Opportunities and Challenges in Multi-Model, Multi-Dimensional Image Analysis for Drug Discovery

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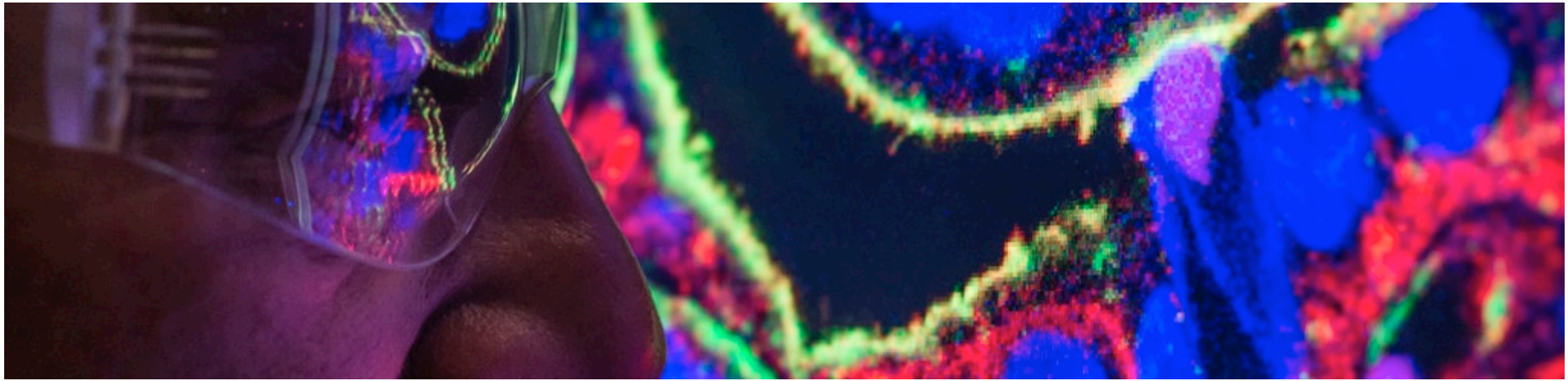
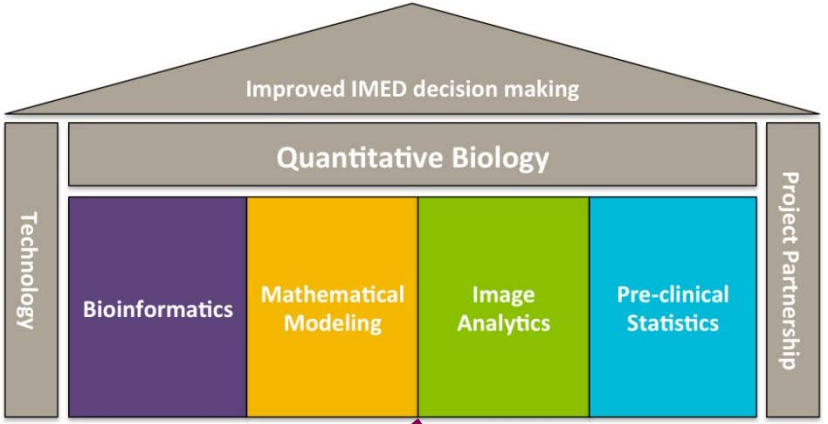
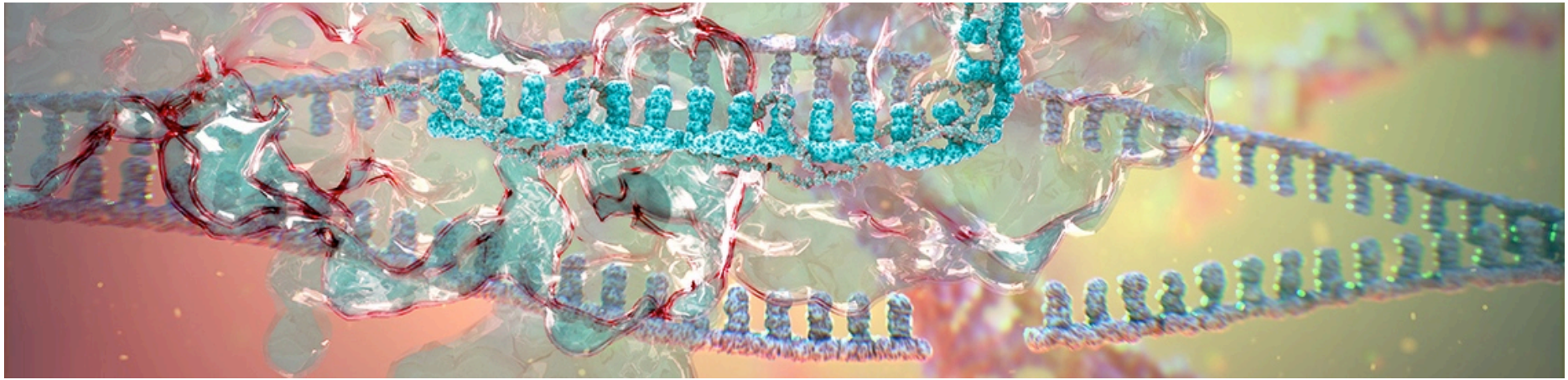


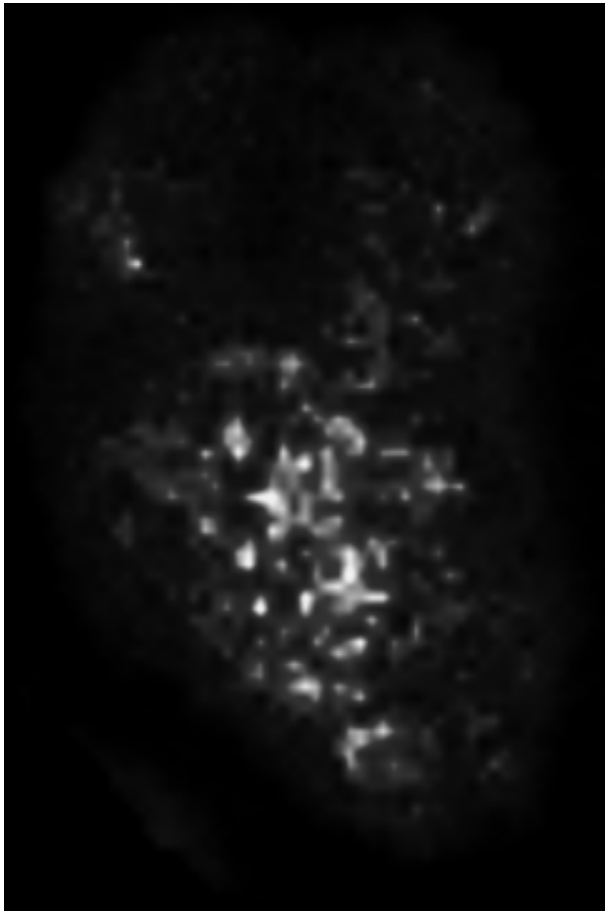
the Quantitative Biology Department (QuBi)

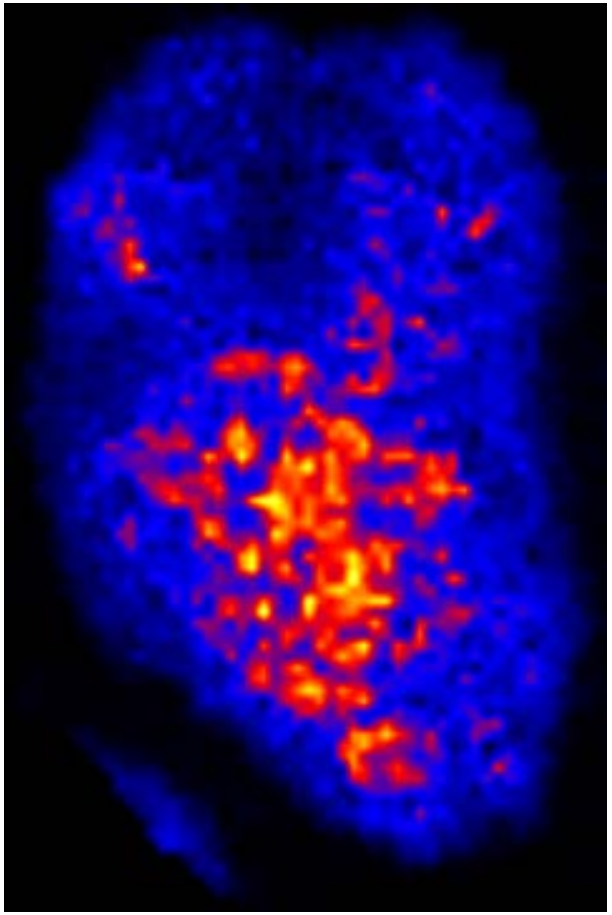


Mass Spectrometry Imaging (MSI)



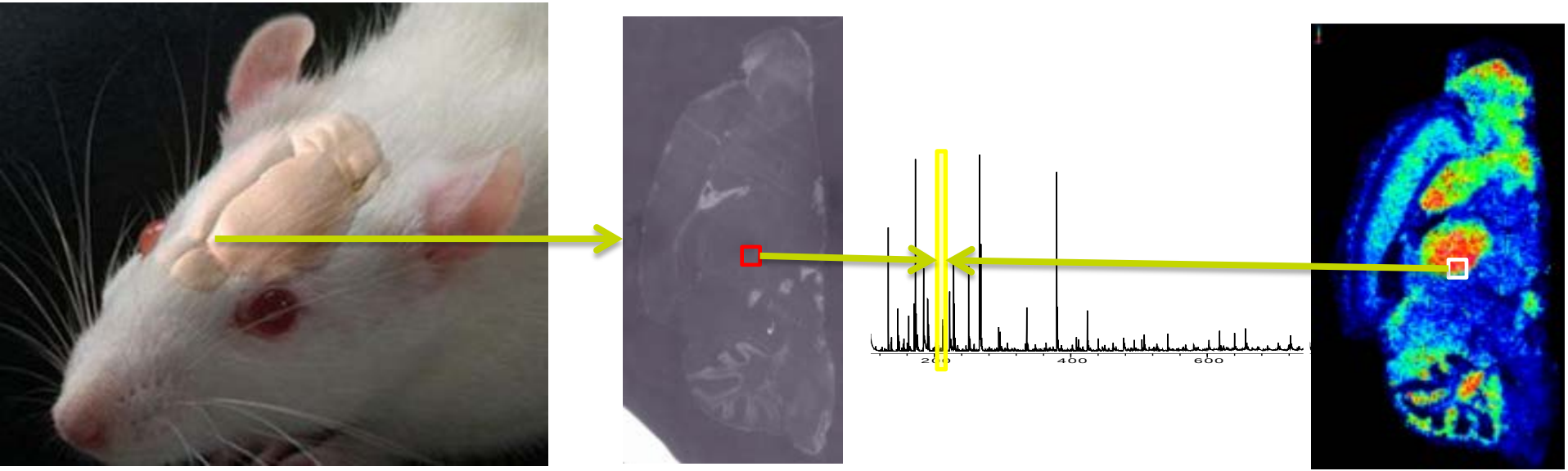
Mass Spectrometry Imaging





What is Mass Spectrometry Imaging?

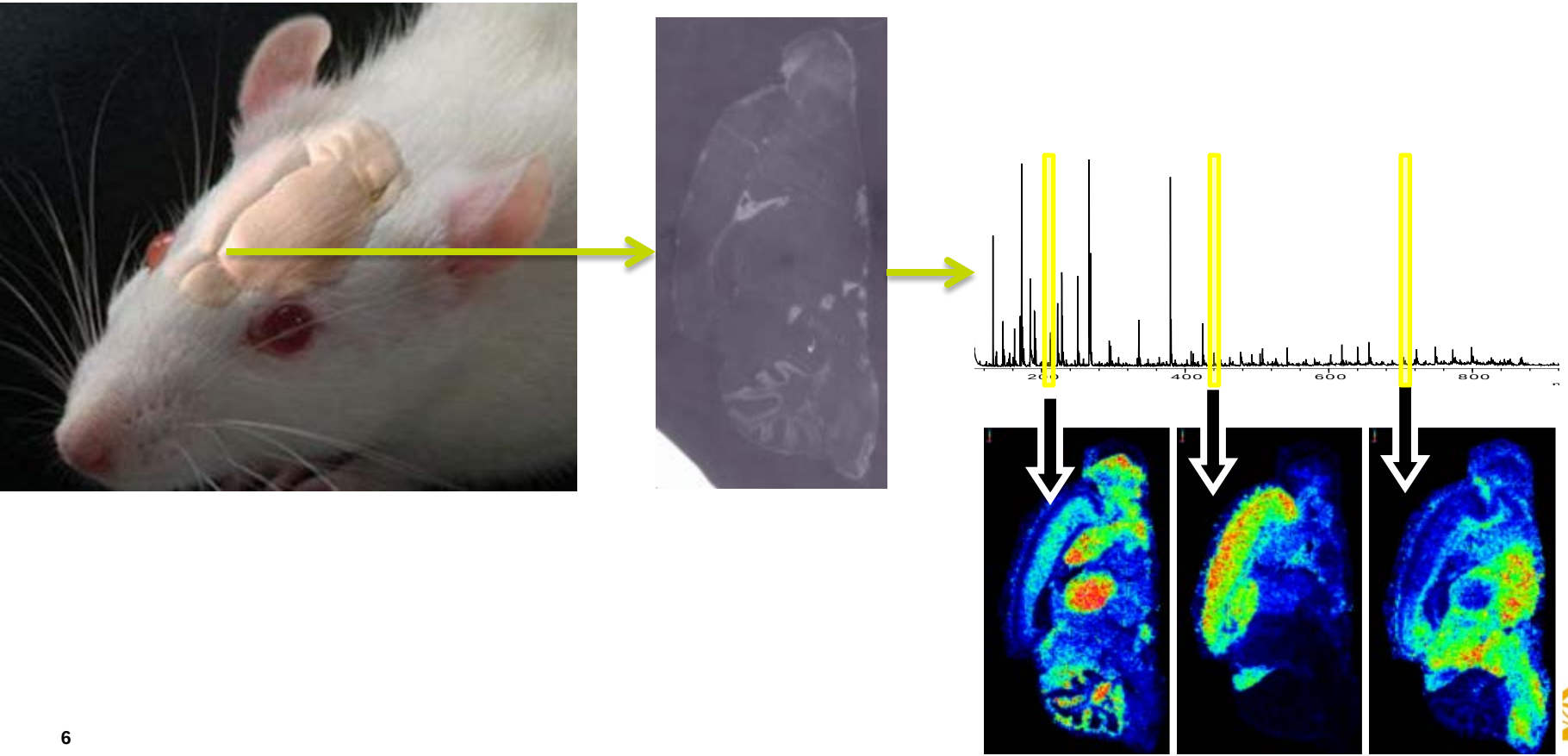
A single pixel in an MSI image is corresponding to a vector of numerical values.



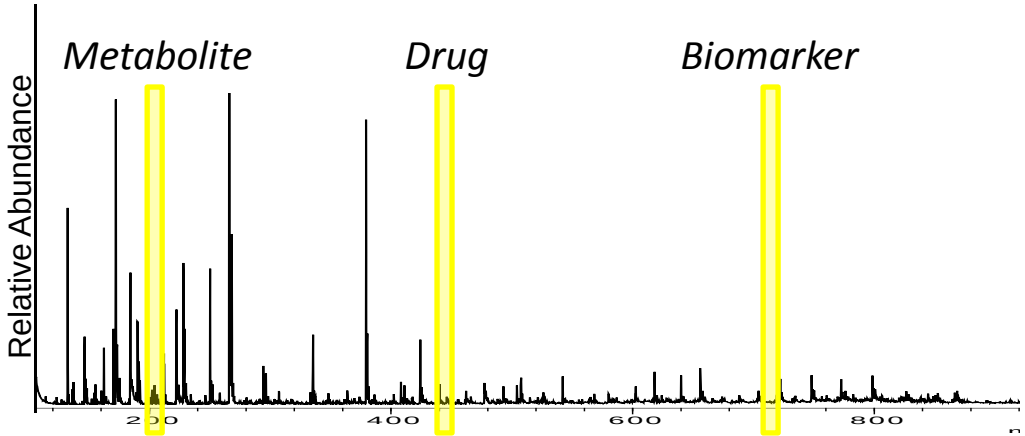
Fresh frozen sample

an MSI image

What is Mass Spectrometry Imaging?

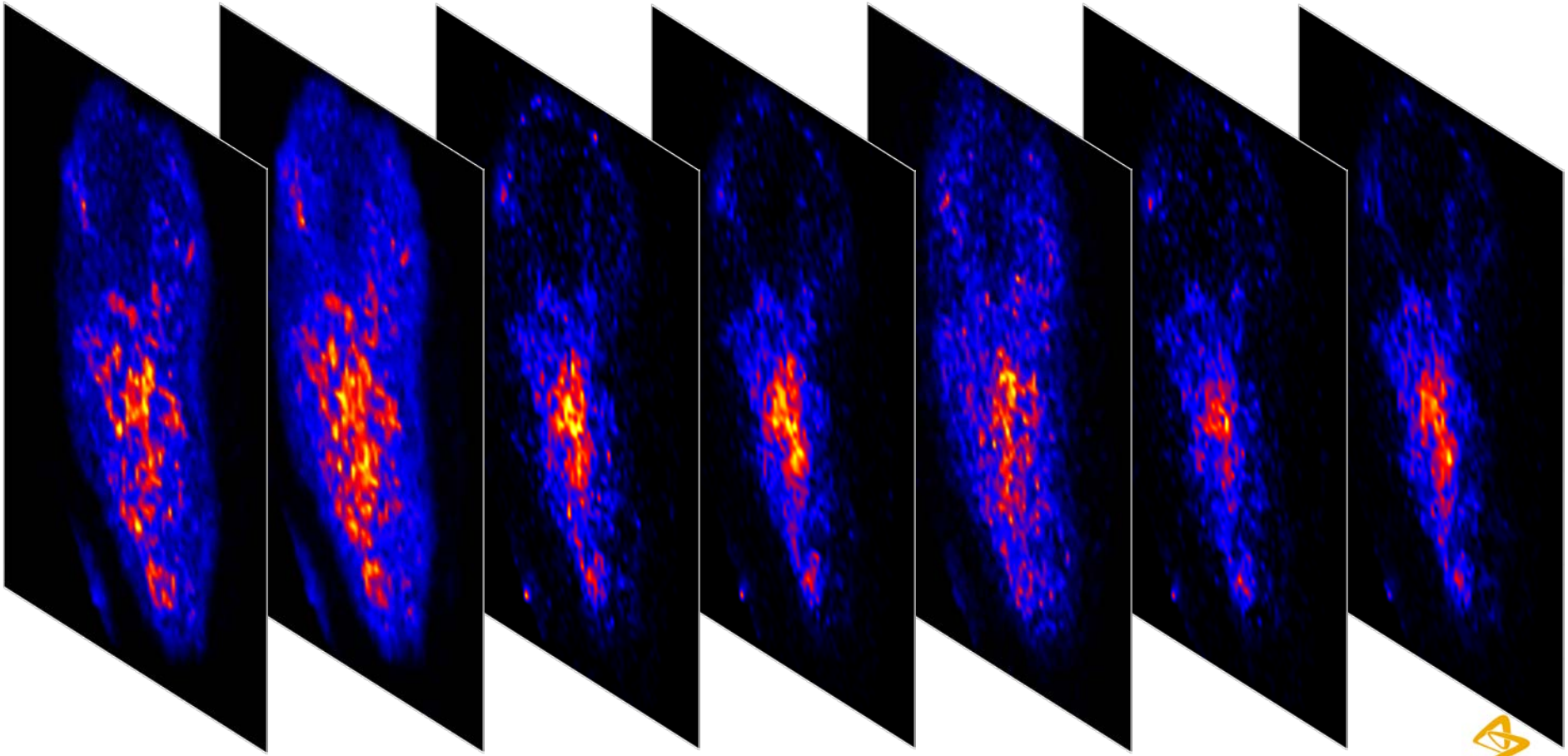


Why Mass Spectrometry Imaging?



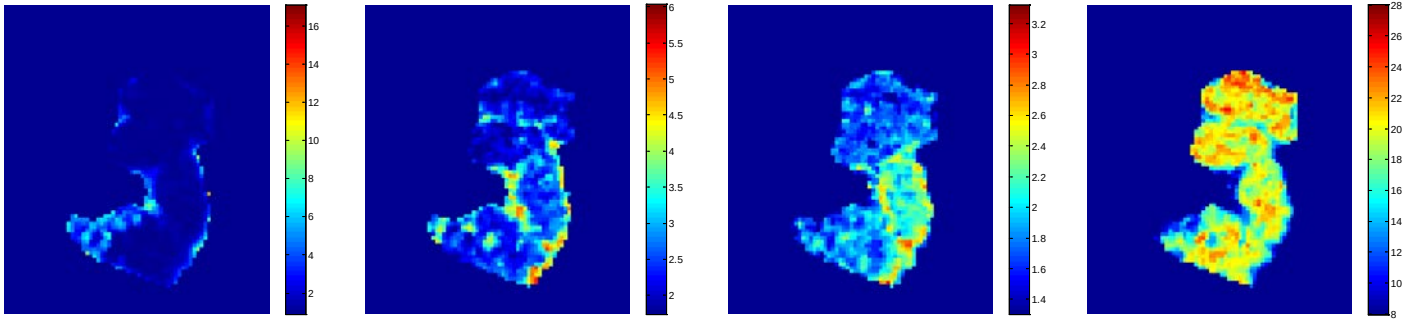
1. MSI is able to detect and visualise the chemical composition.
2. MSI has ability to describe metabolite, drug concentration and biomarkers simultaneously.
3. MSI is applicable to investigate drug's efficacy and safety.
4. MSI is label-free.

MSI – Relationship Among Metabolite, Drug & Biomarker

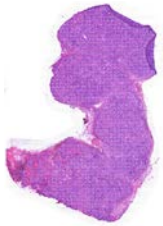


*J. Cappell, University of Maastricht, unpublished work.

MSI + H&E



MSI images

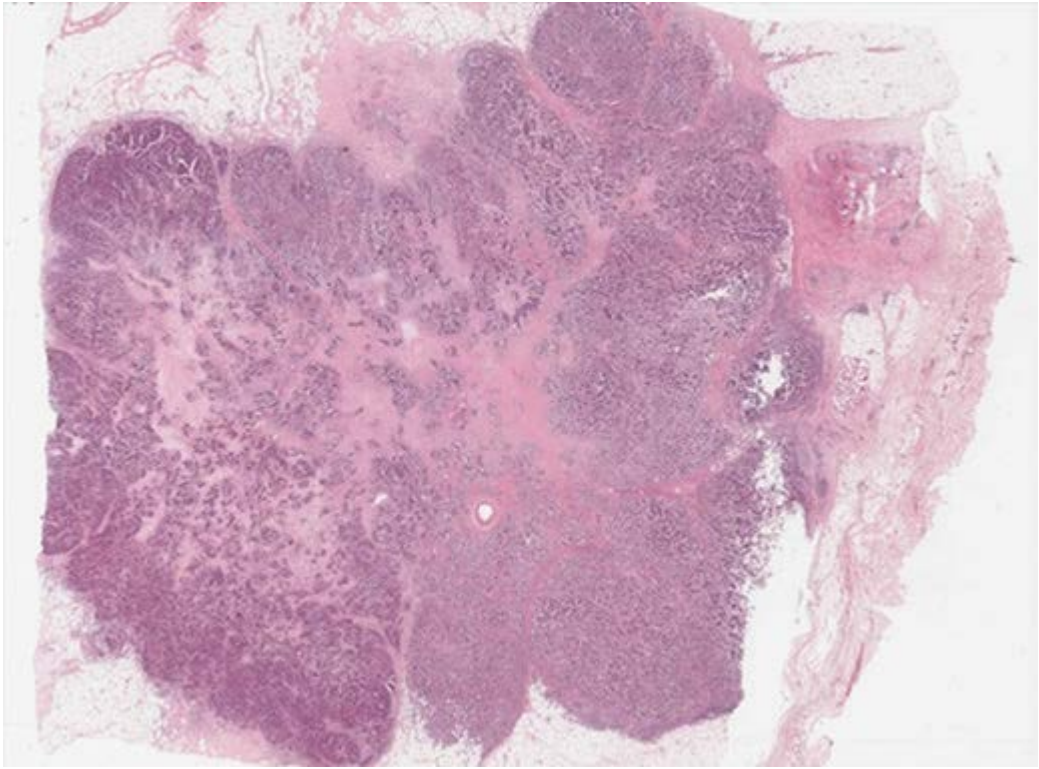


Haematoxylin & Eosin (H&E)

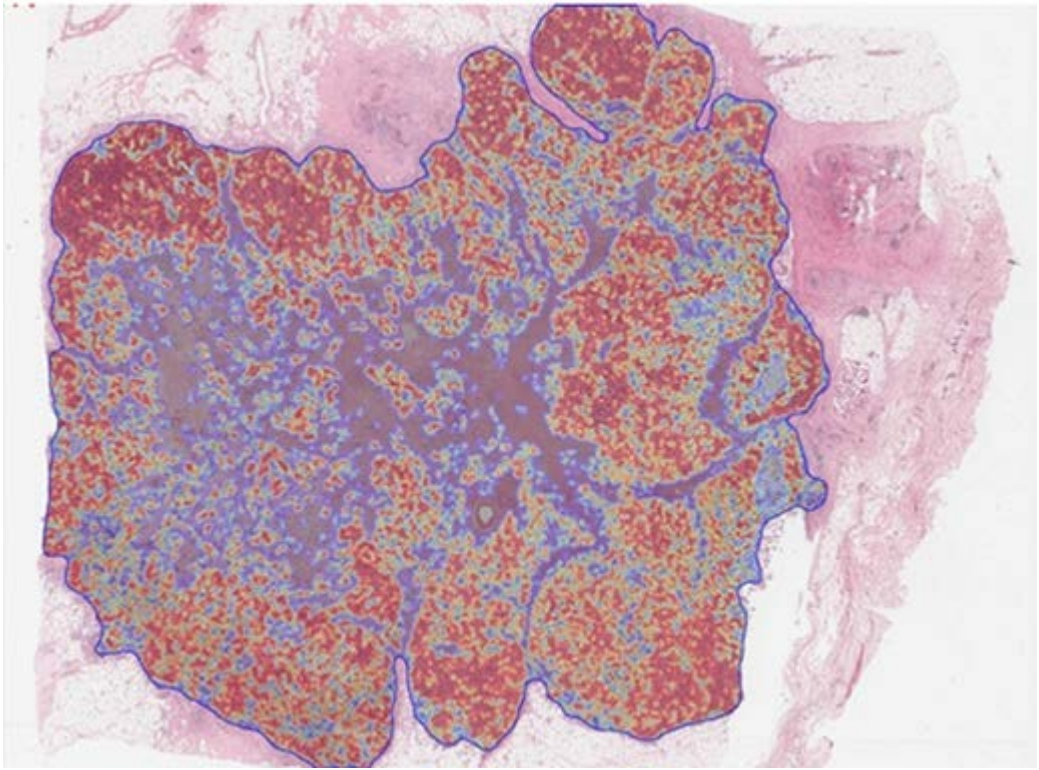
To look at the morphology, tissue structure

*J. Cappell, University of Maastricht, unpublished work.

H&E



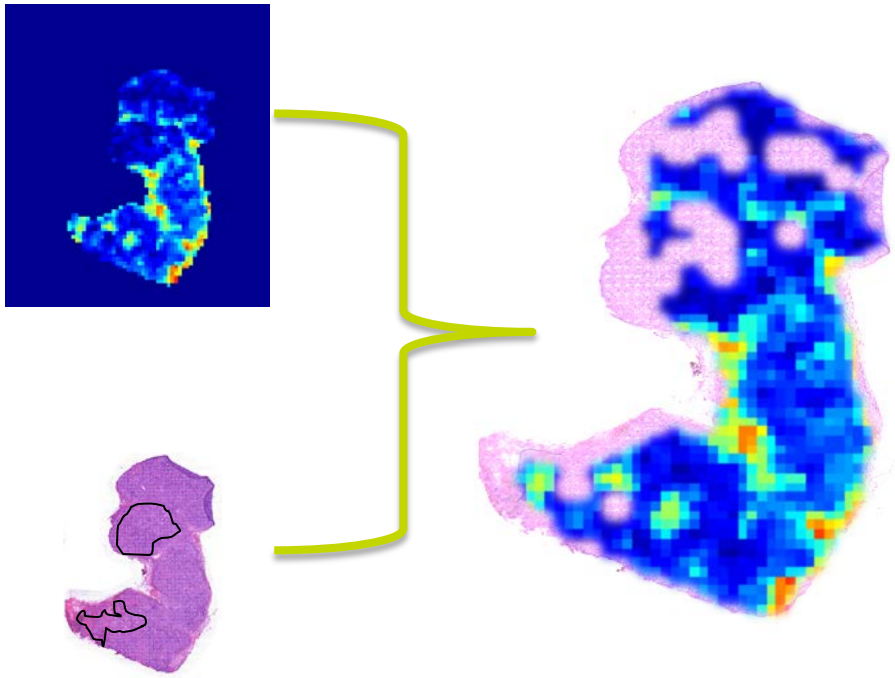
H&E



11 Y. Wang, et al. "Automated tumor analysis for molecular profiling in lung cancer." *Oncotarget* 6.29 (2015): 27938.

H&E + MSI (Metabolite)

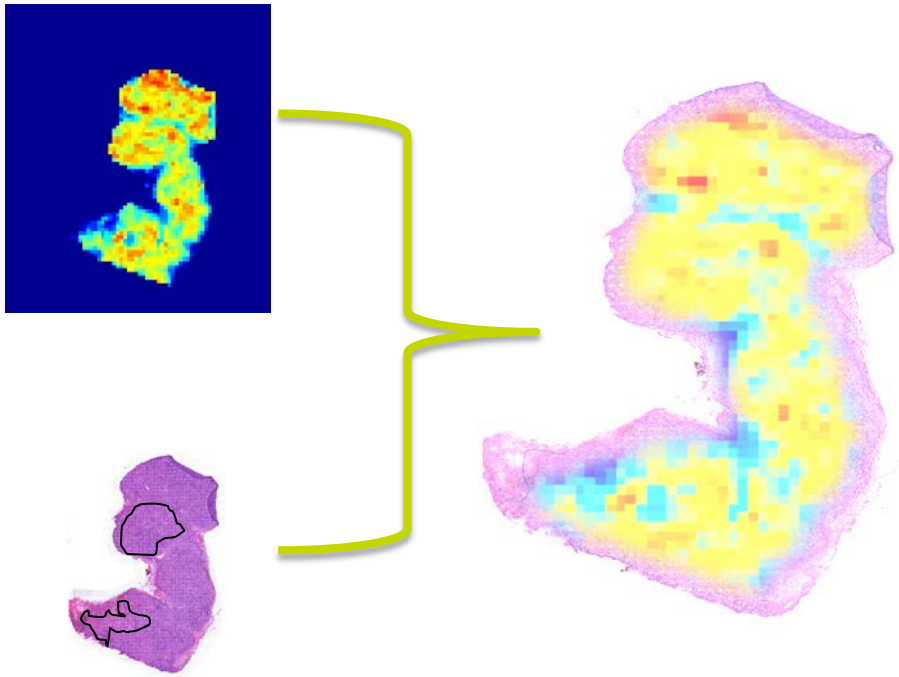
- The spatial distribution of metabolite
- The correlation between tissue morphology with metabolite molecules



H&E + MSI (Drug)

- The spatial distribution of drug X
- The relative concentration of drug X at different tissue locations
- The relationship between drug X and tissue morphology

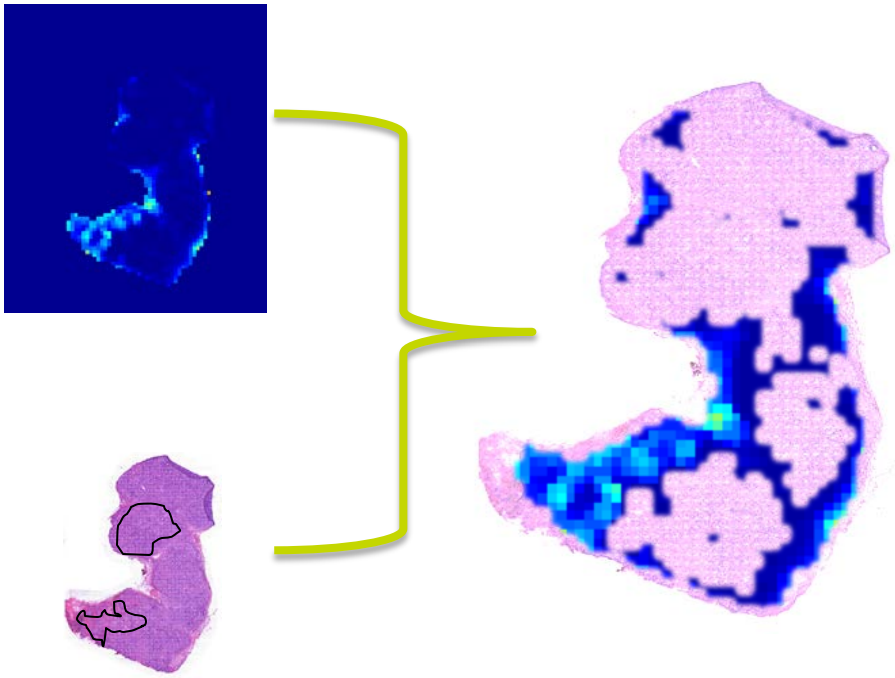
Drug X



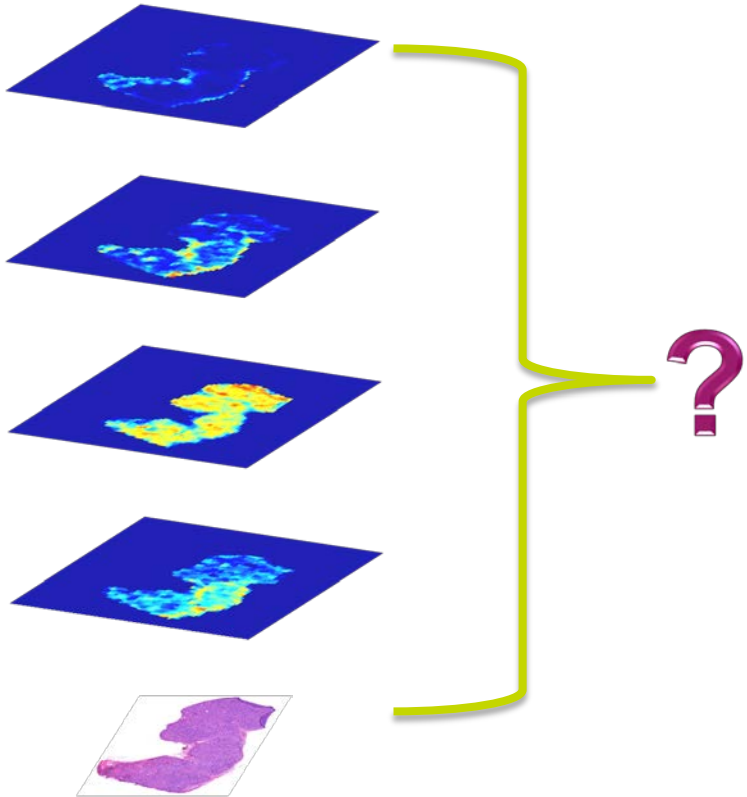
H&E + MSI (Biomarker)

- The location and spatial distribution of biomarker A
- The relative level of expression of biomarker A
- The relationship between biomarker A and tissue morphology

Biomarker A



H&E + MSI (Metabolite, Drug, Biomarker)

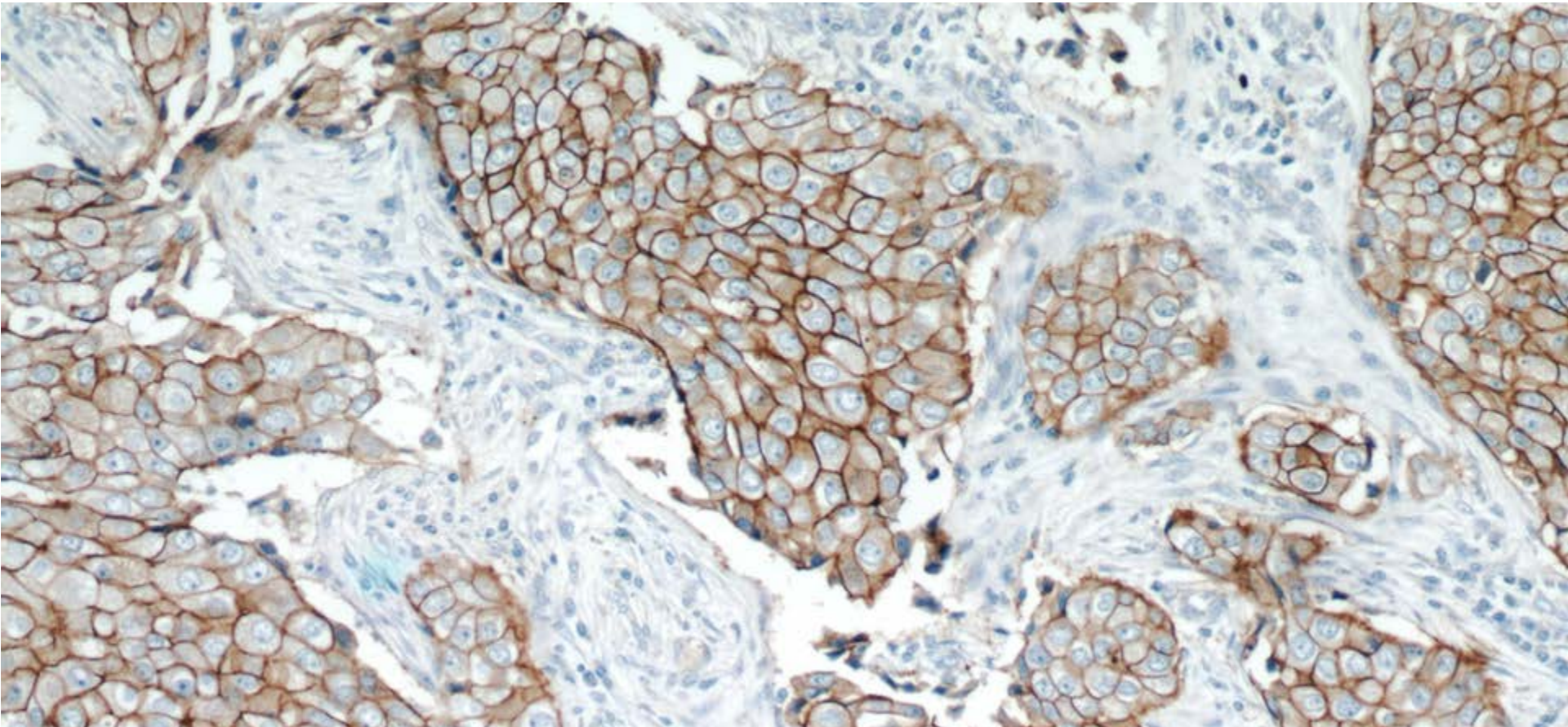


Foreseeable problems:

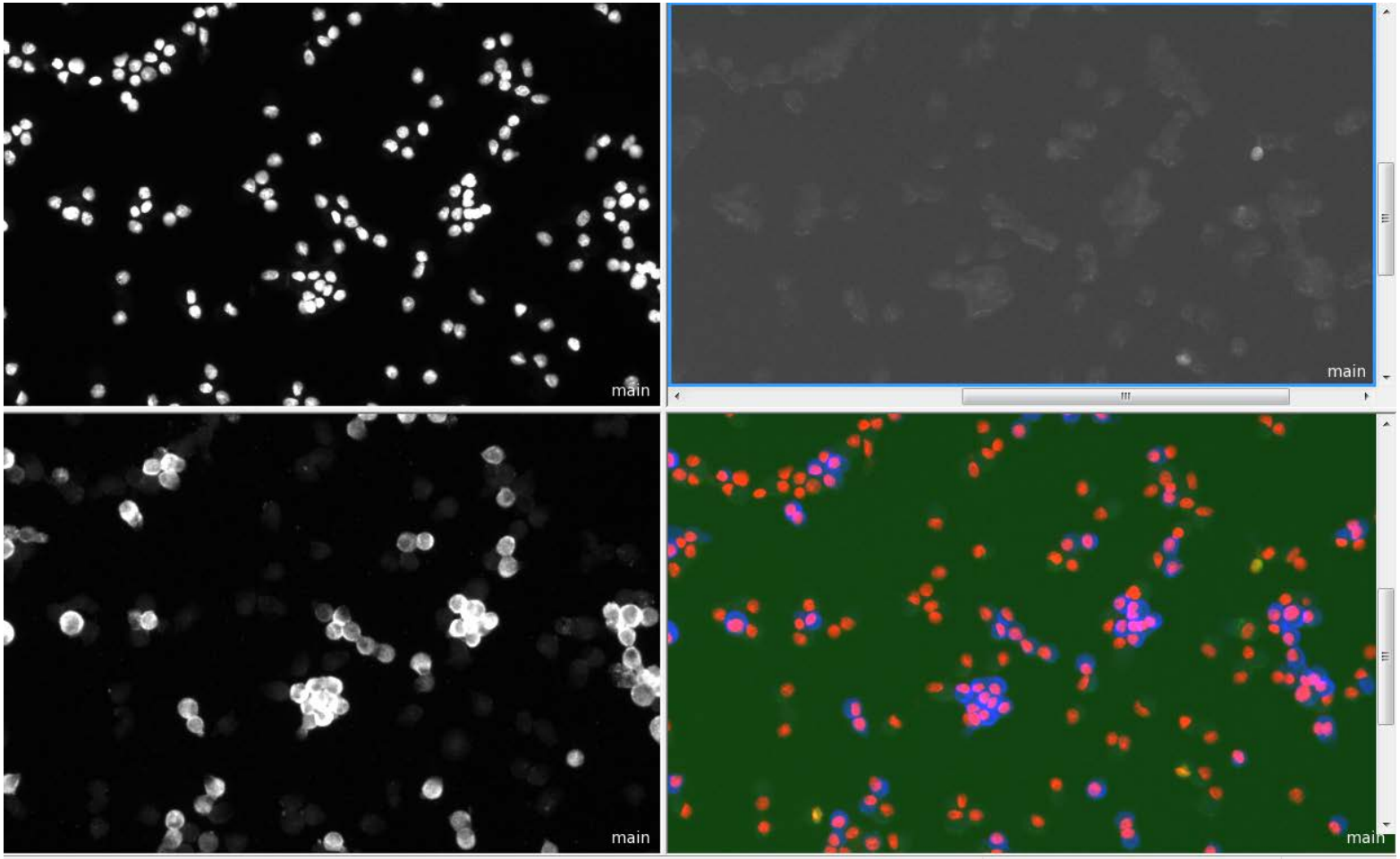
1. Image Registration between MSI and H&E
2. Visualisation
3. Tissue image processing (e.g. machine learning for the recognition of tumour *)
4. Multi-dimensional data analysis:
   - Multiple MSI images
   - MSI intensity + spatial locations
   - H&E tissue structure
   - Regional relationships
   - Relationship among metabolite, drugs and biomarkers)
   - Machine learning for rapid matching

*Y. Wang, et al. "Assisted diagnosis of cervical intraepithelial neoplasia (CIN)." *IEEE Journal of Selected Topics in Signal Processing,* 3.1 (2009): 112-121.

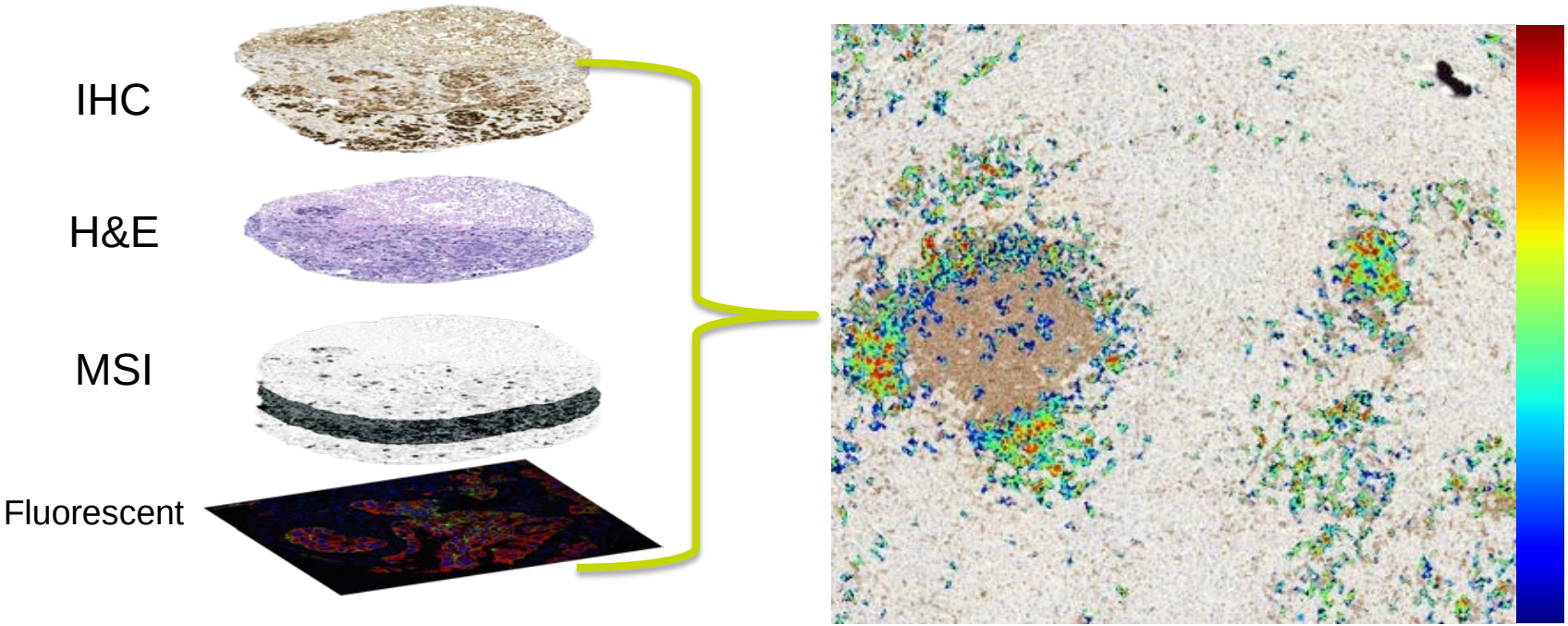
Immunohistochemistry (IHC)



Fluorescent Multiplexing

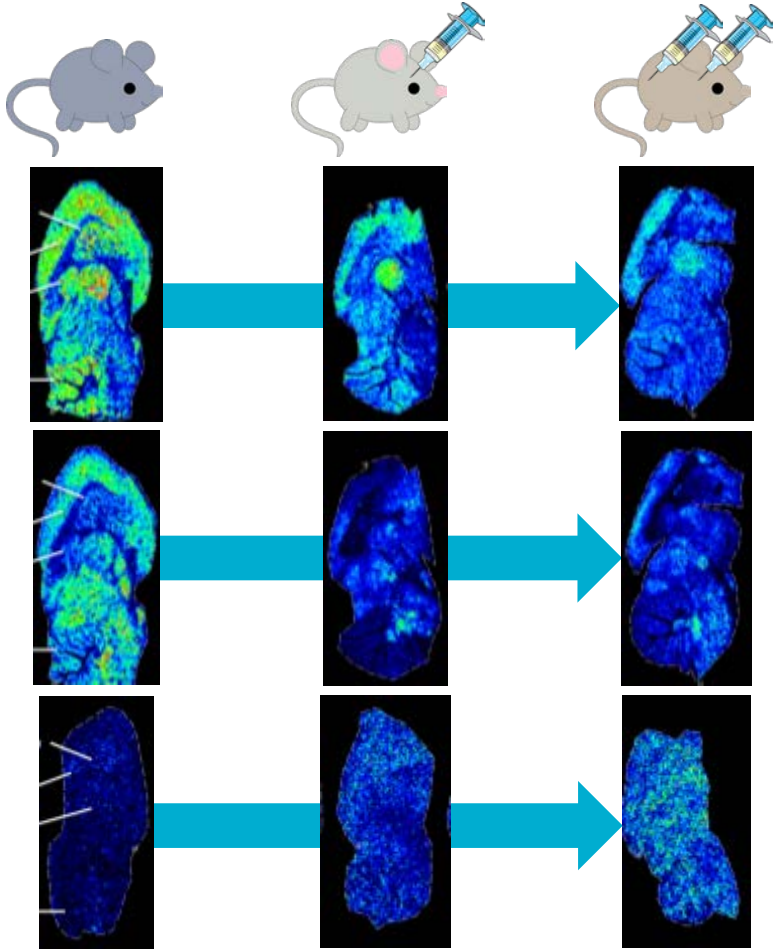


MSI + H&E + Immunohistochemistry (IHC) + Fluorescent



Multiple image modalities: ***m*** **IHC +** ***n*** **H&E +** ***p*** **MSI +** ***k*** **Fluorescent**

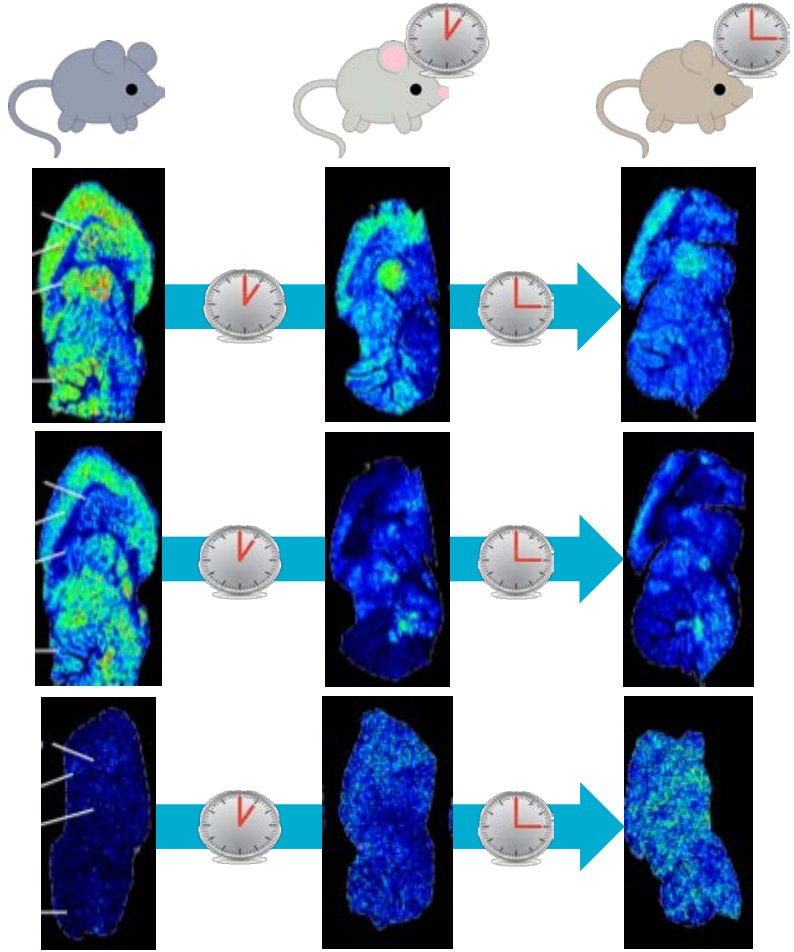
MSI for Dose Responses



Foreseeable problems:

1. Extra dimension of data
2. MSI Image registration (not from a same host)
3. The comparison of dose responses

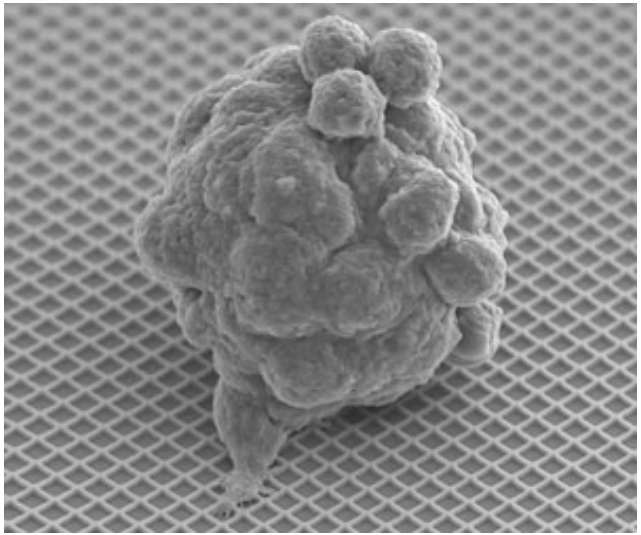
MSI for Kinetics



Foreseeable problems:

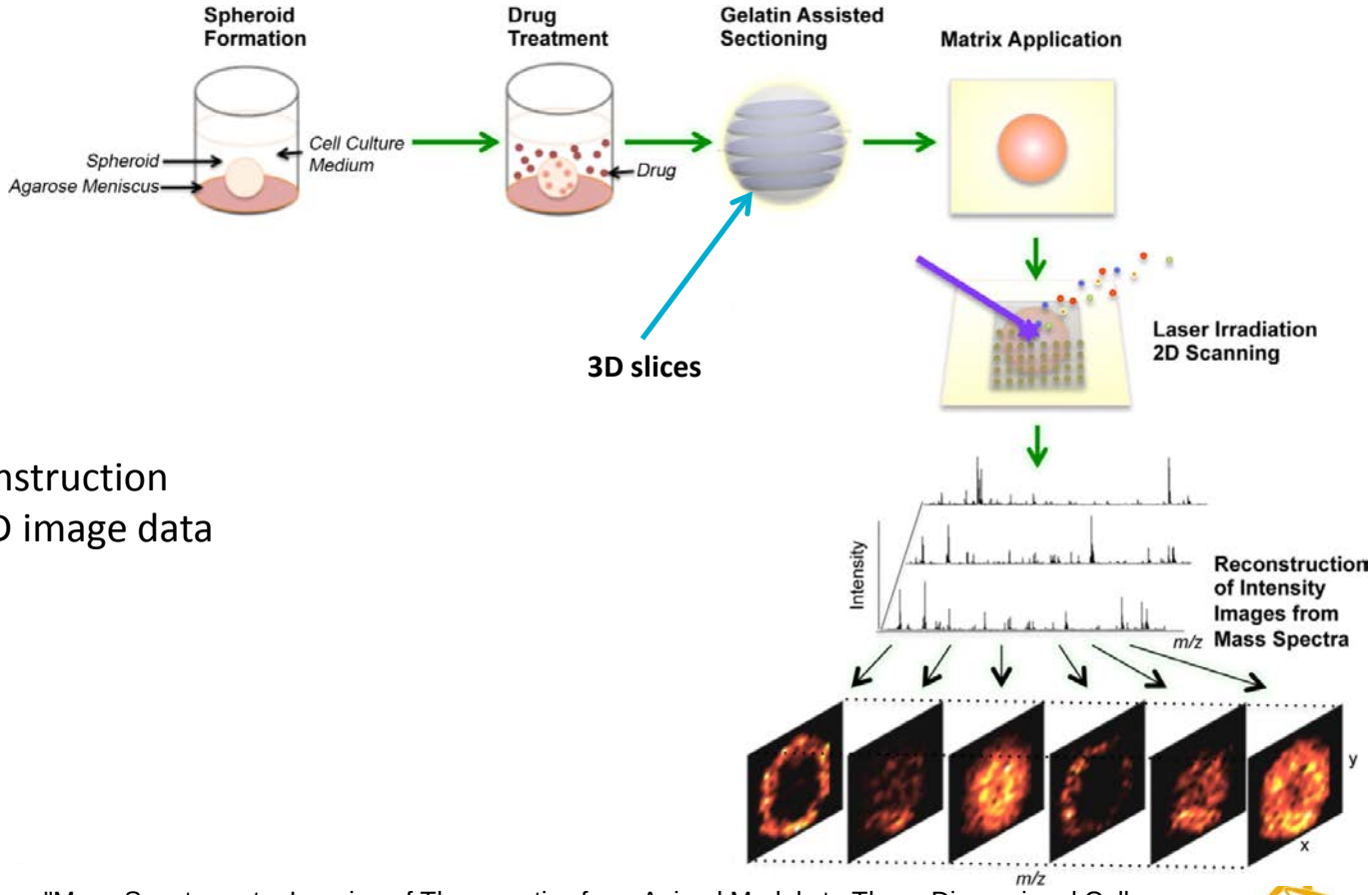
1. Extra dimension of data
2. MSI Image registration (not from a same host)
3. The comparison of drug responses over a period of time

The 3D Spheroid Model



85% of early clinical trials for novel drugs fail.

MSI for 3D Spheroid Models



Foreseeable problem:

3-dimensional image reconstruction
Comparison of complex 3D image data

Liu, Xin, and Amanda B. Hummon. "Mass Spectrometry Imaging of Therapeutics from Animal Models to Three-Dimensional Cell Cultures."*Analytical chemistry* 87.19 (2015): 9508-9519.

MSI Image Analysis

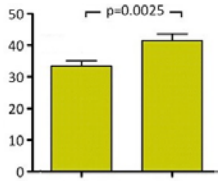
Multiple image modalities:

m IHC + *n* H&E + *p* MSI + *k* Fluorescent

Multiple image dimensions:

2D + colour channels + dose responses + kinetics + 3D

£1 million + 1TB + 6 months later



Difficult

Readily performed

Formalin fixed paraffin embedded
Cross-linking Diffusion Suppression

Archived samples
Incorrect collection and storage

Free drug from total
Does break interactions

Antibodies or ADC
Low copy number/detection

Sub-cellular
Instrument limitations

Proteomics
Mass range limited (<20kDa)

Covalently bound
Doesn't break bonds

Clinical samples
Sample collection

Terminal sampling required
No monitoring

Drug and metabolite
Differentiate by *m/z*

On-tissue quantitation
Multiple approaches

Pathology support
Label-free and multiplexed

Investigatory
Comparing tissue for unknowns

Target engagement
Biomarker analysis

Efficacy
Studying unanticipated outcomes

Blood poor surrogate
Blood brain barrier / tumours

What Machine Learning Could Do to Help?

- MSI images are a stack of images.
  - The matching between tissue morphology/structure (from H&E) and MSIs
  - The matching between IHC expression and MSIs
  - The matching between Fluorescent signals and MSIs

- We expect machine learning to play a key role in MSI image analysis, and be aware of the following factors:
  - Expert input
  - Uncertainty
  - Unknown

Summary

1. At AstraZeneca, we are investigating novel imaging modalities.

2. We are generating a large amount of multi-modal image data, and in turn leads to a large amount of multi-dimensional numerical data.

3. We are pursuing better image and data analytical methods, machine learning approaches to
   - Unleash the power of multiple image modalities (IHC + H&E + MSI + Fluorescent)
   - Unleash the power of multiple dimensional data (2D + colour channels + dose responses + kinetics + 3D)
   - To better understand biology and drugs' mechanism of actions.

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