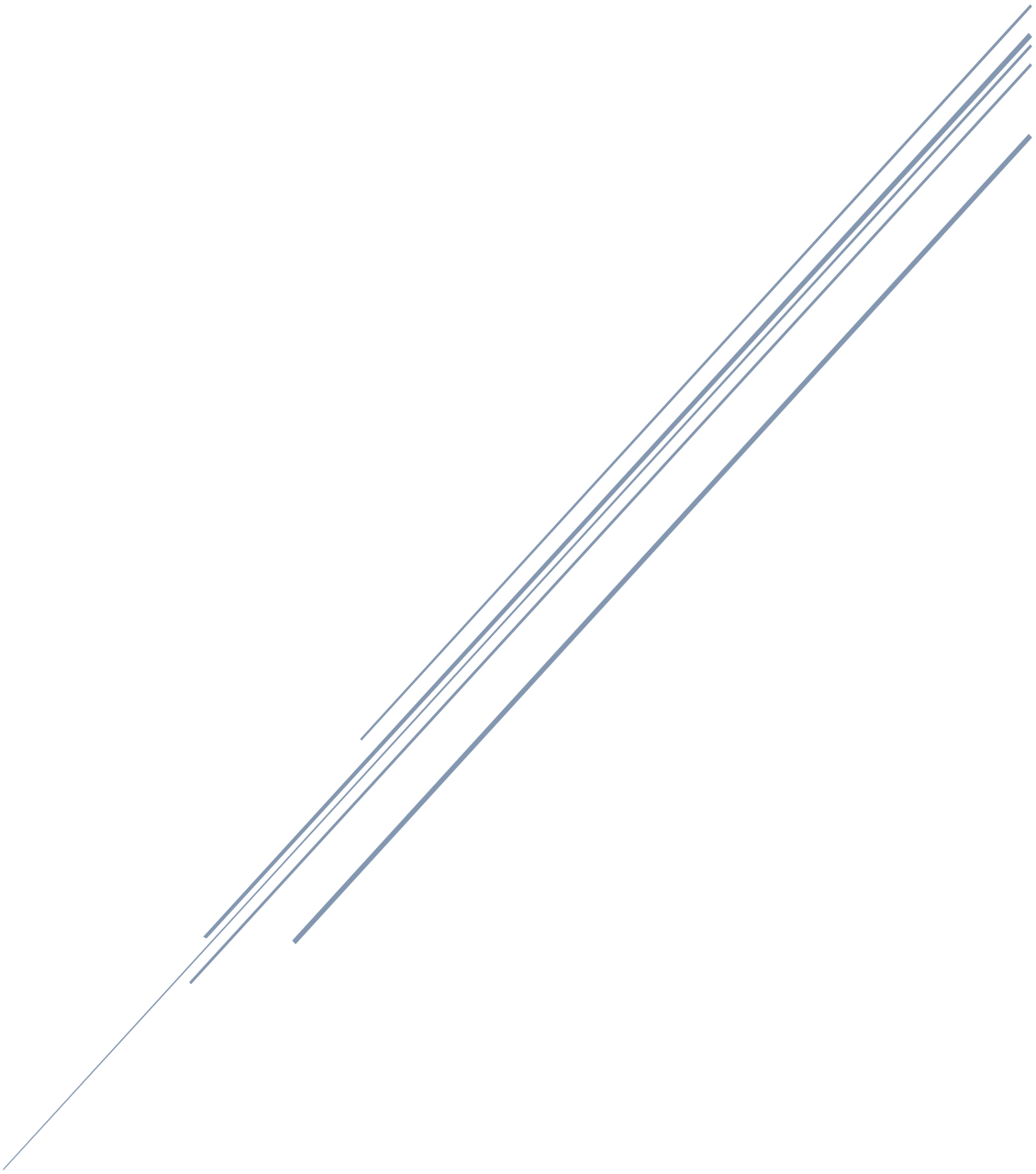
BREAKOUT SESSIONS



Breakout Session 1
Spatial transcriptomics - methodology to study the tumor ecosystem

Joakim Lundeberg
SciLifeLab

Tissue represents an ecosystem of different cells carrying out different tasks. Specific types of cells exist in every organ and serve specialized functions defined by the specific genes and proteins active in each cell type. Comprehensive maps of molecularly defined human cell types are underway through the Human Cell Atlas effort using primarily single-cell RNA sequencing. The technologies to assemble spatial molecular maps that describe and define the cellular basis of health and disease are becoming increasingly available. Indeed, Nature Methods awarded spatially resolved transcriptomics (SRT) the Method of the Year in 2020, demonstrating the increased interest in the field. The two main approaches will be introduced: sequencing-based SRT and imaging-based SRT.

We have developed and established the Spatial Transcriptomics (ST) technology, in which tissue imaging is merged with spatial sequencing and resolved by computational means. Spatial Transcriptomics technology was the first method to provide unbiased whole transcriptome analysis with spatial information from tissue using barcoded array surfaces and has, since its initial publication, been used in multiple biological systems in health and disease. This presentation will introduce methodological and analytical aspects in the context of biological applications of cancer.

Breakout Session 1
Spatial transcriptomics - methodology to study the tumor ecosystem

Alejandro Mossi Albiach
Dept. of Medical Biochemistry and Biophysics

Glioblastoma is spatially organized by neurodevelopmental programs and a glial-like wound healing response

Glioblastoma is the deadliest brain cancer, characterized by great cellular diversity and unique histology. Recently, single cell RNA sequencing studies have revealed that cell states present in GBM resemble those of human foetal development and human adult brain: astrocyte-like, oligodendrocyte precursor cell-like, neural progenitor cell-like with an additional cell state named mesenchymal. The proportion of these states varies highly across tumour sample and patients; and the ability of GBM cells to transition between states is thought to be a key factor in resistance to current treatments. Heterogeneity has been used as an umbrella keyword to describe GBM biology, both referring inter/intra patient molecular and cellular diversity. To understand the spatial organization of transcriptional cell states, we leveraged EEL-FISH (Enhanced ELectric single molecule Fluorescence *in situ* Hybridization) to map the expression of 888 genes in 57 centimetre-scale tissue sections from 41 unique surgical samples of 27 patients: 25 GBM (IDH-wildtype) cases and two oligodendrogliomas (IDH-mutant and 1p19q co-deleted). We found a hierarchy of cellular states akin to normal brain development, including proliferating and differentiated cells interacting with the stroma. We discovered that mesenchymal-like glioblastoma cells comprised a major glial-like wound-response component and a distinct gliosarcoma-specific malignant fibroblast type. Our analysis highlighted hypoxia, tissue damage, and wound healing as major factors in glioblastoma spatial organization. Tumor microenvironment varied along the hypoxia gradient, inducing the recruitment of monocytes and pro-tumorigenic macrophages, and propagating wound response program activation in malignant glial cells. Our study reveals the dynamic progression of glioblastoma organization independent of its mutational profile, in response to tumor-induced injury.

Keywords: Glioblastoma, spatial transcriptomics

Breakout Session 2
From academia to industry and how to collaborate?

Claire Heride and Louise Slater
Cancer Research Horizons

Cancer Research Horizons Therapeutic Innovation

Therapeutic Innovation (TI) is part of Cancer Research Horizons, the innovation arm of Cancer Research UK (CRUK). TI comprises six drug discovery centres, each with complementary state-of-the-art drug discovery technology platforms, operating under one leadership team, with a shared portfolio and budget. We engage closely with CRUK-funded researchers (~4,000) and a global research community through strategic partnerships (e.g., Oncode Institute, Netherlands and Karolinska Institutet, Sweden). Our aim is to identify and progress novel ideas in close partnership with academic researchers, with the objective of discovering breakthrough medicines for cancer patients. CRUK has a long track-record of translating academic science into the clinic, having played a role in the discovery and/or development of ten cancer medicines.

Our purpose is to ensure the translation of emerging cancer biological knowledge and discoveries. We are interested in novel targets and emerging areas of cancer biology or approaches to known challenging cancer targets with promising therapeutic potential in areas of unmet need. We have the expertise to progress small molecule or biological approaches to modulate cancer targets. Our approach is centred on collaboration, working closely with individual academic researchers, academic institutes, and commercial entities to enable us to drive progression of our portfolio further, faster, together.

Breakout Session 3
Artificial Intelegence in cancer research in KI

Fredrik Strand
Dept. of Oncology-Pathology

AI for breast cancer risk prediction and screen-reading ”

Mammography screening is the cornerstone of early detection of breast cancer. A long-standing practice in Sweden has been to offer all women mammography (and nothing else) and to have two radiologists reviewing each screening examination to identify signs of potential malignancy. Now, artificial intelligence (AI) is about to change both of these practices. In collaboration with KTH, we have developed an AI model for breast cancer risk prediction and are finalizing the randomized clinical trial ScreenTrustMRI where we use our AI model to select women for supplemental MRI after negative screening. We have recently published results of the prospective ScreenTrustCAD study, in Lancet Digital Health, comparing the cancer detection rate and unnecessary recalls of healthy women between various combinations of AI and radiologists in the initial screen-reading.

Breakout Session 3
Artificial Intelegence in cancer research in KI

Abhinav Sharma
Dept. of Medical Epidemiology and Biostatistics

A methodology for direct selection of image areas important for classification in weakly supervised CNN-based modelling of cancer pathology images

Introduction:
In computational pathology, there is rise of weakly supervised learning models where slide-level labels are used for training, since pixel or tile level annotations may not be available, or in cases where the label is on patient or tumour level, for example, histological grade classification or patient outcome. However, spatial interpretability is often desirable to understand which tissue areas are important in the classification but is not intrinsically available in weakly supervised tile-based models. In this study, we have proposed a direct methodology based on backward selection to determine Whole Slide Image (WSI) regions that are necessary for the classification of a WSI in the context of a weakly supervised CNN model.
Materials and Methods:
We optimised and validated ResNet-18 CNN models for breast cancer histological grade 1 vs 3 classification on the training set of SöS-BC-4 cohort (n = 1695 WSIs) using 5-fold CV. Two different tile-to-slide level aggregator functions were evaluated: the 75th percentile of the tile-level predictions probabilities as the slide-level score, and an attention layer trained on tile-level feature vectors derived from the CNN model to provide the slide-level score. In both modelling strategies, for each slide, we iteratively remove the highest-ranking tile and recalculate the slide-level score until the slide-level score reaches the classification threshold, which we define as the set of tiles, and corresponding tissue area, that drives the classification by the CNN model.
Results:
The proposed methodology provides means for spatial visualisation of the regions of interest. We observed an average of 32.34% (95% CI: 29.69% - 34.99%) and 44.97% (95% CI:41.69% - 48.26%) of the WSI regions that contributed to the classification of Grade 3 in the CNN with a 75th percentile and attention layer based tile-to-slide level aggregator respectively. The two different aggregation functions had similar 49% of areas driving the classification.
Conclusion:
There is a need for interpretability and understanding of the decision-making of weakly supervised deep CNN models in both research and clinical applications. Here we proposed and evaluated a methodology for interpretability that is directly linked to predictions provided by weakly supervised tile-based deep learning models, which can improve understanding of the classification decisions.

Keywords: Breast cancer, Deep learning, Interpretability

Breakout Session 4
Meet the Scientist

Matthew P. Goetz, M.D.
Professor of Oncology and Pharmacology, Mayo Clinic

Matthew P. Goetz, M.D., is a consultant in the Division of Medical Oncology, Department of Oncology, at Mayo Clinic in Rochester, Minnesota. Dr. Goetz serves as Enterprise Deputy director, Translational Research, in Mayo Clinic Comprehensive Cancer Center. He joined the staff of Mayo Clinic in 2003 and holds the academic rank of Professor of Oncology and Pharmacology, Mayo Clinic College of Medicine and Science. He is recognized with the distinction of the Erivan K. Haub Family Professorship in Cancer Research Honoring Richard F. Emslander, M.D.

Dr. Goetz received his B.A. in music at Wheaton College and his M.D. at the University of North Dakota School of Medicine. He completed an internship in internal medicine and a residency in internal medicine at the University of Michigan in addition to a postdoctoral fellowship in hematology and oncology at Mayo Clinic School of Graduate Medical Education.

Dr. Goetz leads breast cancer research activities at Mayo Clinic where he is co-leader of the Women's Cancer Program within the Mayo Clinic Comprehensive Cancer Center and Director of the National Cancer Institute (NCI)-funded Mayo Clinic Breast Cancer Specialized Program of Research Excellence (SPORE). He holds Master's faculty privileges in Biochemistry and Molecular Biology in Mayo Clinic Graduate School of Biomedical Sciences.

Dr. Goetz has been extensively involved in both translational research as well as in the conduct of early- and late-phase clinical trials, with a focus on germline and tumor factors that alter endocrine responsiveness. A notable area of research focus has been the pharmacogenetics of tamoxifen, where Dr. Goetz has led multiple studies demonstrating the importance of CYP2D6 genetic variation as a predictor of tamoxifen response, resulting in Clinical Pharmacogenetics Implementation Consortium guidelines for use of CYP2D6 genotype for tamoxifen dosing. Emanating from this work, and in collaboration with the Developmental Therapeutics Program of the NCI. Dr. Goetz has led a team of investigators in the development of a novel formulation of endoxifen for the treatment of estrogen receptor positive breast cancer through both phase I and II clinical studies.

In addition, Dr. Goetz co-led prospective "multi-omic" studies, including the Breast Cancer Genome-Guided Therapy (BEAUTY) and PROMISE (A Prospective Study to Evaluate the Role of Tumor Sequencing in Women Receiving Palbociclib for Advanced Hormone Receptor (HR)-Positive, Breast Cancer) studies, wherein blood and tumor biopsies are obtained for comprehensive "omic analyses" and patient-derived xenografts (PDX). Together, the combined "omic", PDX, and clinical trial outcome data provide a resource to drive new therapeutic approaches for treatment-resistant breast cancer. Based on this latter work, Dr. Goetz and the BEAUTY team receive the Mayo Clinic Team Science Award in 2019.

Nationally and internationally, Dr. Goetz is recognized by serving on the steering committees for the NCI Breast Cancer Steering Committee, the Translational Breast Cancer Research Consortium, and the Early Breast Cancer Trialists' Collaborative Group. He currently serves as Vice Chair of the Academic and Community Center Research United (ACCRU) Executive Committee.

Breakout Session 4
Meet the Scientist

Juha Klefström, PhD
Research Professor, Finnish Cancer Institute, Helsinki University Hospital and University of Helsinki
Visiting Professor, UCSF Department of Cell and Tissue Biology

Juha Klefström is a renowned scientist who has made significant contributions to the field of basic and translational cancer research. He received his Ph.D in Molecular Genetics from the University of Helsinki, Finland in 1997. During his post-doctoral research, he received scientific training in the laboratory of Prof Gerard Evan at ICRF/CRUK, London and later at UC San Francisco, where he studied the mechanisms of MYC oncogene induced apoptotic cell death. Since 2003, Dr. Klefström has been leading an independent lab at the University of Helsinki, Finland and he has current affiliations with Finnish Cancer Institute, University of Helsinki, Helsinki University Hospital and UCSF. Klefström lab's primary research goal is to develop new cancer therapies by exploiting specific oncogene signaling pathways that render cancer cells vulnerable to programmed cell death. The lab has developed various patient-derived ex vivo culture and in vivo mouse model systems to understand how oncogenes reprogram the cell metabolism, epithelial plasticity and cell death machinery to drive tumorigenesis. Klefström lab also focuses on the development of new therapeutic approaches that would selectively kill cancer cells and simultaneously activate tumor immune microenvironment through modulation of immunometabolism and immunogenic cell death.

Dr. Klefström is currently a FICAN Research Professor in Finnish Cancer Institute (FCI) with Research Director position at the University of Helsinki in Research Program in Cancer Medicine. He also holds a part-time position in Helsinki University Hospital, The Southern Finland Regional Cancer Center FICAN (FICAN South). He also serves as a Visiting Professor in the UCSF Department of Cell and Tissue Biology. Overall, Klefström's expertise, research and cross-organizational collaborations continue to advance the discovery and development of novel innovative cancer therapies.

Dan Grandér's Memorial Prize Awardee
Karin Dembrower
Dept. of Oncology Pathology
Monday 25th, 15:00

Deep Learning in Breast Cancer Screening

My PhD dissertation revolves around the use of AI in screening mammography to detect breast cancer. The first study describes the curation of a large dataset of images linked to clinical outcomes. In the second study, we demonstrated that training a deep neural network can outperform traditional mammographic density when it comes to predicting which women will be diagnosed with breast cancer within the next few years. In the third study, we examined how AI aimed at cancer detection may also be used to refine the current screening workflow by reliably assessing a large proportion of mammograms as normal not needing any radiologist assessment, and to contribute to reducing future interval cancer and next-round screen-detected cancer. The fourth paper discussed the practical implications, in terms of workload and cancer detection, of various alternatives in how the cut-off threshold for the abnormality score was chosen. In parallel with the last part of my PhD, we started a prospective clinical study, ScreenTrustCAD, at my hospital Capio S:t Göran, which included 55,000 women and showed that AI plus one radiologist would lead to increased cancer detection without any increase in false positive assessments. This study led directly to clinical implementation of AI. Since June 2023 an AI algorithm replaced one reader in a double reading setting for screening mammograms. The work load has been less heavy for our breast radiologists and time has been released to perform more advanced diagnostics for women with a breast cancer diagnosis.