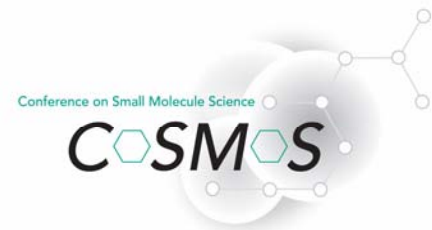


# **Imaging Mass Spectrometry for Direct Tissue Analysis of Pharmaceuticals**

**Yunsheng (Tony) Hsieh**

**Drug Metabolism and Pharmacokinetics Department  
Schering-Plough Research Institute**

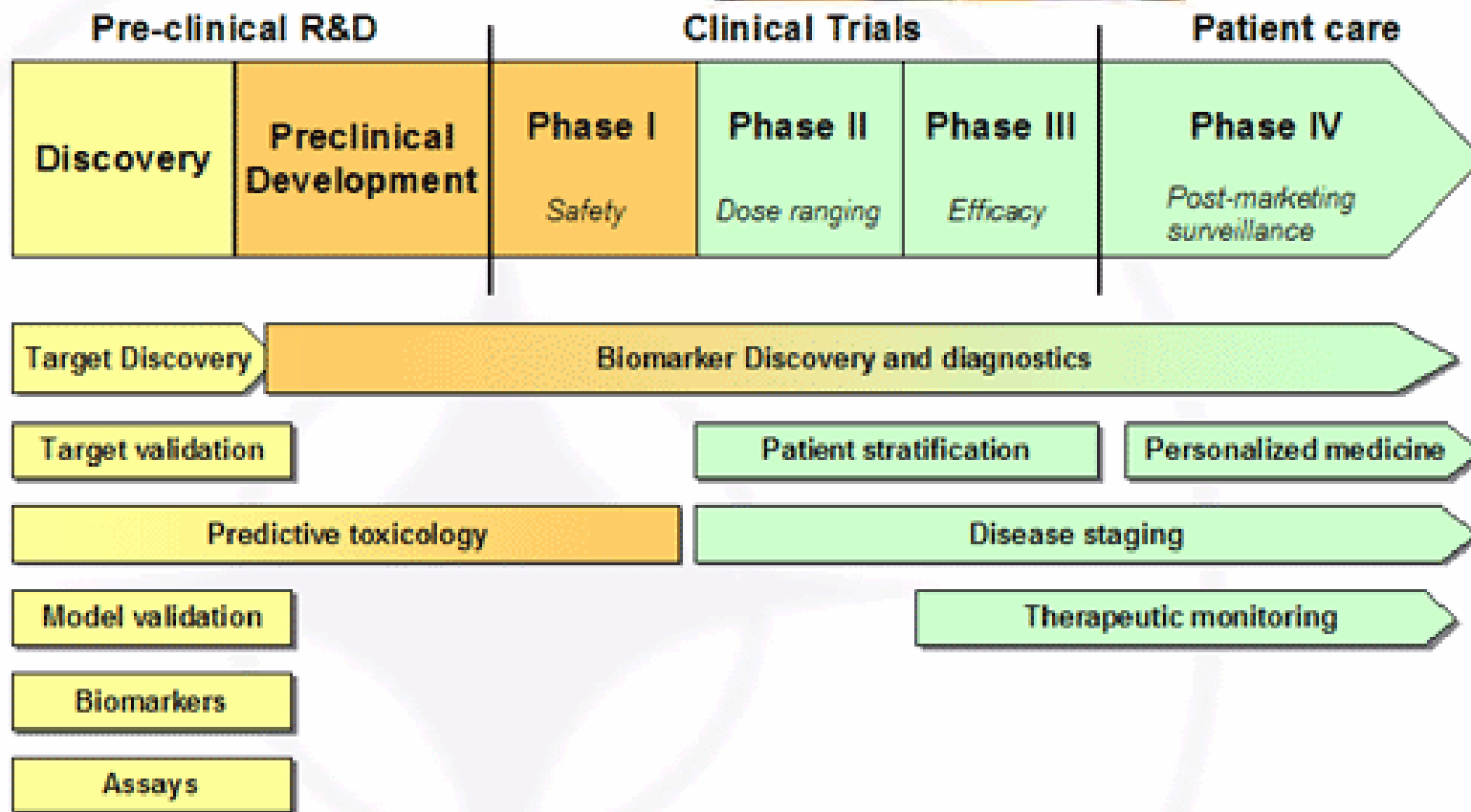


# Agenda

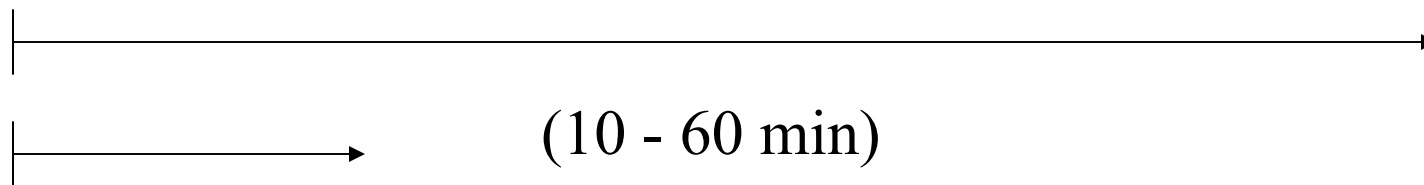
1. Objectives
2. LC-MS/MS methods
3. MALDI-MS imaging methods
4. Applications



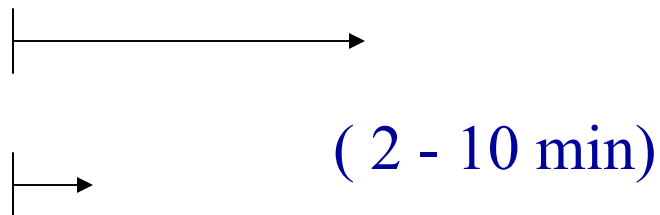
# Timeline for bringing to market



# Bioanalytical Methods for Drug Analysis

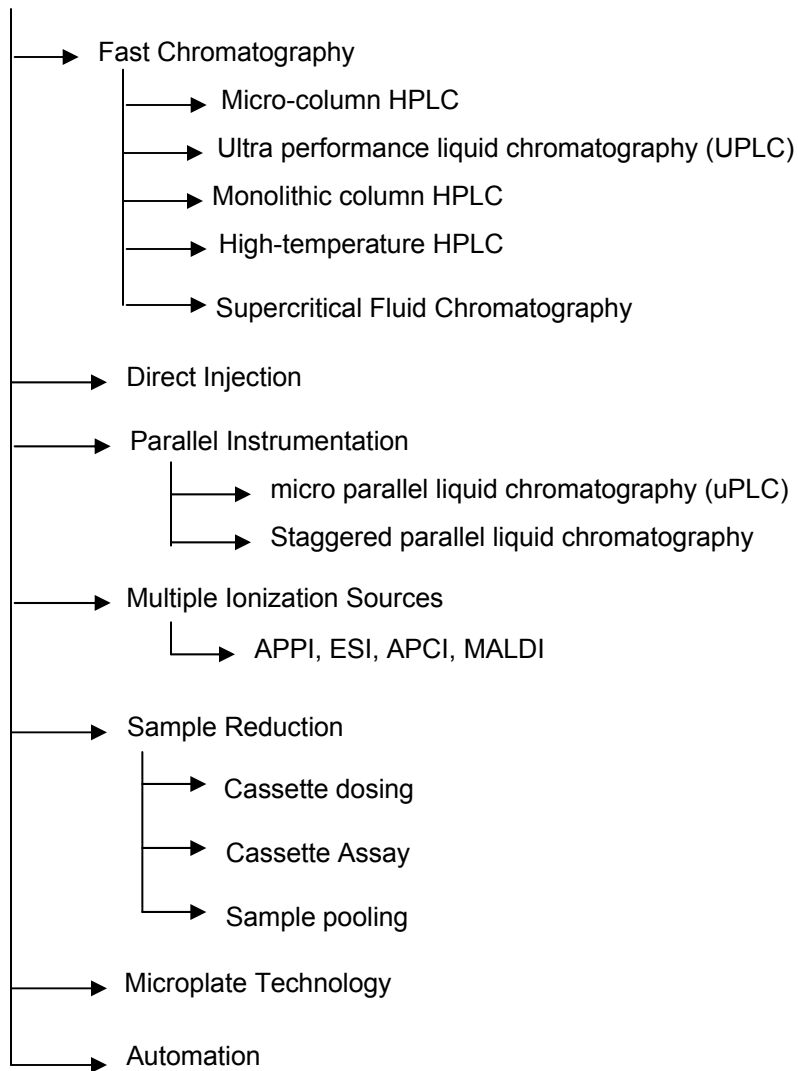


**HPLC**

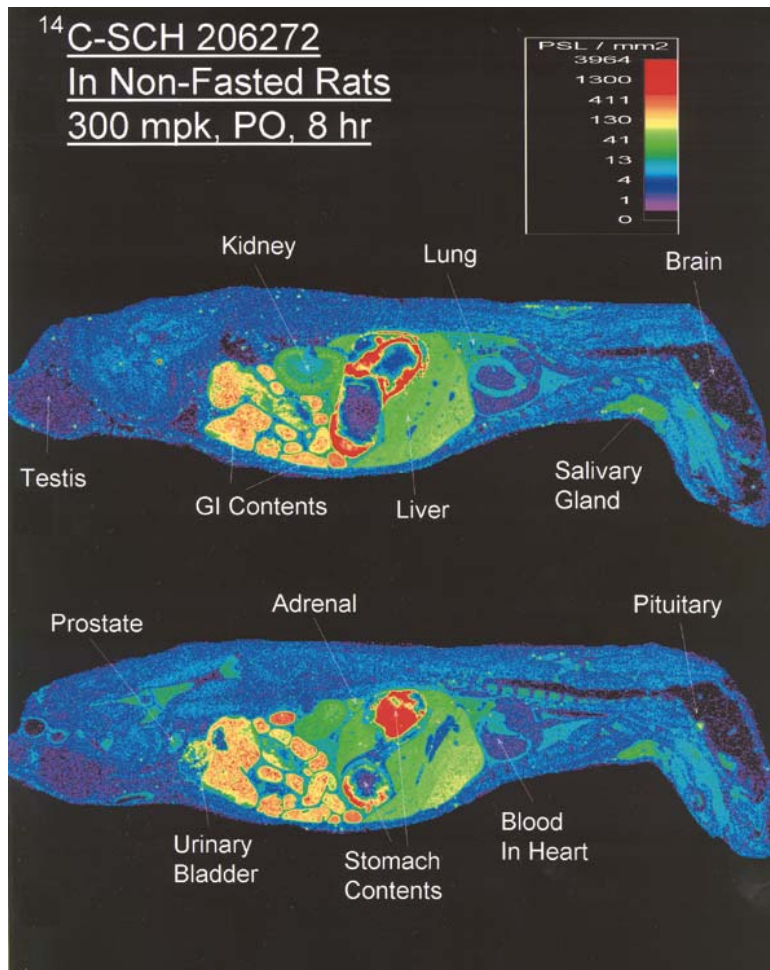


**LC-MS/MS**

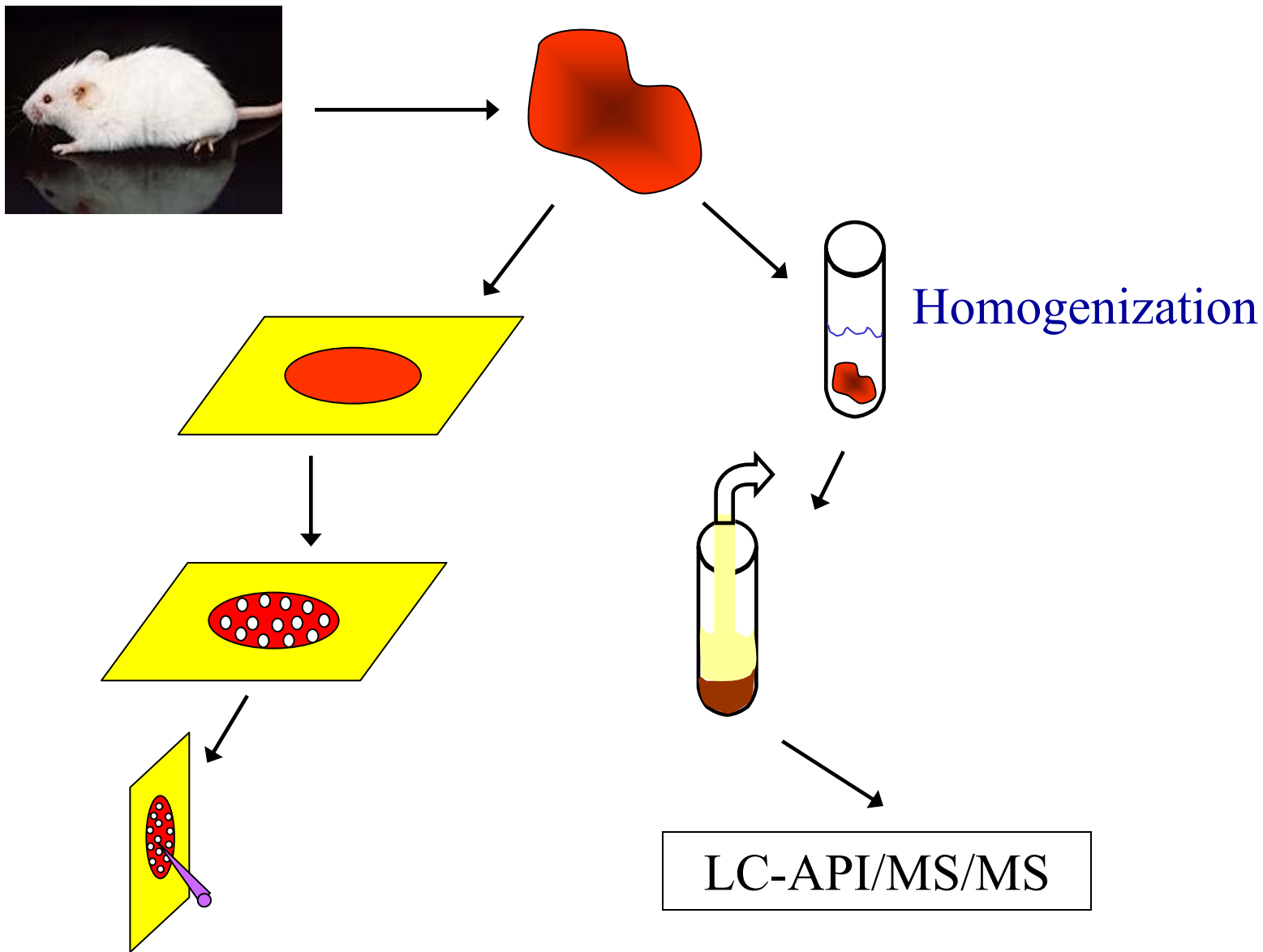
## Higher-Throughput LC-MS Strategies in Drug Discovery



# Whole Body Auto-radiograph of $^{14}\text{C}$ -SCH 206272 in Rat

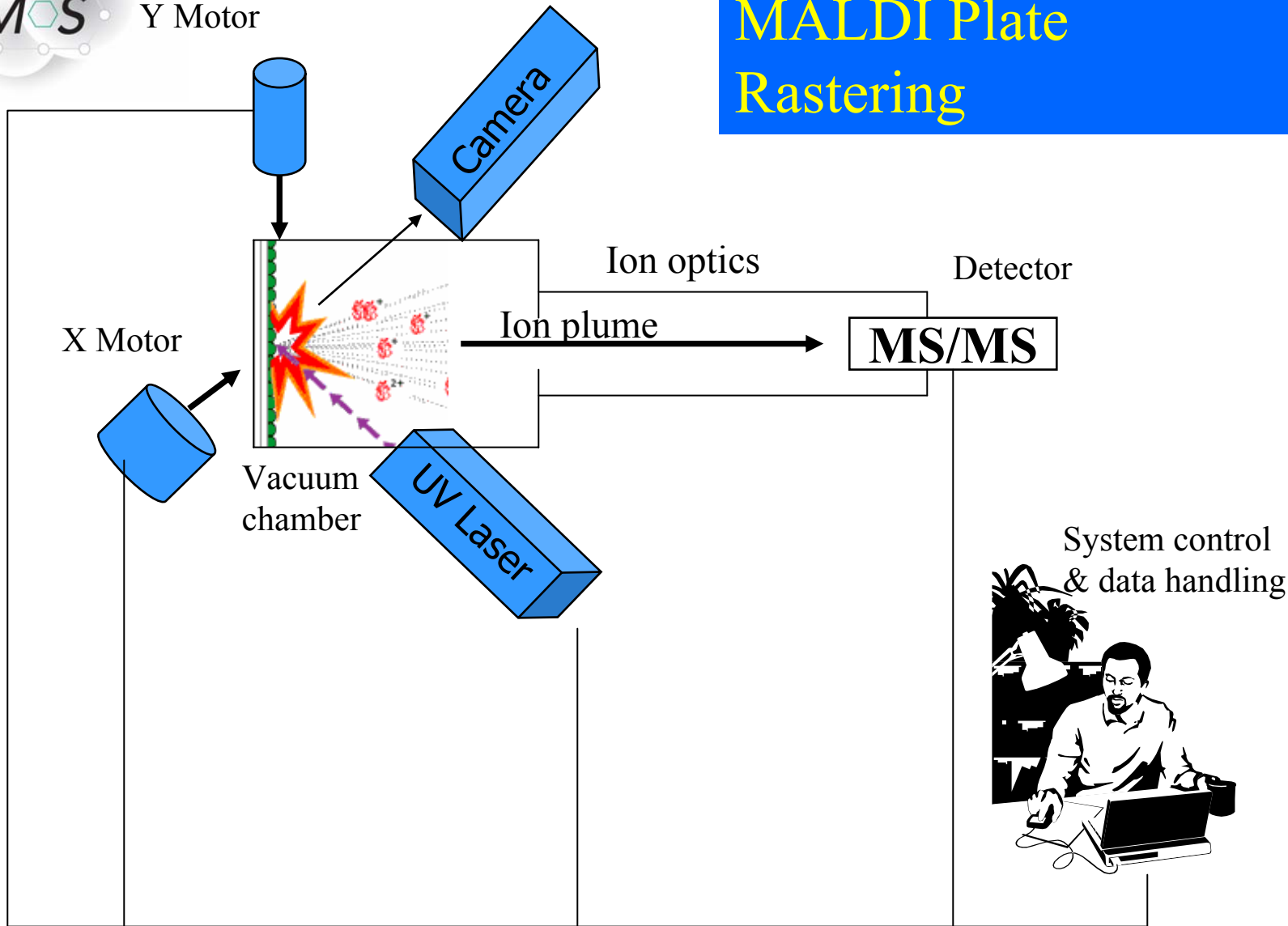


# Analysis of drugs in tissue by mass spectrometry

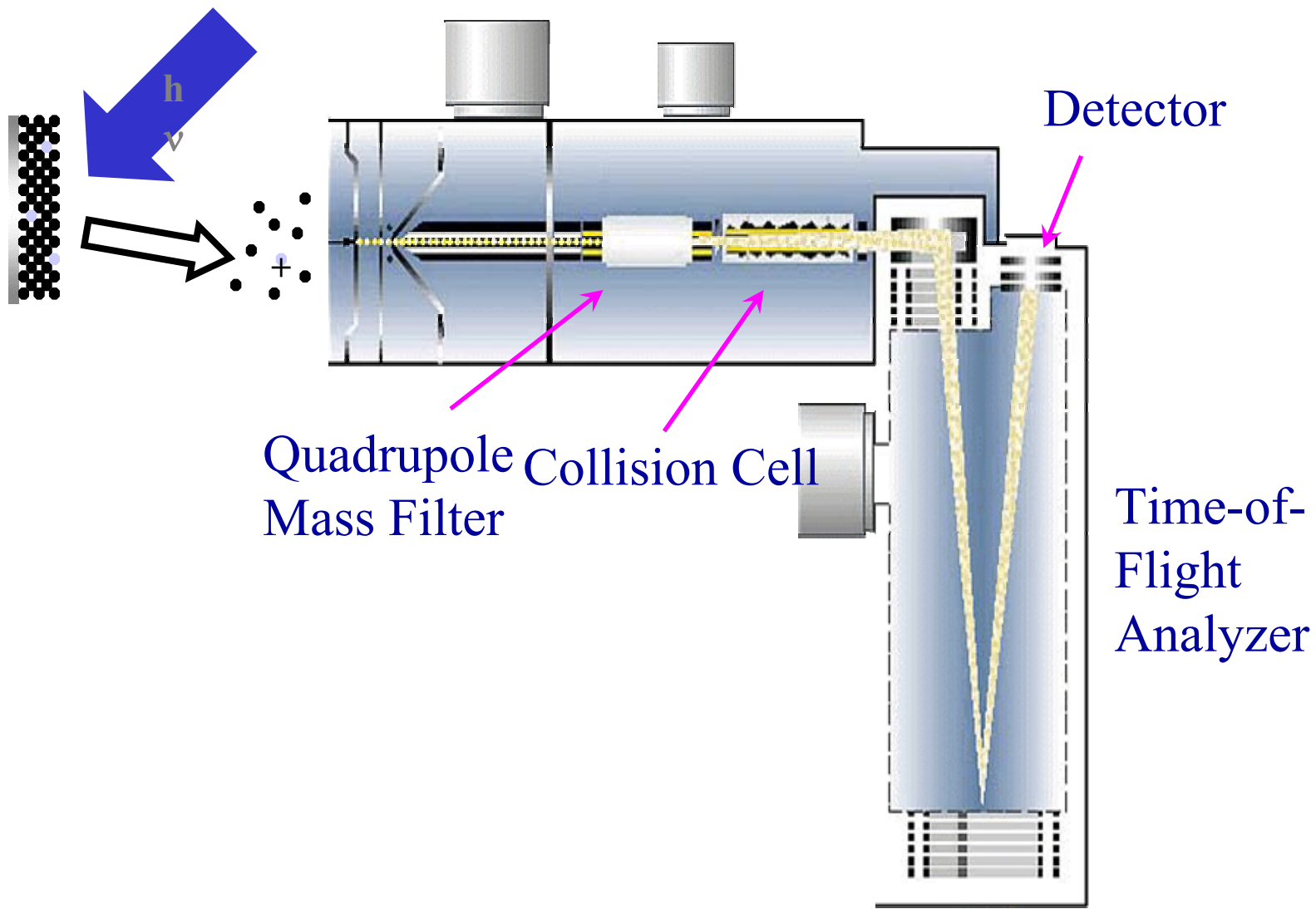




# MALDI Plate Rastering

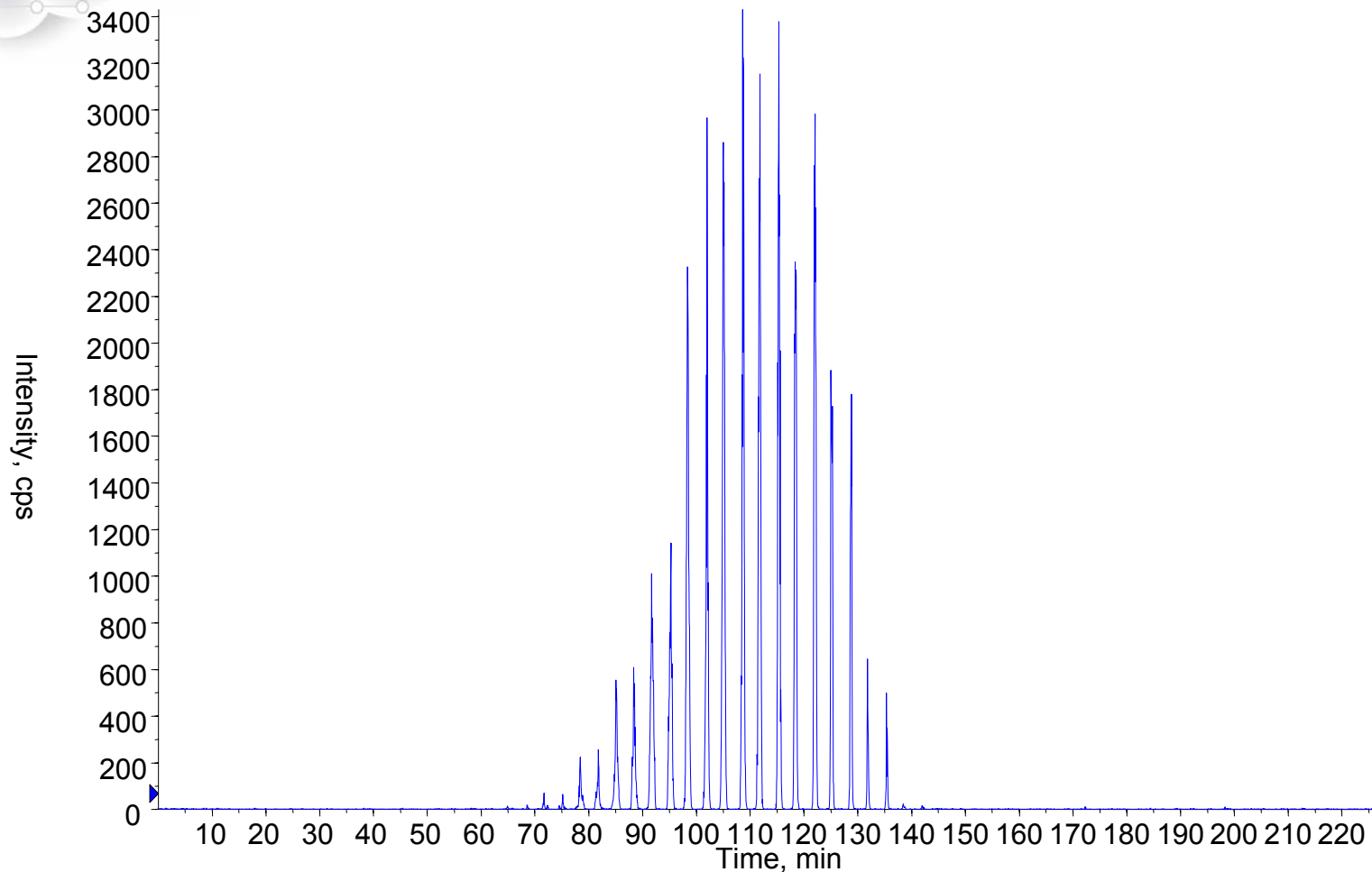


# MALDI QqTOF

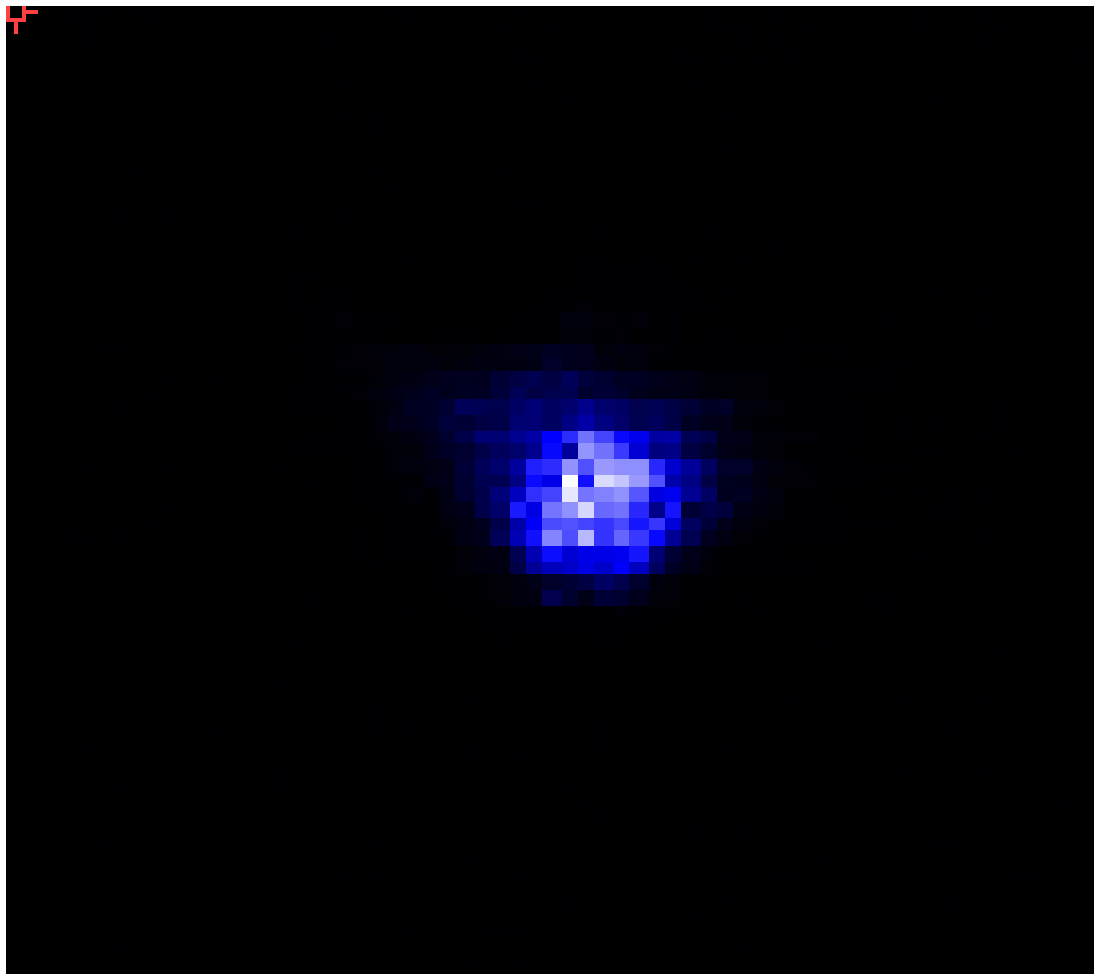


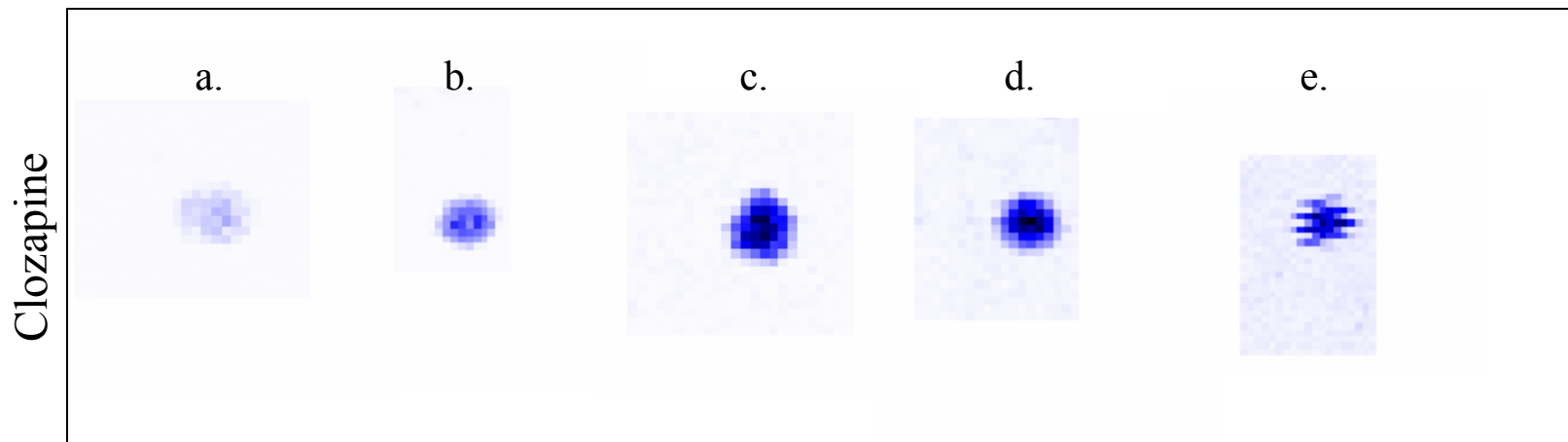
# oMALDI 2 on QSTAR Pulsar *i*



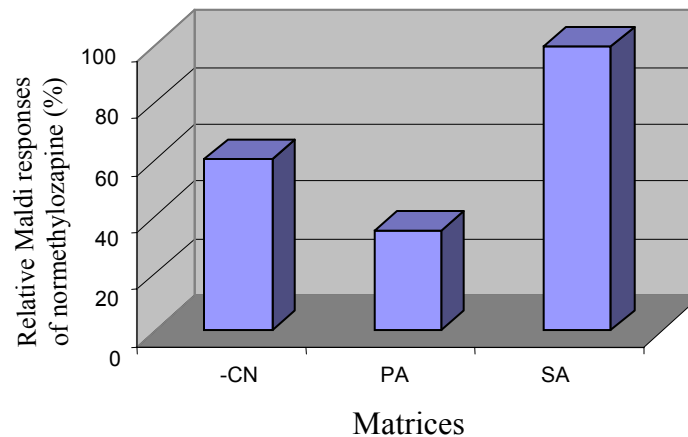
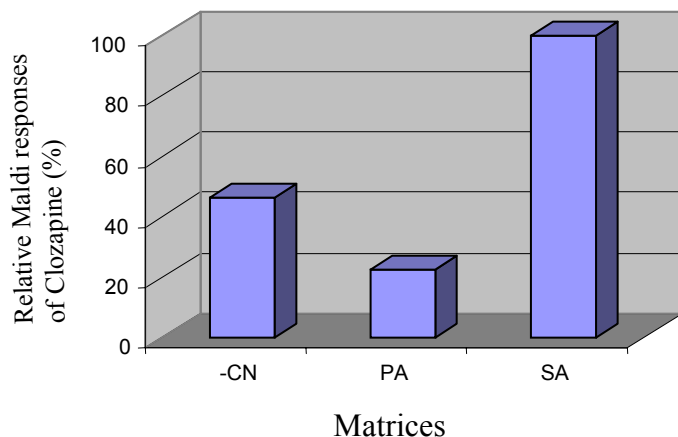
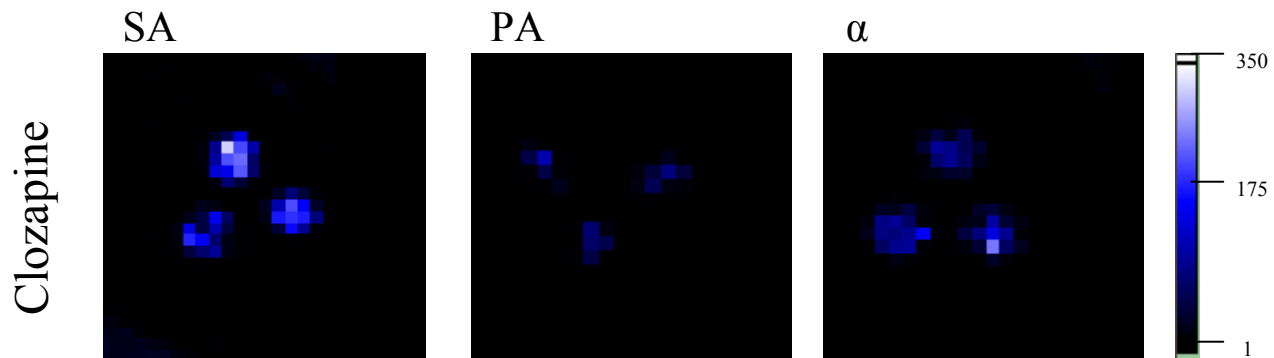


**MALDI signal as a function of drug distributions on tissue**

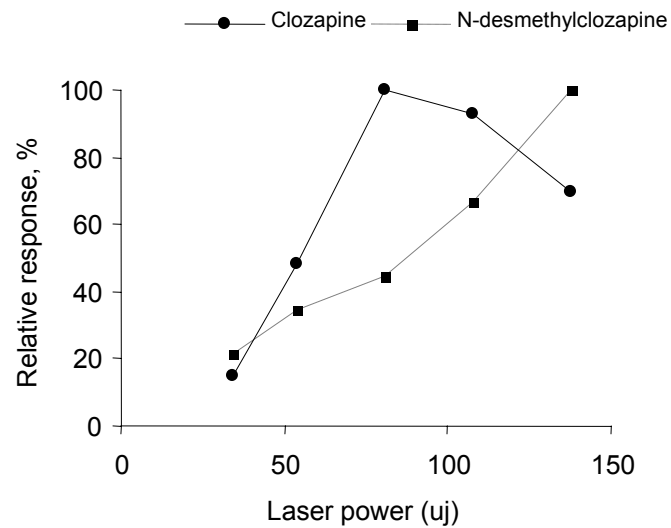




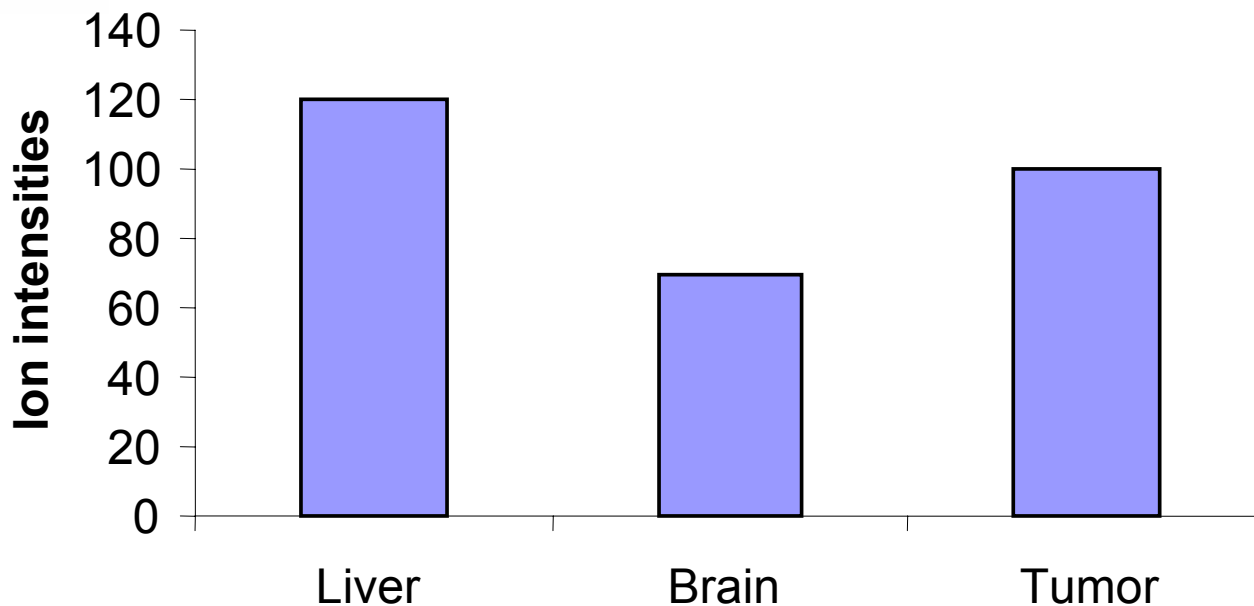
**Maldi responses of clozapine as a function of laser power**



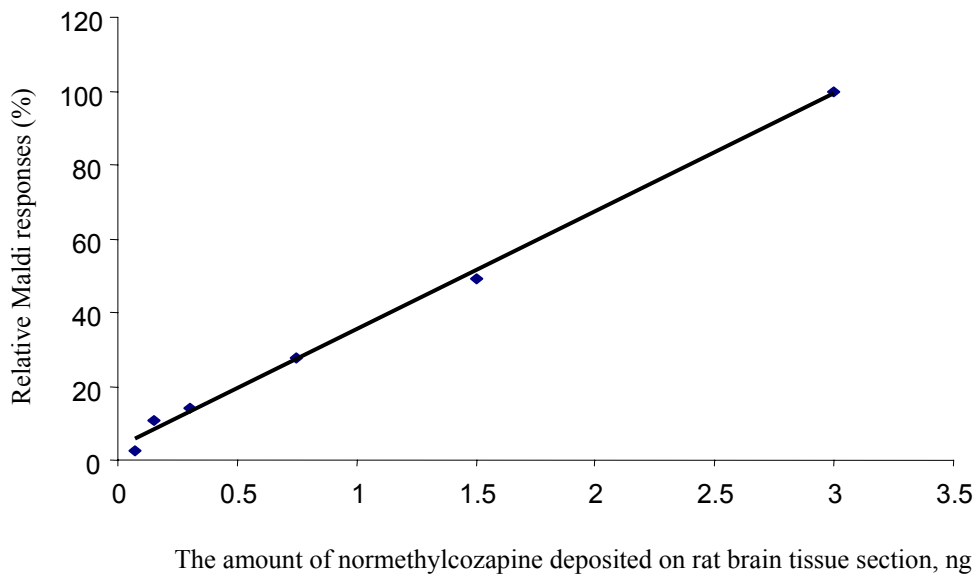
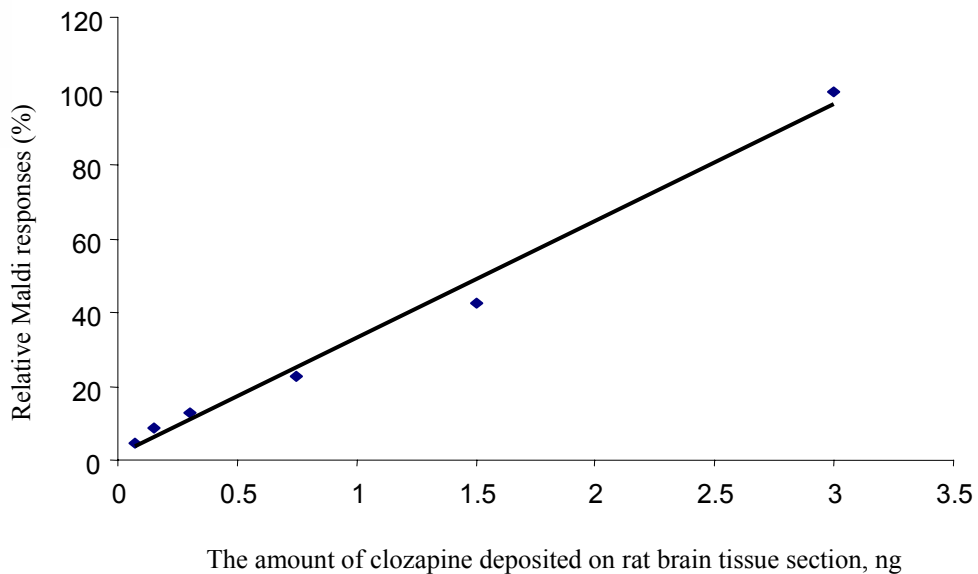
(Top panel) Imaging of three separate droplets containing clozapine spotted in rat brain tissue section using three kinds of matrix, SA, CHCA and 3-hydroxy picolinic acid;  
 (Bottom panel) Relative average MALDI responses of (left) clozapine and (right) norclozapine in rat brain tissues using SA, CHCA and 3-hydroxy picolinic acid.

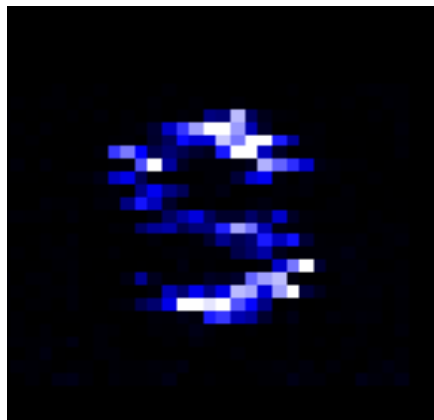


**Maldi responses of clozapine and N-desmethylozapine as a function of laser power**

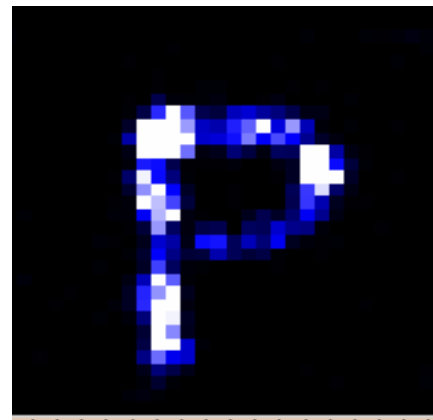


Effects of ionization efficiency of clozapine  
in liver, brain and tumor slices



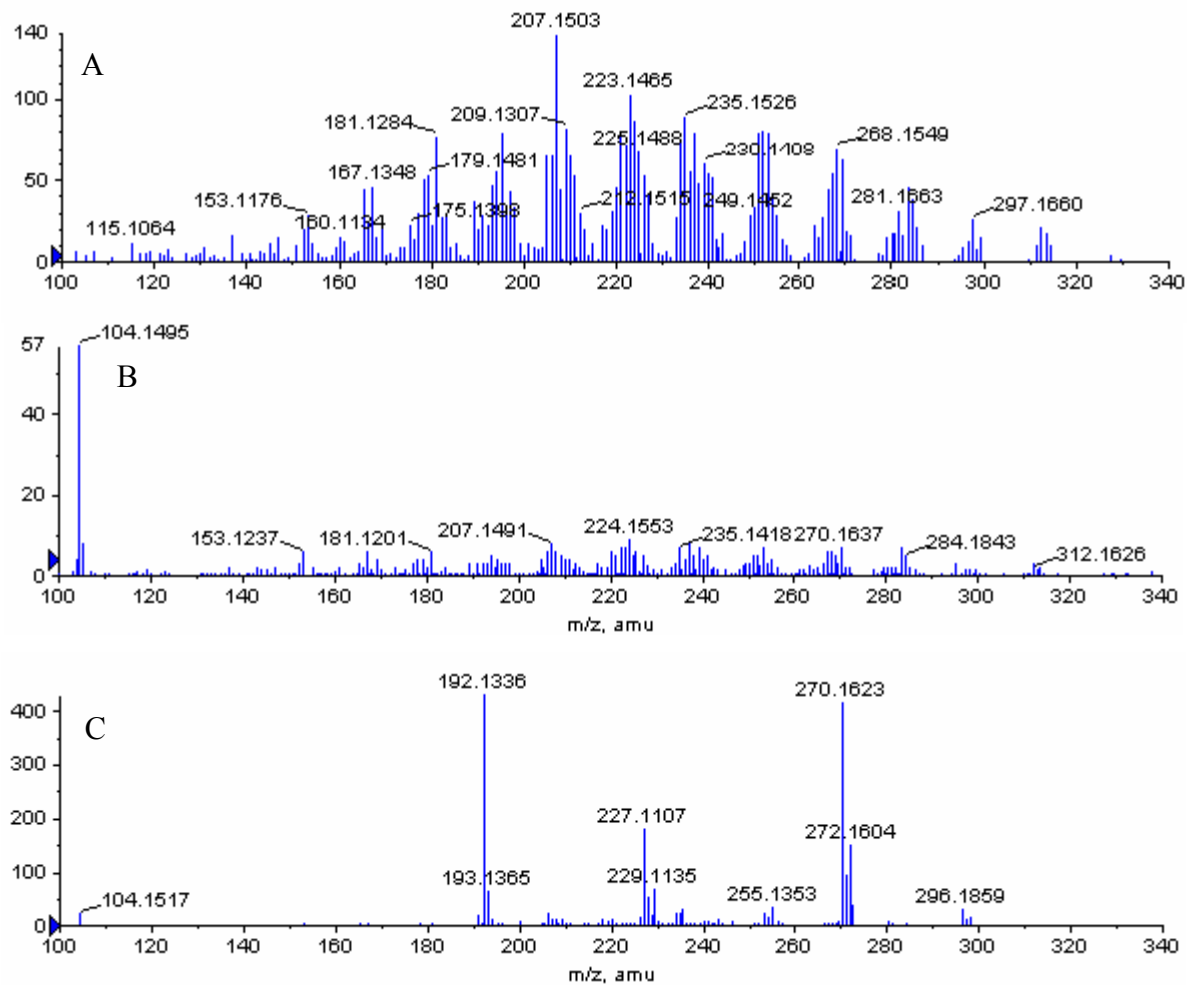


N-desmethylclozapine on rat brain tissue



Clozapine on rat brain tissue

MALDI-MS images of letters S and P containing clozapine  
in rat brain slices.

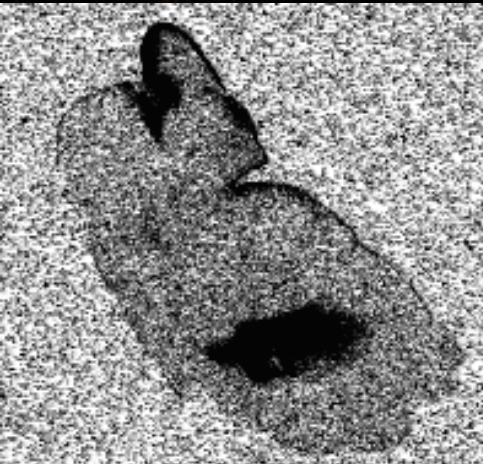


MALDI spectra of spots from (A) outside the tissue slice, (B) the bright area within the tissue and (C) dark area within the tissue.

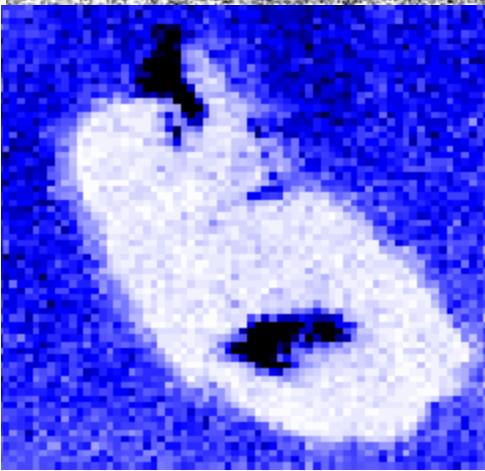


1000  $\mu\text{m}$

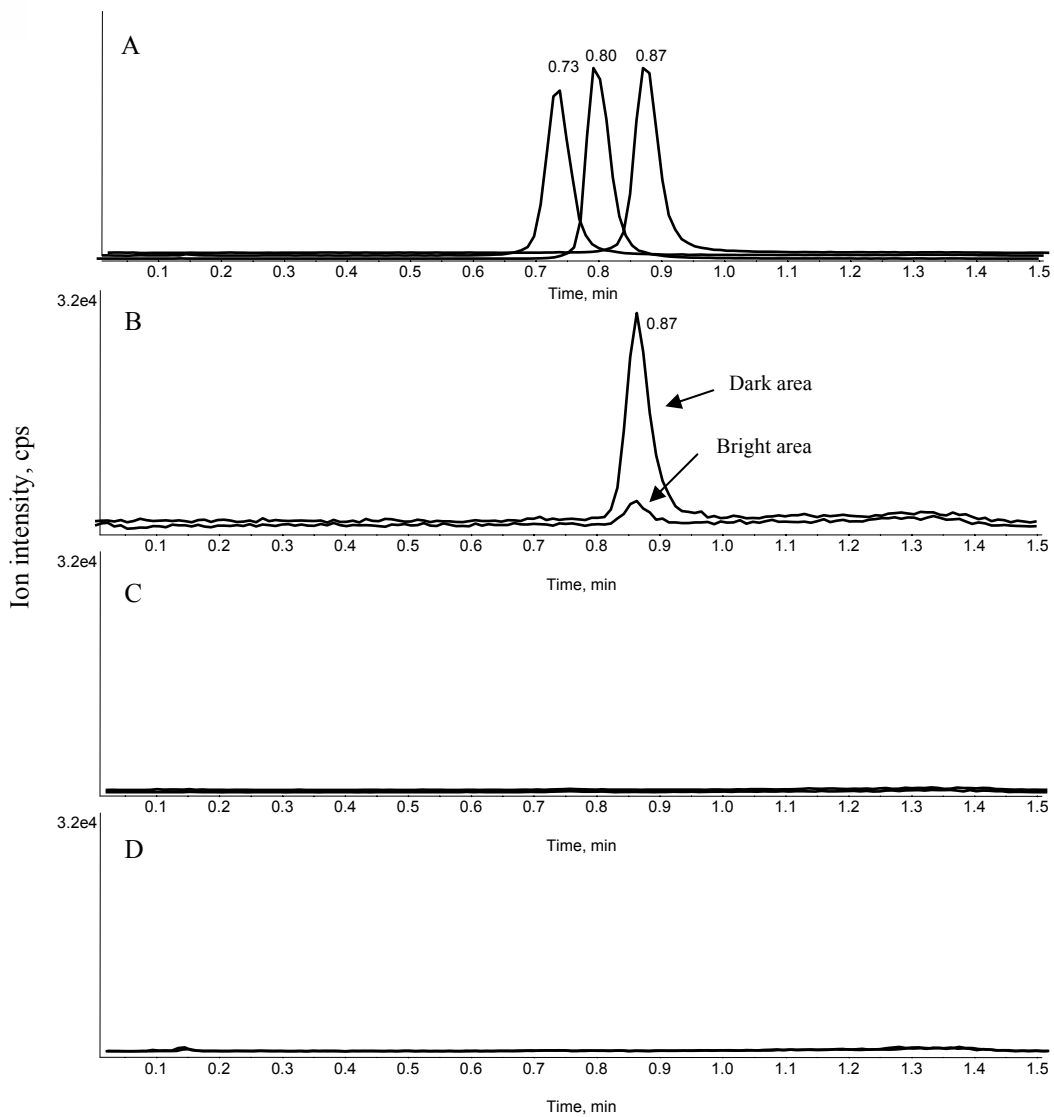
← Optical Image

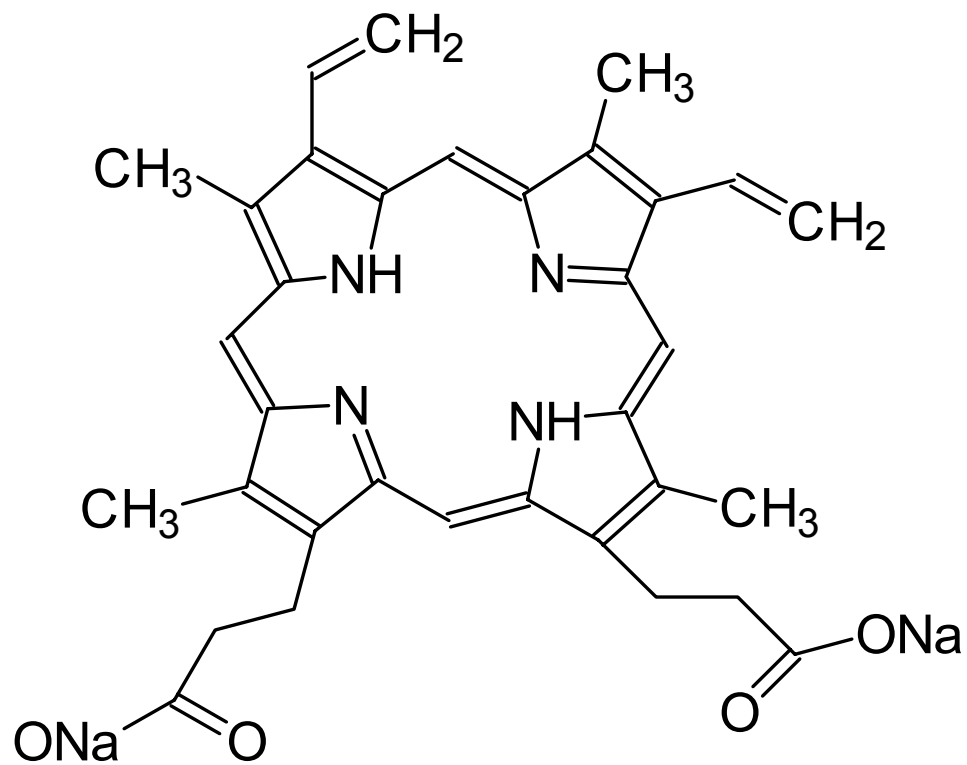


← Radioautographic Image



← MALDI-MS Image





Protoporphyrin I

# Image of compound X in mouse tumor tissue

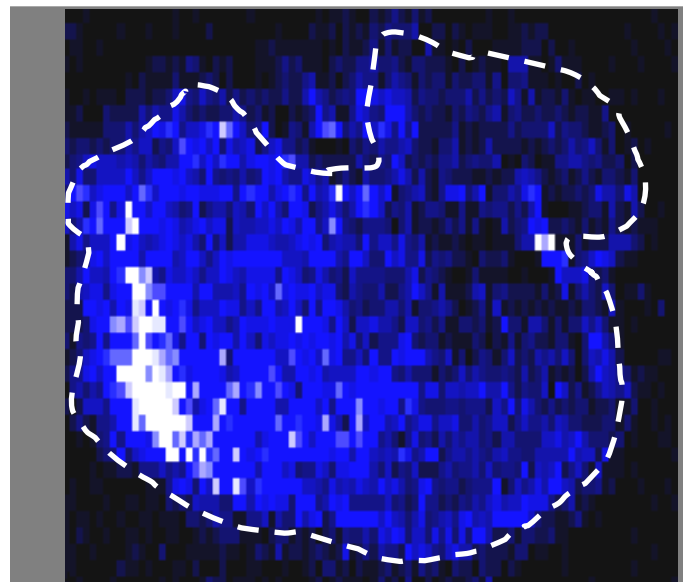
Conference on Small Molecule Science

C<sub>SM</sub>S

Optical image of tissue section – coated with matrix



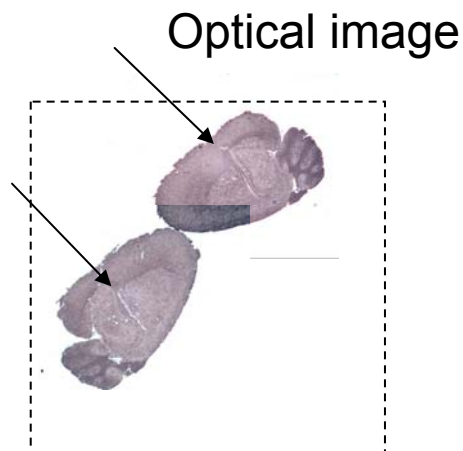
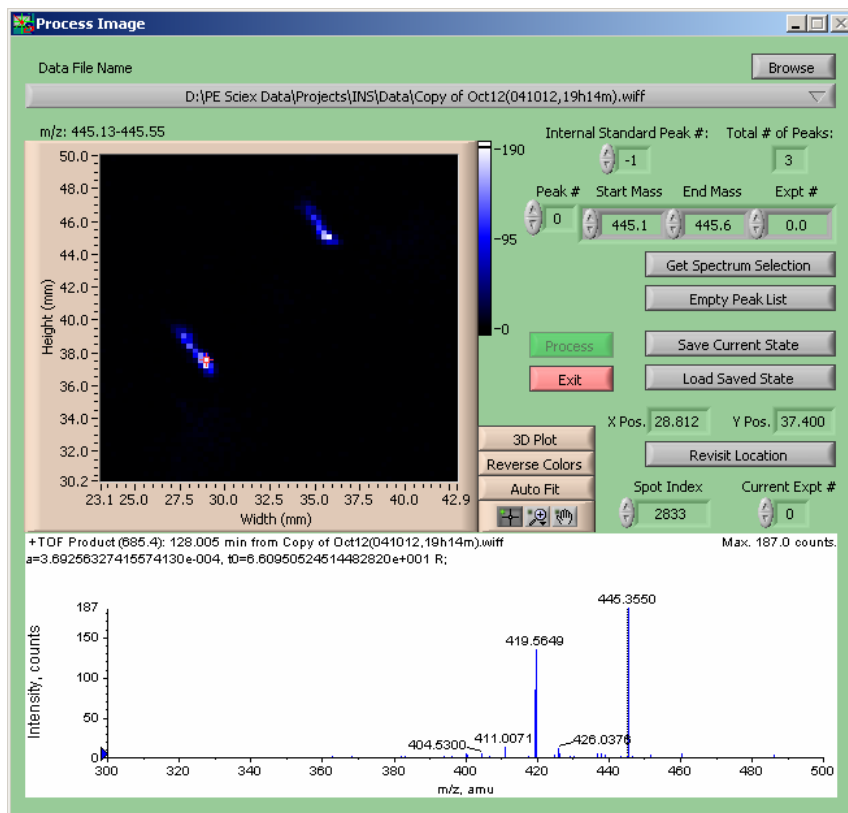
MS image of tissue section



- ◆ Mouse dosed at 80 mg/kg
- ◆ Tissue removed 7 hr after last dose

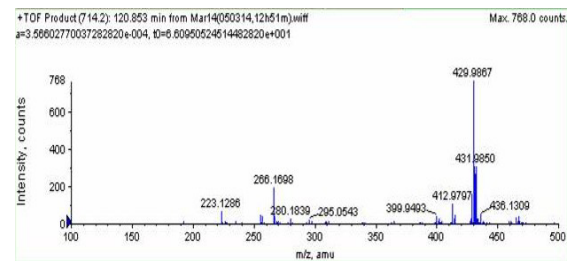
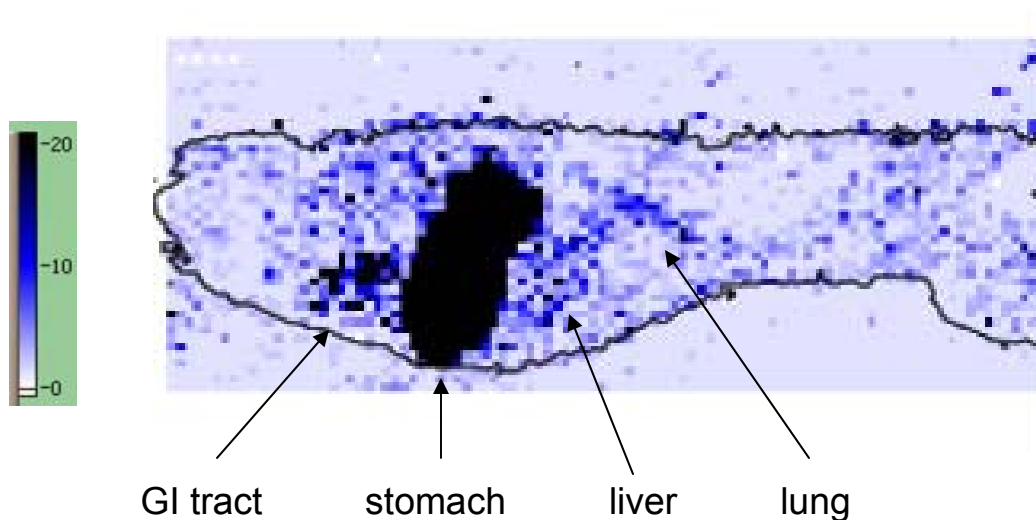
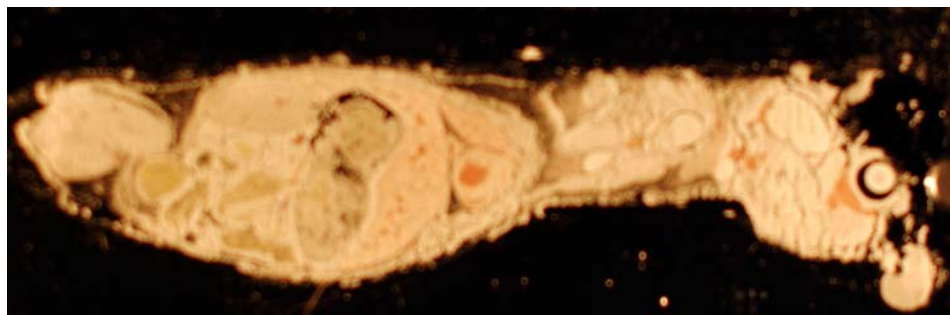
- ◆ MS image
  - 200  $\mu\text{m}$  x 400  $\mu\text{m}$  resolution
  - Area imaged  $\sim 260 \text{ mm}^2$

# Mouse Brain Slices (2 h), Ion Image

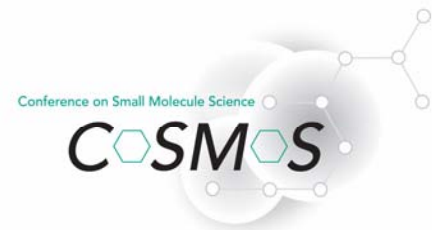


Mass spectrum from a "bright" spot shown, S/N > 200  
 Note: m/z numbers were changed to avoid compound information

## Mouse Whole Body Dosed with SCH 226072



Mass spectrum of a spot from the stomach

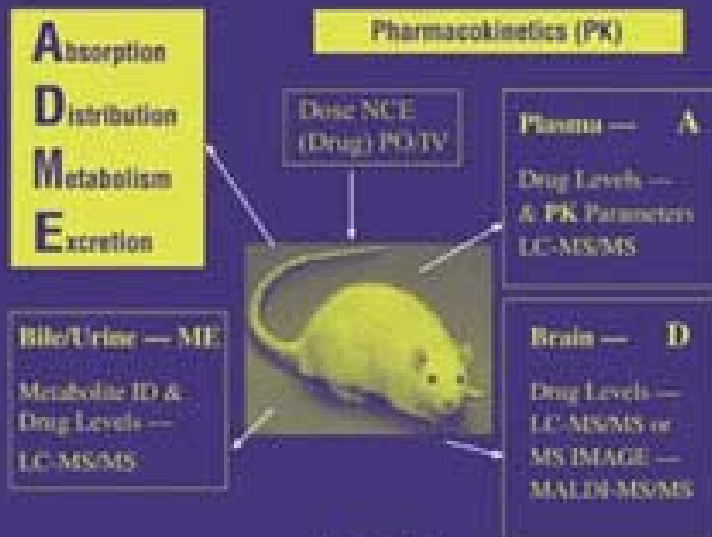


# Further Applications?

Biomarker, metabolomics studies

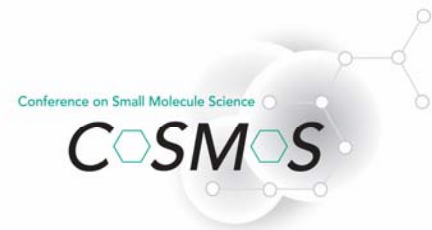
**Dr. Michelle Reyzer and Prof. Richard Caprioli**  
**Mass Spectrometry Research Center,**  
**Vanderbilt University, Nashville, TN**

# USING MASS SPECTROMETRY FOR DRUG METABOLISM STUDIES



EDITED BY

Walter A. Korfmacher



# Acknowledgement

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**Prof. Ganfeng Wang**

**Jean-Marc Brisson**

**An open position**

# Thank you for your invitation!

