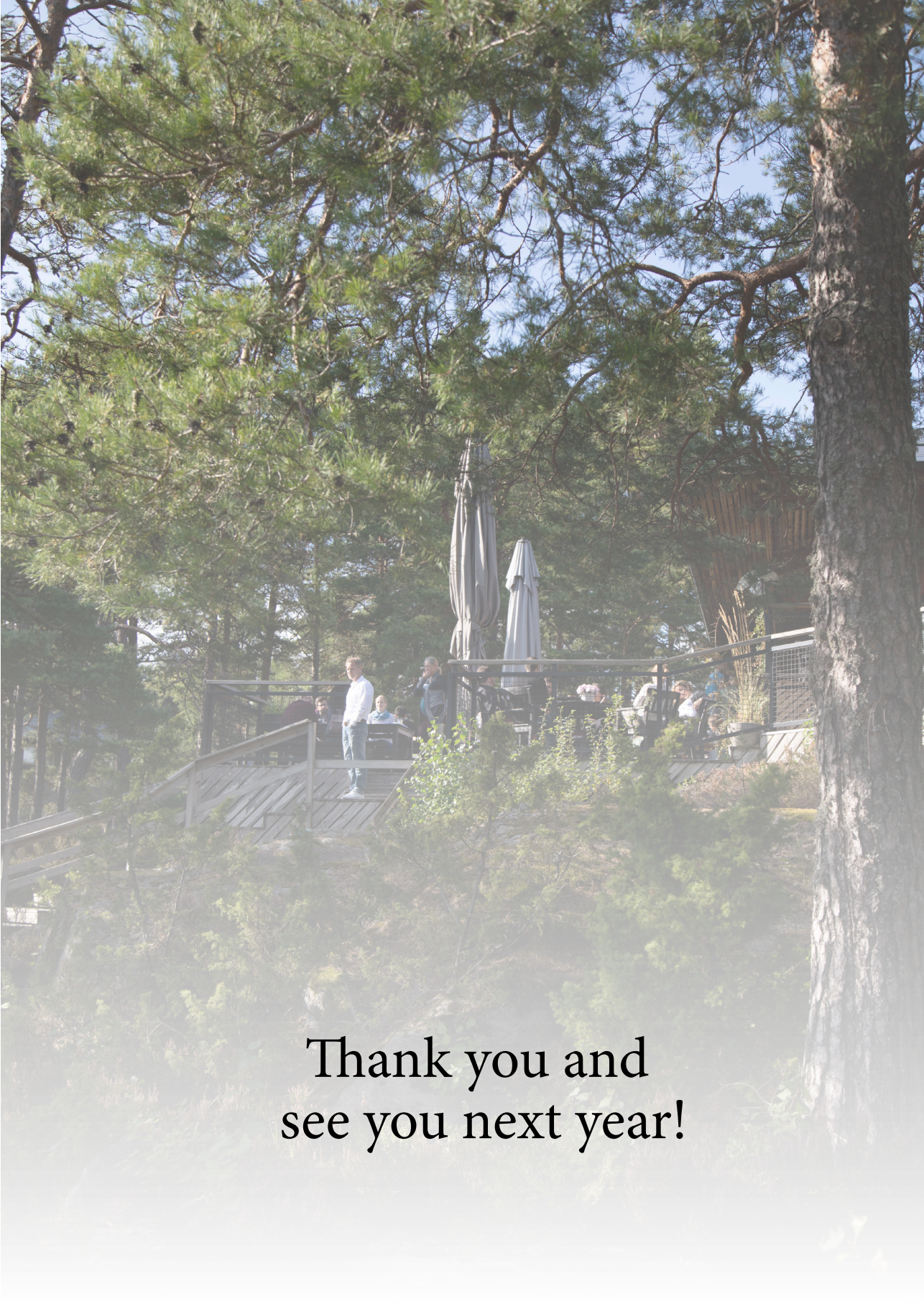
~350 PIs in cancer research at KI 22 Departments

The Executive Board

Jonas Bergh, Elias Arner, Yvonne Wengström, Margareta Wilhelm, Ingemar Ernberg, Matthias Löhr, Simon Ekman, Linda Lindström, Johanna Ungerstedt, Päivi Östling, Jonas Fuxe, Ninib Baryawno, Pedro Fonseca, Lise-lott Eriksson (Chair of the Blood Cancer Association), 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

Notes



Thank you and
see you next year!