Development of a Multi-Modal Imaging Platform for the Analysis of Patient Biopsies In Translational Studies

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November 2023

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What is a biopsy for?

"Medical procedure that involves taking a small sample of body tissue so it can be examined under a microscope"

But what if we want to look at what's happening at the molecular level – what you can't see under a microscope?

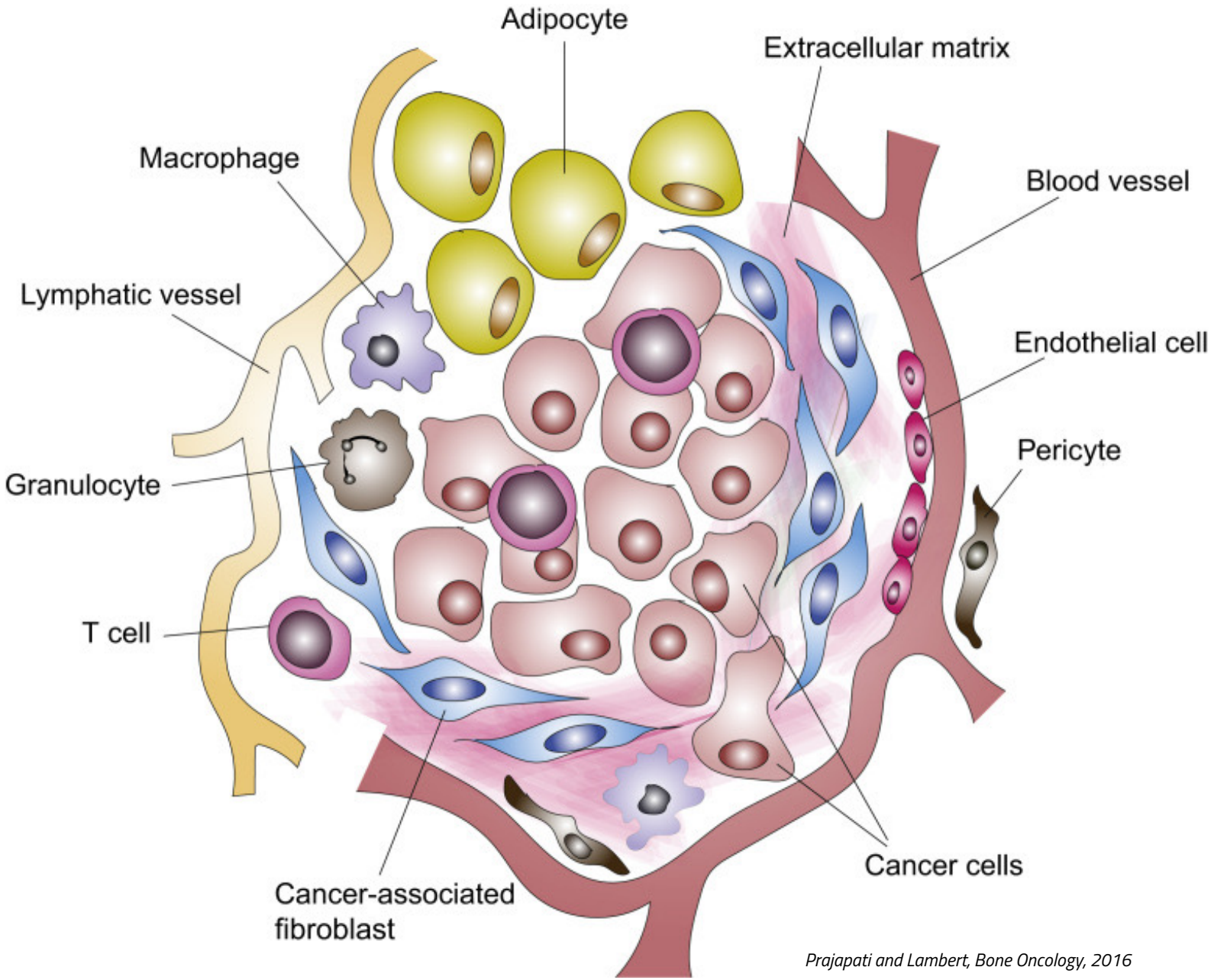
Drug discovery and drug metabolism

- Pharmacokinetic (PK)
- Pharmacodynamic (PD)

Two approaches to process patient biopsy

- Mash it up "grind and find" (homogenise)
- *in situ* analysis

Tissue is a lot more complex…



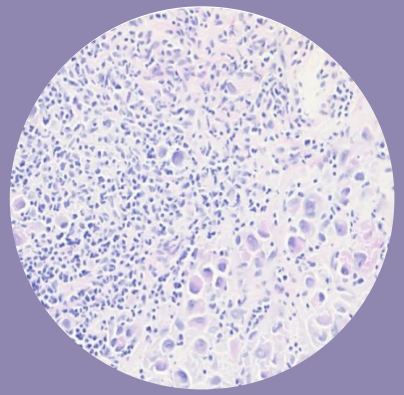
Prajapati and Lambert, Bone Oncology, 2016

- Understanding of the cellular microenvironment
- Tissue architecture
- Immune microenvironment
- Phenotyping

Imaging Toolkit

High Throughput

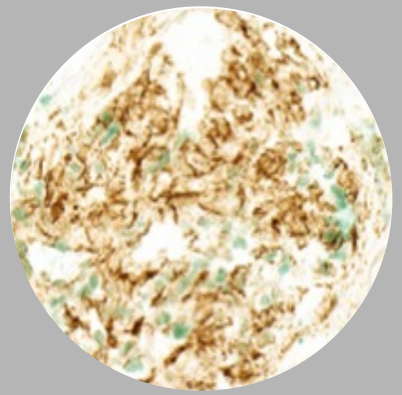
Large Data Volumes



Histology

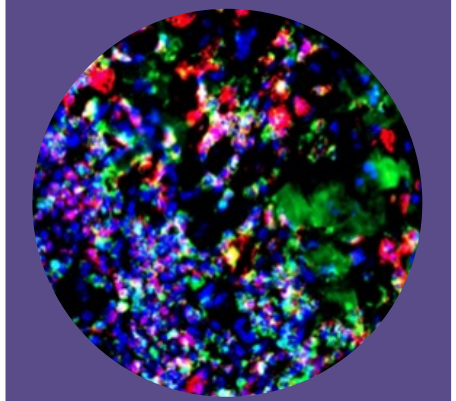
Pathology

Morphology



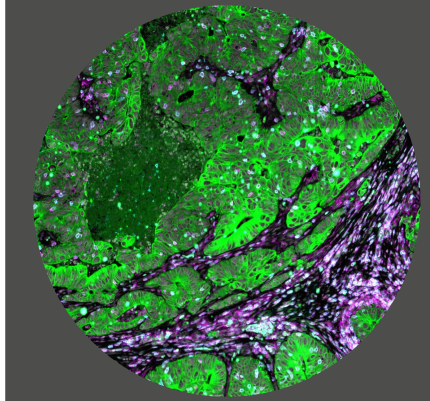
mIHC

Immuno-Histochemistry



mIF

Immuno-Fluorescence



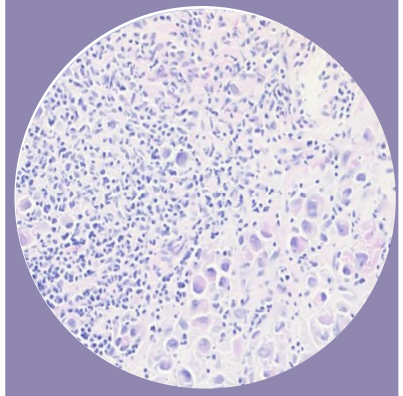
ST

Spatial Transcriptomics

Data Integration for AI and Machine Learning

Imaging Toolkit

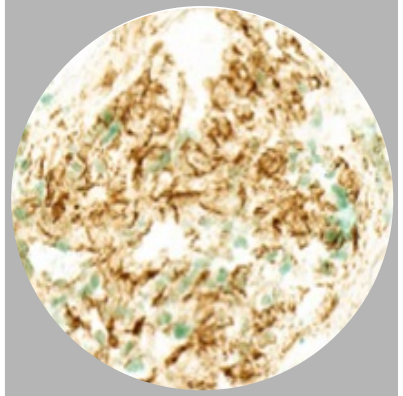
High Throughput → **Large Data Volumes**



Histology

Pathology

Morphology



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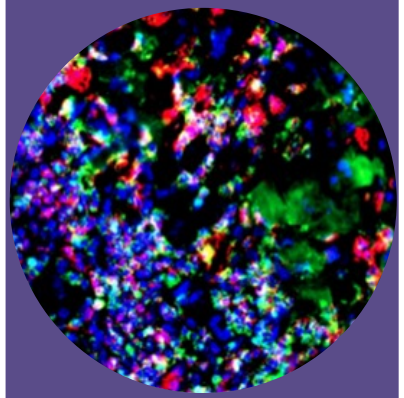

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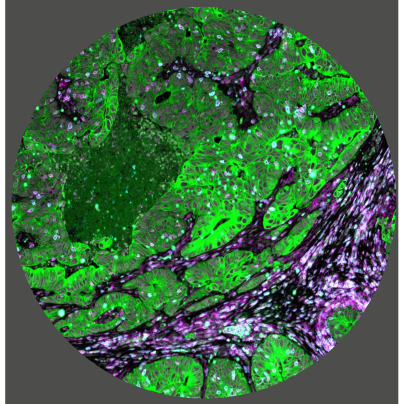
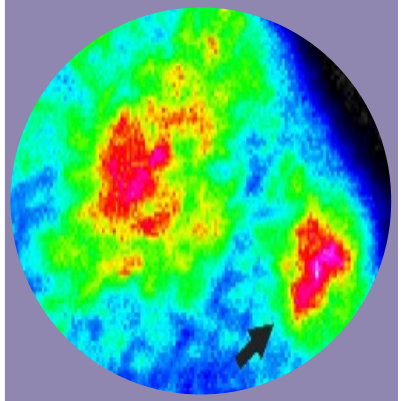


ST

Spatial Transcriptomics

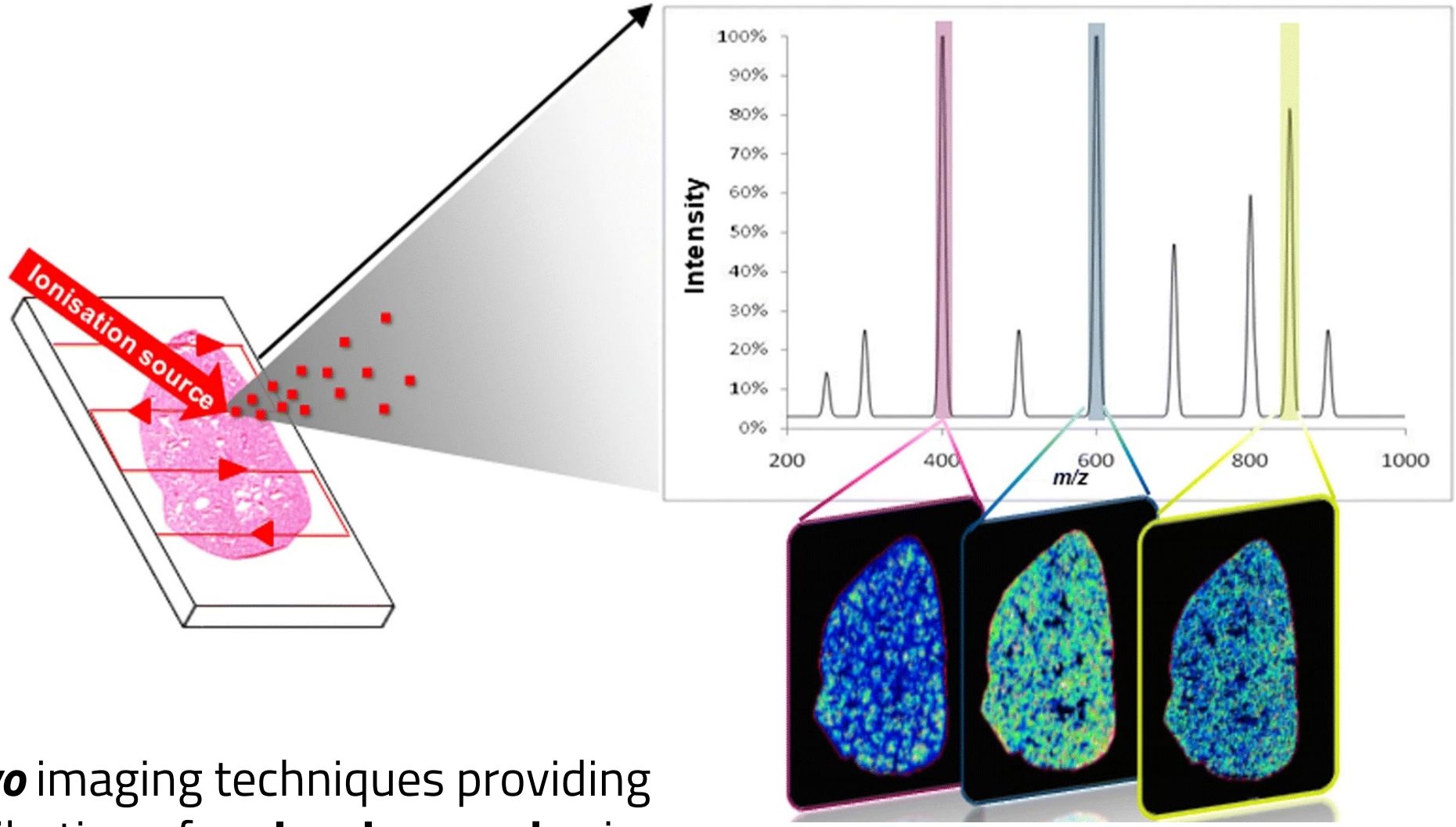


MSI

Mass Spectrometry Imaging

Data Integration for AI and Machine Learning

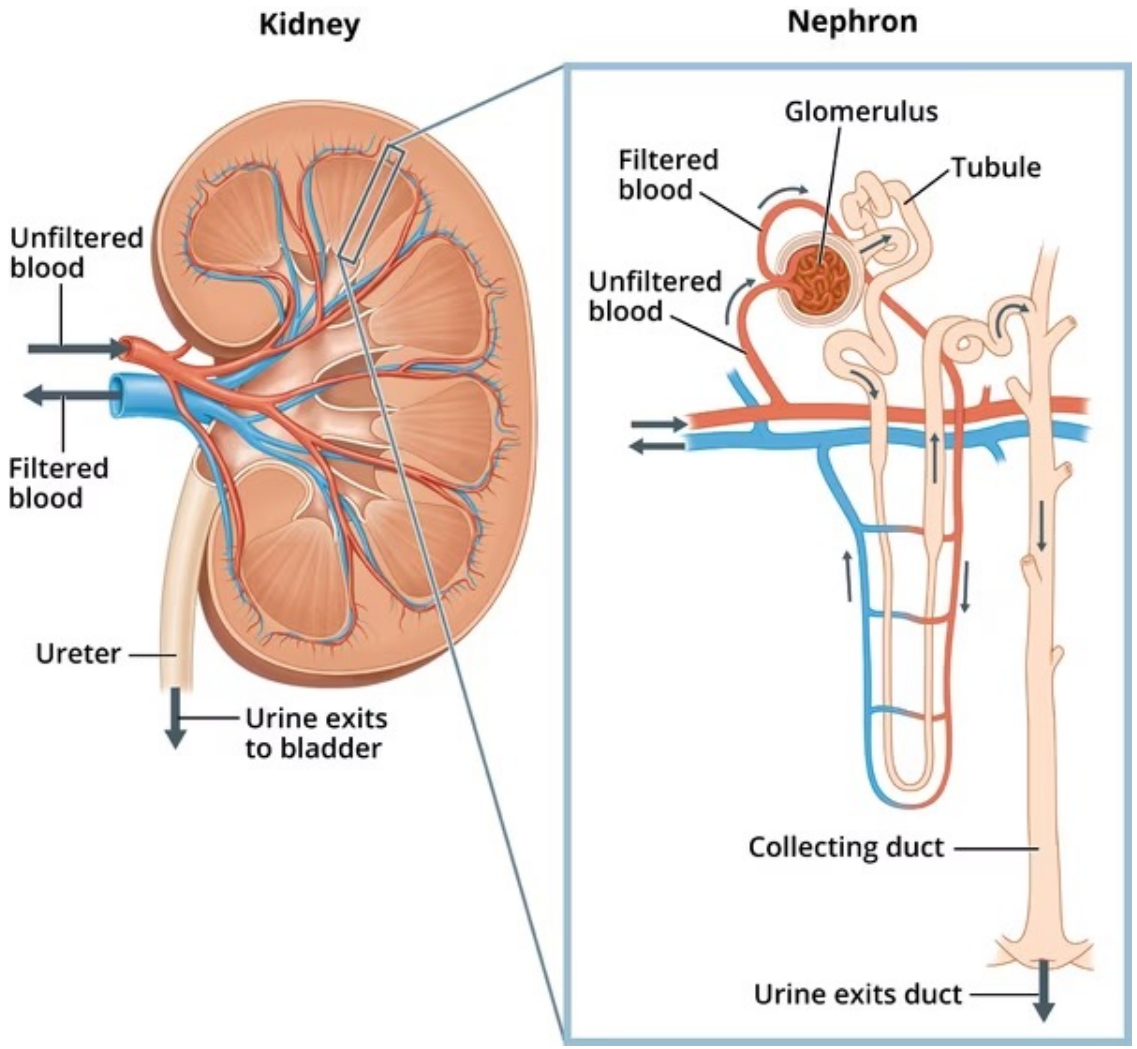
Mass Spectrometry Imaging (MSI)



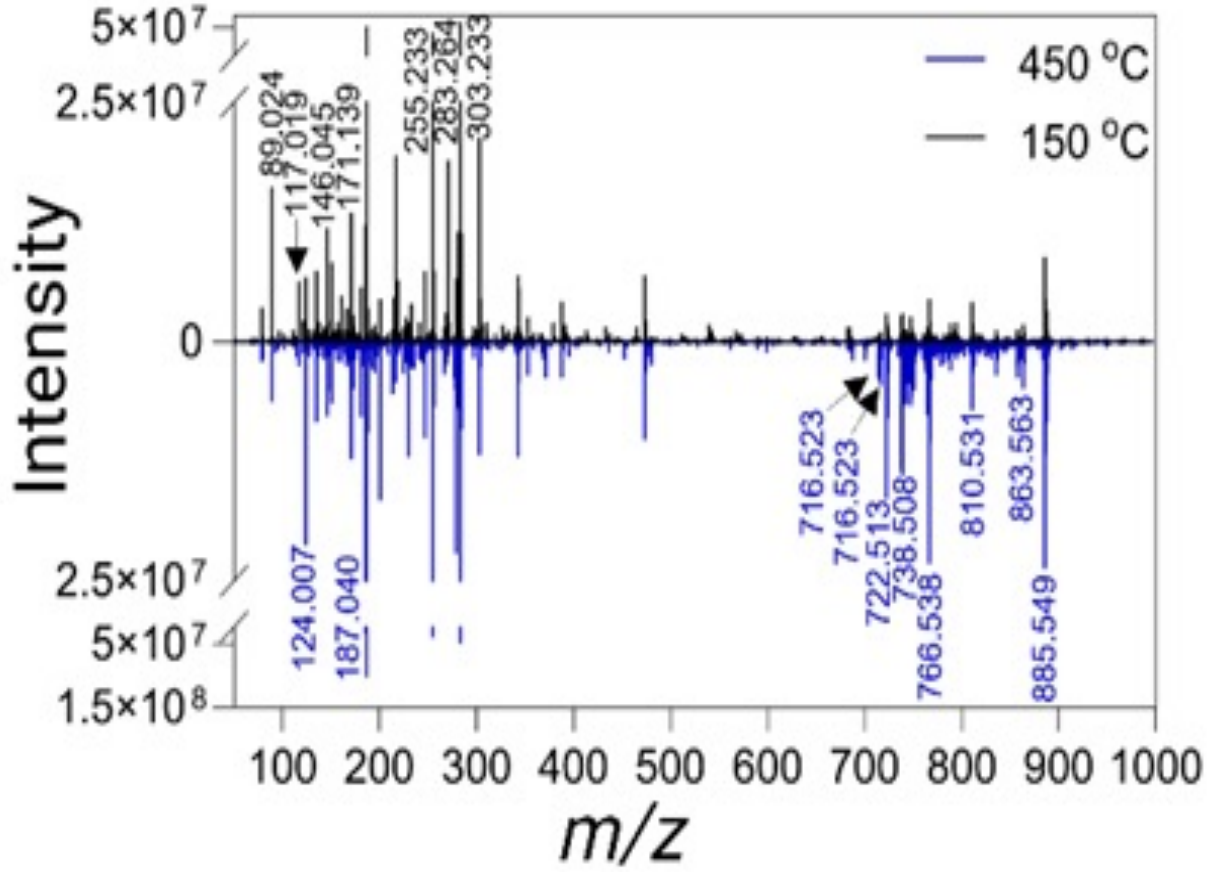
Set of ***ex-vivo*** imaging techniques providing spatial distribution of **molecular species** in **biological tissue**

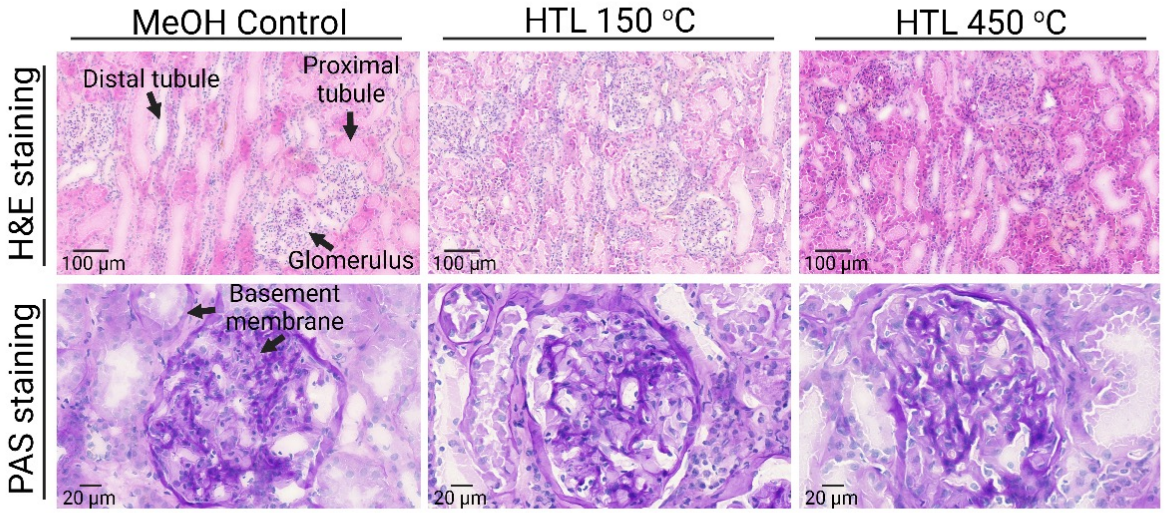
*Porta Siegel et al. Mass Spectrometry Imaging and Integration with Other Imaging Modalities for Greater Molecular Understanding of Biological Tissues. Mol Imaging Biol **20**, 888–901 (2018).*

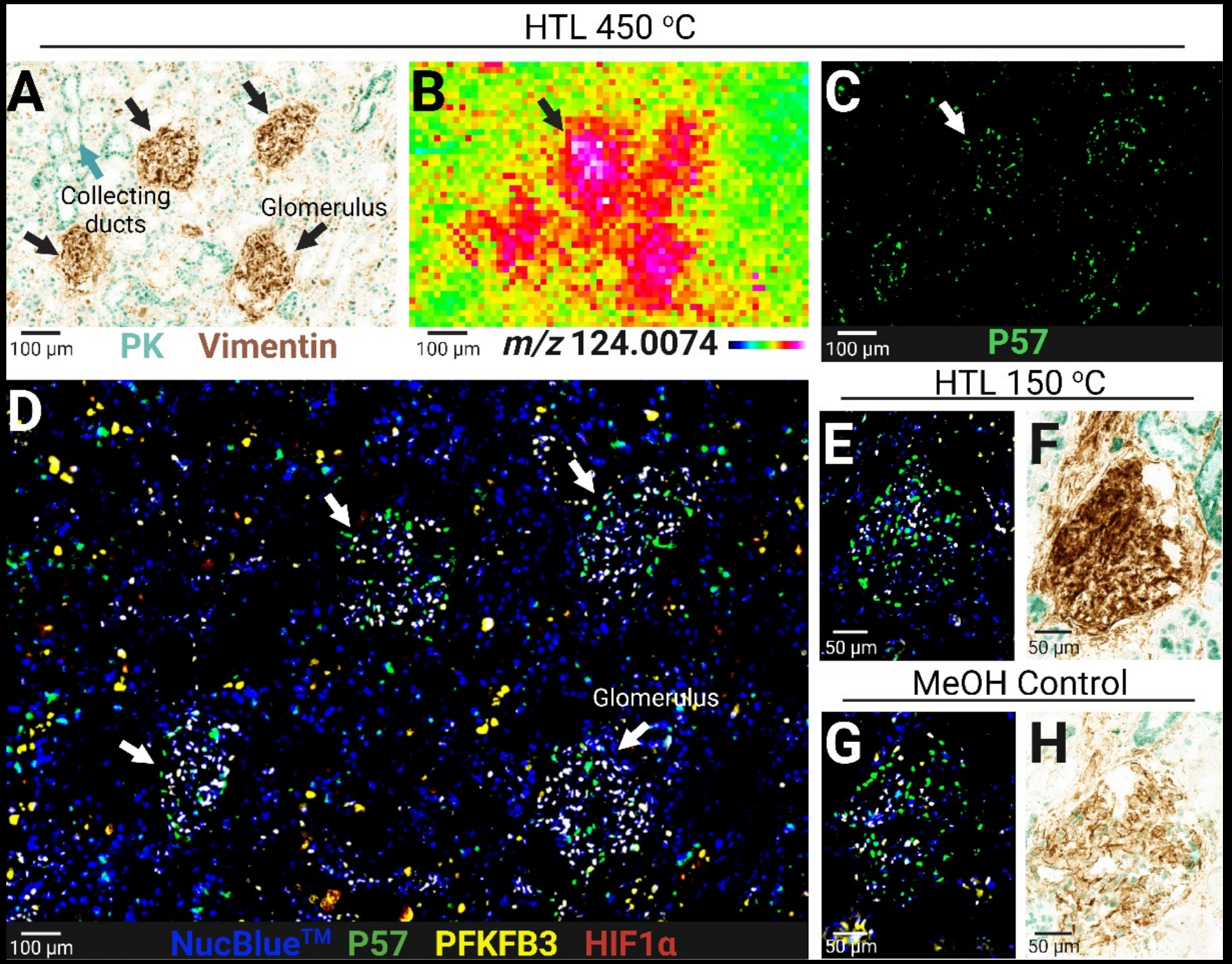
Take the kidney for example...



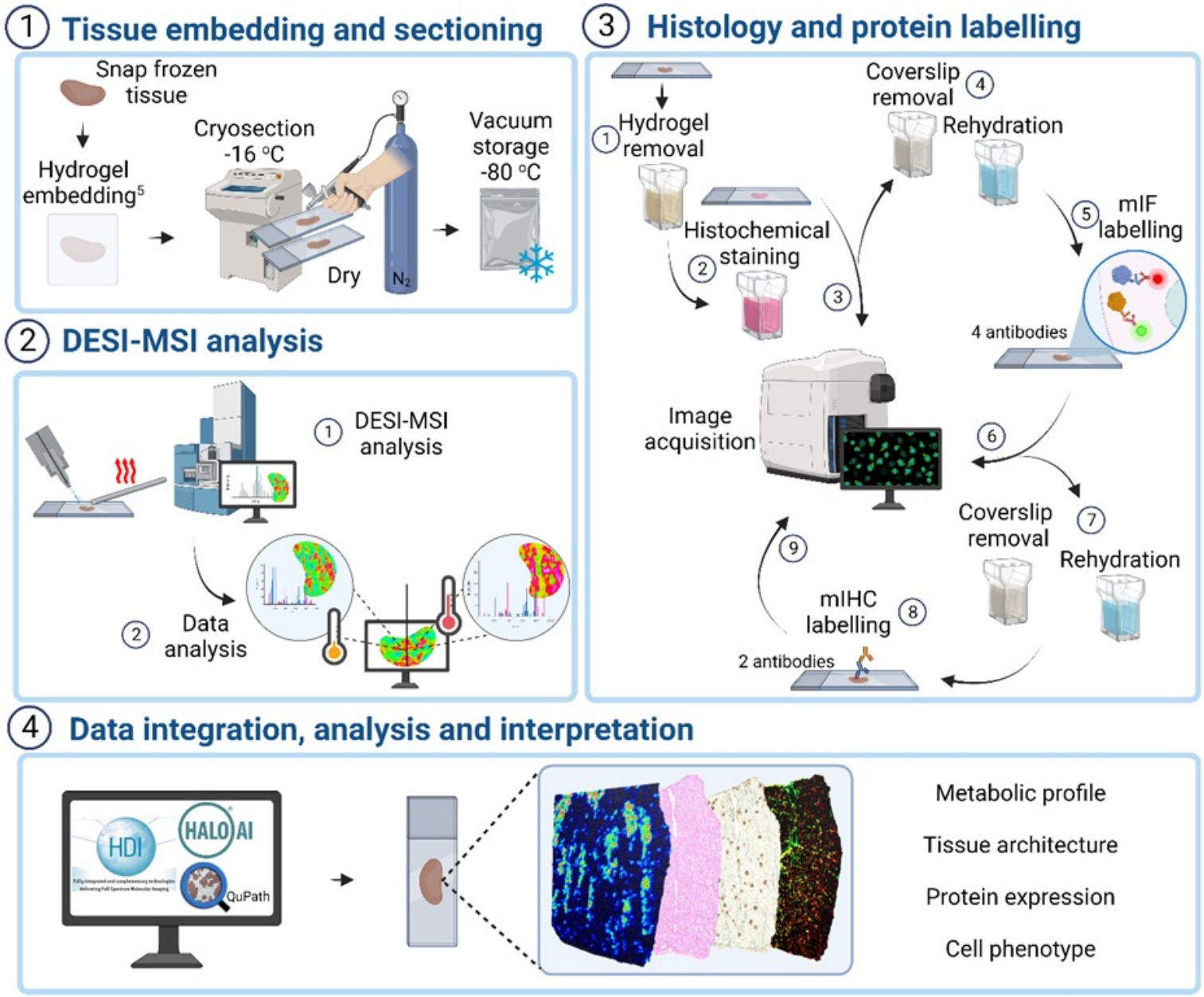
What's cooking with DESI-MSI?



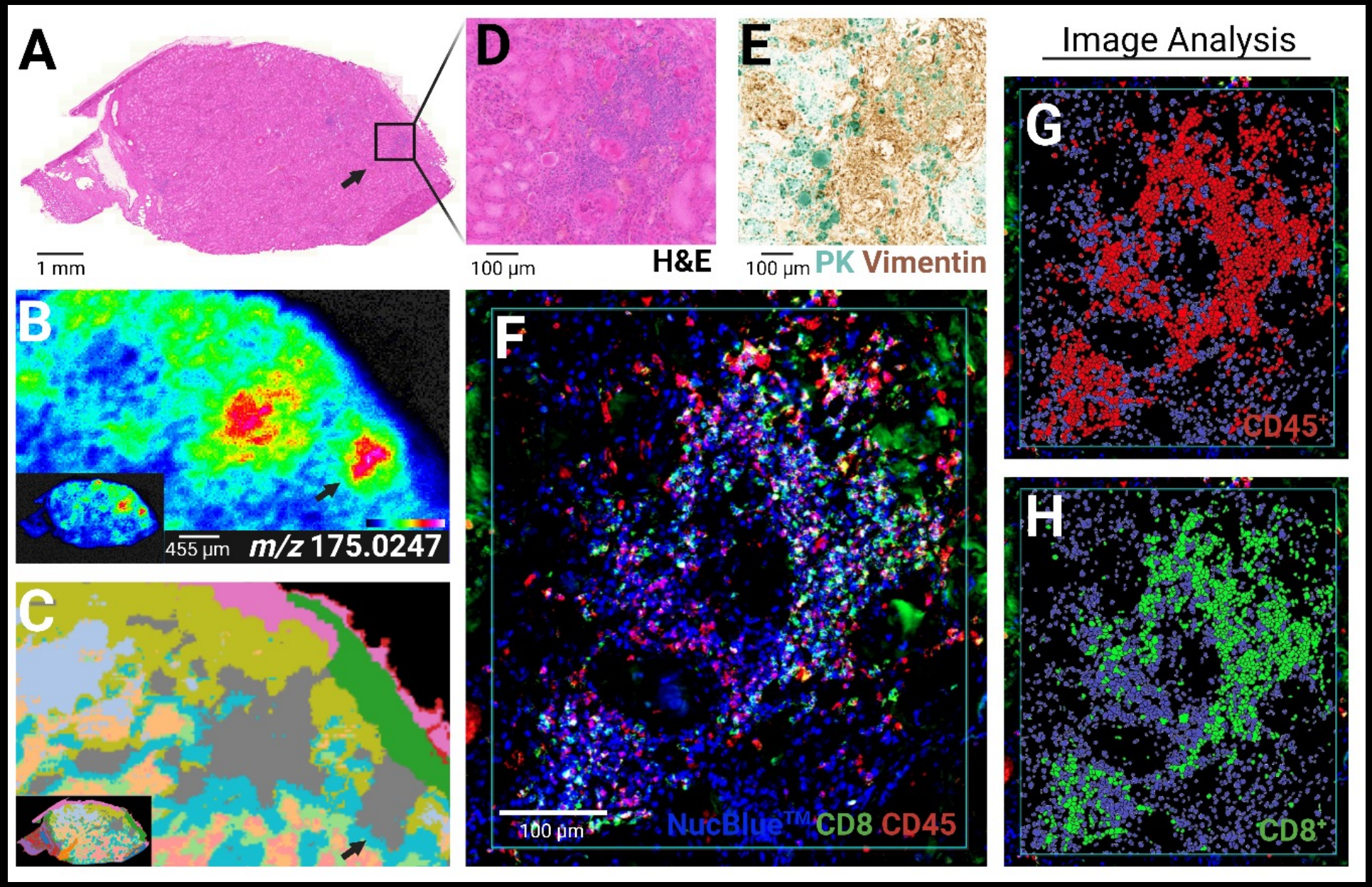



HTL 450 °C
A
Collecting ducts
Glomerulus
100 µm
PK
Vimentin
B
100 µm
m/z 124.0074
C
100 µm
P57
HTL 150 °C
D
Glomerulus
100 µm
NucBlue™
P57
PFKFB3
HIF1α
E
50 µm
F
50 µm
MeOH Control
G
50 µm
H
50 µm

Vast amounts of data from a single tissue section

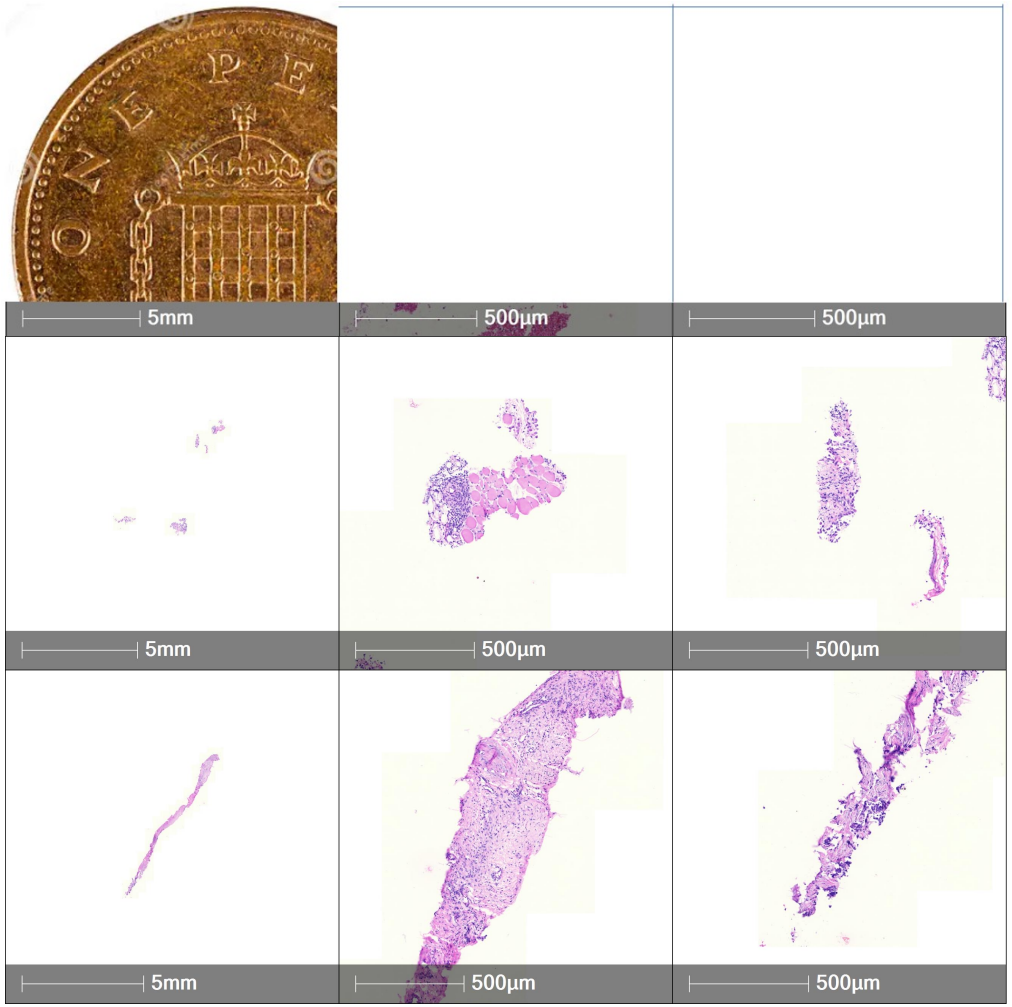


Application of the workflow – scarring and immune cell infiltration

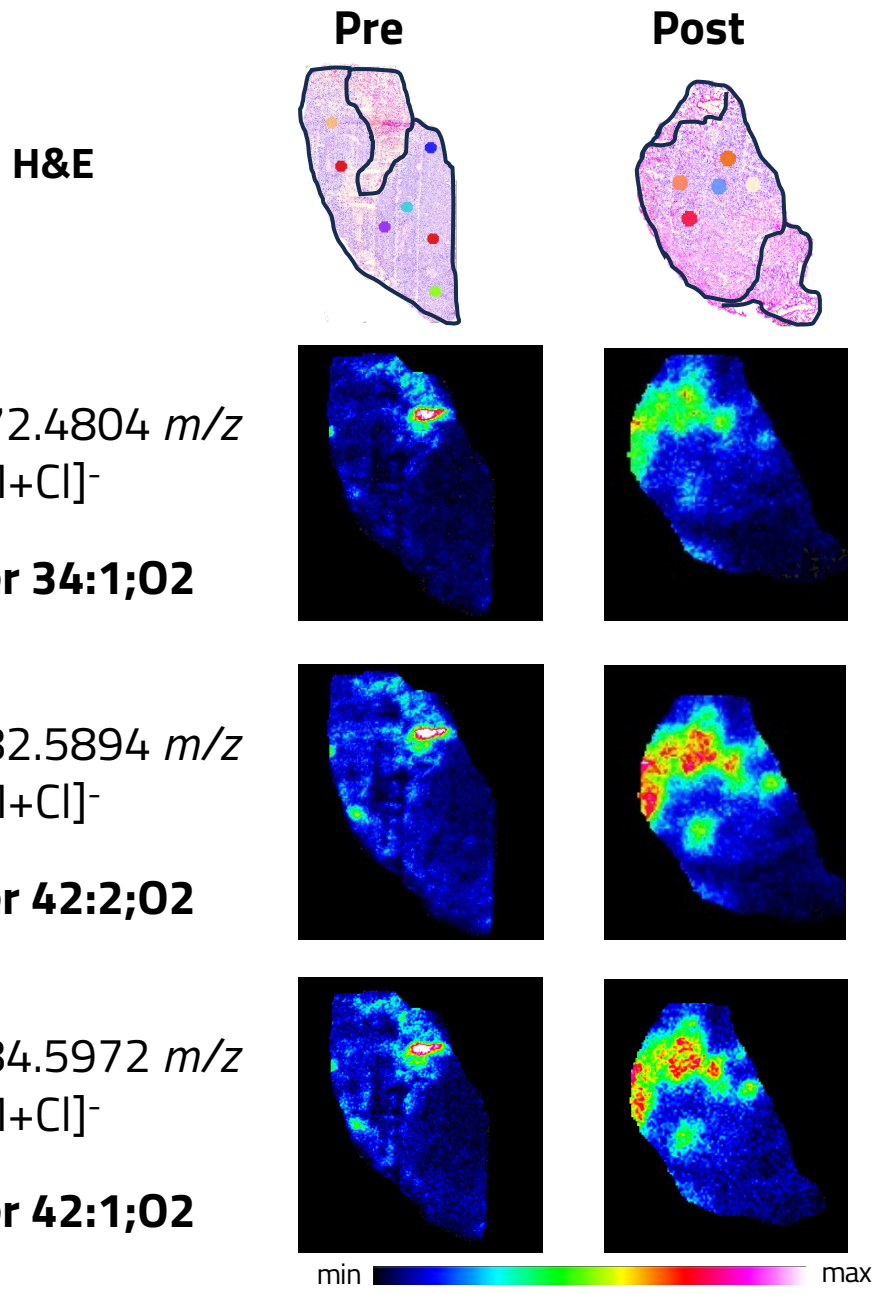


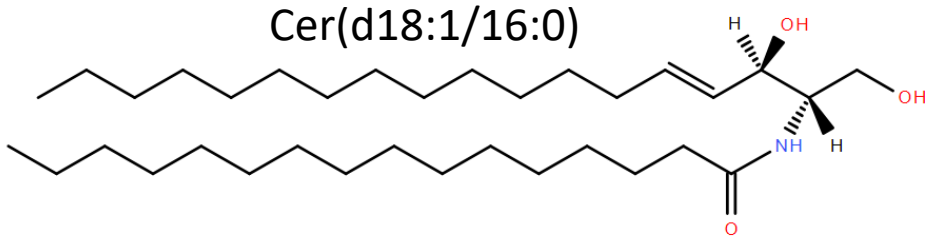
Translational Studies – biomarker discovery

- **Translational medicine** “from bench to bedside“ - requires a multidisciplinary approach
- Benefits of a well-designed clinical study allow **Paired** pre and on-treatment biopsies from patients in on-going Phase I/II clinical studies
- Challenges in getting tissue from patients with cancer
- Crucial that we obtain as much data as possible from a small sample

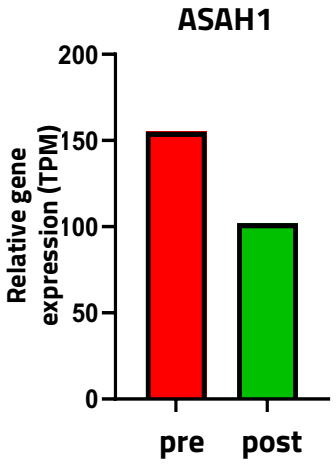


Case 1: necrotic tissue and dense areas of cancer cells

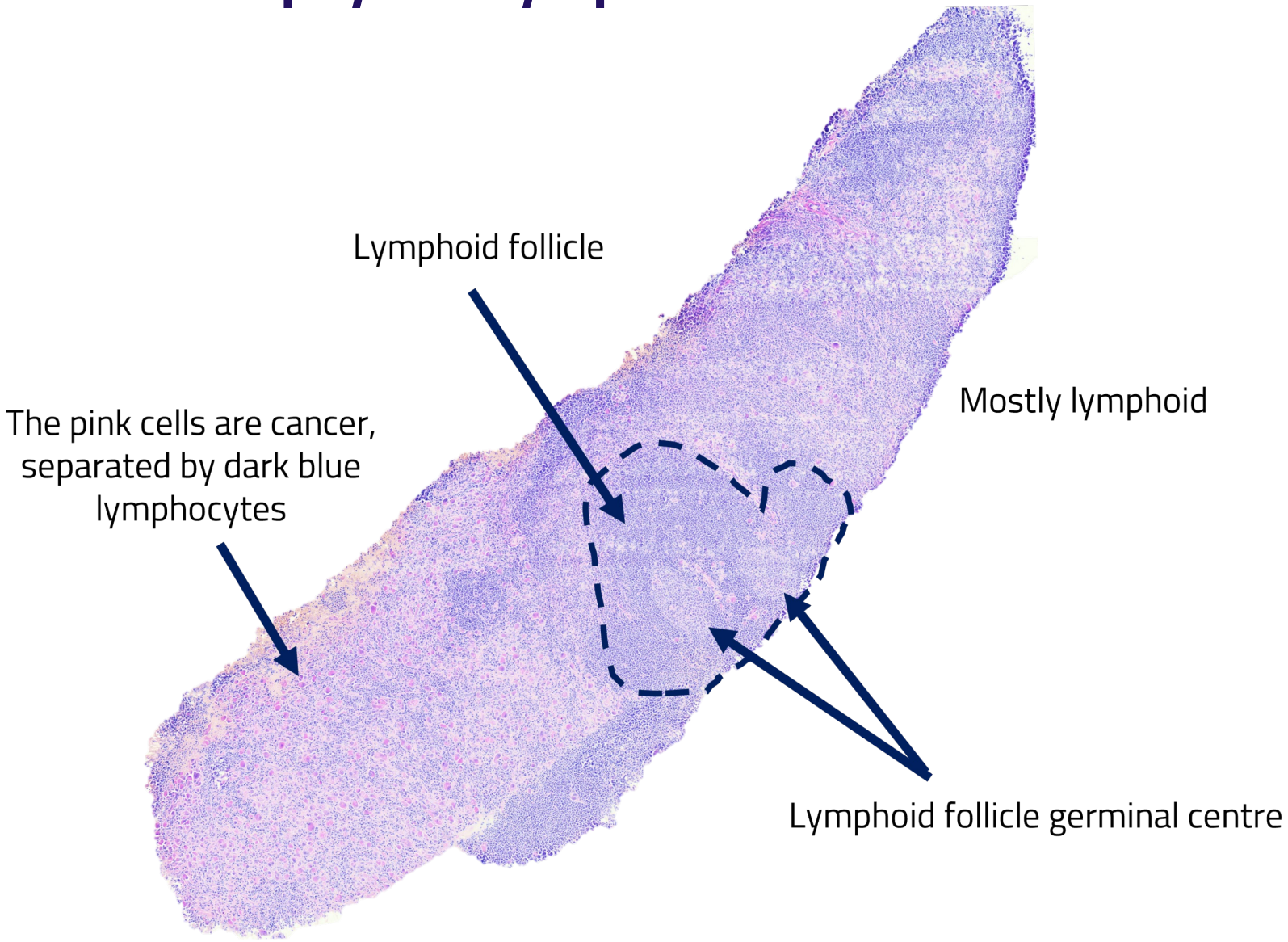




- 3 Ceramide (Cer) species significantly increased (|d| > 5) following treatment
- Bulk RNAseq of same biopsy shows a reduction in the expression of ASAH1, the gene that encodes the enzyme acid ceramidase (AC)
- AC is involved in metabolism of ceramides and often overexpressed in certain cancers
- Ceramides are pro-apoptotic

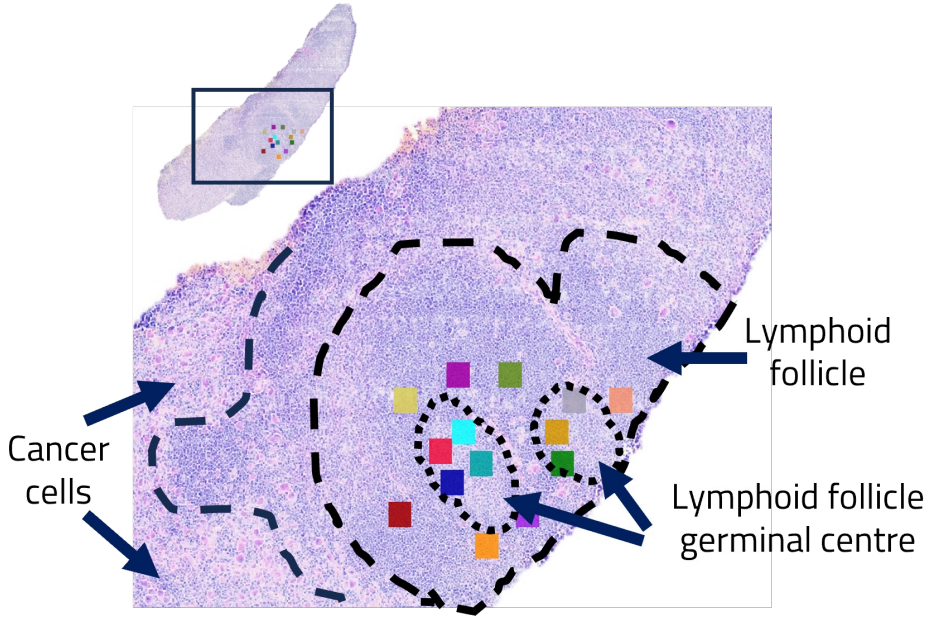


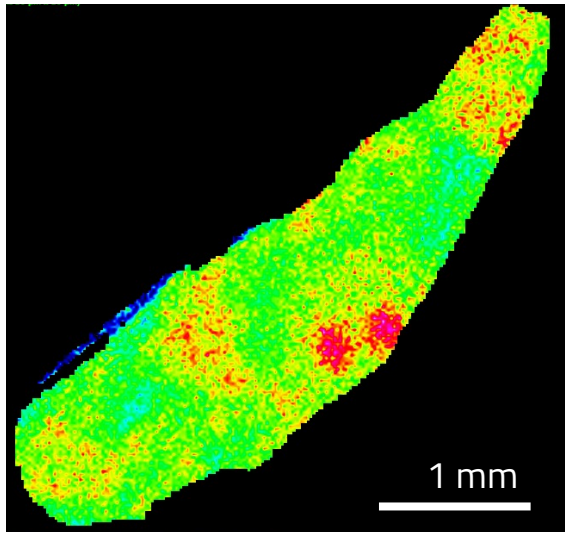
Case 2: Pre-Treatment biopsy of a lymph node

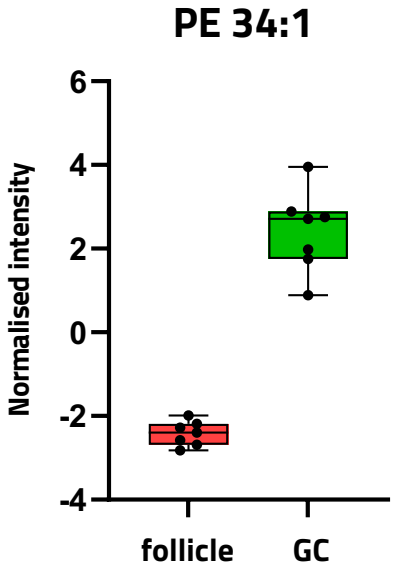


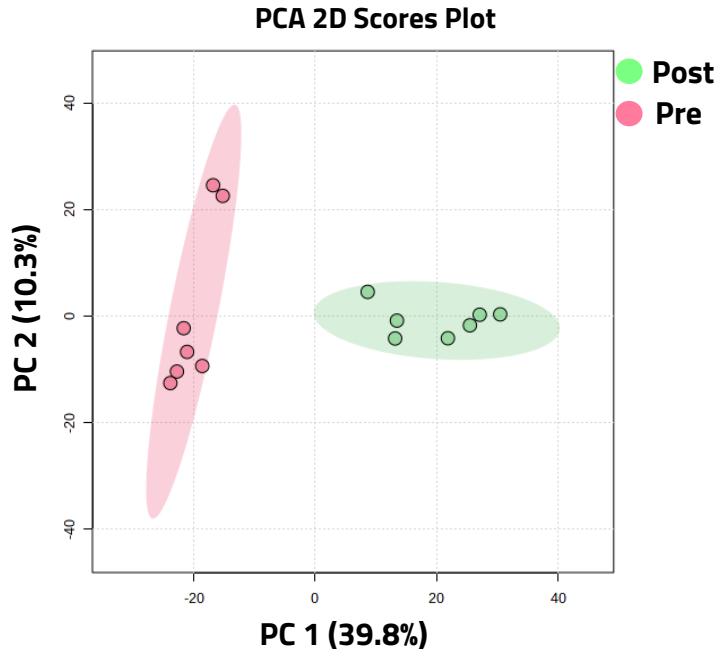
- Germinal centres, contain few T cells as these are full of maturing B cells

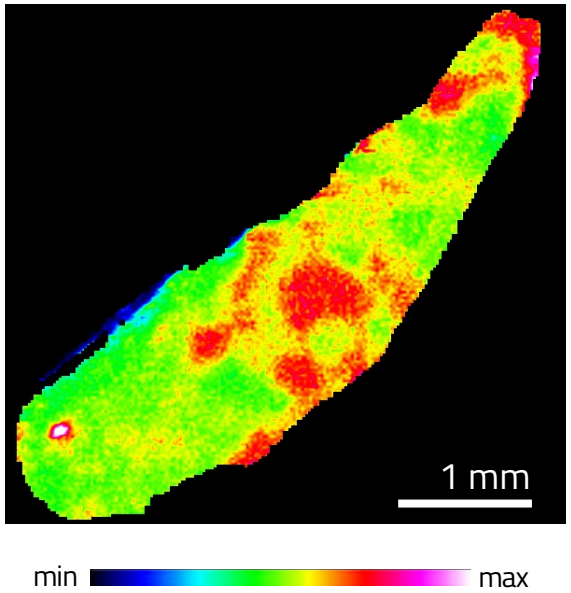
Metabolic changes revealed by MSI show an immune response in action

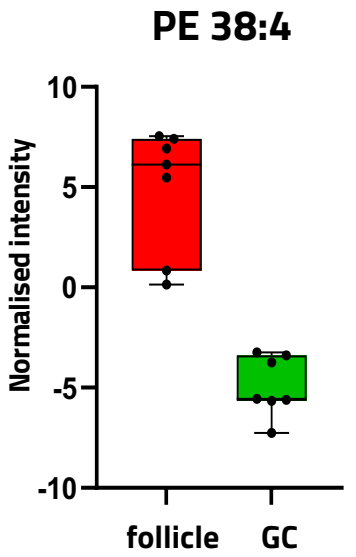




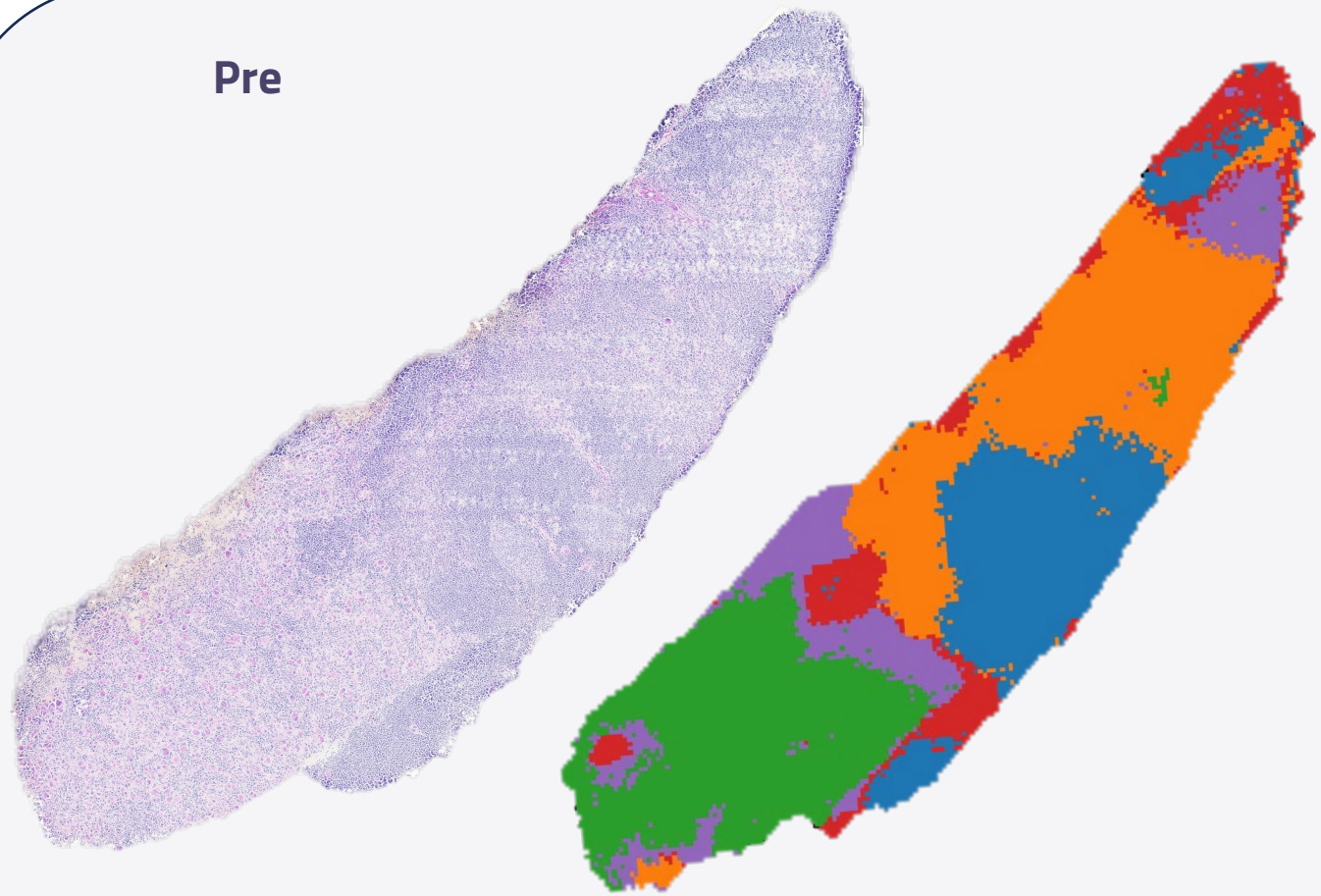


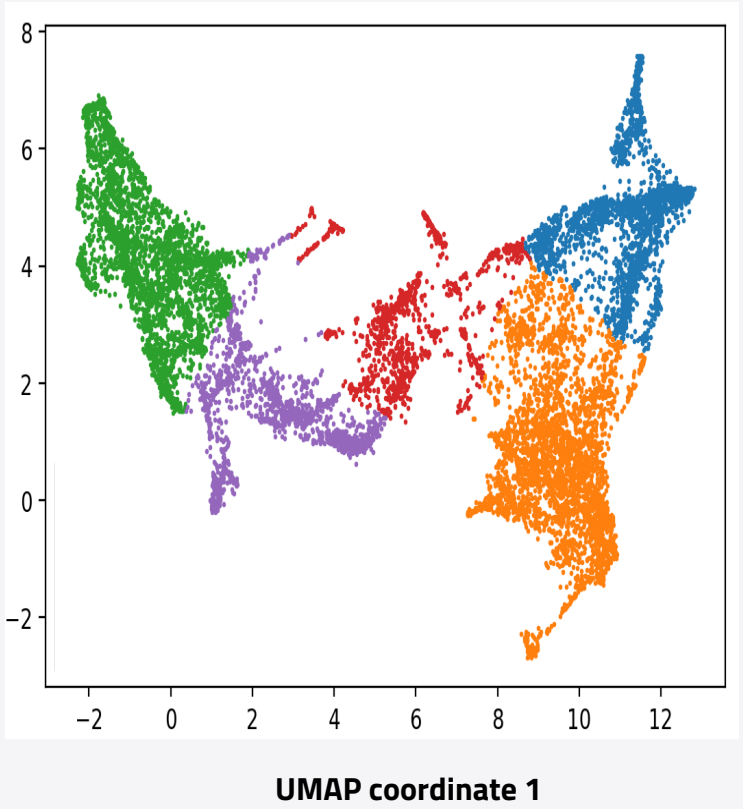






Pre and Post treatment biopsies – heterogeneity





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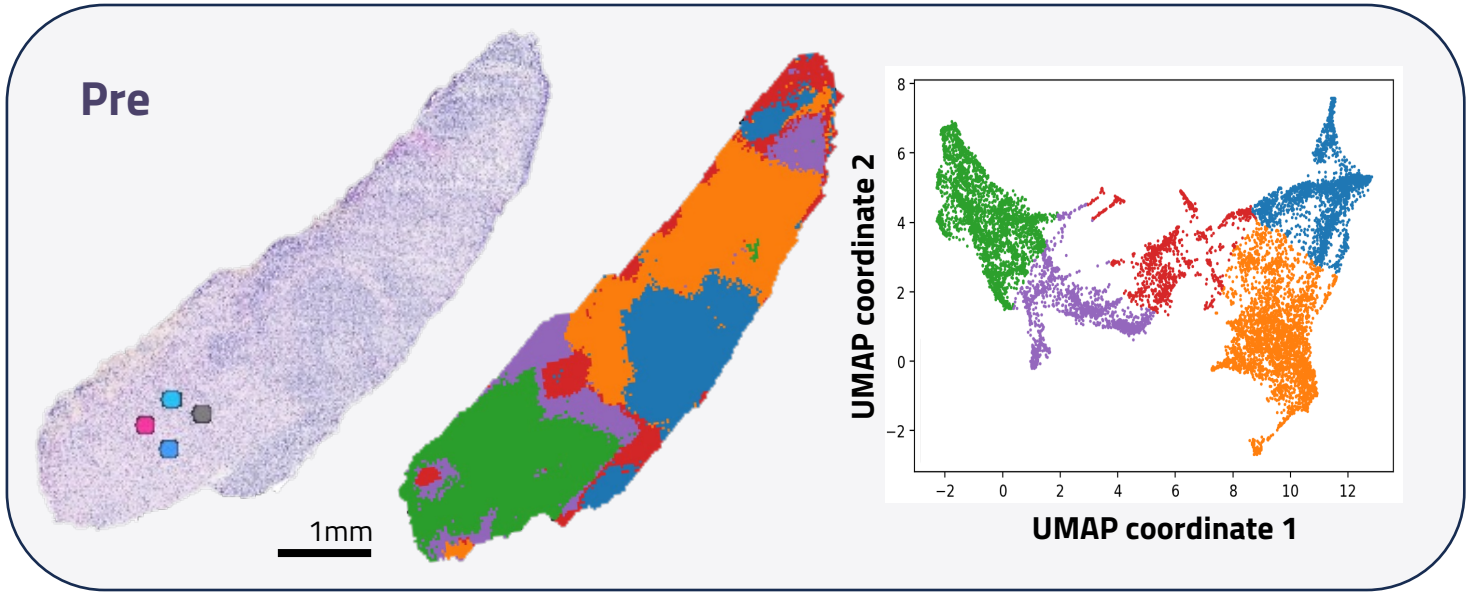
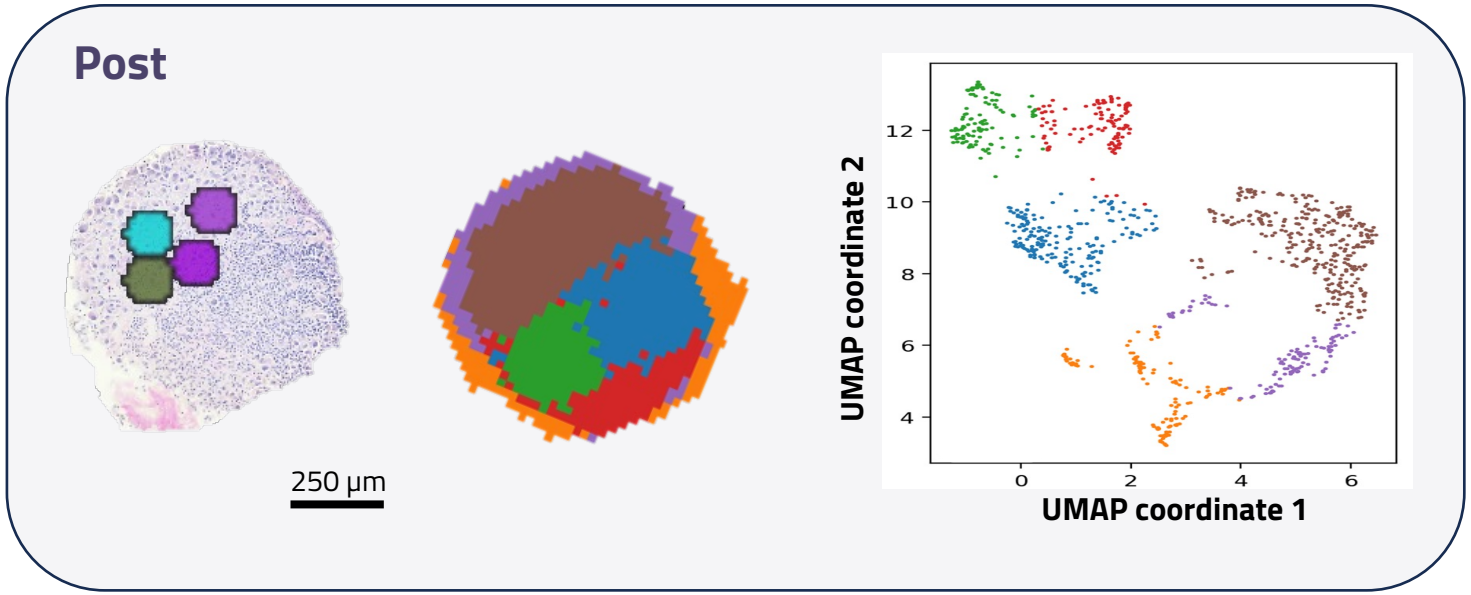
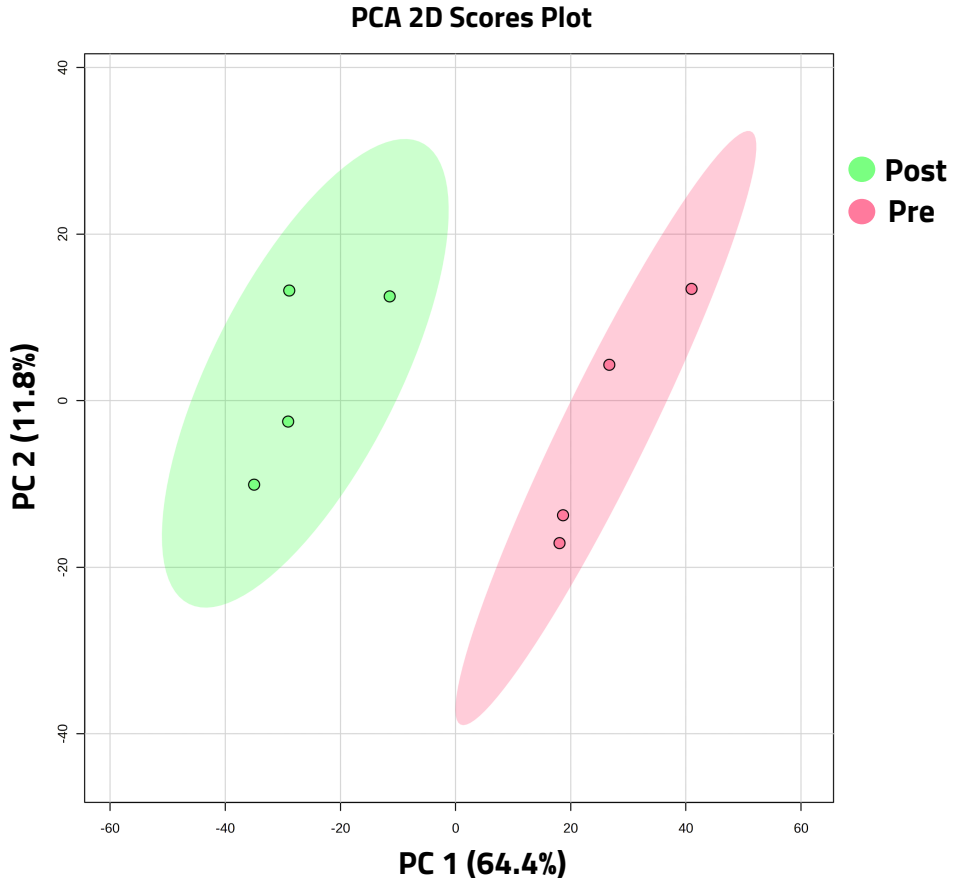
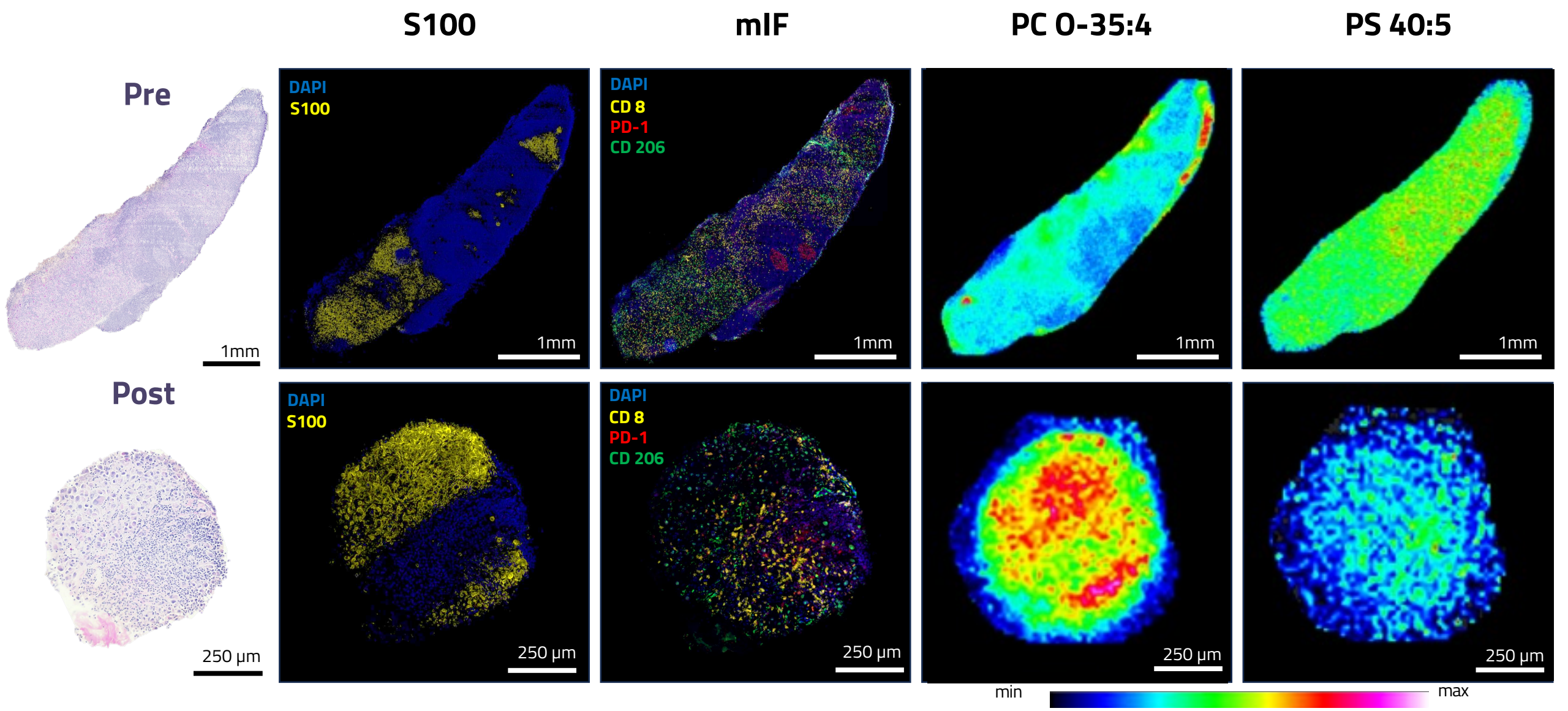




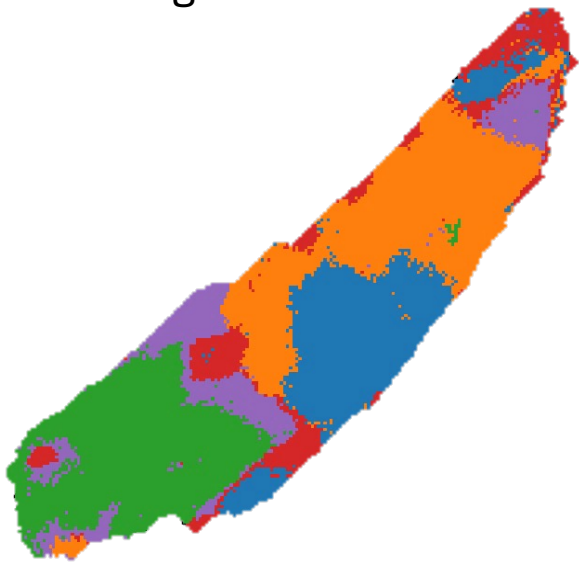


Pre and Post treatment biopsies – metabolome and protein changes



MSI data integrated into AI enabled image analysis software

UMAP Clustering of MSI data



Metabolite annotation layer

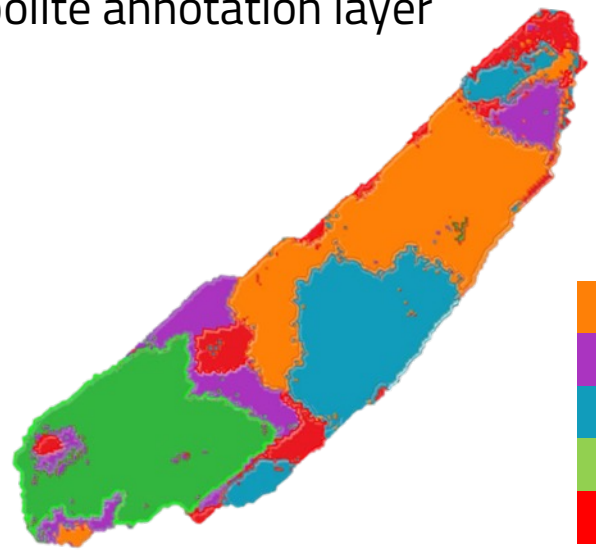
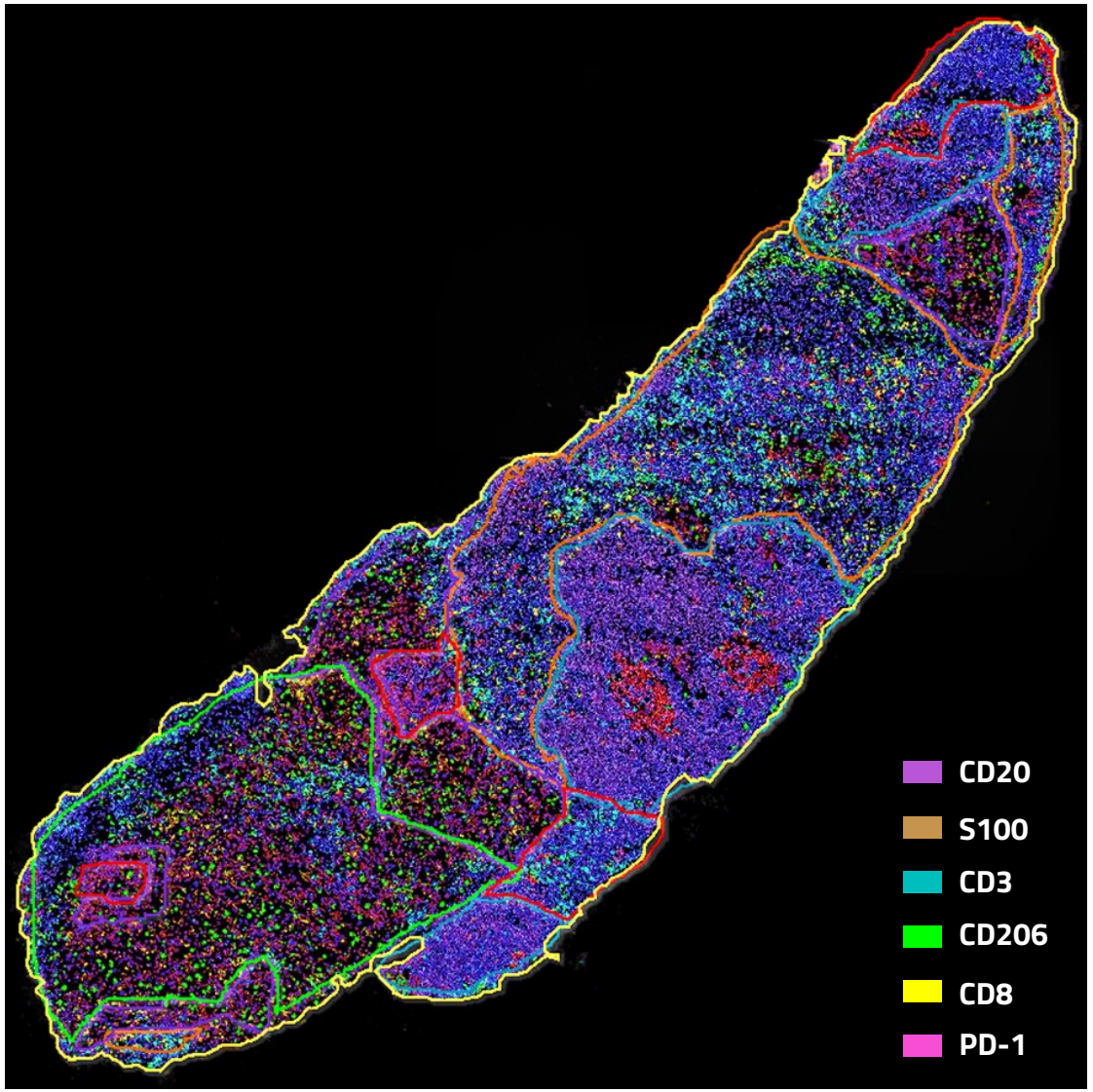


Image Analysis



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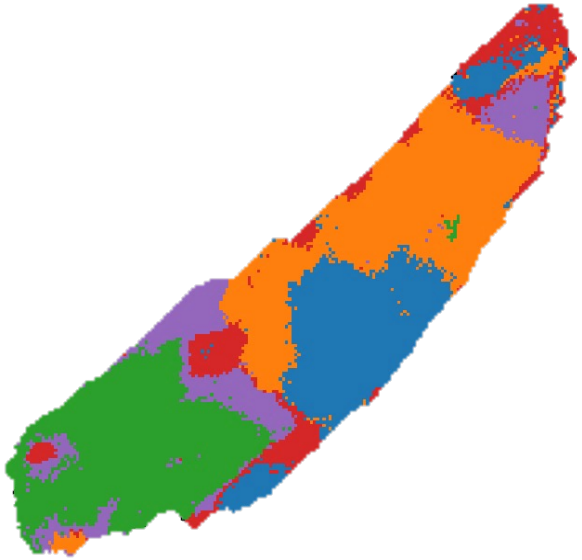

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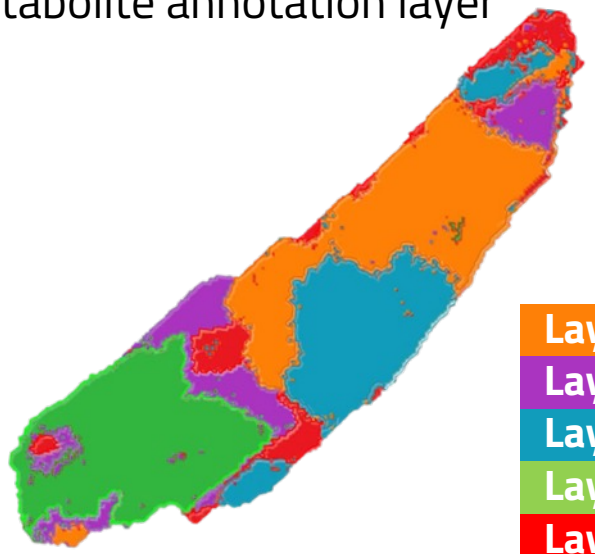

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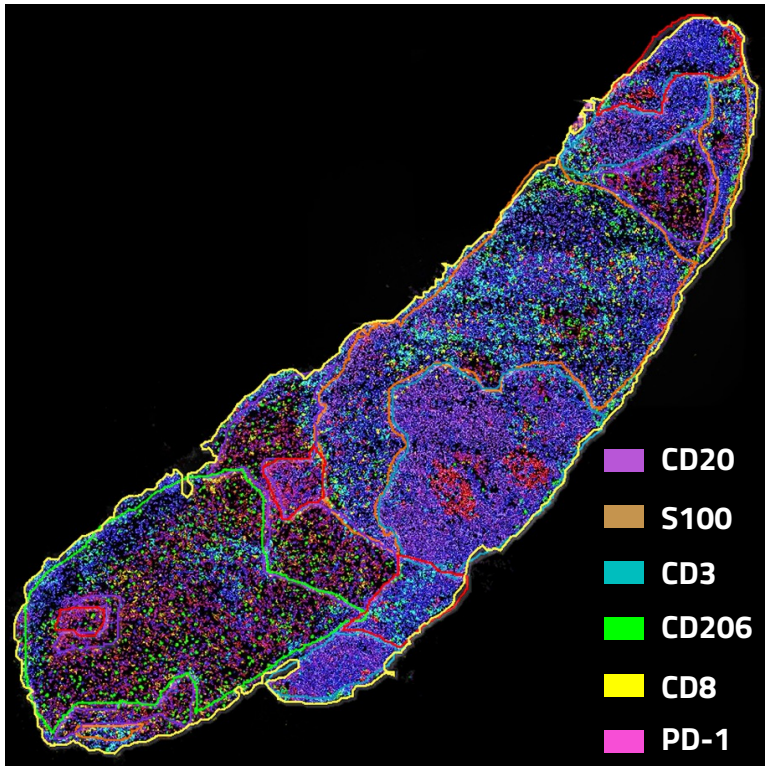
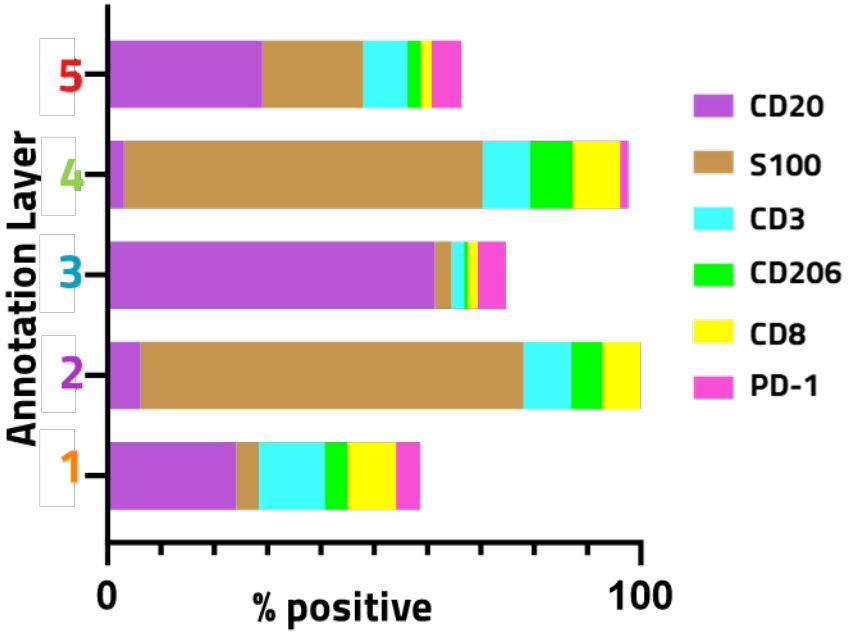
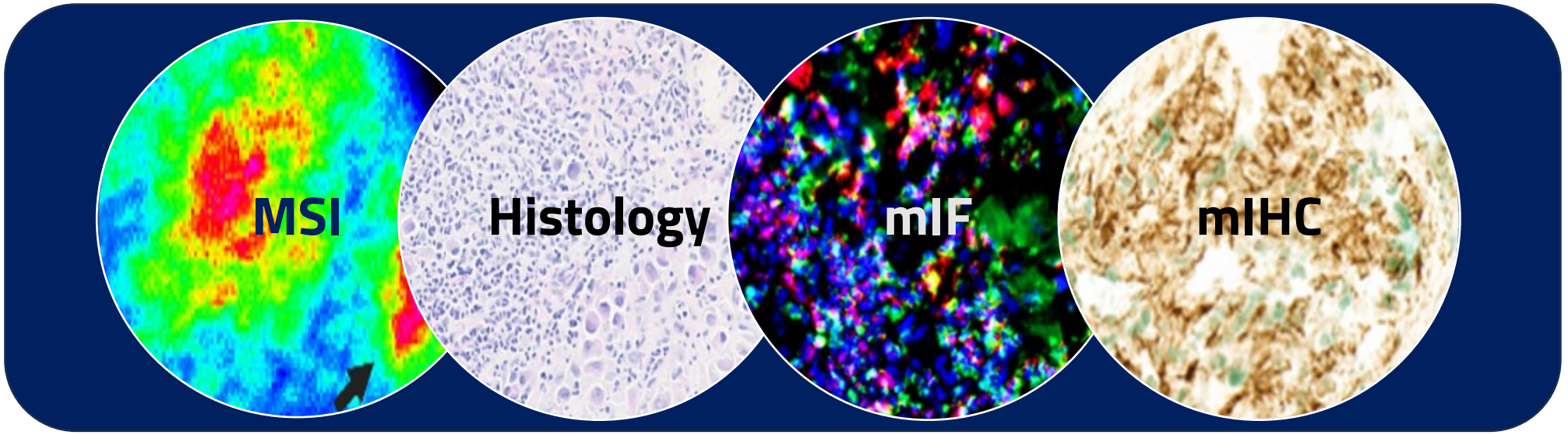




Summary: Using a single 10 µm tissue section…



- DESI MSI – successfully incorporated into image analysis workflows using a single tissue section
- AI enabled pipeline that incorporates histology, mIHC, mIF following DESI-MSI
- Well-designed clinical studies provide opportunities to investigate a patient cancer and PD response to therapy
- Metabolic changes from MSI coupled to histology reveal immune responses
- Metabolomic changes are occurring between regions of interest of high cancer cell density pre and post treatment
- Metabolic signatures can be integrated into AI analysis software for molecular phenotyping

Collaborators/Network

University of St Andrews Imaging and AI Team

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In Hwa Um
David Harrison

NuCana plc Translational Team

Mustafa Elshani
Ying Zhang

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Aglaia Skolariki
Noor Md Haris
Zhuang Boh
Sarah P Blagden
Natalie Cook
TR Jeffry Evans
E. Ruth Plummer

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