Visualising the biodistribution of Complex Drugs in tissues with Mass Spectrometry Imaging

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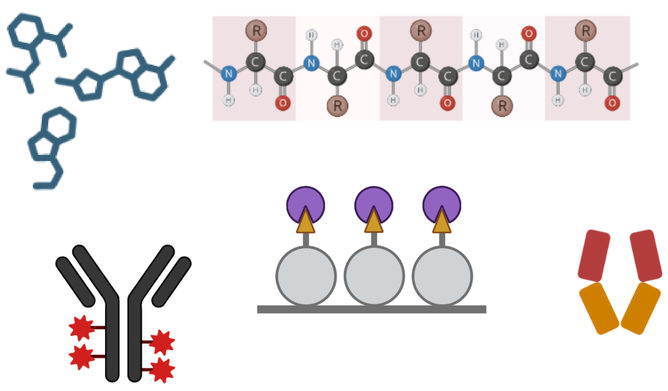
Introduction

Advances in biotechnology research have accelerated the development of innovative therapies, often referred to as 'Complex Medicines'. This term includes biologics, and conjugated complexes with active ingredients, complex formulations, or complex mechanisms of delivery. Understanding the biodistribution of these therapeutics used in targeted treatment is key for the development of new therapies.

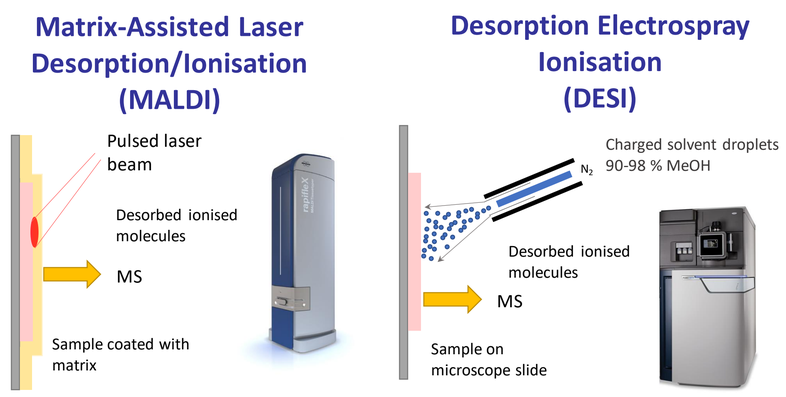
At Medicines Discovery Catapult, one of our main areas of focus is the ex vivo assessment of complex drug candidates using Mass Spectrometry Imaging (MSI). Here, we present two case studies in the preclinical phase where a complex formulation was administered in a targeted way (non-systemic) in vivo, and assessment was carried out ex vivo using either DESI-MSI or MALDI-MSI.

MSI strategies: Method development and image acquisition



Project planning

Setting the aim of the biodistribution study, defining the target complex medication and target organs. Complex medications include biological and non-biological active ingredients such as drug products, peptides, antibody conjugates or any other complex dosage form or product with a complex route of delivery.



Method development

Analytical methods enabling targeted imaging of the spatial distribution of a compound. During the method development, the ionisation of the compound of interest and the detection limit are assessed. Ion suppression and detection of the target molecule is also tested in a biological matrix environment.

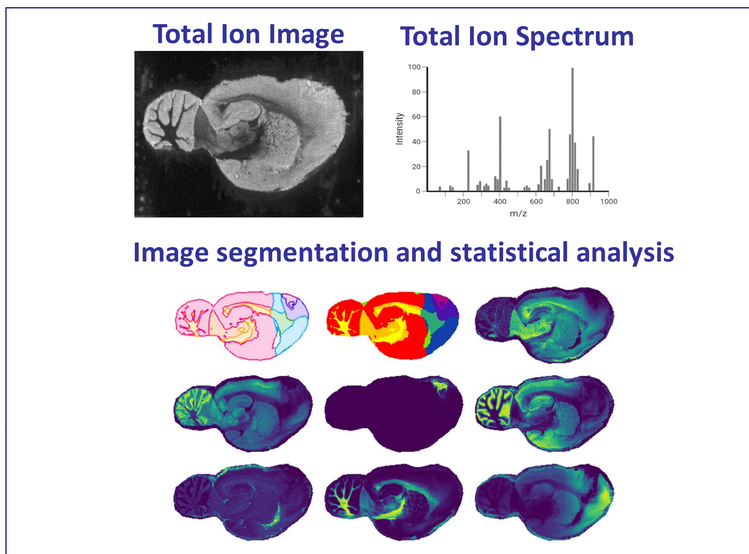


Image acquisition and Data processing

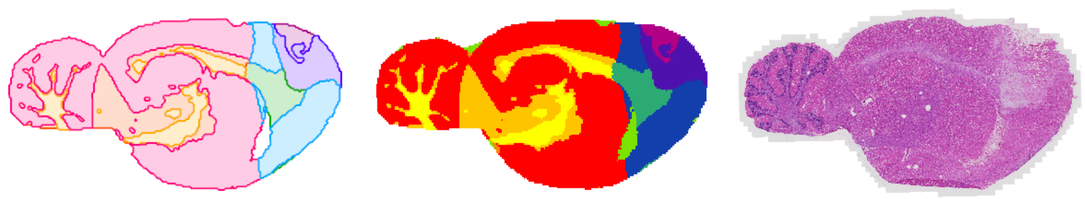
MSI data is acquired and processed to evaluate the biodistribution of the target complex therapy using statistical approaches. A semi-quantification approach is applied when an internal standard is available.

Case 1- Biocompatible hydrogel formulation to treat glioblastoma post surgery, with local administration

TARGTEX
TARGETED THERAPEUTICS

TargTex engineered a hydrogel formulation containing a small molecule to treat Glioblastoma (GBM) post-surgery. This complex formulation is implanted after tumour removal to eliminate the remaining GBM cells. At MDC, a biodistribution method was developed applying DESI-MSI to the targeted analysis of the active compound to evaluate its biodistribution ex vivo.

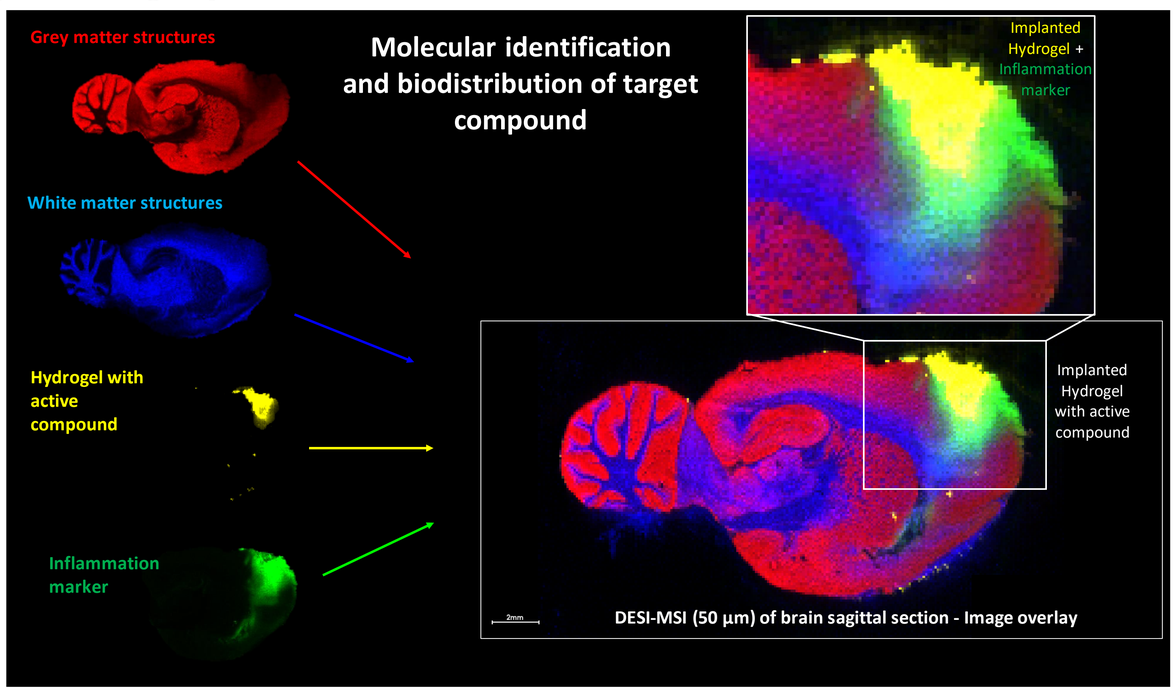
DESI-MSI of a brain implanted with a hydrogel formulation



Anatomical regions selected based on PLSA and segmentation

Image segmentation Bisecting k-means

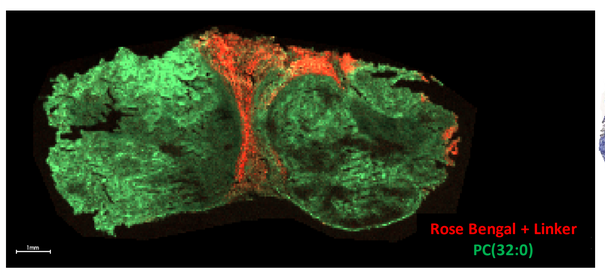
Post-MSI H&E staining



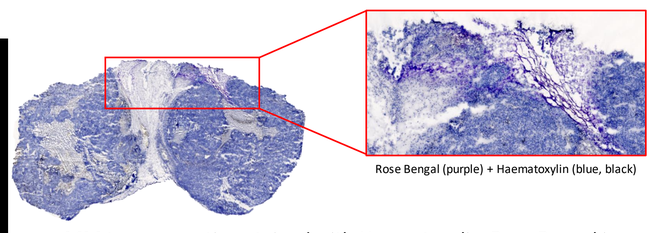
Case 2- Targeted peptide-conjugate to treat Metastatic Melanoma (MM) in combination with photodynamic therapy

MALDI-MSI of a preclinical MM section treated with peptide-conjugate and PTD

MALDI-MSI (50 µm)
Image overlay showing the distribution of RB+linker and PC(32:0) as a cell marker



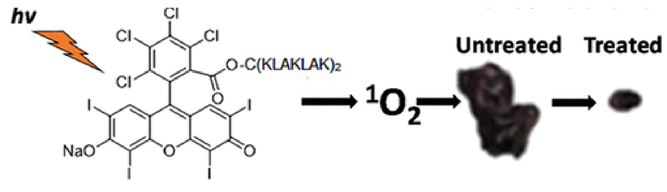
Post-MSI histological staining to validate the distribution of RB



MM tumour section stained with Haematoxylin. Rose Bengal is observed in dark purple

KLAS Therapeutics developed a Rose Bengal- peptide conjugate, RB-C(KLAKLAK)$_2$, to treat Metastatic Melanoma (MM). This is achieved by combining the photosensitising compound, Rose Bengal and the antimicrobial peptide in combination with photodynamic therapy (PDT). A method using MALDI-MSI was successfully developed to evaluate the biodistribution of the peptide-conjugate in preclinical MM models ex vivo.

KLAS Therapeutics



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