BREAKOUT SESSIONS

XXII Cancer Research KI Retreat

22-23 September, 2025

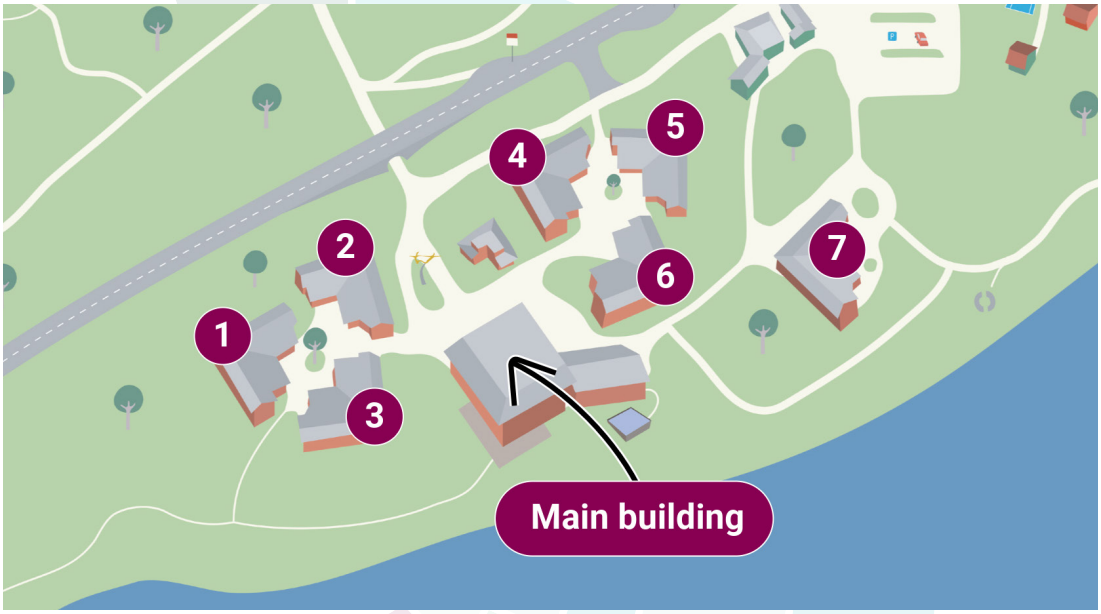
Djurönäset

BREAKOUT SESSIONS

Monday 22, 16:00 - 17:30

The sessions will take place simultaneously in various smaller rooms throughout the Djurönäset complex. Please **refer to the map below to find your way to the correct session**.

Keep in mind that **session capacity is limited**, and **you must attend the session you registered for**. If you have not registered for a session or experience any difficulty finding your room, please approach a member of the Cancer Research KI staff for assistance.



Breakout session 1: Patient Perspectives

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

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

Melanoma
Hildur Helgadottir, House 3 (Room 3A)

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

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

Breakout session 2: Scientific Presentations

Chairs: Dimitris Kanellis and Conny Tümmler

House 7 (Conference Room 7A)

Breakout session 3: Meet the Scientist

Prof. Michelle Monje, House 1 (Coffee Lounge)

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

MEET THE SCIENTIST

Michelle Monje

Professor of Neurology

Howard Hughes Medical Institute, Stanford University

Location: House 1, Coffee Lounge

About Prof. Michele 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

Location: House 2, Coffee Lounge

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.

PATIENT PERSPECTIVE

Pancreatic Cancer

Chair: **Matthias Löhr**

Location: House 1 (Room 1A)

About Matthias Löhr

Matthias Löhr was appointed Professor of Gastroenterology & Hepatology at Karolinska Institutet in 2007, following his tenure at the University of Heidelberg and DKFZ. From his MD thesis through his PhD and beyond, his work has focused on various aspects of the pancreas, spanning clinical medicine, translational research, and basic science.

He leads the Pancreas Research Team at Gastrocentrum and coordinates the KICancer Diagnose-Related Network for HPB tumors. At the European level, he has served on several committees within the United European Gastroenterology (UEG) and currently holds the position of President of UEG.

Research

Matthias Löhr's research centers on the pancreas, covering:

- Clinical pancreatology: hereditary and autoimmune pancreatitis, biomarkers, endoscopic therapy (ERCP), function tests.
- Pancreatic cancer: early clinical studies exploring novel therapeutic concepts.

Translational and basic research is conducted in the PaCaRes lab, led by Rainer Heuchel. The lab focuses on the connective tissue reaction in pancreatic cancer and its role in chemoresistance, including the development of a novel 3D model combining pancreatic cancer cells and stromal cells.

Funding sources include VR, CF, RaHFo, Wallenius Stiftelsen, among others. Current projects include:

- PRECODE (MSC program)
- PANCAIM, PANCAID, and GUIDE.MRD (EU-funded projects)

Teaching

Matthias Löhr lectures at pregraduate, graduate, and postgraduate levels on all aspects of the pancreas. He also leads Pancreas 2000, an educational initiative for future pancreatologists in Europe, now integrated into the European Pancreatic Club (EPC).

Hereditary Cancer

Chair: **Svetlana Bajalica Lagercrantz**

Location: House 2 (Room 2A)

About Svetlana Bajalica Lagercrantz

Svetlana Bajalica Lagercrantz is an Adjunct Professor of Cancer Genetics, specializing in hereditary cancers. Her research aims to improve patient management in clinical oncology, with a particular focus on lymphoma and breast cancer.

Her team's projects explore the use of circulating tumor DNA (ctDNA) as a biomarker for prediction and treatment in breast cancer, as well as the characterization of mutations in the Swedish germ-line TP53 cohort.

Circulating Tumor DNA as a Biomarker for Breast Cancer

Emerging evidence suggests that future screening tests will rely on molecular biomarkers found in bodily fluids. Tumors release circulating tumor DNA (ctDNA) into the bloodstream through necrosis and apoptosis. This ctDNA carries the same genetic alterations as the tumor tissue, allowing for accurate genotyping via a simple blood test.

This minimally invasive method enables repeated sampling to monitor tumor progression in breast cancer patients and can also be used to track tumor development in healthy high-risk mutation carriers.

The Swedish Constitutional TP53 Cohort

Li-Fraumeni Syndrome (LFS) is linked to constitutional TP53 mutations, a rare condition associated with a high risk of cancers such as osteosarcoma, soft tissue sarcomas, breast, brain, and adrenocortical tumors, especially in children and young adults. TP53 mutations are also implicated in hereditary breast cancer.

To better understand and manage these risks, a national clinical TP53 study group was established in Sweden in 2013. The group aims to:

- Create a nationwide registry for families with TP53 mutations.
- Develop and implement a clinical surveillance program for molecularly defined LFS families.

The project's goals are to:

- Characterize the mutation spectrum in families with LFS or LFS-like histories compared to those with hereditary breast cancer.
- Increase knowledge of the disease panorama in TP53 mutation carriers.
- Evaluate and refine a surveillance program to improve survival outcomes for affected families in Sweden.

Melanoma

Chair: **Hildur Helgadottir**

Location: House 3 (Room 3A)

About Hildur Helgadottir

Hildur Helgadottir is a specialist oncologist and researcher, serving as the Chair of the Swedish Melanoma Study Group (SMSG). Her research is dedicated to malignant melanoma, with a focus on understanding its incidence, biology, genetics, and strategies for prevention and treatment.

Research Focus

Epidemiological Studies

Using health and population registers, the team maps factors linked to melanoma, contributing to a deeper understanding of disease patterns and risk factors.

Preventive Studies

Efforts are made to:

- Identify high-risk individuals, including those with genetic predispositions.
- Discover novel genetic factors associated with melanoma.

Melanoma in Young Individuals (MELCAYA Project)

This project investigates early-onset melanoma, aiming to uncover factors related to its development and treatment in young patients.

Immunotherapy and Precision Radiation (PROMMEL Study)

A Phase II clinical study exploring whether precision radiation to metastases can enhance the effectiveness of immunotherapy in melanoma patients.

Biomarkers for Treatment Prediction (BioMelanoma)

Research focuses on identifying molecular markers that can predict treatment response in patients with metastatic melanoma.

Tumor Models and Mechanisms of Resistance

Clinically relevant questions, such as genetic predisposition, treatment prediction, and the emergence of resistance, are addressed through in vitro and in vivo studies using tumor models.

Lung Cancer

Chair: **Simon Ekman**

Location: House 4 (Room 4A)

About Simon Ekman

Simon Ekman, born in Umeå in 1971, earned his medical degree and defended his doctoral thesis at Uppsala University in 2000. He completed his postdoctoral fellowship at the Rudbeck Laboratory (Uppsala University) between 2002-2005, and was a visiting research fellow at the University of Colorado, Denver in 2011-2012. He was appointed docent in 2015.

Since 2004, Simon Ekman has specialized in oncology. He worked at Uppsala University Hospital until 2015, after which he became Chief Physician at Karolinska University Hospital. On January 1, 2023, he was appointed Professor of Oncology at Karolinska Institutet.

Research Focus

Simon Ekman's research centers on thoracic oncology, with a primary focus on lung cancer. His work spans clinical, translational, and preclinical studies, aiming to:

- Identify new treatment targets and biomarkers for prognosis and treatment response.
- Understand and overcome resistance to therapy, particularly in relation to tyrosine kinase inhibitors (EGFR and ALK) and immunotherapy.
- Advance precision cancer medicine through improved diagnostics, imaging, treatment strategies, and cancer registry data.

To support these goals, his team has established patient cohorts with detailed clinical data and tumor material for molecular analysis. These include patients treated in routine clinical care at Karolinska University Hospital and participants in various clinical studies.

Another major research area is brain metastasis, a condition with poor prognosis in lung cancer patients. The team investigates:

- Molecular mechanisms driving brain metastasis.
- Development of novel therapeutics targeting brain metastases.
- Analysis of brain metastasis tissue and cerebrospinal fluid (CSF), focusing on targeted therapies.

A key method involves exosome analysis, as exosomes released from tumor cells carry DNA and RNA that reflect the molecular profile of the tumor.

In a related study, the team has used PET imaging with radiolabeled EGFR tyrosine kinase inhibitors to examine drug uptake in the brain, aiming to better understand treatment response and resistance in brain metastases.

Childhood Cancer

Chair: **Nikolas Herold**

Location: House 5 (Room 5A)

About Nikolas Herold

Nikolas Herold is a Paediatric Oncologist at Astrid Lindgren's Children's Hospital, Karolinska University Hospital, and an Associate Professor of Paediatrics. His clinical and research work is dedicated to improving outcomes for children with cancer, particularly through understanding and optimizing combination chemotherapy.

Historically, paediatric cancers were considered universally lethal, with treatment viewed as unethical experimentation. However, the introduction of chemotherapy in the late 1940s by Sidney Farber revolutionized the field. Today, 85% of childhood cancer cases are curable, yet 15% of patients still succumb to their disease despite intensive combination therapies. In adult cancers, such as acute myeloid leukaemia, the prognosis remains significantly worse.

Research Focus

Nikolas Herold's research seeks to uncover the cellular and molecular mechanisms behind the success or failure of combination chemotherapy. Despite its widespread use, the synergistic effects of drug combinations are still poorly understood.

The central hypothesis driving his research is that genetic factors influence the degree of cellular and clinical drug synergy in combination treatments. Understanding these factors could:

- Enable the development of predictive biomarkers for chemotherapy combinations.
- Guide the creation of new drugs that target cellular mechanisms blocking synergy.
- Inform alternative treatment schedules that bypass resistance mechanisms.

By identifying these genetic determinants, the research aims to personalize and improve combination chemotherapy strategies, ultimately enhancing survival and reducing toxicity for paediatric cancer patients.

SCIENTIFIC PRESENTATIONS

Scientific Presentations

Location: House 7 (Conference Room 7A)

Program

16:00 - 16:10 **Amos Tuval**
"Exploiting the correlation between p53 conformation and function for therapeutic targeting of p53-dysfunctional myeloid neoplasms"

16:15 - 16:25 **Silvia Angori**
"Exploring the effect of SAMHD1 on tumor suppression in cutaneous melanoma"

16:30 - 16:40 **Susanna Hellberg**
"Modeling the colon tumor microenvironment: A 3D silk-scaffold in vitro network to investigate the role of estrogen and hypoxia"

16:45 - 16:55 **Gurwinder Kaur**
"Retrospective Clinical Validation of AI-based Tumor Segmentation in Breast MRI"

17:00 - 17:10 **Ingrid Lilienthal**
"Addition of hydroxyurea enhances the efficacy of fludarabine/cytarabine-based salvage regimens against acute myeloid leukemia"

Silvia Angori

Postdoctoral Researcher

Department of Oncology-Pathology, Karolinska Institutet

Time and location: 16:15, House 7

Exploring the effect of SAMHD1 on tumor suppression in cutaneous melanoma

Cutaneous melanoma (CM) is one of the most aggressive of all skin cancers and has the highest mortality. Although treatments with immune checkpoint inhibitors (ICIs) have improved the survival rate of CM patients, approximately 50% of these patients still die from the disease. SAMHD1, a key regulator of innate immune responses and DNA damage repair, can act as a tumor suppressor in various malignancies. We hypothesize that SAMHD1 expression confers a survival advantage by enhancing the anti-tumor immune response in CM. We propose that the loss of SAMHD1 in CM promotes tumor progression through dual mechanisms: first, by dysregulating dNTP pools, leading to replication stress and cell cycle disruptions, and second, by hyperactivating the STING pathway, which enhances the expression of immune-suppressive molecules like PD-L1, thereby limiting immune cell infiltration and contributing to immune evasion. This project aims to investigate the impact of SAMHD1 in inhibiting the STING-TBK1 axis in CM, which may result in improved response to immunotherapy in melanoma.

Our data showed that higher SAMHD1 expression is significantly associated with better overall survival (458 CM patients, TCGA data) with a proportion of high-expressers as long-term survivors after adjustment for lymphocyte infiltration. This result supports the hypothesis that the expression of SAMHD1 has a positive effect on survival in CM. Next, we have corroborated the association between loss of SAMHD1 and STING pathway activation in SAMHD1-wt and -KO melanoma cell lines. Indeed, cells lacking SAMHD1 showed hyper-activation of the STING pathway by increased expression of downstream target genes such as ISG15, IFI16, and CXCL10. Moreover, we evaluated if the presence of SAMHD1 can influence the immune response by co-cultures of NK cells from healthy donors and SAMHD1-wt and -KO melanoma cells alone or after treatment with STING inhibitors (STINGi). Our results showed that IFNγ secretion is higher when co-culturing NK cells with SAMHD1-wt cells than SAMHD1-KO cells, and it increases upon treatment with STINGi. Furthermore, SAMHD1-KO cells were more resistant to NK killing compared to SAMHD1-wt cells. Finally, we observed that loss of SAMHD1 can hamper DNA damage response in SAMHD1-KO cells by treatment with a double strand breaks (DSB)- inducing agents. Overall, by exploring the role of SAMHD1 in CM and examining its modulation of the immune landscape and genome instability, we aim to lay the groundwork for novel therapeutic strategies that could improve outcomes for CM patients.

Susanna Hellberg

PhD Student

Department of Medicine, Huddinge, Karolinska Institutet

Time and location: 16:30, House 7

Modeling the colon tumor microenvironment: A 3D silk-scaffold in vitro network to investigate the role of estrogen and hypoxia

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death. Men have a higher incidence of CRC than age-matched pre-menopausal women. Notably, estrogen has been shown to have a protective effect against CRC. Estrogen acts via two nuclear receptors, estrogen receptor (ER) alpha and beta, and the transmembrane receptor G-protein coupled receptor (GPER1). It is demonstrated that intestinal-specific ERβ knock-out (ERβKOvil) in the colitis-induced colon tumor mouse model (AOM/DSS) leads to increased tumor numbers in males and increased tumor size in females. ERβ has a protective role against colon tumor development in mice of both sexes, trough both anti-inflammatory and anti-tumorigenic activities. Cell lines are commonly used to model cancer in vitro and to allow mechanistic studies. However, their 2D culture often fails to recapitulate the in vivo tumor and lacks the complexity of the tumor microenvironment (TME), limiting the correlation between in vitro and in vivo data. For this reason, complex 3D culture models have been suggested as a bridge to better mimic the complexity of the in vivo TME by offering improved oxygen- and nutrient gradients, extracellular matrix (ECM) composition, and cell-cell interactions. Among 3D models, recombinant spider silk functionalized with the ECM protein fibronectin (FN-silk) provides a scaffold that facilitates cell growth while upholding cell characteristics.

In this study, we set up a 3D FN-silk-scaffold-based cell culture model for CRC cells and investigated the impact of estrogen signaling and hypoxia on CRC cells. Colon cancer cells lines expressing ERβ or mock were cultured in either FN-silk scaffold or traditional 2D system under different oxygen level conditions. The models were compared, and the impact on key cellular processes such as proliferation and apoptosis was evaluated using immunostainings and gene expression analysis. This work aims to provide insights into the molecular mechanism of action of the estrogen signaling in a more physiologically relevant cell model. Moving forward, the aim is to add complexity to the 3D-model and build up a TME-like model to investigate whether and how estrogen signaling in colonic cells impacts the recruitment and interaction of immune cells such as macrophages and NK-cells.

Gurwinder Kaur

PhD Student

Department of Oncology-Pathology, Karolinska Institutet

Time and location: 16:45, House 7

Retrospective Clinical Validation of AI-based Tumor Segmentation in Breast MRI

Purpose: AI has the potential to support radiologists by improving consistency, reducing workload, and enabling scalable access to automated expert-level interpretation for breast magnetic resonance imaging (MRI) exams. This study evaluates the performance of an AI-based segmentation model for breast cancer dileantion by analyzing localization concordance with expert radiologist annotations, and tumor size error compared to actual tumor size in the surgical specimen.

Methods and Materials: We collected all breast MRI exams performed for women diagnosed with breast cancer from 2008 to 2021 at Karolinska University Hospital in Stockholm, using 1.5T and 3.0T scanners (GE, Philips, Siemens). Two expert radiologists annotated tumors, breast volume, nipple, and lymph nodes on Maximum Intensity Projection of Dynamic Contrast-Enhanced MRI. One radiologist served as the reference standard for model development, while the other—the annotator—was used for this performance evaluation. A patient-level split was used for training, validation and testing. We trained the state-of-the-art nnU-Net on 800 exams. We report results on the held-out test set, using Dice Similarity Coefficient (DSC), 95th percentile Hausdorff Distance (HD95), and tumor size error relative to post-surgical pathology reports.

Results: From the held-out test set of 74 breast MRI exams from 72 patients with biopsy-confirmed cancer, 6 studies with a DSC of zero were excluded, leaving 68 exams. For tumor size estimation, 9 additional studies were excluded due to missing radiology and pathology reports, leaving 59 exams. Our trained model achieved a mean DSC of 0.76 and HD95 of 14.95 mm— for mass lesions: DSC 0.79, HD95 17.6 mm and for non-mass lesions: DSC 0.74, HD95 11.5 mm.

Comparing three image interpreters: (i) our AI model, (ii) the original radiology report, (iii) and the study annotator: the Spearman's correlation coefficient with pathology-reported tumor size was 0.83 (95% CI: 0.65–1.00), 0.63 (95% CI: 0.34–0.92), and 0.53 (95% CI: 0.17–0.89); the median tumor size error was 20.1%, 17.2%, and 20.3%; overestimation by more than 5 mm occurred in 21, 21, and 23 cases; and underestimation by more than 5 mm was observed in 3, 2, and 3 cases, respectively.

Conclusion: We demonstrated the AI model achieving performance in both tumor size estimation and localization comparable to clinical experts with high consistency across mass and non-mass lesion types, exhibiting notably lower variability for non-mass lesions.

Clinical Relevance/Application: This study highlights the potential of AI-based segmentation to support radiologists by providing consistent and accurate tumor size estimates in breast MRI, reducing uncertainty in treatment planning. This might be especially valuable in settings where there is a deficit in expert breast MRI radiologists.

Ingrid Lilienthal

Postdoctoral Researcher

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

Time and location: 17:00, House 7

Addition of hydroxyurea enhances the efficacy of fludarabine/cytarabine-based salvage regimens against acute myeloid leukemia

Despite intensive treatment, patients with relapsed or refractory acute myeloid leukemia (AML) have a dismal prognosis and only one-third of adults and children with relapsed/refractory disease will become long-term survivors. This indicates a need for therapy improvement, particularly to overcome drug resistance. A cornerstone therapy for relapsed/refractory AML is a combination of fludarabine (F-ara-A) and cytarabine (ara-C), so-called FLA. FLA is based on data showing an increase in ara-C active metabolites when F-ara-A is given before ara-C. FLA is often enhanced with idarubicin and/or venetoclax to further boost response. As the enzyme SAMHD1 mediates resistance to both ara-C and F-ara-A, we investigated whether SAMHD1 inhibition via hydroxyurea (HU) could improve FLA efficacy.

Using cell proliferation inhibition assays, we found that HU sensitized AML cell lines to F-ara-A and FLA in a SAMHD1-dependent manner. These findings were confirmed in primary pediatric and adult AML samples. Patients expressing high levels of SAMHD1 were most susceptible to increased FLA efficacy with HU. Using HPLC-MS/MS we found reduced levels of active metabolites of ara-C (ara-CTP) and F-ara-A (F-ara-ATP) in the FLA combination compared with single treatments. Addition of HU to FLA, however, significantly increased levels of ara-CTP and F-ara-ATP in cell lines and patient samples. Moreover, FLA-HU significantly increased exposure to these active metabolites over time. Neither addition of idarubicin or venetoclax, nor the timing of the HU addition, altered the efficacy of the FLA-HU combination. In an immunocompetent mouse model of AML, we found that FLA-HU significantly increased survival and did not introduce additional cytotoxicity when compared to FLA alone. Furthermore, leukemic SAMHD1 protein expression negatively correlated with overall survival in a cohort of FLA-treated refractory AML patients.

Our findings suggest that addition of HU, a cheap and globally used drug, improves the efficacy of FLA-based regimens and warrant clinical trials to test the safety and efficacy of this combination in patients. To this end, we are currently preparing a clinical trial protocol called FLAsH-IV for adults with relapsed/refractory AML, with the hope that this combination will offer these patients a better chance at survival.

Amos Tuval

Postdoctoral Researcher

Department of Oncology-Pathology, Karolinska Institutet

Time and location: 16:00, House 7

Exploiting the correlation between p53 conformation and function for therapeutic targeting of p53-dysfunctional myeloid neoplasms

Most patients with TP53-mutated myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) have a median survival of less than one year and their malignant clones are characterized by genomic alterations that affect both TP53 alleles (bi-allelic). TP53 encodes the p53 transcription factor whose activity is tightly correlated with its conformation that enables proper binding to DNA. A majority of TP53 mutations are missense and affect p53's DNA-binding domain. p53 mutants can be divided to "structural variants" that have a misfolded conformation and "DNA-contact variants" that maintain wild-type conformation. However, p53 can become dysfunctional even in the absence of mutations: 5% of MDS patients with wild-type TP53 have dysfunctional p53 and similar survival rates as patients with bi-allelic TP53 genomic alterations. This dysfunction can be explained in part by misfolding of wild type p53 and acquisition of a mutant-like conformation (so called "Pseudo-Mutant p53", PMp53). In pre-leukemic hematopoietic stem and progenitor cells, the dynamic equilibrium between properly folded and misfolded p53 is shifted toward PMp53 (Tuval et al. Haematologica 107:2548-61, 2022). To explore the correlation between p53 conformation and function at single cell resolution, we developed a single-cell methodology for concomitant whole-transcriptome and p53 conformation analyses. We used p53 conformation-specific monoclonal antibodies that were custom-conjugated to oligonucleotides and optimized an intra-nuclear staining protocol to make it compatible with single-cell proteo-transcriptomic technology (AbSeq, BD Biosciences). To identify altered molecular pathways in cells with PMp53 we applied this protocol in a seemingly homogenous TP53-wild type AML cell line population. We found that 33% of the cells harbor misfolded p53 and show downregulation of molecular pathways that involve p53, thus demonstrating a remarkable and unexpected heterogeneity in p53 folding and function. Our further studies of the molecular basis for this heterogeneity may identify targetable cancer-cell vulnerabilities. Moreover, we shall use our single-cell proteo-transcriptomic technology to explore mechanisms of synergistic cell death induced by the p53- and redox-targeting compound APR-246 and selected other compounds using a panel of isogenic AML cells that express structural (unfolded) and DNA-contact (largely folded) TP53 variants. The identification of therapeutic vulnerabilities in cancer cells with PMp53 and the extent and role of p53-refolding in synergistic cell death should facilitate the design effective tailored treatments for individual patients with myeloid neoplasms that have p53 dysfunction.

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.

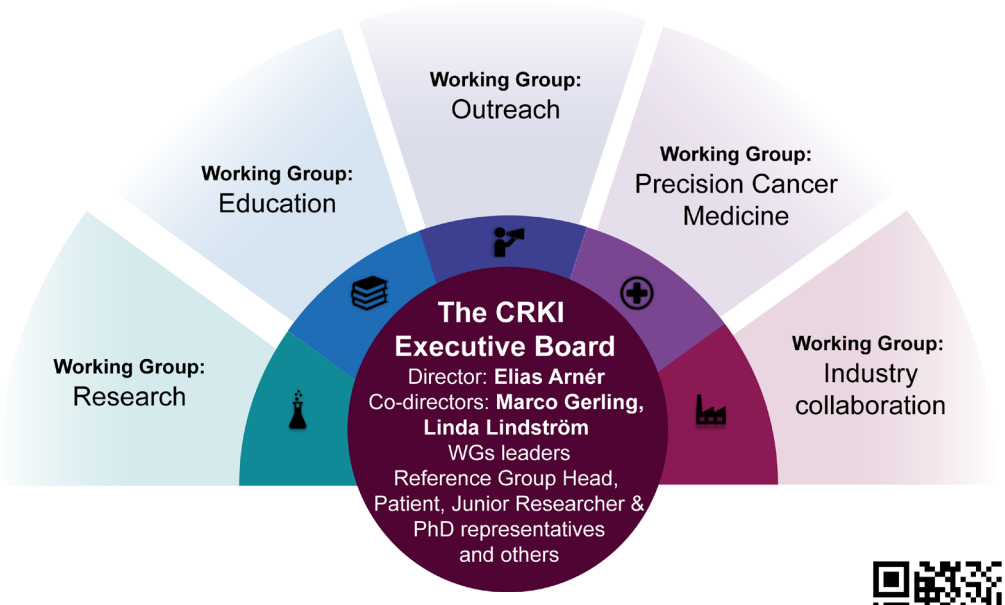
An umbrella organization for cancer research at Karolinska Institutet

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



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