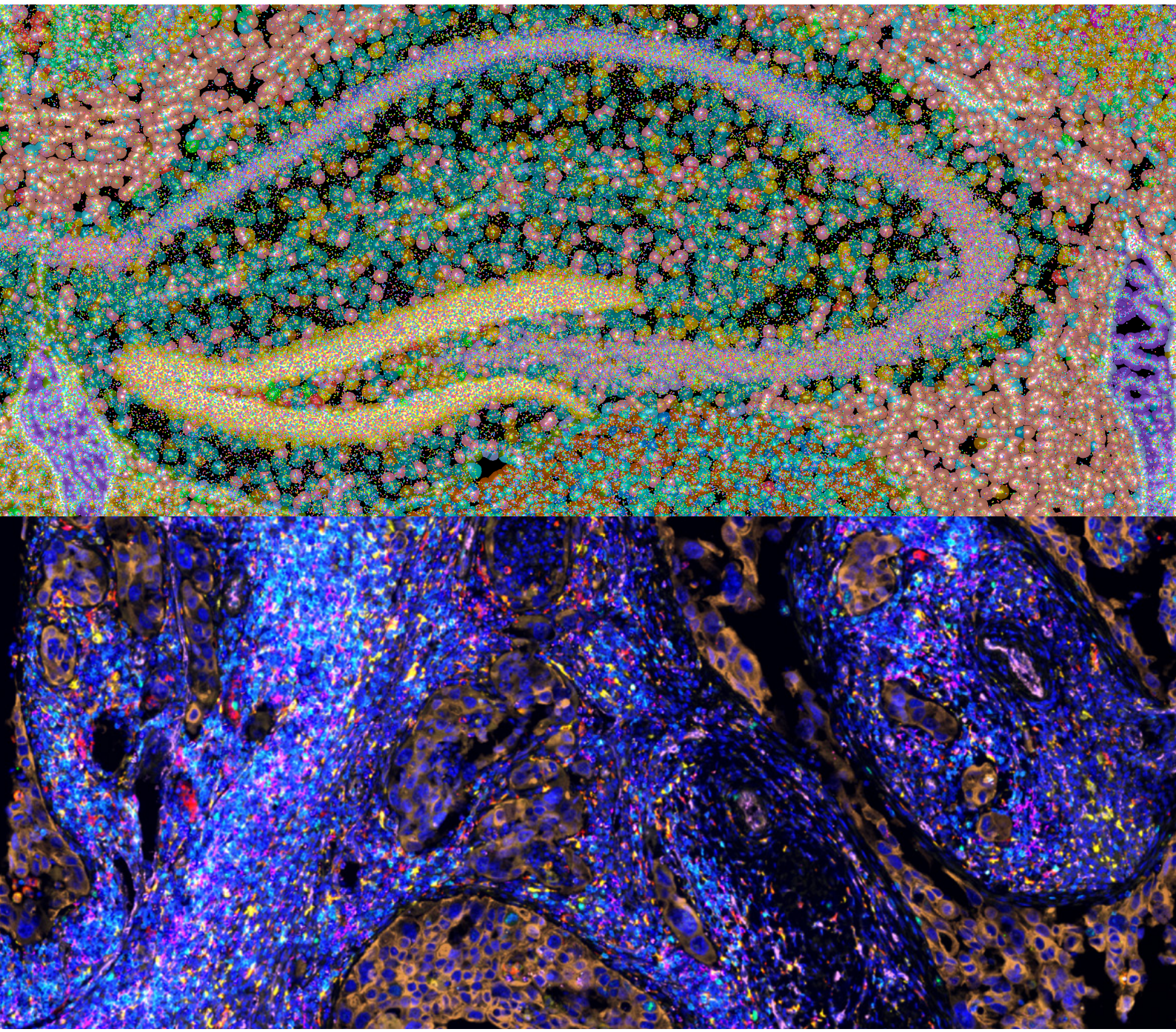
Science Summit 2024 October 1

Spatial Biology
Uppsala Konsert & Kongress

Speaker abstracts



SciLifeLab

09:50 - 10:20
Sinem Saka
EMBL, Germany

Oligodendroglia in Development and Multiple Sclerosis: Insights from Single-Cell and Spatial Omics

DNA is not only a fundamental constituent of cells, but has also great capacity for information storage. We leverage the predictability of DNA hybridization kinetics and orthogonality of DNA sequences to utilize DNA oligos as tagging and barcoding tools for improving the major limitations of in situ visualization of molecules. We have previously developed multiplexed imaging approaches such as SABER-FISH and Immuno-SABER that utilize DNA barcoding and a flexible in situ signal amplification system for efficient visualisation of many protein, DNA or RNA targets in cells and tissues.

More recently, we have implemented DNA barcoding for a new spatial transcriptomics approach, Light-Seq, which directly integrates fluorescence imaging and whole-transcriptome next-generation sequencing of the same cells in fixed biological samples. Light-Seq combines spatially-targeted, rapid photocrosslinking of DNA barcodes onto cDNAs in situ with a novel one-step DNA stitching reaction to create pooled, spatially-indexed sequencing libraries. This light-directed barcoding enables imaging-based in situ selection of multiple cell populations in intact fixed tissue samples for full transcriptome sequencing based on location, morphology, or protein stains, without cellular dissociation.

Applying Light-Seq to mouse retinal sections, we discovered new biomarkers for a very rare neuronal subtype, dopaminergic amacrine cells, from only 4-8 individual cells per section. Light-Seq provides an accessible workflow to combine in situ imaging and protein staining with next-generation sequencing of the same cells, leaving the sample intact for further analysis post-sequencing. We are using these methods to directly link multi-dimensional and high-resolution microscopic phenotypes to transcriptomic profiles for diverse sample types.

10:25 - 10:45

Gonçalo Castelo-Branco
Karolinska Institutet, Sweden

Oligodendroglia in Development and Multiple Sclerosis: Insights from Single-Cell and Spatial Omics

Oligodendroglia (OLG) mediate myelination of neurons, a process that allows efficient electrical impulse transmission in the central nervous system. An autoimmune response in multiple sclerosis (MS) leads to OLG cell death, loss of myelin and neuropathology. Using single cell transcriptomics, we have previously identified disease-specific OLG populations in the EAE mouse model of MS and in human MS brain archival tissue, characterized by the expression of immune genes.

By assessing chromatin accessibility and the transcriptome simultaneously at the single cell level at different stages of the disease course, we found that immune genes exhibit a primed chromatin state in mouse and human OLG in a non-disease context, compatible

with rapid transitions to immune-competent states in MS. Moreover, we found dynamic and distinct transcriptomic and epigenomic responses of OLG subpopulations to the evolving environment in EAE mouse model of MS, which might modulate their response to regenerative therapeutic interventions in MS.

While single-cell genomics are powerful for investigating disease-specific cellular states, these methods involve isolating the tissue under study from its niche, leading to a loss of spatial information. Such information is essential for determining cell-to-cell communication in disease niches. We have applied in situ sequencing to investigate disease evolution in MS at a spatial level, both in the EAE mouse model of MS and in human post-mortem MS samples. We annotated disease neighborhoods during lesion evolution and found centrifugal propagation of active lesions. We demonstrated that disease-associated (DA)-glia arise independently of lesions and are dynamically induced and resolved over the disease course.

We have also applied dBIT-Seq, a ligation-based method for deterministic barcoding in tissue, to probe different histone modifications and chromatin accessibility in the mouse brain tissue sections, either in an unimodal or simultaneously with transcriptomics. This spatial epigenome–transcriptome co-profiling has allowed us to identify cellular lineage progression and epigenomic priming events that precede transcription during development with spatial resolution. We are currently applying these methods to disease paradigms in MS, to uncover how transitions to pathological cellular states occur at epigenomic and transcriptomic levels.

11:45 - 12:15

Arutha Kulasinghe
The University of Queensland, Australia

Uncoupling Pathways Involved in Immunotherapy Resistance: Insights from Deep Tissue Profiling

Spatially resolved multi-omic phenotyping is revolutionizing how we study tissue and immune responses to cancer treatments. In this talk, we will describe our integrated approaches to characterizing the tumour microenvironment in head and neck, lung, and skin cancers using ultra high-plex spatial proteomics and transcriptomics, benchmarking to ground truth, and developing functionally characterised immuno-metabolic signatures associated with resistance and sensitivity to immunotherapy.

12:20 - 12:40

Cecilia Lindskog
Uppsala University, Sweden

A spatio-temporal single-cell type map of the human proteome based on transcriptomics, high-resolution antibody-based imaging and artificial intelligence

For a fundamental understanding of human health, molecular medicine and targeted treatment, it is necessary to map processes unique to each tissue and cell type. We here aimed to set up a stringent, workflow for mapping human tissues at the single-cell type level, and utilized this workflow to create high-resolution

spatio-temporal maps of tissue or cell type-specific proteins in human tissues. One of these tissues is testis, which is a complex organ with spermatogenesis involving thousands of genes and proteins activated or repressed through multiple cell states, from spermatogonial stem cells to mature sperm. Understanding the intricate functions and mechanisms at each step of this process requires a multi-dimensional approach that integrates both quantitative and qualitative methods.

Based on single-cell RNA sequencing data, we identified 12 distinct cell types and subsets of germ cells in testis, some of which cannot be distinguished by regular immunohistochemistry. Using a multiplex immunofluorescence pipeline, we then built antibody panels specifically outlining each of these cell types. The fixed antibody panels were stained together with the candidate protein of interest, one at a time, to pinpoint the exact protein localization at a cellular and subcellular level. Using artificial intelligence, the high-resolution images were quantified using an automated image analysis workflow. The integrated data allowed us to study temporal mRNA and protein expression gradients along with maturation processes and identify which mRNAs that are consistently translated into proteins from those that vary from a spatio-temporal aspect. We were also able to assign presumed functions to numerous uncharacterized proteins not previously described in the context of human reproduction.

In summary, we present a strategy for high-resolution spatio-temporal mapping of human tissues and cells, presented as a single-cell type reference map of adult human testis. The data which is freely available on www.proteinatlas.org decodes the complexity of human germ cells and links quantitative data with tissue morphology, and the validated workflow has the potential to be used for other tissues, contributing to valuable insights into molecular function and processes linked to disease.

14:05 - 14:35

Jeffrey Spraggins
Vanderbilt University, Nashville, USA

Bringing human disease into focus through integrated multimodal molecular imaging

Cellular interactions within tissue micro-environments form the basis of health and disease for all organisms. Exposure to nutrients, toxins, and neighboring cells triggers coordinated molecular responses that impact cellular function and metabolism in a beneficial, adaptive, or detrimental manner. Acquiring molecular information at cellular resolution is thus crucial for developing a comprehensive understanding of the biology of an organism.

Matrix-assisted laser desorption/ionization (MALD) imaging mass spectrometry (IMS) addresses this need by combining the spatial fidelity of classical microscopy with the molecular specificity of a mass spectrometer.

This presentation will highlight our work developing new, high-performance technologies for improving the spatial resolution, sensitivity, and specificity of MALDI IMS for metabolite, lipid, and protein mapping. This will include the utilization of novel MALDI methods and development efforts using high spatial resolution Q-TOF platforms to address the molecular complexity associated with direct tissue analysis.

Further, I will describe recent advances in integrated, multimodal methods that correlate molecular signals to specific biological tissue features and cell types. These

technologies will be demonstrated through various biomedical research applications that include the construction of molecular atlases and understanding the molecular drivers of normal aging and disease

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14:40 - 15:10
Ron Heeren
Maastricht University, The Netherlands

Spatial biology and translation life sciences

Modern molecular analytical technologies in the “omics” arena plays a crucial role in many scientific disciplines ranging from material sciences to clinical diagnostics. Technological advances have increased methodological sensitivity allowing researchers to acquire detailed molecular information of smaller and smaller samples. The biggest challenge is to put that concerted information in the context of the biological problem the samples originate from. This lecture describes how innovative mass spectrometry based molecular imaging technologies, have impacted translational clinical research and beyond.

Or: how a mass spectrometer can be used as a sensitive and selective molecular microscope in modern spatial biology. Targeted and untargeted imaging technologies now offer new insights in the complexity that can be employed for systems medicine. Innovations in mass spectrometry based chemical microscopes have now firmly established themselves in translational molecular research. One key aspect of translational success is the ability to obtain this molecular information on thousands of molecules on a timescale relevant to translation. Single cells can be analyzed in great molecular detail and in the context of their native tissue. Combined this offers a true multi-omics approach that reveals contextual molecular complexity for systems medicine.

16:00 - 16:20
Joakim Lundeberg
KTH, Sweden

Tissue ecosystems in time and space

Tools in spatial biology offer a wide range of technologies that quantify different types of biomolecules in tissue sections. These technologies provide information about distinct aspects of tissue anatomy, such as its morphology, genome, transcriptome, proteome, and metabolome. Here, several multiomics computational and experimental methodologies approaches that capture the tissue ecosystem from a single tissue section will be described.

16:25 - 16:45
Carolina Wählby
Uppsala University, Sweden

Measuring tissue morphology in spatial biology

Spatial omics has transformed our understanding of tissue architecture by preserving spatial context of gene expression patterns. Simultaneously, advances in imaging AI have enabled extraction of morphological features describing the tissue. The intersection of spatial omics and imaging AI presents opportunities for a more holistic understanding: morphological features can be translated or integrated into spatial omics analyses. By translation we mean finding morphological features that spatially correlate with gene expression patterns with the purpose of predicting gene expression.

Such features can be used to generate super-resolution gene expression maps or infer genetic information from clinical H&E-stained samples. By integration we mean finding morphological features that spatially complement gene expression patterns with the purpose of enriching information. Such features can be used to define spatial domains, especially where gene expression has preceded morphological changes and where morphology remains after gene expression.