Pharmacokinetics in Pulmonary Lesions/MALDI-MS Imaging Studies of Drug Distributions

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Analytical methods for drug distribution

- dissection of animal
- limited spatial resolution
- only parts of animal

- label required
- total radioactivity
- not specific
MALDI-MSI

Dissection  →  Sectioning

Matrix application

Acquisition

Image reconstruction

ROI quantification

m/z
Semi-Quantitation

Co-crystallization of matrix/analyte/internal standard?
⇒ solvation of analyte
⇒ spreading, resolution

Crystal size
⇒ sensitivity
⇒ image resolution
Importance of spatial resolution –
laser averaging
The need to assess lesion drug penetration

- Existing drug regimens were developed before standard PK measurements existed
- Need to optimize dosing regimens of existing TB drugs (concentrations and combinations)
- Use detailed lesion penetration information for developing novel anti-TB compounds
Clinical pathology

H&E

Massan Trichrome
Multi-modal lesion studies

MSI

Histology (staining)

Drug Binding

Non-invasive (PET, MRI)

Quantitation

Microscopy and labeling
Animal Models
Lesion processing

A. Sample for Imaging MS
   Snap-frozen with surrounding tissue
   -> 2D map of drugs by MALDI-TOF

B. Sample for Drug Quantitation by MS
   Dissected out (if cavity, caseum and wall processed separately)
   Weighed and frozen
Pyrazinamide

MW 123.113

Pyrazinoic acid

MW 124.10
Clinical (1500mg)

3.3h  5h  11h  24h

PZA
Rabbit (30mg/kg)

2h 6h 24h

RIF

Des-RIF
Penetration of RIF into caseum at late timepoints

22h
Steady-state dosing

1 day (16h)  3 days (2h)  10 days (2h)  Clinical (24h)
Clofazimine

MW 473.396
Clinical (steady-state)

Steady-state Patient #1

Steady-state Patient #2

Steady-state Patient #3

CFZ
Clofazimine v RIF distribution

Clofazimine | Cholesterol | Rifampicin
Summary

Rapid diffusion into caseum, rapid elimination

Slow caseum penetration and accumulation

Poor to no caseum penetration

Lesion distribution information is important for optimizing existing therapies and developing novel drugs!!!
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