XXII Cancer Research KI Retreat

22-23 September, 2025

Djurönäset

Welcome to the Cancer Research KI Retreat 2025

This annual retreat brings together PhD students, postdocs, and scientists from Karolinska Institutet, Karolinska University Hospital, and other Stockholm hospitals for a two-day meeting to strengthen interactions, foster interdisciplinary exchange, and spark new collaborations..

Organized by Cancer Research KI (CRKI)—a hub for all researchers and clinicians in the cancer field at Karolinska—the retreat reflects CRKI's commitment to inclusivity, transparency, and collaboration. We warmly invite you not only to share and discuss science, clinical care, and patient perspectives, but also to take an active role in shaping the future of cancer research in the Stockholm region. Cancer Research KI has remained active in several areas over the past year, and we briefly describe some of the key initiatives here. Our **Annual Report**, presented during the **Karolinska Comprehensive Cancer Centre (KCCC) Day**—a day dedicated to showcase the latest research conducted at Karolinska CCC—, summarized the breadth of our activities and achievements. We also hosted the **second edition of the PI Retreat** in February at Djurönäset, following the success and high demand of the first edition—an initiative we plan to continue next year.

Public outreach remains a basis of our mission. The latest edition of **"En dag för cancerforskning"**, held in Swedish and aimed at the general public, attracted over 1000 registered participants and highlighted the impact of cancer research at KI. We also expanded our communication efforts through curated **film screenings**, including *Cracking the Code: Phil Sharp and the Biotech Revolution* and *Jim Allison: Breakthrough*.

A major milestone this year was the **re-accreditation of the Karolinska Comprehensive Cancer Centre**, making it the first Comprehensive Cancer Center in Sweden to achieve this recognition—a significant achievement for our region and evidence of the strength of our collaborative efforts.

Our seminar and workshop series has grown substantially. We hosted a **radiotherapy workshop** in Stockholm in collaboration with the **National Institute of Oncology (NIO)** in Budapest as part of the twining agreement between both centers. In collaboration with **KI Science Park**, we organized seminars on **AI in cancer research** and **startups** run by scientists who developed their research ideas into a company, both of them followed by a networking afterwork. Our **Intellectual Property seminar**, together with the External Engagement Office at KI and KI Innovations, tailored for young researchers, was met with extremely positive participation and feedback, and future editions are already in the planning. We also held an **Ethics seminar** together with the Compliance & Data Office, now available on KI Play to watch. A seminar in collaboration with **Cancerfonden** featured three KI researchers funded under the **"Clinical Treatment Studies"** call, along with practical advice for future applicants, which is also available on KI Play. Our **Patient Workshop**, held online in Swedish, focused on common cancers in women, with an upcoming edition dedicated to cancers in men.

Cancer Research KI continues to strengthen its international presence. We welcomed the **Cancer Core Europe (CCE) Leadership** for a site visit to KI and Karolinska University Hospital, reinforcing our role within the European network. KI researchers also participated in the **CCE Summer School in Translational Cancer Research** in Portugal, aimed at PhD students, postdocs, and clinician-scientists from around the world. As part of the ECHoS project, we organized the **First Cancer Mission Fair** in Warsaw, focusing on patient and

citizen engagement. We look forward to the launch of a **Swedish Cancer Mission Hub** in the coming years. In addition, we hosted the **EUnetCCC launch** in Stockholm last November, further strengthening our role in shaping the future of European cancer research and care infrastructure.

Finally, we celebrated the **sixth Mayo Clinic and Karolinska Institutet Joint Cancer Research Symposium**, which included presentations from the 2024 Cancer Research Funding Awardees—an event that continues to reinforce our transatlantic collaboration.

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

We are especially honored to welcome our keynote speakers: **Hans Clevers** (Hubrecht Institute, Utrecht University, The Netherlands), **Michelle Monje** (Stanford University, USA), and **Robert Weinberg** (Massachusetts Institute of Technology, USA).

A warm welcome also to all invited speakers, patient representatives, 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 in planning the event, and **Elekta**, our **poster prize sponsor**.

On behalf of Cancer Research KI, a warm welcome to you all!

The Directors of Cancer Research KI

Elias Arnér, Marco Gerling, and Linda Lindström

Share your experience on social media using the hashtag

#CRKIretreat2025

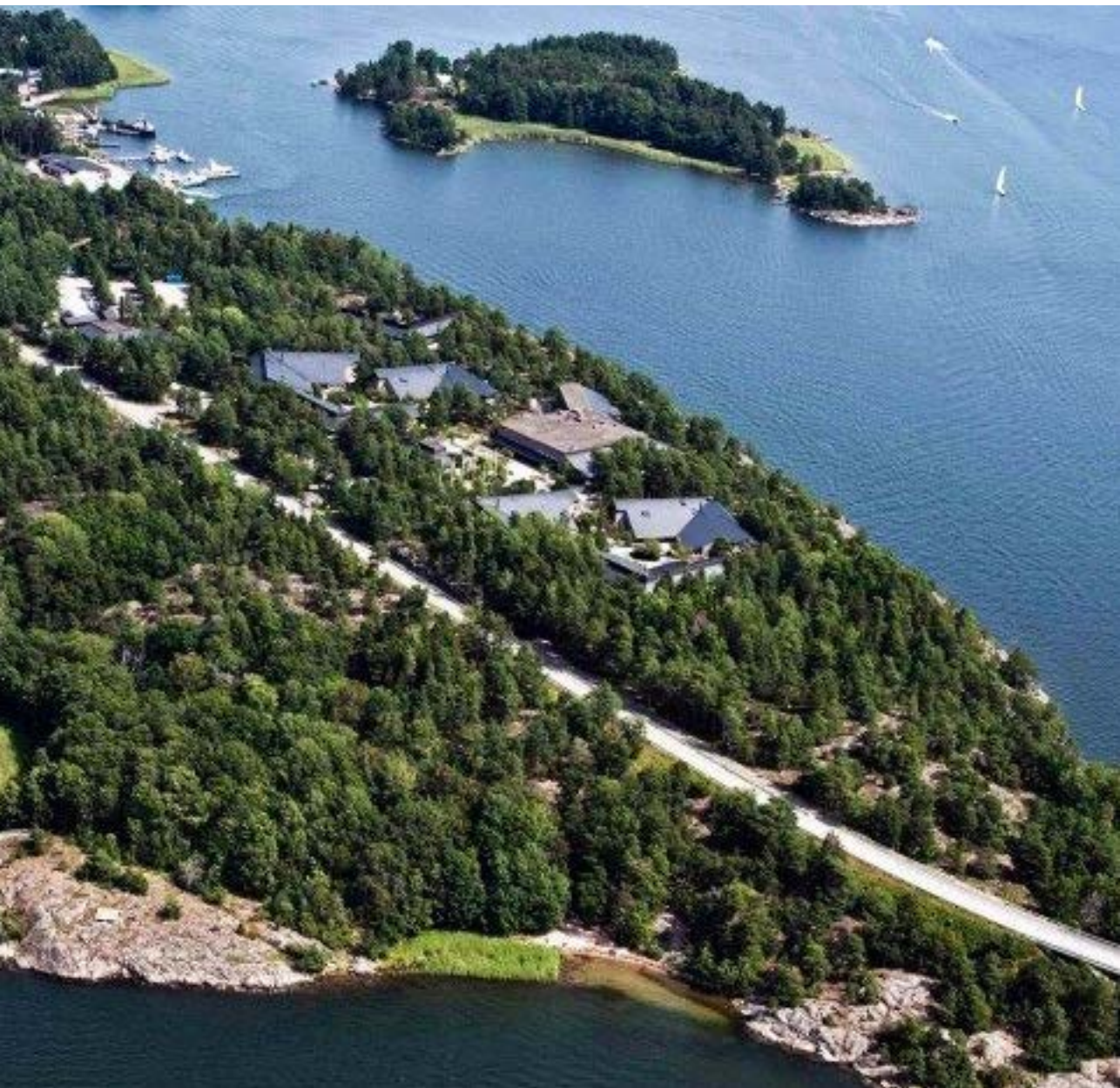
To access the **extended version** of the program, please scan this QR code

About Elekta

Our Poster Prize Sponsor

As a leader in precision radiation therapy, Elekta is committed to ensuring every patient has access to the best cancer care possible. We openly collaborate with customers to advance sustainable, outcome-driven and cost-efficient solutions to meet evolving patient needs, improve lives and bring hope to everyone dealing with cancer. To us, it's personal, and our global team of 4,700 employees combine passion, science, and imagination to profoundly change cancer care. We don't just build technology, we build hope.

Elekta is headquartered in Stockholm, Sweden, with offices in more than 40 countries and listed on Nasdaq Stockholm.



PRACTICAL INFORMATION

TRANSPORTATION (STOCKHOLM – DJURÖNÄSET – STOCKHOLM)

Buses will depart from **Cityterminalen** (Klarabergsviadukten 72) on **Monday, September 22 at 08:30** sharp.

Please check the monitors for the gate number for our buses labeled **"KI till Djurönäset."** The journey takes approximately one hour. Return buses will depart from Djurönäset on **Tuesday afternoon, September 23**, arriving at Cityterminalen around 17:00, depending on traffic conditions.

REGISTRATION

Upon arrival at Djurönäset, you will receive a **name badge** and a printed copy of the **program**. Please wear your badge visibly at all times during the conference.

Coffee/tea and sandwiches will be served before the conference begins at **10:05**. Luggage will be stored temporarily until check-in.

ACCOMMODATION

Room keys will be distributed during the afternoon coffee break at **15:30**. **Check-out** is scheduled for **Tuesday, September 23 at 08:45**, before the morning session begins.

Note: Students will be accommodated in shared rooms.

MEALS

Lunches will be served buffet-style in the restaurant located in the main building. If you have informed us of any dietary requirements, please speak directly with the restaurant staff as they have been notified.

Dinner on **Monday, September 22** will be served at **18:00**, and **breakfast** on **Tuesday, September 23** will be available from **07:00 to 08:45**.

POSTERS

The **poster session** will take place on **Monday evening at 20:00** in the main hall. Posters should be mounted between 17:30 and 18:00.

Please refer to the **digital abstract book** to find your poster number, as the poster frames will be numbered accordingly.

INTERNET

WiFi is available free of charge throughout the Djurönäset complex. Network name: **djuronaset-guest**. Each room also includes a wired internet connection.

LEISURE FACILITIES

The conference center features a 25-meter swimming pool, gym, and sauna, open on **Monday, September 22 from 15:30 to 23:00** (bar service available). The seaside **wooden sauna** will be open from **21:00 to 23:00** (pre-order your drinks in the main building until 21:00).

On **Tuesday, September 23**, the spa will be open from **06:00 to 08:00**.

PROGRAM

To access the extended version of the program, please scan the QR code.

1-7 Konferenslokaler och hotellrum / Conference and 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 och badtunnor / Wood burning sauna and hot tubs
14 Svit och Längan / Suite and Hotel rooms

A Varm infinitypool / Hot outdoor infinity pool
B Cyklar / Bicycles
C Naturstig / Nature trail
D Badstrand / Beach
E Äventyrscenter / Adventure Center
F Helikopterplatta / Helipad
G Motionsslinga / Running trail
H Utegymstationer / Outdoor gym stations
I Busshållplats / Bus stop
J Tennisbana / Tennis court
K Folkparken / Outdoor event area
L Gästhamn / Guest harbour
M Mötesplats / Meeting spot
P1 Parkering / Parking
P2 Parkering Seregården och Folkparken / Parking for Seregården and Folkparken

XXII Cancer Research KI Retreat

September 22-23, 2025

GENERAL PROGRAM OUTLINE

Monday, September 22:

Bus departure from Stockholm: **08:30**

Arrival, coffee, and registration: **09:30**

Welcome and introduction: **10:05**

Morning session: **10:05**

Group photo: **12:40**

Lunch: **12:50**

Afternoon session: **13:45**

Coffee break and collection of keys: **15:30**

Breakout sessions: **16:00**

Mingle and welcoming drink: **17:30**

Dinner: **18:00**

Poster session: **20:00**

Tuesday, September 23:

Breakfast and check out: **07:30**

Morning session: **09:00**

Coffee break: **10:05**

Lunch: **11:25**

Afternoon session: **12:30**

Coffee break: **13:55**

Bus departure: **16:00**

Arrival to Stockholm: **17:00**

Keynote Speakers:

Prof. Hans Clevers, Hubrecht Institute, Utrecht University

Prof. Michelle Monje, Howard Hughes Medical Institute, Stanford University

Prof. Robert A. Weinberg, Whitehead Institute for Biomedical Research, MIT

Monday, September 22

08:30 Departure by bus from Cityterminalen, Klarabergsviadukten 17, Stockholm

09:30 Arrival at Djurönäset (estimated)

10:05 - 12:40 **Morning session**

10:05 - 10:15 **Opening and Welcome Remarks**
Elias Arnér and Linda Lindström

Chairs: **Matthias Löhr** and **Sara Abu Ajamieh**

10:15 - 10:55 **Keynote Lecture: Hans Clevers**, Hubrecht Institute, Utrecht University
"Modeling development and disease with human organoids"

11:00 - 11:15 **Janne Lehtiö**, Dep. of Oncology and Pathology, KI Proteomics platform SciLifeLab
"Cancer proteomics - adding molecular phenotypic information in precision medicine"

11:20 - 11:25 **Active break**
Svetlana Bajalica Lagercrantz

Chairs: **Hanna Brauner** and **Panagiotis Alkinoos Polychronopoulos**

11:30 - 11:45 **Qiang Pan Hammarström**, Dep. of Medical Biochemistry and Biophysics
"Genomic and transcriptomic studies: towards precision medicine in B cell lymphomas"

11:50 - 12:00 **Ahmed Osman**, Dep. of Women's and Children's Health
"Harnessing liquid biopsies for defining the mechanisms of the nervous system cancer progression and resistance to therapies"

12:05 - 12:15 **Mohammed Rasul**, Dep. of Women's and Children's Health
"Progesterone Receptor Modulator: Novel Avenues in Breast Cancer Prevention"

12:20 - 12:35 **Richard Rosenquist Brandell**, Dep. of Molecular Medicine and Surgery
"Towards precision medicine in chronic lymphocytic leukemia"

12:40 - 12:50 **Group Photo**

12:50 - 13:45 **Lunch**

13:45 - 15:30 **Afternoon session**

Chairs: **Ingemar Ernberg** and **Madeleine Barrett**

13:45 - 14:00 **Luigi de Petris**, Dep. of Oncology-Pathology; Phase I Unit, KCCC
"Applying Data-driven approaches to Real-World Data in Small-Cell Lung Cancer: Bridging the Evidence Gap to Inform Clinical Practice"

14:05 - 14:20 **Karin Ekström Smedby**, Dep. of Medicine, Solna
"Recent developments in treatment, survival and precision medicine in malignant lymphomas"

14:25 - 15:05 **Keynote lecture: Robert A. Weinberg**, Whitehead Institute for Biomedical Research, MIT
“Mechanisms of Metastatic Awakening”

15:10 - 15:30 **Poster pitches**

15:30 - 16:00 **Coffee break and collection of keys**

16:00 - 17:30 **Breakout sessions** (see detailed program on the next page)

17:30 - 18:00 **Mingle and mounting of posters**

18:00 - 20:00 **Dinner**

20:00 - 22:00 **Poster session**

Breakout Sessions

Monday, September 22 (16:00 - 17:30)

Please note:

- **Pre-registration is required for all sessions.** If you haven't registered yet, please contact the organizers to check if there are any available spots.
- Abstracts and additional information about the speakers can be found in the **extended abstract booklet available online**.

Scan the QR code to access more information about the breakout sessions

Breakout session 1: Patient Perspectives

In these sessions, you will have the opportunity to join one of our oncologists and their patients in a conversation about their journey and perspectives. Each session will begin with a brief introduction to the topic, followed by a discussion between the oncologist and the patient. The session will conclude with an open dialogue, giving the audience a chance to ask questions and engage in the conversation.

Pancreatic Cancer
Matthias Löhr, House 1 (Room 1A)

Lung Cancer
Simon Ekman, House 4 (Room 4A)

Hereditary Cancer
Svetlana Bajalica Lagercrantz, House 2 (Room 2A)

Childhood Cancer
Nikolas Herold, House 5 (Room 5A)

Melanoma
Hildur Helgadottir, House 3 (Room 3A)

Breakout session 2: Scientific Presentations

In this session, participants will have the opportunity to attend several scientific presentations selected by the Scientific Committee from submitted abstracts. A detailed program and information about each presentation can be found in the digital booklet, accessible by scanning the QR code above.

Chairs: Dimitris Kanellis and Conny Tümmler

House 7 (Conference Room 7A)

Breakout session 3: Meet the Scientist

In these sessions, participants will have the opportunity to engage in conversation with our keynote speakers in a more relaxed and informal setting. This format allows for questions that might otherwise be difficult to ask due to time constraints or their personal nature.

Prof. Michelle Monje, House 1 (Coffee Lounge)

Prof. Robert A. Weinberg, House 2 (Coffee Lounge)

Tuesday, September 23

07:00 - 08:45 **Breakfast and check-out**

09:00 - 11:25 **Morning session**

Chairs: **Margareta Wilhelm** and **Oscar Danielsson**

09:00 - 09:40 **Keynote lecture: Michelle Monje**, Howard Hughes Medical Institute, Stanford University
"The Neuroscience of Cancer"

09:45 - 10:00 **Hildur Helgadottir**, Dep. of Oncology-Pathology
"Treating metastatic melanoma and ongoing academic translational studies: PROMMEL, BioMelanom and SWE-NEO"

10:05 - 10:15 **Glancis Luzeena Raja**, Dep. of Medical Biochemistry and Biophysics
"Uncovering novel microproteins driving chemoresistance in pancreatic ductal adenocarcinoma"

10:20 - 10:30 **Cheng-De Liu**, Dep. of Oncology-Pathology
"Bridging the Heterogeneity Gap: Single-Cell Transcriptomic Heterogeneity Measurement as a Guide to Enhance Neuroblastoma Organoid Diversity"

10:05 - 10:35 **Coffee break**

Chairs: **Klas Wiman** and **Sara Söderqvist**

10:35 - 10:50 **Susanne Schilisio**, Dep. of Oncology-Pathology
"Intratumor Heterogeneity and Plasticity in Neuroblastoma and Paraganglioma: From Developmental Origins to Therapy Resistance"

10:55 - 11:05 **Damien Kaukonen**, Dep. of Medical Epidemiology and Biostatistics
"The Risk of HER2+ Breast Cancer; Before and After Diagnosis"

11:10 - 11:20 **Hala Habash**, Dep. of Women's and Children's Health
"Drugging the undruggable target: Gemcitabine and cytarabine kill Ewing sarcoma cells through inhibition of SAMHD1 and degradation of the Ewing sarcoma fusion protein"

11:25 - 12:30 **Lunch**

12:30 - 15:00 **Afternoon session**

Chairs: **Dhifaf Sarhan** and **Mattias Hammarström**

12:30 - 12:45 **Simon Ekman**, Dep. of Oncology-Pathology
"Overcoming Treatment Resistance to Targeted Therapies in Lung Cancer – Development of Novel Therapies using a Multiomics Approach"

12:50 - 13:00 **Mingzhi Liu**, Dep. of Microbiology, Tumor and Cell Biology
"Germline ALK-R1275Q Mutation Drives a Proliferative, Undifferentiated State and Accelerate Neuroblastoma Initiation"

13:05 - 13:15 **Berenice Fischer**, Dep. of Medicine, Solna
"Spatially dissecting the role of macrophages in cutaneous lymphoma"

13:20 - 13:35 **Kamila Czene**, Dep. of Medical Epidemiology and Biostatistics
"Incidence, Genetics, and Outcomes of Interval Breast Cancer: Toward Personalized Screening"

13:40 - 13:50 **Ann-Britt Johansson**, Karolinska Comprehensive Cancer Center
"Uniting Science and Care: Karolinska CCC's Comprehensive Mission"

13:55 - 14:30 **Coffee break**

Chairs: **Galina Selivanova** and **Nan Sophia Han**

14:30 - 14:40 **Ingemar Ernberg**, Dep. of Microbiology, Tumor and Cell Biology
"Unresolved enigmas in understanding the biology of nasopharyngeal carcinoma (NPC)"

14:45 - 14:55 **Dan Grandér Prize** for best dissertation in cancer research in 2024

15:00 - 15:15 **Conclusions; Poster prizes**

16:00 **Bus departure**

17:00 **Arrival to Stockholm Cityterminalen** (estimated)

KEYNOTE SPEAKERS

Hans Clevers

Professor of Molecular Genetics

Hubrecht Institute, Utrecht University

Time: Monday 22, 10:15

Modeling development and disease with human organoids

Techniques for culturing functional human breast epithelium in three-dimensional (3D) matrices have been championed for more than 30 years by Mina Bissell. Additionally, around a decade ago, Sasai and colleagues pioneered pluripotent stem cell (PSC)–based technology to create organoids that mirror specific parts of the central nervous system (CNS). Lancaster and Knoblich modified this technology and provided particularly notable examples of “mini-brain” structures. While PSCs can be used to model everything ranging from tissues to organismal development, adult stem cells (ASCs) can also be isolated to generate organoid models of the primary tissues in which they reside. Specific growth factor cocktails allow long-term expansion of ASC organoids by mimicking the organ stem cell niche, as first established for mouse and human intestine and airway epithelium. The organoid structures generated from PSCs and ASCs reflect crucial tissue features in terms of overall architecture, the collection of differentiated cell types, and tissue-specific function. Organoids thus represent a model system that can be compared to traditional genetically engineered mouse models (GEMMs), cell lines, and patient-derived xenografts (PDXs).

As a definition, organoids are microscopic self-organizing, three-dimensional structures that are grown from stem cells in vitro. They recapitulate many structural and functional aspects of their in vivo counterpart organs. This versatile technology has led to the development of many novel human cancer models. It is now possible to create indefinitely expanding organoids starting from tumor tissue of individuals suffering from a range of carcinomas. Alternatively, CRISPR-based gene modification allows the engineering of organoid models of cancer through the introduction of any combination of cancer gene alterations to normal organoids. When combined with immune cells and fibroblasts, tumor organoids become models for the cancer microenvironment enabling immune-oncology applications. Emerging evidence indicates that organoids can be used to accurately predict drug responses in a personalized treatment setting. I will illustrate the current state and future prospects of the rapidly evolving tumor organoid field through examples from my lab.

About Prof. Hans Clevers

Hans Clevers is world-renowned for his work in the fields of cell biology, molecular signaling and stem cells. His research groups' discoveries include the detailed characterization of the molecular effectors and integrators of the "Wnt" pathway, which play crucial roles in health and disease, including in stem cells, regeneration and cancer. His group provided important insights into (intestinal) stem cell biology, exploiting LGR5 as a novel stem cell marker. This eventually led him to pioneer "organoids", 3-dimensional in vitro structures that behave anatomically and molecularly like the organ from which they are derived. Organoid biology has revolutionized the way we understand and approach human biology and medicine.

Hans Clevers obtained his MD and PhD degrees from the University of Utrecht, the Netherlands. He holds a professorship in Molecular Genetics from the University of Utrecht. He previously held directorship/President positions at the Hubrecht Institute, the Royal Netherlands Academy of Arts and Sciences and the Princess Maxima Center for pediatric oncology. He has served as Head of Roche's Pharma Research & Early Development (pRED) since March 2022 as member of the company's Enlarged Corporate Executive Committee. In 2023, he oversaw the establishment of the Institute of Human Biology (IHB) in Basel, and currently serves as its ad interim Director. Hans Clevers will remain in charge of the IHB until a successor is appointed, while supervising his research groups at the Hubrecht Institute and the Princess Máxima Center.

He is the recipient of multiple international scientific awards, including the Breakthrough Prize in Life Science. Hans Clevers is a member of the Royal Netherlands Academy of Arts and Sciences (NL), the National Academy of Sciences (USA), the Royal Society (UK) and the Academie des Sciences (France). He is also Chevalier de la Légion d'Honneur and Knight in the Order of the Netherlands Lion, among many other international accolades.

Michelle Monje

Professor of Neurology

Howard Hughes Medical Institute, Stanford University

Time: Tuesday 23, 09:00

The Neuroscience of Cancer

In the central nervous system, neuronal activity is a critical regulator of development and plasticity. Activity-dependent proliferation of healthy glial progenitors, oligodendrocyte precursor cells (OPCs), and the consequent generation of new oligodendrocytes contributes to adaptive myelination. This plasticity of myelin tunes neural circuit function and contributes to healthy cognition, while disruption of myelin plasticity contributes to cognitive impairment in a range of disease states. The robust mitogenic effect of neuronal activity on normal oligodendroglial precursor cells, a putative cellular origin for many forms of glioma, suggests that dysregulated or “hijacked” mechanisms of myelin plasticity might similarly promote malignant cell proliferation in this devastating group of brain cancers. Indeed, neuronal activity promotes progression of both high-grade and low-grade glioma subtypes in preclinical models. Crucial mechanisms mediating activity-regulated glioma growth include paracrine secretion of tumor-promoting factors and synaptic communication between neurons and glioma cells. Glioma cells integrate into neural circuits synaptically through neuron-to-glioma synapses that exhibit synaptic plasticity, and electrically through potassium-evoked currents that are amplified via gap-junctional coupling between tumor cells. This synaptic and electrical integration of glioma into neural circuits is central to tumor progression in preclinical models. Thus, neuron-glial interactions not only modulate neural circuit structure and function in the healthy brain, but neuron-glioma interactions also play important roles in the pathogenesis of glial cancers. The mechanistic parallels between normal and malignant neuron-glial interactions underscores the extent to which mechanisms of neurodevelopment and plasticity are subverted by malignant gliomas, and the importance of understanding the neuroscience of cancer.

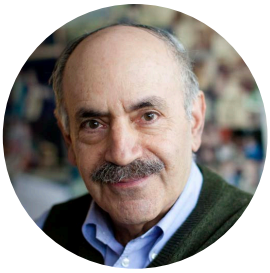
About Prof. Michelle Monje

Michelle Monje, MD, PhD, is a Professor of Neurology at Stanford University and a Howard Hughes Medical Institute Investigator. She received her M.D. and Ph.D. in Neuroscience from Stanford and completed her residency training in neurology at the Massachusetts General Hospital/Brigham and Women's Hospital/Harvard Medical School Partners program, and then returned to Stanford for a clinical fellowship in pediatric neuro-oncology. Her research program focuses at the intersection of neuroscience, immunology and brain cancer biology with an emphasis on neuron-glial interactions in health and oncological disease. Her laboratory studies how neuronal activity regulates healthy glial precursor cell proliferation, new oligodendrocyte generation, and adaptive myelination; this plasticity of myelin contributes to healthy cognitive function, while disruption of myelin plasticity contributes to cognitive impairment in disease states like cancer therapy-related cognitive impairment. Her lab discovered that neuronal activity similarly promotes the progression of malignant gliomas, driving glioma growth through both paracrine factors and through electrophysiologically functional neuron-to-glioma synapses. Dr. Monje has led several of her discoveries from basic molecular work to clinical trials. Her work has been recognized with numerous honors, including an NIH Director's Pioneer Award, a MacArthur Fellowship, the Richard Lounsbery Award from the National Academy of Sciences and election to the National Academy of Medicine.

Robert A. Weinberg

Professor of Biology

Whitehead Institute for Biomedical Research, MIT



Time: Monday 22, 14:25

Mechanisms of Metastatic Awakening

The cell-biological program termed the EMT (epithelial-mesenchymal transition) can become activated in primary carcinoma cells in response to contextual signals that these cells receive from the recruited host-derived stroma. Once activated, it can confer a number of cellular phenotypes on carcinoma cells that have long been depicted as indicators of malignant progression. Thus, carcinoma cells that have been induced to express their EMT programs acquire traits such as invasiveness, motility, a heightened resistance to various types of therapeutics, and even stemness/tumor-initiating powers. Moreover, primary carcinoma cells are empowered to physically disseminate to distant organ sites. Unexplained by this sequence of events, which together constitute many of the steps of the invasion-metastasis cascade, is the fate of the disseminated carcinoma cells after they have extravasated into the parenchyma of a distant tissue. As described, we find that the great majority of these cells enter into a non-proliferative state in which they can persist for extended periods of time, representing the state of “metastatic dormancy”. Our recent work reveals that dormant disseminated carcinoma cells can be provoked to re-enter into the active growth-and-division cycle through inflammation that is inflicted on the host tissue in which these cells are lodged. Mechanisms such as this would seem to explain how in diseases such as human breast cancer, patients are often apparently cured by elimination of all detectable neoplastic cells in their bodies, only to suffer months or years later a metastatic relapse with the eruption of life-threatening metastatic growths.

About Prof. Robert A. Weinberg

Over the past four decades, Dr. Weinberg's research has been focused on the molecular and biochemical determinants of neoplastic cell transformation. His lab isolated the first human cancer-causing gene, the Ras oncogene, and the first known tumor suppressor gene, Rb, the retinoblastoma gene.

Dr. Weinberg is an elected Member of the U.S. National Academy of Sciences and a fellow of the American Academy of Arts and Sciences. Among many honors and awards, he received Discover Magazine's 1982 Scientist of the Year, the Sloan Prize of the General Motors Cancer Research Foundation, the Bristol-Myers Award for Distinguished Achievement in Cancer Research, and the 1997 National Medal of Science. He has written or edited several books including the widely used The Biology of Cancer textbook and published more than 400 articles. His three most recent books include *One Renegade Cell*, *Racing to the Beginning of the Road: The Search for the Origin of Cancer* and *Genes and the Biology of Cancer*, the latter co-written with Dr. Harold E. Varmus, former Director of the National Institutes of Health.

Personal statement

Research in my laboratory is focused on attempting to elucidate the biochemical and cell-biological mechanisms that enable carcinoma cells in primary tumors to invade and disseminate, resulting in the formation of metastases in distant sites. Much of this work depends on our analyses of the cell-biological program termed the epithelial-mesenchymal transition (EMT). In addition to conferring on epithelial carcinoma cells traits such as motility and invasiveness, activation of this program heightens their resistance to chemotherapeutic attack. In recent years, we have also found that activation of a previously latent EMT program places both normal and neoplastic epithelial cells in a position from which they can enter into a stem cell state. In the case of carcinomas, the tumor-initiating powers resulting from this shift indicates the formation of cancer stem cells (CSCs), which are qualified to serve as founders of new metastatic colonies in distant anatomical sites. With the passage of time, our research increasingly focuses on the interaction of CSCs with recruited inflammatory cells and on the later steps of the invasion-metastasis cascade that enables disseminated carcinoma cells to extravasate, thereby setting the stage for the formation of micro- and macroscopic metastatic colonies.

INVITED SPEAKERS

Kamila Czene

Professor

Department of Medical Epidemiology and Biostatistics, Karolinska Insitutet

Time: Tuesday 23, 13:20

Incidence, Genetics, and Outcomes of Interval Breast Cancer: Toward Personalized Screening

Early detection remains the cornerstone of breast cancer control, offering the greatest chance for curative treatment and long-term survival. While mammography has significantly reduced mortality overall, up to 30% of breast cancers in screening programs are interval cancers, diagnosed after a negative screen but before the next scheduled exam. These tumors are often biologically aggressive, progress rapidly, and disproportionately contribute to breast cancer deaths, underscoring persistent gaps in current screening strategies.

In a population-based cohort study of more than 527,000 women screened in Stockholm over 30 years, we found that the proportion of interval cancers has remained unchanged across three decades. Risk is elevated among women with dense breasts, those using hormone replacement therapy, and those with a family history of breast or other cancers. Strikingly, women with a family history of interval cancers or estrogen receptor–negative disease are at highest risk, highlighting both heritable and biological determinants.

Genetic analyses demonstrate that interval cancers are enriched for rare protein-truncating variants in *BRCA1/2*, *PALB2*, and other major breast cancer susceptibility genes. Carriers of these variants not only face an increased likelihood of interval diagnosis but also experience significantly poorer survival outcomes. This suggests a distinct molecular profile differentiating interval cancers from screen-detected cancers, presenting opportunities for targeted risk assessment.

Outcome analyses confirm that interval cancers are linked to worse breast cancer–specific survival, as well as elevated risks of contralateral breast cancer and other malignancies. Unique prognostic indicators include early-onset family history and low mammographic density, both associated with aggressive tumor biology in interval cancers.

Collectively, these findings call for a paradigm shift from age-based to risk-adapted screening. By integrating mammographic features, family history, and genetic susceptibility, we can identify women most likely to develop interval cancers and tailor prevention, surveillance, and early detection strategies accordingly. Such a precision approach moves breast cancer screening from reactive to proactive, fulfilling the promise of early detection to save more lives.

Luigi de Petris

Medical Lead

Phase I Unit, Karolinska Comprehensive Cancer Center; Dep. of Oncology-Pathology, Karolinska Institutet

Time: Monday 22, 13:45

Applying Data-driven approaches to Real-World Data in Small-Cell Lung Cancer: Bridging the Evidence Gap to Inform Clinical Practice

Small-cell Lung Cancer (SCLC) is a complex and aggressive malignancy with limited prognosis despite advances in treatment. While molecular subtyping has provided new insights into the biological heterogeneity of SCLC, current clinical staging systems often fail to capture the nuances that influence prognosis and treatment outcomes. In recent years, the use of real-world data (RWD) has gained traction as a valuable resource for understanding disease patterns, treatment responses, and prognostic factors in oncology. However, RWD often poses significant challenges due to variability in data quality, incomplete records, and the need for advanced methods to handle unstructured datasets. Machine learning (ML) approaches have emerged as powerful tools to address these challenges, enabling the identification of meaningful prognostic subgroups and stratifying patients based on risk. In addition, SCLC poses significant challenges for recruitment to randomized controlled trials (RCTs) due to its aggressive nature and the urgent need for treatment initiation. The patient population is typically older, with multiple comorbidities, and often presents with symptomatic disease or brain metastases, necessitating immediate therapy and limiting opportunities for trial enrollment. These challenges lead to underrepresentation of SCLC in clinical trials, limiting the development of robust treatment strategies. While RCTs are considered the gold standard for establishing efficacy, their restrictive criteria often exclude patients with poor performance status or comorbidities. RWD, collected from broader clinical populations, offers a complementary perspective by capturing diverse patient outcomes and treatment patterns. We developed a novel ML framework to explore discrepancies between RCT and RWD outcomes, focusing on the impact of patient selection criteria and operational conditions, improving the applicability of clinical trials to real-world populations. Our studies, conducted within a KI-KTH partnership, integrate statistical and machine learning methods to create a robust framework for analyzing RWD, aiming to improve risk stratification and treatment decision-making for SCLC, and set the pavement for Real-World Evidence.

Simon Ekman

Professor, Senior Consultant in Oncology

Theme Cancer, KCCC, Karolinska University Hospital; Dep. of Oncology-Pathology, Karolinska Institutet

Time: Tuesday 23, 12:30

Overcoming Treatment Resistance to Targeted Therapies in Lung Cancer – Development of Novel Therapies using a Multiomics Approach

Lung cancer is responsible for most cancer-related deaths worldwide and with non-small cell lung cancer (NSCLC) being the most common subtype (80%). Survival has improved with the use of targeted therapies, including tyrosine kinase inhibitors (TKIs) of mutated epidermal growth factor receptor (EGFR) and rearranged anaplastic lymphoma kinase (ALK) and inhibitors of the KRAS G12C mutation (in total 1/3 of NSCLC patients). Unfortunately, treatment resistance will inevitably develop leading to disease progression and eventually death of the patients. In at least 50% of the cases the resistance mechanisms are unknown on a DNA level demanding further investigations. With a multiomics approach of RNA expression and proteomics profiling we aim to develop novel therapies against treatment-resistant NSCLC. Patient materials from several ongoing clinical studies are used. State-of-the-art ex vivo models are used to establish treatments in systems mimicking the features of the original tumors. So far, we have identified several miRNAs, mRNAs and proteins involved in treatment resistance, they are now ready for further therapeutic development.

Karin Ekström Smedby

Professor

Dep. of Medicine Solna, Karolisnka Institutet; Dep. of Hematology, Karolinska University Hospital, Solna

Time: Monday 22, 14:05

Recent developments in treatment, survival and precision medicine in malignant lymphomas

Malignant lymphomas are a heterogeneous group of malignancies with large variations in morphology, molecular biology and clinical course. Aggressive subtypes may be cured whereas indolent forms are often chronic. With the addition of targeted therapies to chemotherapy about 20 years ago, and more recently of cellular therapies, the outcome of B-cell lymphomas has steadily improved whereas T-cell lymphomas still fare worse. Recent survival trends are monitored in the national Swedish Lymphoma register initiated in the year 2000. Precision medicine is only implemented to a limited extent in the everyday clinical care of lymphoma patients but is developing rapidly. In the prospective clinical BioLymph study, ongoing since 2019 at the hematology clinic, Karolinska hospital Solna, we're aiming to identify additional diagnostic, prognostic and predictive markers to support clinical decision making and treatment choices and to improve patient outcomes in lymphoma patients. In multidisciplinary collaboration with the depts of clinical genetics and hematopathology, we're evaluating the impact of targeted panel sequencing of tumor tissue and cell-free tumor-DNA as new tools for lymphoma subtyping, prognostication, treatment stratification and monitoring of measurable residual disease (MRD). First analyses show that NGS can be carried out on paraffin-embedded lymphoma tumor tissue, and that the NGS results add to diagnostics, prognostics and subtyping in aggressive B- and T-cell lymphomas. In Hodgkin lymphoma, preliminary results indicate that rapid ctDNA clearance is associated with a favourable outcome, and that ctDNA MRD monitoring during follow-up may allow for early relapse detection. Measurement of ctDNA in the cerebrospinal fluid may also offer a valuable tool to detect and monitor lymphoma involvement in the CNS.

Hildur Helgadottir

Associate Professor; Senior Consultant in Oncology

Dep. of Oncology-Pathology, Karolinska Institutet; Karolinska University Hospital

Time: Tuesday 23, 09:45

Treating metastatic melanoma and ongoing academic translational studies: PROMMEL, BioMelanom and SWE-NEO

Metastatic melanoma was until the recent decade considered incurable. With the entrance of immune checkpoint inhibitors (ICI) and targeted therapies, the outlook for patients with metastatic melanoma has markedly improved. In this period there has been a learning curve on how to optimally combine and sequence these treatments. We conduct the BioMelanom study, where sequential sampling is conducted in patients undergoing treatment for metastatic melanoma. In the PROMMEL study stereotactic radiotherapy is given concomitantly with ICI in melanoma patients progressing on ICI. In SWE-NEO, we compare ICI single agent (anti-PD-1) or combination (anti-PD-1/anti-CTLA-4) therapy as neoadjuvant treatment before operating melanoma metastases. The studies include sequential sampling for translational analyses and biomarker discovery and include study of plasma proteins, extracellular vesicles, immune cells in the blood as well as single cell DNA/RNA sequencing and in situ analyses of tumors.

Ann-Britt Johansson

Coordinator

Karolinska CCC Project Unit, Karolinska University Hospital

Time: Tuesday 23, 13:40

Uniting Science and Care: Karolinska CCC's Comprehensive Mission

Karolinska Comprehensive Cancer Center (Karolinska CCC) brings together cutting-edge expertise in highly specialized cancer care and cancer research. The center is a collaboration between Karolinska University Hospital and Karolinska Institutet and was the first accredited Comprehensive Cancer Center in Sweden.

The accreditation as a Comprehensive Cancer Center (CCC) means that the operation has a quality seal according to criteria set by the Organisation of European Cancer Institutes (OECI). This non-profit, non-governmental organisation was established in 1979 with the aim of promoting collaboration between European healthcare providers and research institutes in the field of cancer. Today, there are over 40 Comprehensive Cancer Centers worldwide.

The requirements to be able to call oneself a Comprehensive Cancer Center include the following:

- Cancer care is individualized and the approach is multidisciplinary and innovative.
- Good conditions for cancer research in terms of infrastructure, expertise and innovative power.
- Cancer research covers the full spectrum of basic, translational and clinical research.
- A well-developed network that includes all aspects of research, education, care and prevention in the field of cancer.
- There is constant development work with a focus on improving professional skills, organization, quality of care and collaboration.

As Sweden's first CCC, we are also the first to conduct a re-accreditation, which involves a thorough self-assessment against OECI's quality standards.

The work began in the fall of 2023 and included answering 900 qualitative measures and 385 quantitative questions, as well as submitting over 700 documents as evidence for the self-assessment. The self-assessment work took six months to complete and concluded with a successful 2-day audit in November. An international review team of 7 people represented OECI.

Day 1 was held in Solna and day 2 in Huddinge. The team visited our operations and interviewed nearly 200 committed employees from cancer care, research and education, as well as representatives from our patient network.

OECI in brief

The Organisation of European Cancer Institutes (OECI) mission to:

- Reduce cancer incidence and death and provide support to cancer patients.
- Linking the expertise and competence of the European Cancer Institutes in care and research.
- Strengthen cancer institutes and promote communication and collaboration between them.

The Comprehensive Cancer Centre accreditation program started in 2008 with the aim of:

- All cancer patients in Europe should have equal access to high-quality cancer care.
- Assist European cancer institutes in implementing quality systems for cancer care through standards/indicators and peer review/audit.

Scan the QR code to access more information about Karolinska Comprehensive Cancer Center

Janne Lehtiö

Professor

Dep. of Oncology-Pathology; KI Proteomics Platform, SciLifeLab; Div. of Pathology, Karolinska Univ. Hospital

Time: Monday 22, 11:00

Cancer proteomics - adding molecular phenotypic information in precision medicine

The explosion of genomics data has greatly advanced our understanding of cancer in recent years. However, systems-level knowledge of how genomic aberrations affect the functional proteome remains limited, hindering effective selection of anti-cancer drug combinations in precision medicine. Proteome data reflects the combined effects of epigenetic, transcriptional, and translational regulation, and encompasses virtually all drug targets.

Recent advances in proteomics methods now enable detailed molecular phenotyping of cells, tissues, and plasma, providing a systems-level view of disease biology. Integrating proteome data with genomics and imaging-based modalities offers significant opportunities to improve predictive diagnostics and guide the selection of anti-cancer drugs and their combinations.

In this talk, I will present examples of proteome-driven multi-omics research, focusing on predicting response to immunotherapy and targeted therapies in lung cancer, breast cancer, and leukemia. To facilitate clinical implementation, we have developed DIA-based cancer subtyping approaches for lung cancer and leukemias, along with clinical reporting tools integrated within the Molecular Tumor Board portal.

Qiang Pan Hammarström

Professor

Dep. of Medical Biochemistry and Biophysics, Karolinska Institutet

Time: Monday 22, 11:30

Genomic and transcriptomic studies: towards precision medicine in B cell lymphomas

Lymphomas account for approximately 5% of all cancers worldwide, with B-cell lymphomas comprising over 90% of all lymphoma cases. The most common types of B-cell lymphomas are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), both of which are clinically and genetically highly heterogeneous. Through integrated whole genome sequencing and transcriptomic analyses, we present the first molecular classification of FL. We identified three clinically relevant genetic subtypes. These include: C1, associated with favorable prognoses and enriched for BCL6-related translocations and mutations in the NOTCH, NF-κB, and immune evasion pathways; C2, characterized by *BCL2-IGH* translocations and mutations in chromatin-modifiers; and C3, associated with poorer prognosis, lacking *BCL2-IGH* and *BCL6*-related translocations but exhibiting increased copy number variations. Transcriptionally, C1 and C3 tumors display signatures resembling activated-B-cell-like DLBCL, whereas C2 tumors showed features of germinal-center B-cell-like DLBCL. Furthermore, C1 tumors are distinguished from C3 by gene signatures indicative of age-associated B cells and an inflamed tumor microenvironment. Preliminary results regarding the molecular classification of DLBCL will also be present at the meeting. Together, our findings illustrate the molecular heterogeneity of the two major types of germinal center-related B cell lymphomas, offering opportunities for personalized therapeutic strategies.

Richard Rosenquist Brandell

Professor; Senior Physician in Clinical Genetics

Department of Molecular Medicine and Surgery, Karolinska Institutet; Karolinska University Hospital

Time: Monday 22, 12:20

Towards precision medicine in chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in the Western world, characterized by a highly variable clinical course and outcome. Although targeted therapies, such as Bruton's tyrosine kinase (BTK) and BCL2 inhibitors, have significantly improved survival in patients with aggressive disease, resistance inevitably develops, and CLL remains an incurable condition. An expanding array of genetic tests is now routinely employed to identify high-risk patients and guide treatment decisions. These tests include molecular cytogenetic analyses to detect recurrent chromosomal alterations, particularly del(17p), and targeted sequencing of key genes (IGHV and TP53). This talk will provide an overview of the current genomic landscape of CLL and showcase recent advances with potential clinical applications. Particular attention will be given to the emerging roles of splicing and ribosomal mutations in the initiation and progression of CLL. Looking ahead, there is an urgent need for more comprehensive genomic profiling techniques that can capture the full spectrum of genetic alterations, as well as highly sensitive assays capable of detecting subclonal mutations linked to drug resistance. Additionally, the potential of emerging technologies, including single-cell sequencing and multi-omics approaches, particularly proteogenomics, will be illustrated for their role in refining disease classification and advancing precision medicine in CLL.

Susanne Schlisio

Senior Lecturer

Department of Oncology-Pathology, Karolinska Institutet

Time: Tuesday 23, 10:35

Intratumor Heterogeneity and Plasticity in Neuroblastoma and Paraganglioma: From Developmental Origins to Therapy Resistance

Acquired cancer therapy resistance is a direct consequence of intratumor heterogeneity, a hallmark of high-risk pediatric neuroblastoma (NB) and malignant paraganglioma (PPGL). Beyond genetic mosaicism driven by clonal mutations, these tumors display remarkable phenotypic plasticity, a transcriptionally regulated capacity of tumor cells to shift identity in response to treatment or microenvironmental cues. Understanding the cellular origins and mechanisms of such plasticity is critical for developing durable therapies.

We employ spatially resolved single-cell and single-nucleus transcriptomics, combined with mass spectrometry and lineage tracing in mouse models, to dissect the developmental trajectories and cell-state dynamics of NB and PPGL. Our recent work identifies SOX2+ sustentacular glial cells in the postnatal adrenal medulla, organ of Zuckerkandl, and paraganglia as previously unrecognized chromaffin progenitors and potential tumor cells of origin in VHL-mutant PPGL. These findings, now available as a preprint, demonstrate that sustentacular progenitors contribute to the plasticity and heterogeneity of sympathoadrenal tumors, thereby shaping therapeutic response and resistance.

By integrating spatial transcriptomics, scRNA-seq, and functional models, our studies uncover lineage hierarchies and signaling pathways governing tumor evolution. This work establishes a framework for linking tumor cell plasticity to developmental programs, with the ultimate goal of informing precision medicine strategies in NB and PPGL.

SELECTED FROM ABSTRACTS

Ingemar Ernberg

Professor

Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet

Time: Tuesday 23, 14:30

Unresolved enigmas in understanding the biology of naso-pharyngeal carcinoma (NPC)

Among human cancers nasopharyngeal carcinoma (NPC) shows many particular features. The world wide epidemiology shows local high incidence areas in South East Asia, radiating out from the Southern Chinese provinces around the Pearl river, but also high incidences on Greenland and in North Africa, a stable higher incidence in males, an early onset of disease and close to 100% prevalence of latent Epstein-Barr virus (EBV) infection in the tumors in these endemic regions. Due to lack of consistent patterns of cancer-driving mutations and extensive DNA-methylation in the tumor cells NPC can be considered “an epigenetic” cancer.

Current treatment for advanced metastatic late NPC does not work well, with a 5-year survival below 50%. We are exploring the mechanisms of NPC metastasis with the ultimate aim to improve this situation.

We have shown that NPC has a metabolic profile involving lipid droplet (LD) accumulation and that this correlates to NPC migration and invasion. We also showed that MTSS1 (metastasis suppressor 1/missing in metastasis (MIM)), was downregulated in NPC metastasis, and that restoring its expression inhibited metastasis and LD accumulation. We are further exploring the link between MTSS1 inhibition of metastasis and lipid metabolism.

MTSS1 is expressed in most human tissues and has multiple functions. MTSS1 has attracted the most attention for its role as a tumor suppressor, being absent or expressed at reduced levels in advanced and metastasizing cancers of many types.

MTSS1 is emerging as a central player in cell biology with four well- documented biochemical functions: 1) it induces membrane protrusions (lamellipodia and filopodia) by a direct interaction between the I-BAR domain (Inverse- Bin/Amphiphysin/Rvs) 2) it modulates actin dynamics by slowing down actin nucleation and filament elongation via the WH2 domain; 3) it modulates the accumulation of F-actin at cell–cell borders or at filopodia via the I-BAR domain; and 4) it acts as a scaffolding protein, bringing together many accessory proteins, particularly in the context of cytoskeletal modulation and protein degradation.

We are studying how MTSS1 regulate metastasis of NPC and how this links to lipid metabolism.

Berenice Fischer

Postdoctoral Researcher

Department of Medicine, Solna, Karolinska Institutet

Time: Tuesday 23, 13:05

Spatially dissecting the role of macrophages in cutaneous lymphoma

While early-stage cutaneous T cell lymphoma (CTCL) presents with thin patches and plaques up to one-third of CTCL patients progress to advanced diseases, which includes infiltrating tumors and a more unfavorable prognosis. There are few treatments available for advanced CTCL and better understanding of the mechanism of progression, including the role of immune cells, is needed. During progression of CTCL a shift towards an Th2 environment and an increase in myeloid cells and tumor promoting M2 macrophages was observed. Our aim is to uncover how different areas in the tumor alter the phenotype of macrophages either to a tumor promoting or suppressing one, to understand how tissue localization and spatial distribution drives disease progression. We collected and analyzed 190 regions of interest from seven CTCL biopsies, three patches, three plaques and one tumor, investigating macrophages through digital spatial profiling using an extensive immuno-oncological panel covering 570 protein targets. We stained macrophages by CD68 and suspected tumor cells using CD4 as a surrogate marker, enabling us to collect data from macrophages, tumor cells and total tumor area separately. We defined regions of interest as tumor margin versus center and tumor enriched areas compared to tumor poor areas. We found that macrophages in the tumor margin express more galectin-3 (gal-3), a β-galactosides-binding lectin, compared to macrophages in the center. Galectin-3 can be nuclear, cytoplasmic and is also secreted by cells. Secreted gal-3 can promote the migration of tumor cells and suppress the function of immune cells. As gal-3 was increased in the margin, we investigated the effect of galectin-3 secreted by macrophages on the migration of tumor cells using a transwell system. Our data suggests that recombinant gal-3 can promote CTCL cell migration. However, macrophage-conditioned medium decreased migration of tumor cells, while the inhibition of gal-3 further reduced migration of CTCL cells. Together, this data hints at a complex role of macrophages in the migration of tumor cells. Additionally, macrophages in tumor rich areas express more of glut1, a glucose transporter, suggesting that they underwent metabolic alterations, enabling them to infiltrate high density tumor areas. We will test the effect of glut1 expression by macrophages on phenotype, through inhibition of glut1. Further, we will also test the role of glut1 in the ability of macrophages to infiltrate CTCL tumors, using a tumor spheroid model established by our group. Overall, our data underscores the effect of spatial localization on macrophage phenotypes and potential functional differences.

Hala Habash

PhD Student

Department of Women's and Children's Health, Karolinska Institutet

Time: Tuesday 23, 11:10

Drugging the undruggable target: Gemcitabine and cytarabine kill Ewing sarcoma cells through inhibition of SAMHD1 and degradation of the Ewing sarcoma fusion protein

Ewing sarcoma (ES) is the second most-frequent bone tumour in childhood and adolescence with a peak incidence rate in the second decade of life. Localised ES has a five-year relapse-free survival rate of only around 55% which drops to 21% for metastatic ES. Survival has largely stagnated for the last decades despite several efforts of treatment intensification.

Resulting from a chromosomal translocation, ES is driven by a fusion protein (most frequently EWS-Fli1 or EWS-ERG) with aberrant transcription factor activity that reprogrammes the cellular transcriptome. Cytarabine, widely used for treatment of haematological malignancies, was identified as a drug that can induce degradation of the fusion protein and thereby reverse its transcriptomic effects, and its anti-tumour efficacy was confirmed in animal experiments. However, a phase-II trial with relapsed and refractory ES patients failed to demonstrate meaningful clinical efficacy of cytarabine. We hypothesize that the cytarabine resistance factor SAMHD1 may explain this discrepancy.

Here, we demonstrated differential SAMHD1 expression in a panel of ES cell lines ranging from absent to high, and SAMHD1 levels correlated with sensitivity to cytarabine. In addition, we used immunoblotting to demonstrate the dose-dependent ability of cytarabine to deplete the ES fusion protein. More important, gemcitabine, a drug used for treatment of relapsed bone sarcomas and a substance that we have previously described as a SAMHD1 inhibitor sensitized ES cells to cytarabine in a SAMHD1-dependent manner and dramatically increased cytarabine-induced ES fusion protein depletion. We also suggest causal relationship between SAMHD1 and cytarabine/gemcitabine synergy through the use of SAMHD1-kocked out cell lines. In a next step, we seek to validate these findings in mouse models of ES. Giving the longstanding use of cytarabine and gemcitabine in paediatric oncology, this research promises to lay the ground for a novel treatment strategy of ES that targets its hitherto undruggable cancer-driving fusion protein which could quickly be translated into a clinical trial.

Damien Kaukonen

Postdoctoral Researcher

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

Time: Tuesday 23, 10:55

The Risk of HER2+ Breast Cancer; Before and After Diagnosis

The Human Epidermal growth factor Receptor 2 (HER2) is elevated in 15–20% of breast cancers, serving as a prognostic indicator. The risk factors influencing HER2 status, and the interaction between HER2 status and other prognostic factors, such as Estrogen Receptor (ER) status, require further elucidation. This case-only study investigated the association between established breast cancer risk factors and HER2 status at diagnosis, and the impact of combined HER2 and ER status on patient survival. Odds ratios were computed for known breast cancer risk factors (including family history, parity, and education) in a cohort of 10,905 breast cancer patients from Stockholm to evaluate the risk of HER2 positive (HER2+) disease. Utilizing data from a 2041-woman cohort with available mammographic information, we employed Generalized Estimating Equations to analyse longitudinal changes in breast density, microcalcifications, and masses preceding diagnosis. The prognostic implications of HER2 and ER status were assessed using a cohort of 14,602 breast cancer patients diagnosed in Stockholm. This analysis characterized the combined influence of HER2 and ER status on distant recurrence-free survival (RFS). The association between HER2+ status and family cancer history was less pronounced than HER2-, with odds ratios of 0.82 (95% CI 0.71–0.95) for breast cancer and 0.89 (95% CI 0.79–0.99) for any other cancer. Higher education and delayed age at first childbirth emerged as notable breast cancer risk factors associated with HER2 status, displaying an increased risk for HER2+ (OR 1.38, CI 1.12-1.72 and OR 1.13, CI 0.99-1.28). We observed a significant association between HER2+ and a higher number of microcalcifications ($p=0.003$), which was time-dependent ($p=0.035$), and a reduction in the number of masses ($p=0.049$). A stronger association between higher number of microcalcifications and HER2+ emerged when comparing affected and unaffected breasts within the woman ($p<0.001$). Our analysis of prognosis indicated a time-varying combined effect of HER2 and ER status on RFS ($p=0.037$ for overall effect, $p=0.017$ for the time interaction). Among ER+ patients, the 2.5-year adjusted short-term survival was similar for HER2+ and HER2- patients (HR 1.02, CI 0.76–1.39). In contrast, among ER- patients, HER2+ patients experienced constant risk compared to HER2- from diagnosis until the end of study (HR ~0.50). Finally, we observed that HER2+ patients have a higher rate of first metastasis to the brain compared to HER2- patients ($p< 0.001$). Our analysis reveals a reduced association between HER2+ and inherited breast cancer risk factors, in contrast to a more pronounced association with physiological factors such as microcalcifications. Furthermore, our findings demonstrate a time-dependent effect of HER2 and ER status on RFS. Advanced models integrating ER and HER2 status provide improved prediction of RFS and the risk of site-specific metastasis.

Cheng-De Liu

PhD Student

Department of Oncology-Pathology, Karolinska Institutet

Time: Tuesday 23, 10:20

Bridging the Heterogeneity Gap: Single-Cell Transcriptomic Heterogeneity Measurement as a Guide to Enhance Neuroblastoma Organoid Diversity

Intratumoral heterogeneity in neuroblastoma is a key driver of disease progression, metastasis, and drug resistance. Despite its critical role, heterogeneity is often overlooked in the development of new drug combinations for treating malignancies. This oversight may stem from two major challenges: the inherently low heterogeneity of cell lines compared to patient tumors, and the lack of effective tools to quantify heterogeneity effectively. Conventional measures of heterogeneity typically focus on tumor subclones defined by mutational status. However, drug resistance is frequently driven by epigenetic and transcriptional changes that are not captured by these approaches.

Recent advances in cell barcoding enable high-resolution tracking of millions of tumor subclones within a single experiment. This technique provides a powerful means to trace heterogeneous subclones and identify drugs that selectively target distinct populations. However, for such experiments to yield meaningful results, the starting cell populations must exhibit a level of heterogeneity comparable to that of in vivo tumors. Without sufficient diversity, stochastic events can obscure the true selection of resistant clones during drug treatment, ultimately limiting the translational relevance of the findings.

In this study, we first developed a composite metric to quantify transcriptomic heterogeneity at the single-cell level across diverse sample types. Our analysis revealed that neuroblastoma patient samples display markedly higher transcriptional heterogeneity than in vitro tumoroids and cell lines. To address this discrepancy, we used N-ethyl-N-nitrosourea (ENU) or Cisplatin as mutagenic agents to enhance the transcriptomic diversity of in vitro models.Using cell barcoding, we evaluated whether the heterogeneity enhancement would result in the selection of distinct resistant subclones under treatment with Etoposide and Alisertib.

Our results offer a quantitative assessment of the heterogeneity gap between patient tumors and experimental models, and demonstrate a strategy to bridge this gap—thereby improving the clinical relevance of preclinical studies.

Mingzhi Liu

PhD Student

Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet

Time: Tuesday 23, 12:50

Germline ALK-R1275Q Mutation Drives a Proliferative, Undifferentiated State and Accelerate Neuroblastoma Initiation

Background:

Anaplastic Lymphoma Kinase (ALK) alterations—including amplification or activating mutations—are frequent somatic events in neuroblastoma (NB) and correlate with poor prognosis. Rare familial NB cases harbor germline ALK mutations, such as ALK-R1275Q, which phenocopy recurrent somatic variants. While ALK's oncogenic potential is established, its role in NB initiation remains unclear.

Method:

We generated induced pluripotent stem cells (iPSCs) from fibroblasts of NB patients with a germline ALK-R1275Q mutation and from healthy controls. These were differentiated into trunk neural crest cells (NCCs) and sympathoadrenal (SA) lineage cells using a standardized protocol. Bulk and single-cell transcriptomics were performed at multiple stages. To assess tumorigenic potential, MYCN was overexpressed in both control and patient-derived lines, followed by orthotopic adrenal gland injection in mice.

Results and Conclusion:

The ALK-R1275Q mutation did not affect iPSC reprogramming efficiency, pluripotency marker expression, or differentiation into trunk neural crest cells (NCCs). Divergence became evident at the sympathoadrenal (SA) stage: in contrast to control cells, which downregulated ALK expression upon SA commitment, patient-derived cells maintained abnormally high ALK expression. Single-cell RNA sequencing identified a distinct cluster within the SAP (sympathoadrenal progenitor) stage that was predominantly composed of ALK-mutant cells. These cells retained progenitor-like transcriptional features and exhibited elevated proliferative activity.

Trajectory and pseudotime analyses demonstrated a delay in differentiation progression in patient cells. Gene set enrichment analysis revealed suppression of p53 signaling and neurogenic differentiation pathways, alongside enrichment of DNA replication, protein synthesis, and Fanconi anemia pathways—indicative of a proliferative, undifferentiated state. Pharmacological inhibition of ALK reduced proliferation and partially restored differentiation-associated gene expression at the SAP stage.

In orthotopic xenograft models, ALK-R1275Q alone did not induce tumor formation. However, co-expression of MYCN significantly enhanced tumor initiation and reduced latency compared to MYCN alone. These results indicate that germline ALK activation sustains a progenitor-like population within the SA lineage, creating a transcriptional and proliferative environment permissive to MYCN-driven transformation.

Ahmed Osman

Assistant Professor

Department of Women's and Children's Health, Karolinska Institutet

Time: Monday 22, 11:50

Harnessing liquid biopsies for defining the mechanisms of the nervous system cancer progression and resistance to therapies

We perform temporal proteomic screens on cerebrospinal fluids obtained from our preclinical mouse models for central nervous system (CNS) metastases to identify molecules associated with the growth of metastatic cancer cells and validate these molecules in patient samples. We exploit the identified molecule(s) beyond being a biomarker discovery and uncover their role in metastatic cancer progression and resistance to current standard-of-care therapies. We achieve this by determining the source(s) of the identified molecules and their responder cells to exploit their signaling axes as target therapies to suppress the disease progression and sensitize cancer cells to respond to current therapies. Using this approach, we have recently demonstrated a mechanism by which patients develop resistance to radiation therapy in the setting of leptomeningeal metastasis.

Leptomeningeal metastasis (LM) is a fatal neurological complication of cancer. Proton craniospinal irradiation (pCSI) has emerged as a promising life-prolonging intervention for LM patients, but the response to this treatment varies. We aimed to characterize the molecular basis of pCSI resistance and response. Proteomic analysis of CSF collected from LM patients at baseline (before pCSI), and at multiple time points post-treatment, identified the CXC-motif chemokine, CXCL1, as associated with LM growth. Higher CXCL1 levels in the CSF prior to pCSI correlated with worse response to this treatment. To define the role of CXCL1 in LM, we established syngeneic mouse models of LM-CSI. We found that both metastatic cancer and host cells generate CXCL1. Genetic interruption of Cxcl1 expression in metastatic cancer, but not host cells, impaired cancer cell growth within the leptomeninges. Moreover, a subset of LM cancer cells expressed Cxcr2, the primary receptor for Cxcl1, and this population was enriched over time in the leptomeninges. Transcriptomic profiling of this rare population revealed an enrichment in pathways implicated in cell cycle progression. Finally, interruption of Cxcl1-Cxcr2 signaling with intrathecally-delivered Cxcr2 antagonist hampered LM growth and sensitized the cells to CSI. Our results demonstrate that the Cxcl1-Cxcr2 signaling axis mediates LM growth, and identifies a potential actionable intervention to improve response to pCSI and halt LM progression.

Glancis Luzeena Raja

Postdoctoral Researcher

Department of Medical Biochemistry and Biophysics, Karolinska Institutet

Time: Tuesday 23, 10:05

Uncovering novel microproteins driving chemoresistance in pancreatic ductal adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease projected to increase mortality by 25.7% across the EU by 2040. Most systemic and targeted therapies developed for PDAC are aimed at known genetic and epigenetic drivers, but they largely fail to control disease progression, due to inherent or acquired chemoresistance. It is therefore critical to identify novel drivers of chemoresistance that may be exploited as drug response predictors or chemoresistance biomarkers in PDAC. Microproteins (MPs), small proteins of <100 codons, have been shown to mediate metastatic phenotypes like cell proliferation, metabolism, and oncoprotein synthesis. Despite growing evidence of their significance in regulating oncogenic mechanisms, their role in PDAC is largely unknown. At the Elsässer lab, we aim to systematically identify and characterize MPs underlying PDAC chemoresistance. We are currently curating a high confidence sORF database, complete with genomic mapping and annotation, subcellular localization and functional predictions, which will serve as a repository for further experiments. We are also performing comparative label-free quantitative proteomics and Ribo-Seq in PDAC resistance models to detect MPs differentially enriched in drug resistant versus sensitive cell populations. Initially, we performed a pilot chemoresistance screen and comparative mass spectrometry analysis in a panel of human drug sensitive/resistant PDAC cell lines with a wide range of chemotherapeutic agents in clinical use. Our results highlight significant enrichment and abundance of MPs differentially enriched in both drug resistant as well as sensitive populations. The abundance of detected MPs in this screen falls within the range of the ‘regular’ proteome, demonstrating that MPs could participate in resistance mechanisms much like ‘regular’ proteins. In addition, we see co-enrichment of ´regular´ proteins canonically associated with drug resistance, which suggests a potential co-regulatory function of these MPs in chemoresistant phenotypes, in conjunction with larger proteins. Further, the MPs identified in this screen have not yet been described as chemoresistance regulators, or characterized in detail, making these novel targets to elucidate, particularly in the context of PDAC. This pilot screen not only proves the feasibility of our comparative MS strategy but also gives us a pool of MP candidates associated with a clear oncogenic phenotype that we can probe in further mechanistic studies. Our future studies include a high-throughput pipeline using PDAC tumour spheroids, and multi-omic strategies/tools developed by the Elsässer lab and collaborators, to identify and elucidate the genetic/proteomic interactome of chemoresistance microproteins. This approach will robustly validate microprotein function and genotype-phenotype relationship, in addition to providing leads for biomarker development and personalized PDAC therapy.

Mohammed Fatih Rasul

PhD Student

Department of Women's and Children's Health, Karolinska Institutet

Time: Monday 22, 12:05

Progesterone Receptor Modulator: Novel Avenues in Breast Cancer Prevention

Women with BRCA1 or BRCA2 gene mutation have an increased risk of developing breast and ovarian cancers. Apart from the direct effect on DNA repair mechanisms, BRCA mutations via non-cell autonomous factors, including progesterone, drive cancer initiation. Our multidisciplinary combined clinical and basic research project aims at developing cancer-preventative strategies via evaluating the potential of using progesterone receptor modulators (PRM) like mifepristone. Two groups of premenopausal women are recruited for this study; The first comprises women undergoing surgery for benign breast reduction mammoplasty. The second consists of women carrying BRCA1 or BRCA2 mutations who are undergoing risk-reducing mastectomy. To investigate and validate our hypothesis, we've developed an advanced high-throughput 3D-organoid culture model using freshly isolated breast tissues. Our findings reveal that PRM effectively reduces the proliferation and growth of cancer precursor cells, encompassing luminal progenitor and basal cells, among both individuals with BRCA mutations and those without. Concurrently, it encourages the differentiation and enrichment of mature luminal cells. Intriguingly, the impact of PRM diminishes as breast cells replicate and age over time. Moreover, we've observed that PRM induces apoptosis in breast cells in a dose-dependent manner. These insights underscore the substantial role of PRM in mitigating the risk of cancer initiation and progression, demonstrating its significance for both normal and BRCA mutation carrier women.

The Cancer Research KI Retreat

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About Cancer Research KI

Our Mission:

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

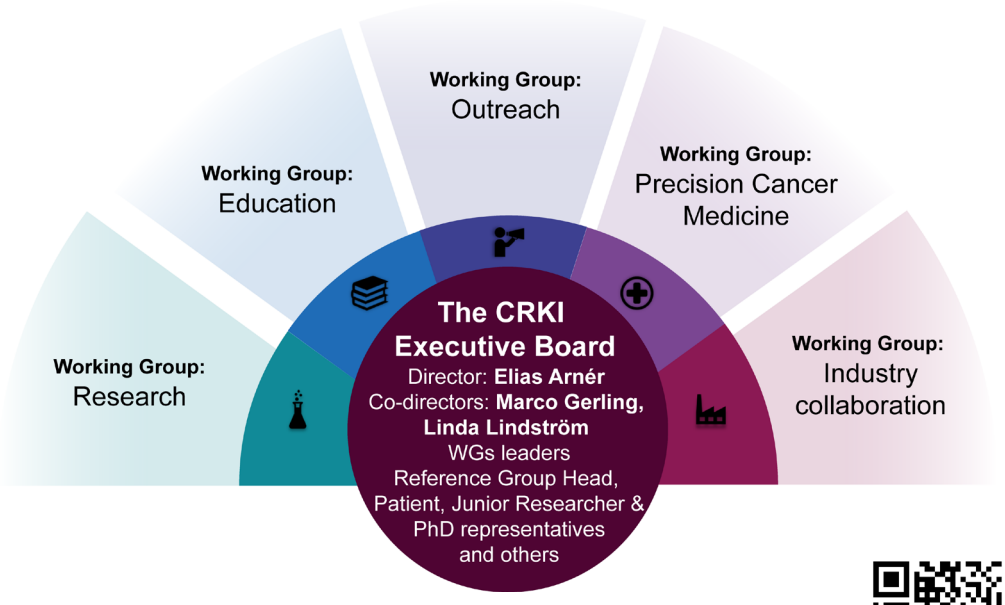
An umbrella organization for cancer research at Karolinska Institutet

A Strategic Research Program in Cancer since 2009 (formerly StratCan)

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

A hub for communicating cancer research at KI to the general public

Over 400 PIs in cancer research representing 21 departments



More information about the Executive Board is available online
Please scan the QR code to access the website

For more information about our activities and how we can support you, please visit our website!

Our website is regularly updated with the latest news and events from Cancer Research KI

And do not forget to subscribe to our newsletter and mailing list to stay informed about upcoming events, seminars, conferences, workshops, and funding opportunities!

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Notes:

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