

Mass Spectrometry Imaging and Localized Omics Studies

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PARIS DESCARTES
SCIENCES PHARMACEUTIQUES ET BIOLOGIQUES

International Summit on
Current trends in Mass Spectrometry
July 13 – 15, 2015
New Orleans, Louisiana

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Outline

- Introduction
- Localized lipidomics
  - Duchenne dystrophy
  - NAFLD
  - Cystic fibrosis
- Special lipids
  - Fabry disease
  - Peptidolipids
  - Cholesterol
- Xenobiotics
  - Environmental pollutant
  - Preservative
  - Anti-acne drug

Sample preparation

Introduction

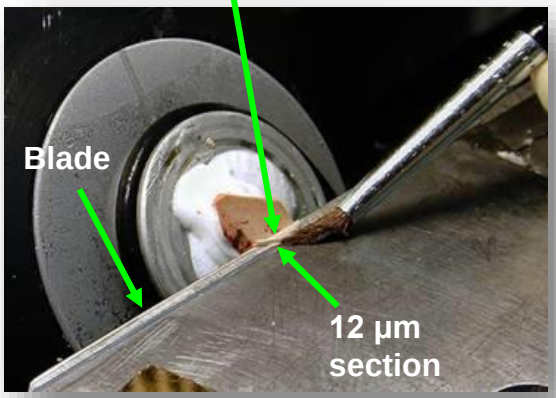
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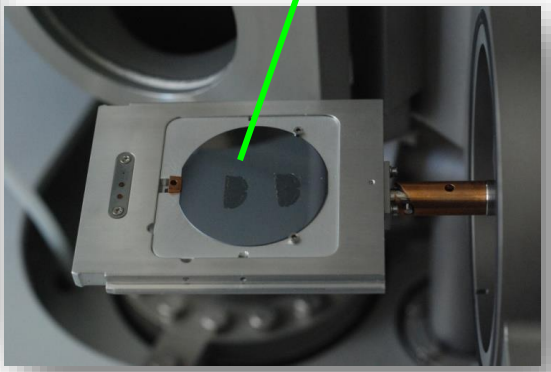


- After dissection, fast freezing at -80°C
- Tissue is maintained with OCT glue
- 12-20 µm sections cut with a cryostat (-20°C)
- Tissue sections are deposited directly onto a stainless steel plate, a silicon wafer, or a glass plate
- Dehydrated under vacuum
- Fixed onto the standard sample holder









Instrumentation: TOF-SIMS IV (Ion-Tof GmbH)

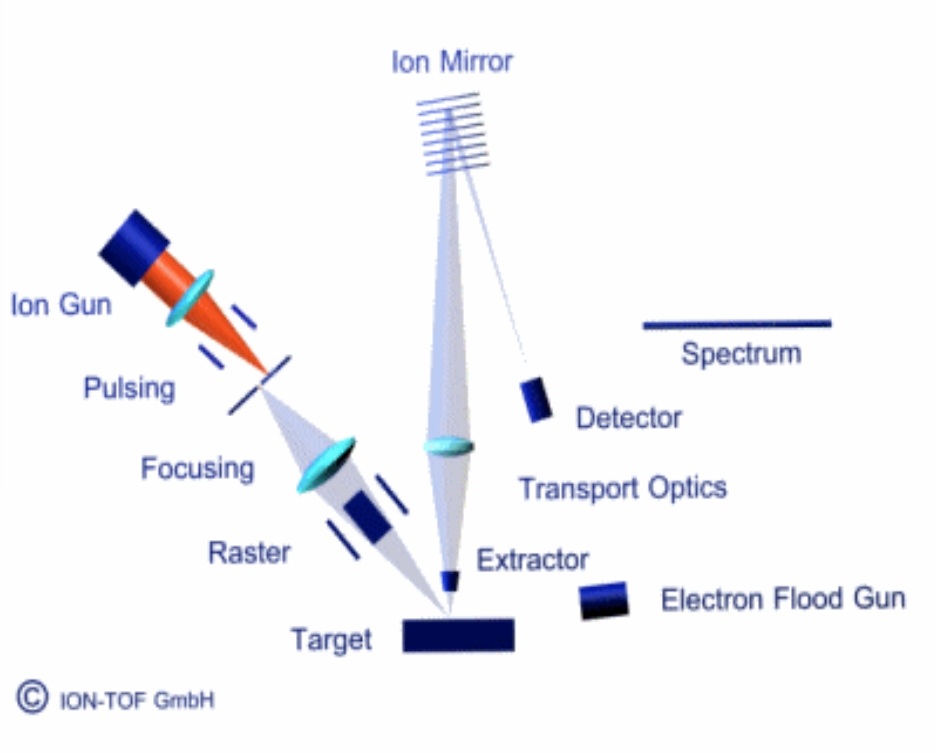
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TOF-SIMS: Bismuth primary ion beams

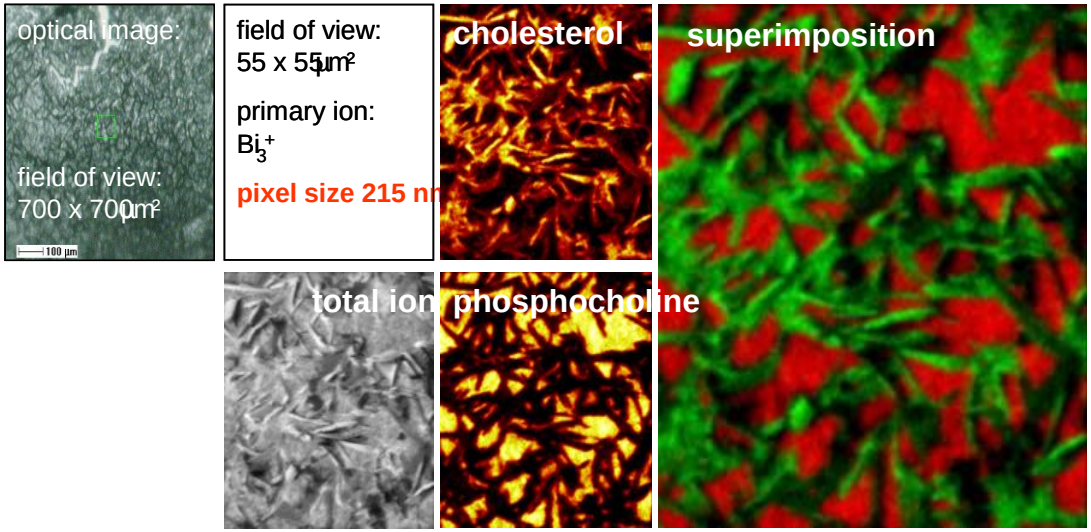
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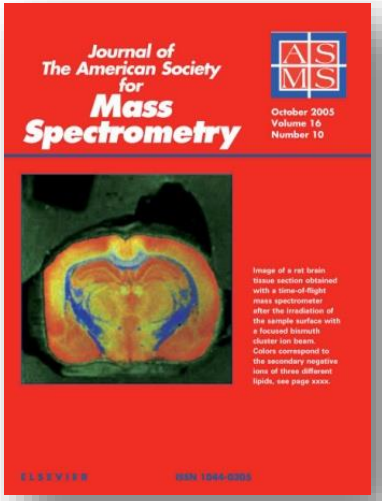
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Very good focus at unit mass resolution



D. Touboul et al.
***J. Am. Soc. Mass Spectrom. 2005**, 16, 1608-1618*



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TOF-SIMS versus other MS imaging/desorption techniques

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DESI : Roger Webb (Monday morning)

MALDI : Mehran F Moghaddam (Monday Morning)

MeV SIMS : Roger Webb (Monday Afternoon)

Low Energy Cs+ SIMS : Purushottam Chakraborty (Tuesday Morning)

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20 KeV Bi^{3+} TOF-SIMS

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MALDI-TOF versus TOF-SIMS imaging

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	MALDI-TOF-TOF	TOF-SIMS
Spatial resolution	10-50 µm	400 nm - 2 µm
Sample	Dehydrated, Homogeneous matrix coating	Dehydrated No fixation No matrix
Mass range	$m/z > 200$	$m/z \leq 1500$
Compounds	Proteins, Peptides, Lipids, Drugs, Metabolites,…	Lipids Glycosphingolipids Cyclopeptides, Drugs, Metabolites, Elements,…
Analyzer	TOF-MS/MS	TOF-MS

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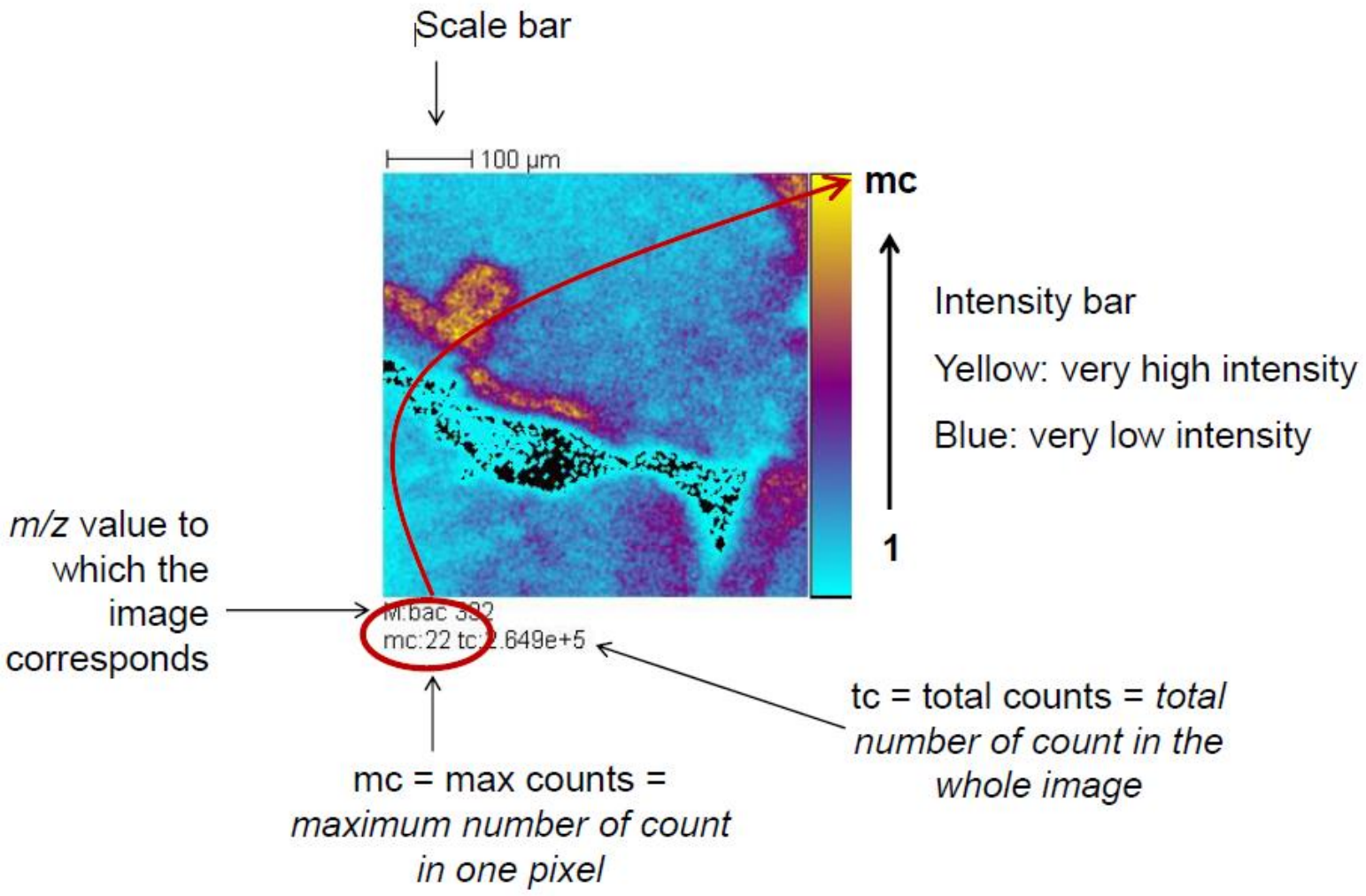
How to read an image ?

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Localized lipidomics:
Most often seen lipids in TOF-SIMS imaging experiments

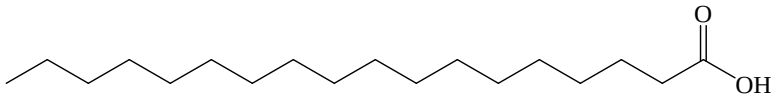
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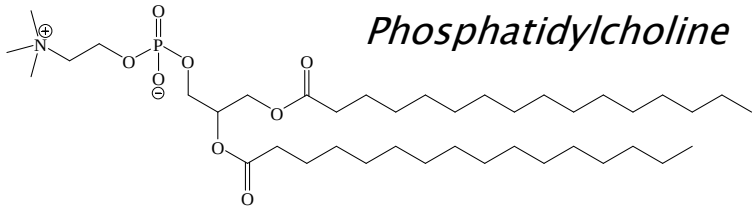
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Fatty acids

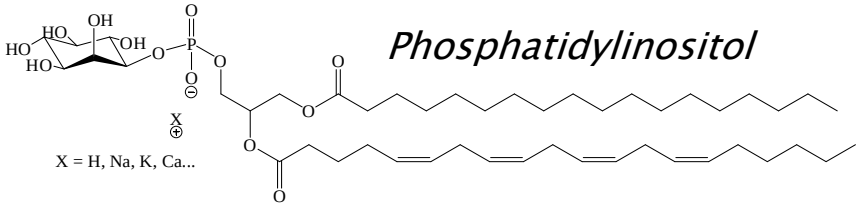


Glycerophospholipids:

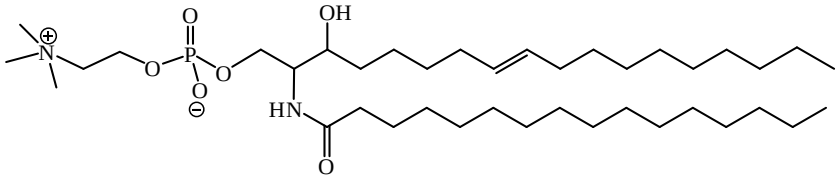
Phosphatidylcholine



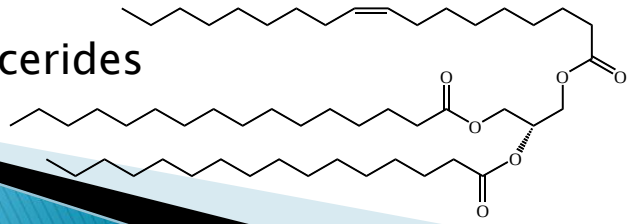
Phosphatidylinositol



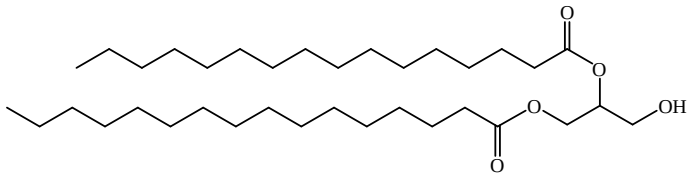
Sphingomyelin



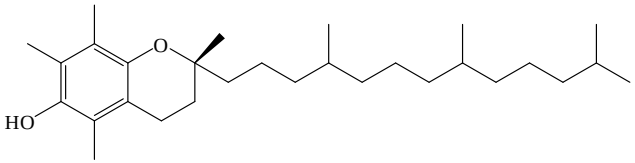
Triglycerides

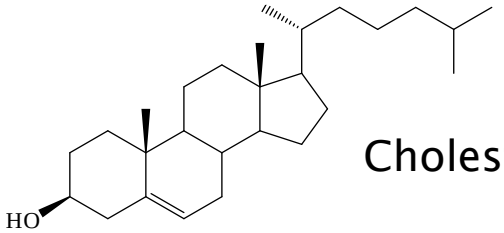


Diglycerides



α-tocopherol (Vit E)





Cholesterol

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Localized lipidomics of Human Duchenne Muscular Dystrophy

Introduction

Localized lipidomics

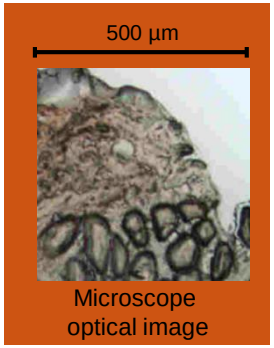
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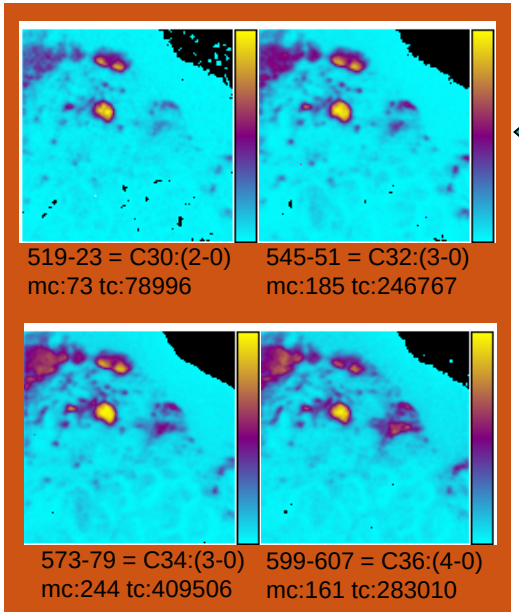
Special lipids

- Fabry disease
- Peptidolipids
- Cholesterol

Xenobiotics

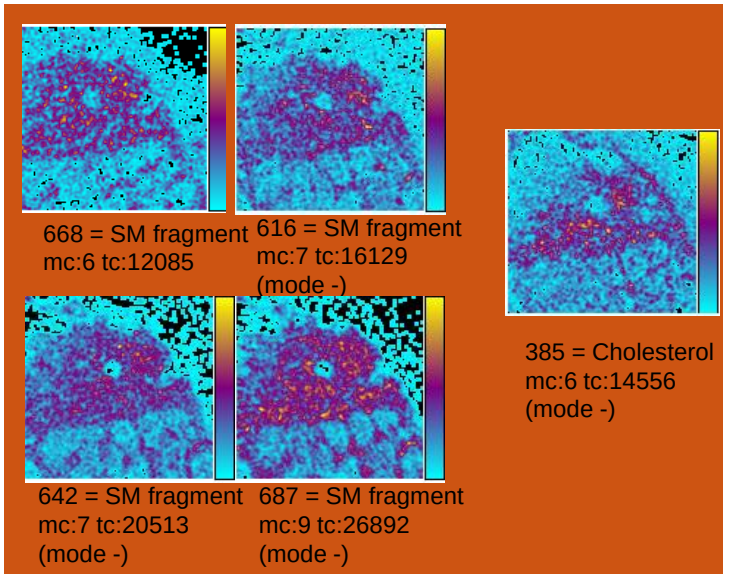
- Environmental pollutant
- Preservative
- Anti-acne drug

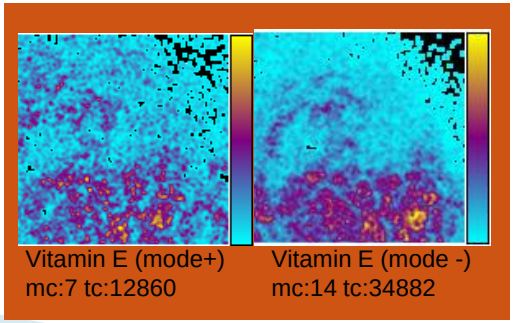




Diglycerides

Sphingomyelins and cholesterol





Vitamin E

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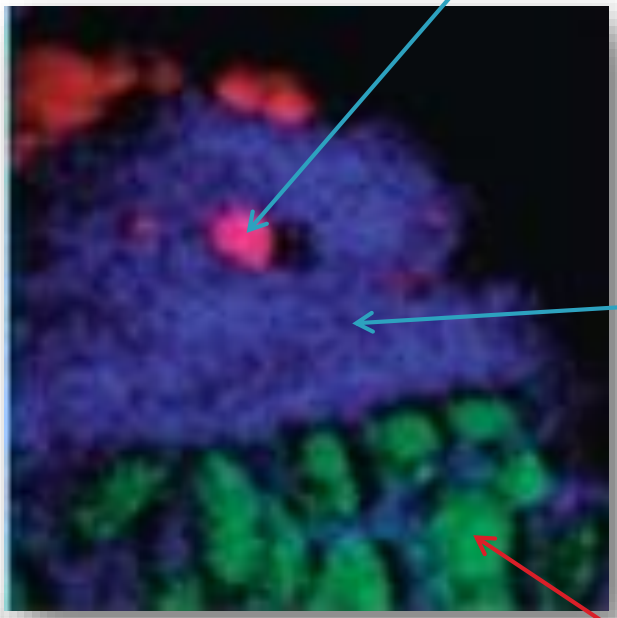
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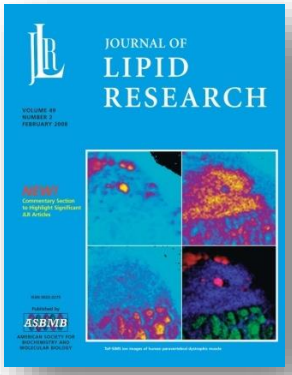
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N. Tahallah, A. Brunelle, S. De La Porte, O. Laprévote, ***J. Lipid Res. 2008****, 49, 438-454*

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Non-alcoholic fatty liver disease (NAFLD)

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Localized lipidomics

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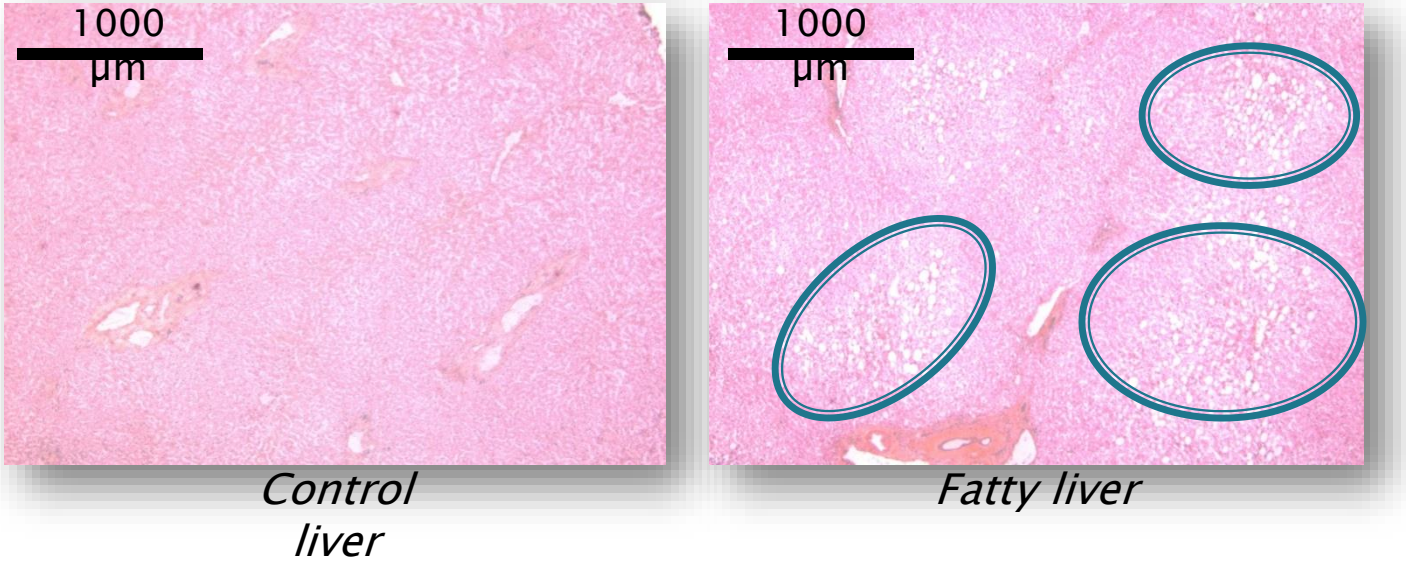
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H&E staining (adjacent sections)



Control liver *Fatty liver*

- Accumulation of lipids (mainly diacyl- and triacylglycerols) in hepatocytes,
- The predominant risk factor for NAFLD appears to be insulin-resistance related to the metabolic syndrome,
- On stained sections, lipid vesicles are observed in fatty liver but are not observable in healthy liver,

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NAFLD: lipid profiles

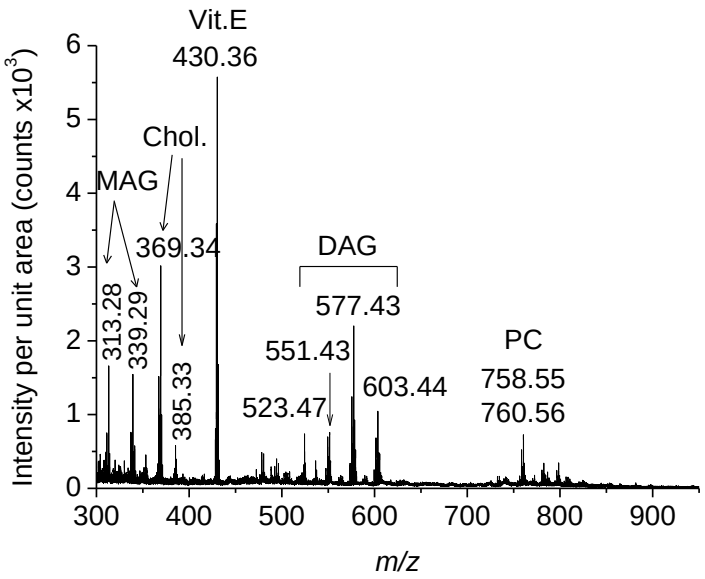
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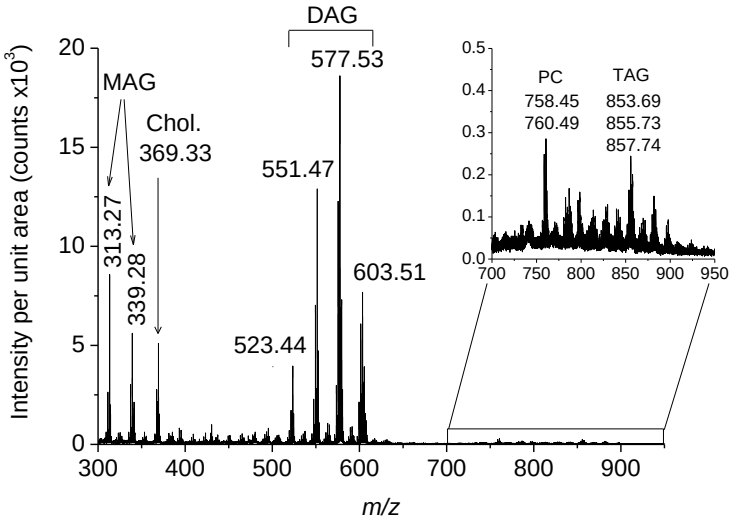
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Control liver

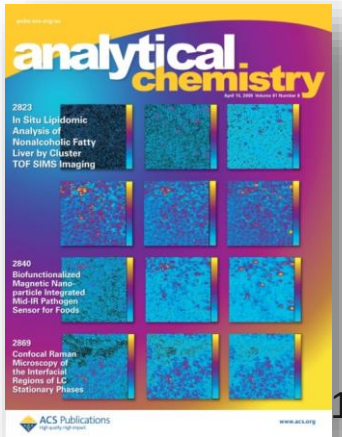


Fatty liver – steatotic area



- Strong decrease of vitamin E signal
- Detection of triacylglycerols
- Strong increase of diacylglycerols

D. Debois et al., Anal. Chem. 2009, 81, 2823-2831



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NAFLD: SIMS images of the steatotic area

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Localized lipidomics

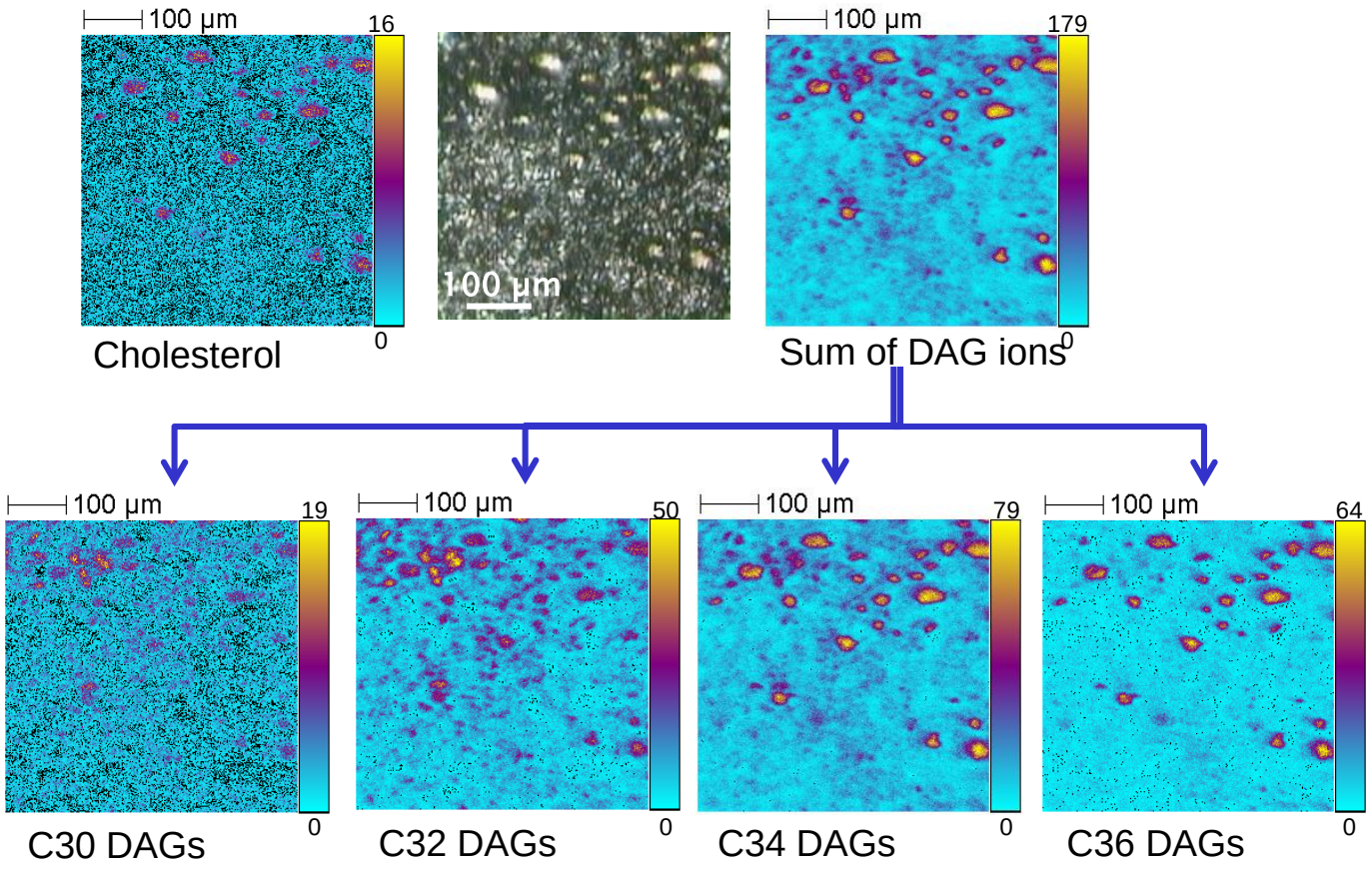
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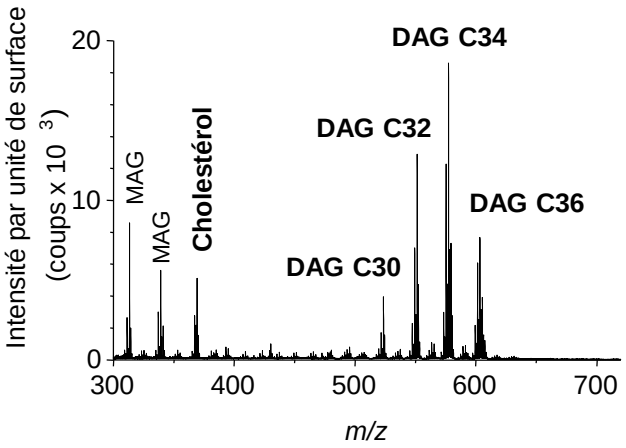
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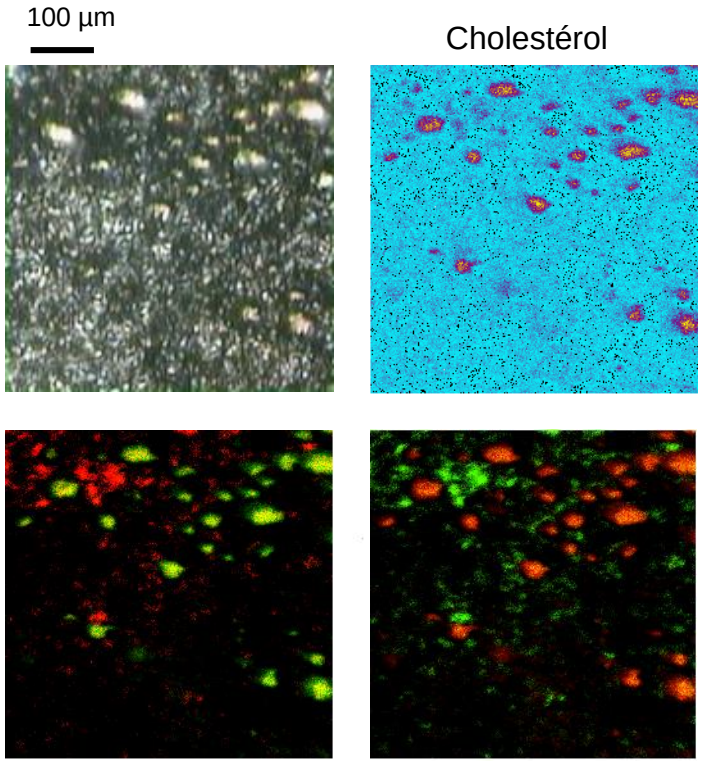
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Red = DAG C30
Green = DAG C36

Red = Unsaturated lipids
Green = saturated lipids

F. Le Naour *et al.*
***Plos One*, 4, issue 10, e7408 (1-10) (2009)**

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Cystic fibrosis: How extracting information from MS images ?

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Usual way

Whole mass spectrum (all pixels)

↓

Extract ion images

↓

Definition of Regions of Interest (ROI) from individual ion images

↓

ROIs Mass spectra

↓

Co(anti)-localization of lipids

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Whole mass spectrum (all pixels)

↓

Extract ion images

↓

Definition of Regions of Interest (ROI) from individual ion images

↓

ROIs Mass spectra

↓

Co(anti)-localization of lipids

Manual process strongly dependant on the operator subjectivity/experience

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Lipid mapping of colonic mucosa by cluster TOF-SIMS imaging and multivariate analysis in *cftr* knockout mice[S]

Marc Brulet,[1,*] Alexandre Seyer,[1,*] Aleksander Edelman,[†] Alain Brunelle,[*] Janine Fritsch,[†] Mario Ollero,[2,*,†] and Olivier Laprévote[*,§]

Centre de Recherche de Gif,* Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France; Inserm,† U845, Faculté de Médecine Paris Descartes, Paris, France; and Chimie Toxicologie Analytique et Cellulaire,§ EA 4463, Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris Descartes, Paris, France

3034 Journal of Lipid Research Volume 51, 2010

Aim: differentiate by TOF-SIMS imaging CF mouse models from WT mices

Samples: colon crypts

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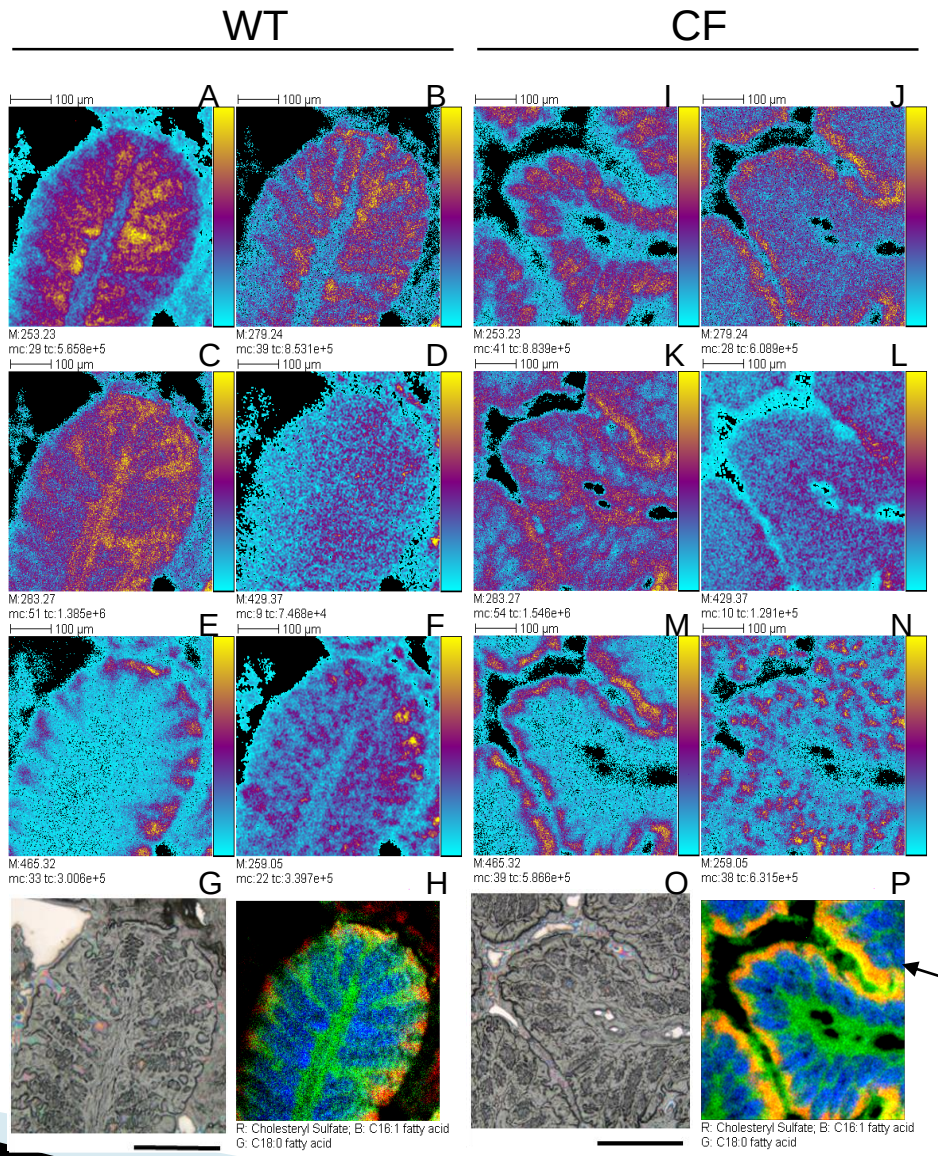
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C16:1 FA (Lieberkühn glands)

C18:2 FA (Border)

Cholesteryle Sulfate (Border)

C18:0 FA (*Lamina propria*)

Vit E

PI or ST fragment (mucosa)

3-color overlay

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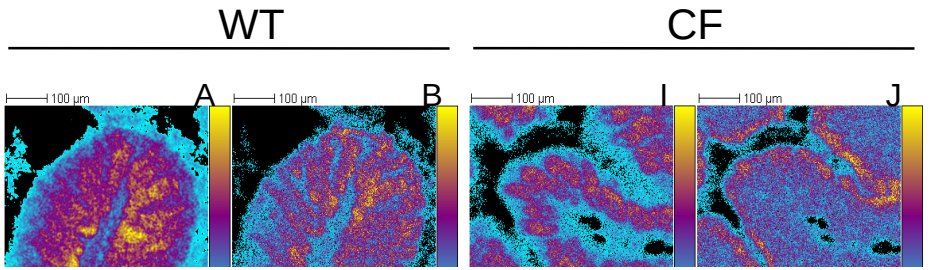
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C16:1 FA (Lieberkü glands)

Different distributions of lipids between the histological substructures

FA
a propria)

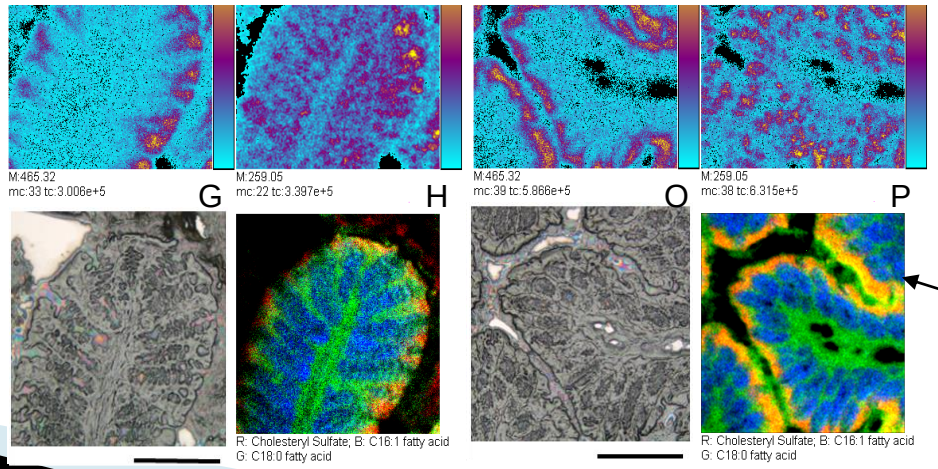
C18:2 FA (Border)

No « clear » differences between CF and WT samples

Vit E

Strong inter-individual variations

Cholesteryle Sulfate (Border)



PI or ST fragment (mucosa)

3-color overlay

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STEP 2
multivariate PCA

→ selection of PCs'

Percent Variance Captured by PCA Model			
Principal Component Number	**Eigenvalue of Cov(X)**	**% Variance Captured by this PC**	**% Variance Captured Total**
1	0.37	**37.45**	**37.45**
2	0.18	**17.97**	**55.42**
3	0.12	**11.65**	**67.06**
4	0.07	**7.29**	**74.35**
5	0.06	5.50	79.85
6	0.05	4.58	84.43
7	0.04	3.80	88.23
8	0.04	3.72	91.95
9	0.03	3.38	95.33
10	0.02	1.90	97.23
11	0.01	1.06	98.30
12	0.01	0.65	98.95
13	0.00	0.49	99.45
14	0.00	0.40	99.85
15	0.00	0.15	100.00

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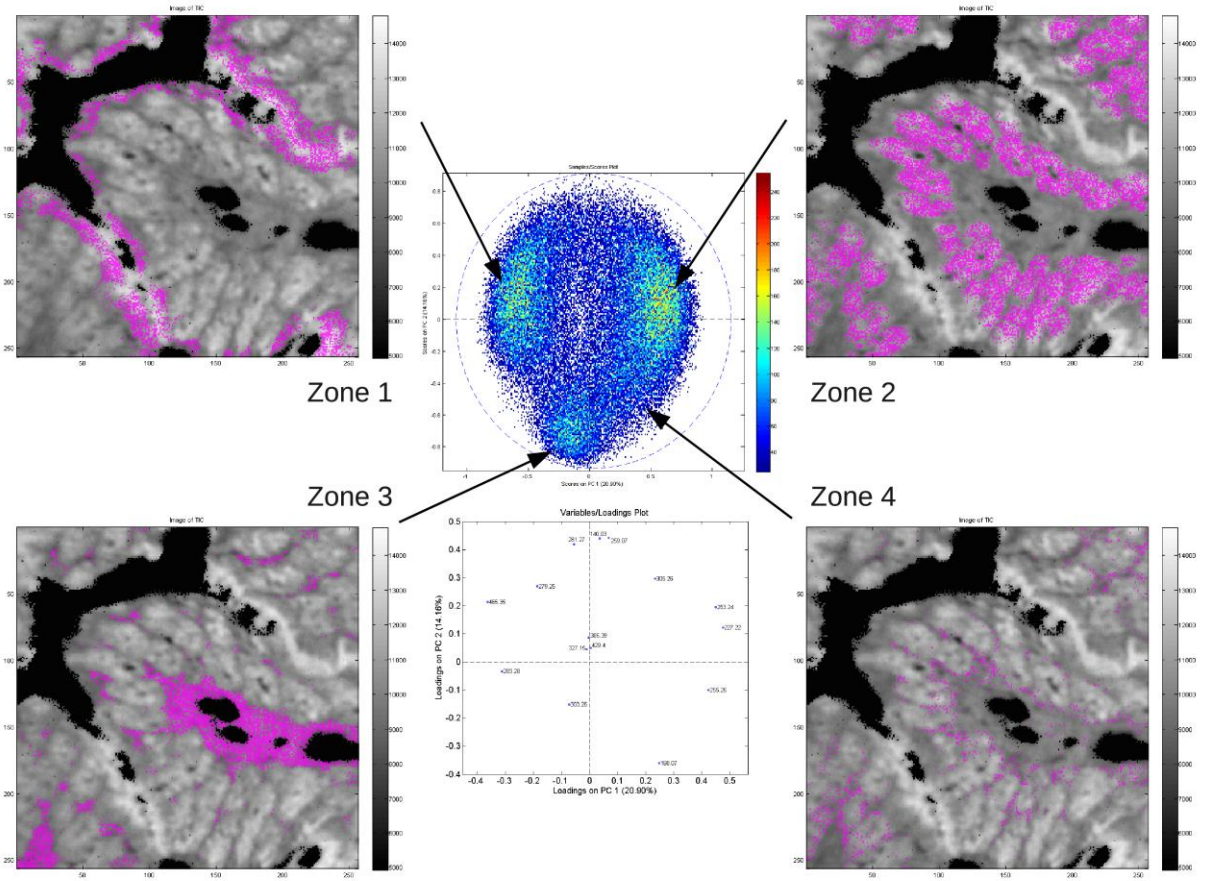
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STEP 3: representing pixels in the space of scores

PC1-PC2 plane

Lieberkühn Glands

Epithelial border



Submucosa

Lamina propria

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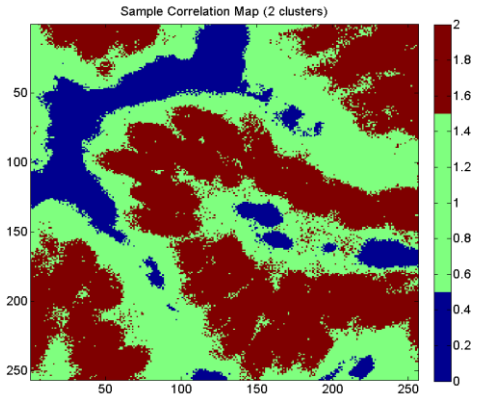
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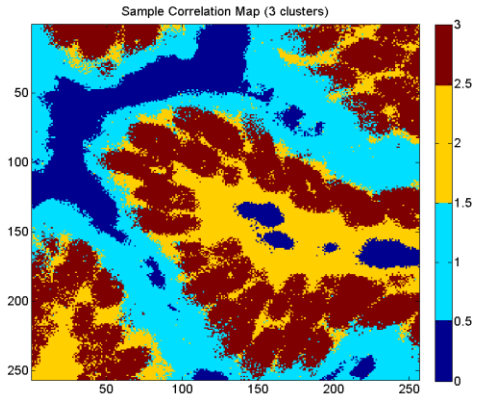
Special lipids
- Fabry disease
- Peptidolipids
- Cholesterol

Xenobiotics
- Environmental pollutant
- Preservative
- Anti-acne drug

STEP 4: partitioning clustering of PCA 1-4 selected variables

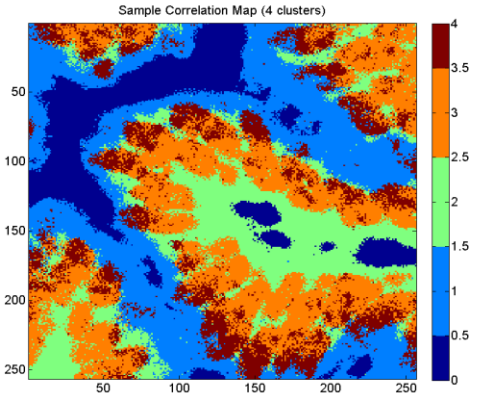
2 clusters

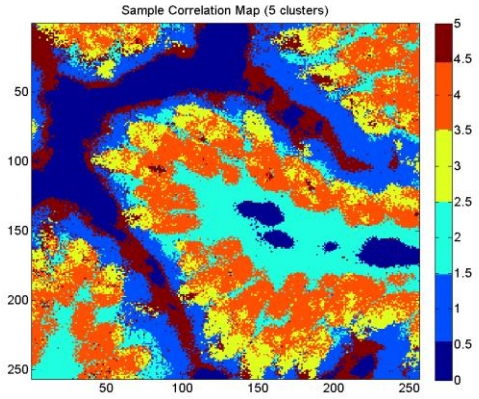




3 clusters

4 clusters





5 clusters

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Cystic fibrosis: How extracting information from MS images ?

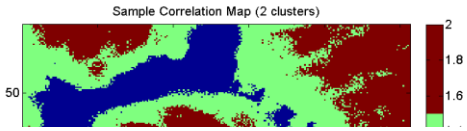
Introduction

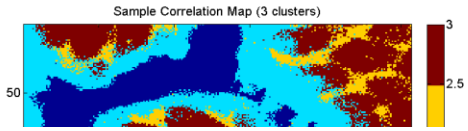
Localized lipidomics
- Duchenne dystrophy
- NAFLD
- Cystic fibrosis

Special lipids
- Fabry disease
- Peptidolipids
- Cholesterol

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- Anti-acne drug

STEP 4: partitioning clustering of PCA 1-4 selected variables





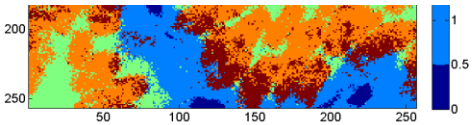
2 clus **RESULTS** **3 clusters**

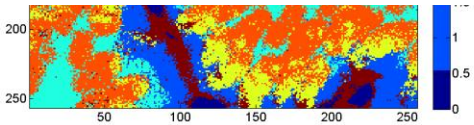
- Well-defined regions of interest (ROIs)

- Selection of ROIs for 7 WT and 6 CF samples allows their comparison by PCA

- A Genetic Algorithm analysis of WT and CF samples provides a list of the most discriminating peaks

4 clusters





5 clusters

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Cystic fibrosis: How extracting information from MS images ?

Introduction

Localized lipidomics

- Duchenne dystrophy
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- Cystic fibrosis

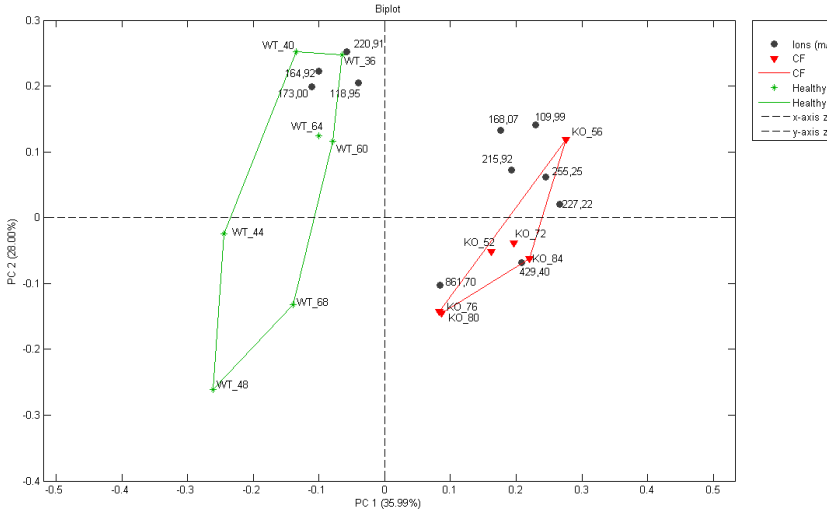
Special lipids

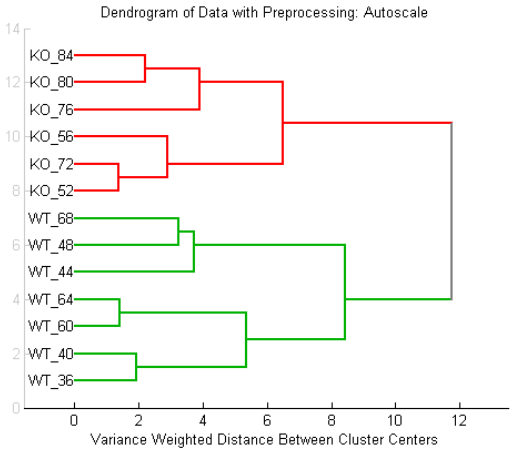
- Fabry disease
- Peptidolipids
- Cholesterol

Xenobiotics

- Environmental pollutant
- Preservative
- Anti-acne drug

Ion mass (*m/z*)	Ion Species	Lipid family
109.99	$[CH_3O_4P]^{\cdot-}$	PE, PC, SM
164.92	fragment	PI
168.08	$[C_4H_{11}NO_4P]^-$	PC, SM
215.92	fragment	CS, ST
220.91	fragment	PI, ST
227.22	C14:0 carboxylate	Fatty Acid
255.25	C16:0 carboxylate	Fatty Acid
429.40	[Vitamine E – H]-	VE
861.70	[TG52:0 – H]-	TG





Glycosphingolipids of the Fabry disease

Introduction

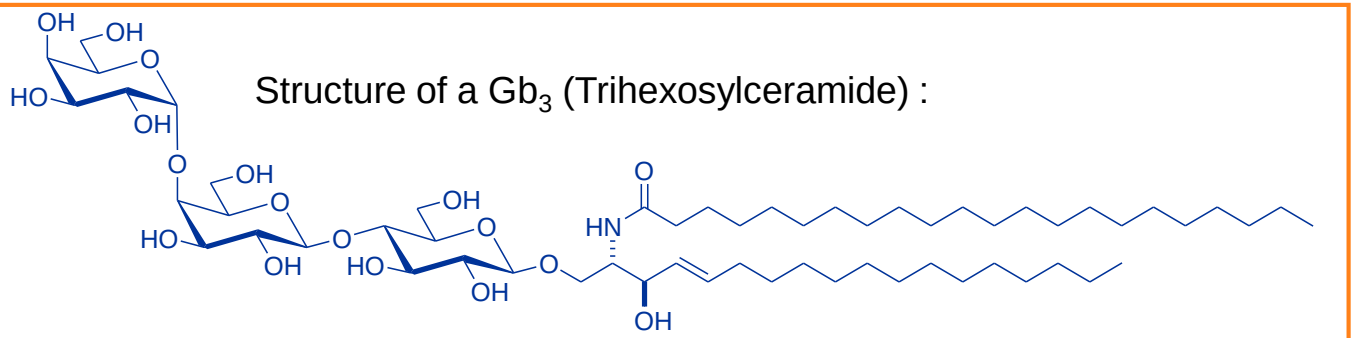
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Lysosomal disease due to a lack of α-D-galactosidase-A (α-GALA) of recessive transmission linked to the X chromosome
(affects 1 over 120 000 people)
Accumulation of Gb_3 and Ga_2 glycosphingolipids in fluids and tissues

Structure of a Gb_3 (Trihexosylceramide) :



Ga_2 (digalactosylceramide), Gal/Gal sequence

➔ kidney deficiencies, neurological and cardiac evolutive lesions and angiokeratomas

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Glycosphingolipids of the Fabry disease

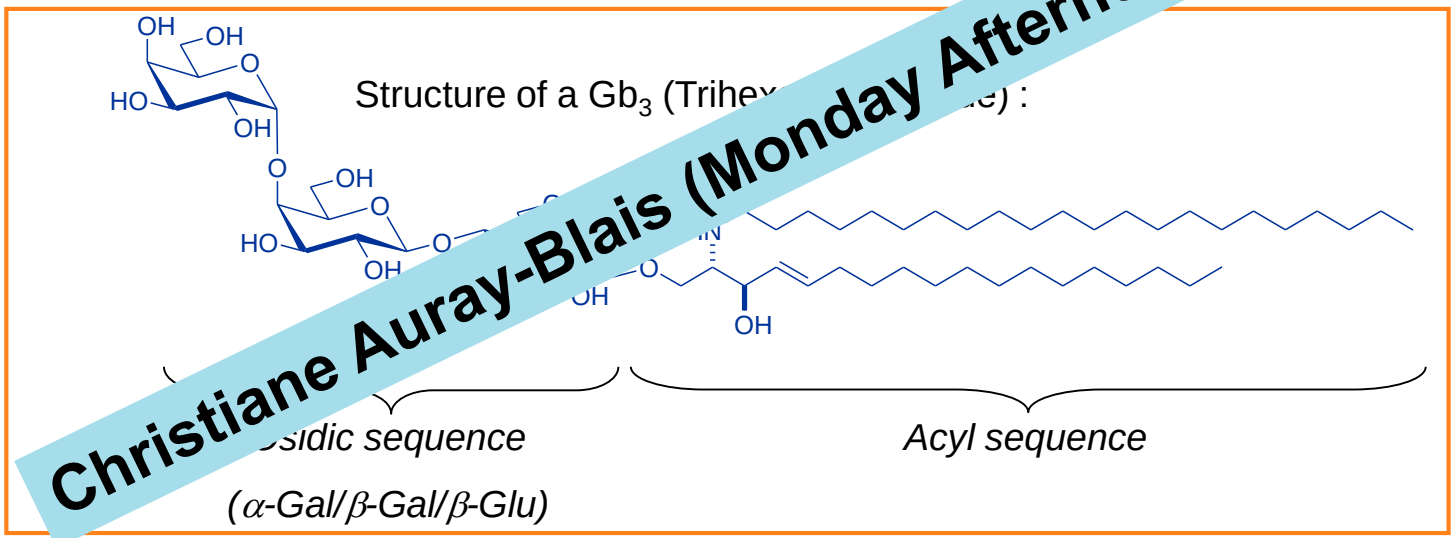
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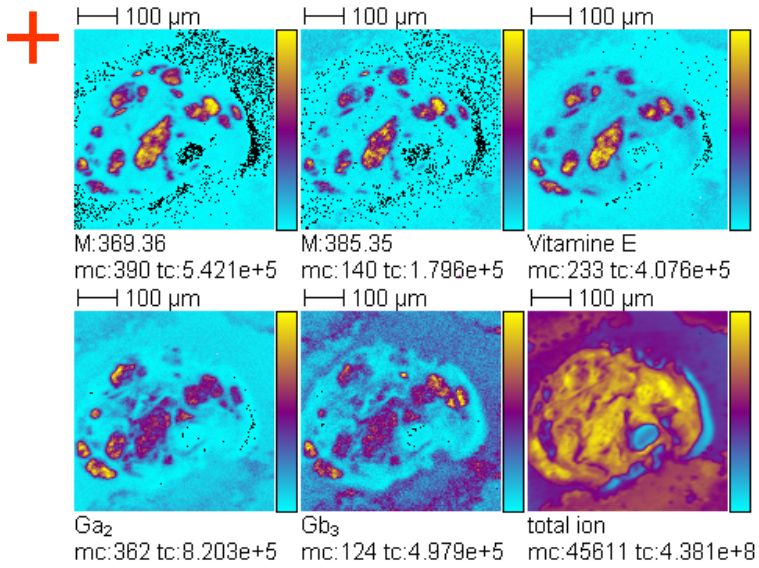
Kidney biopsy of a patient suffering from the Fabry disease

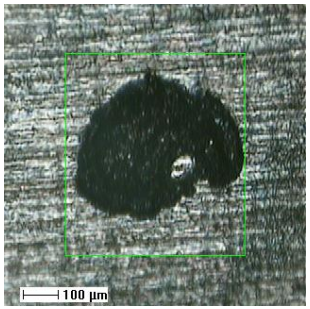
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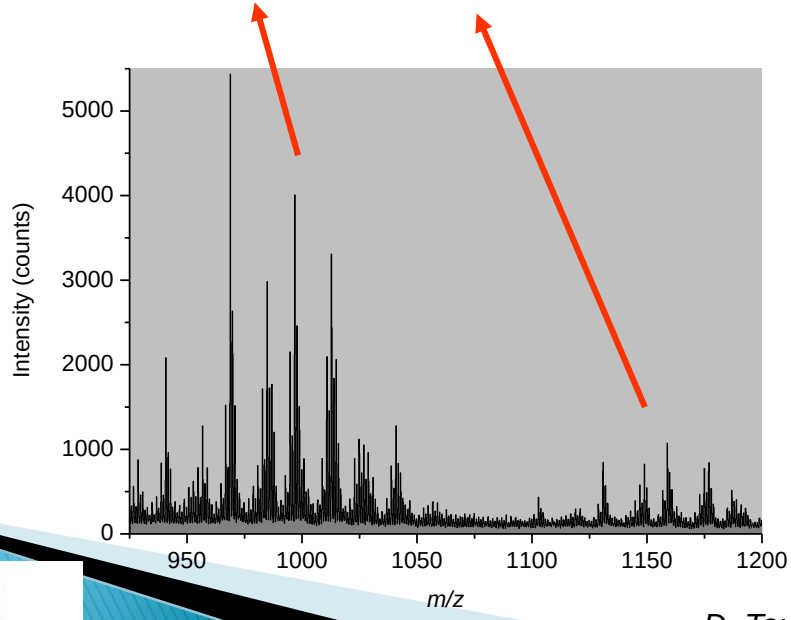
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No treatment of the sample
500x500 µm²
256x256 pixels
Bi_3^+ primary ions
Acquisition time 30 min
Fluence 10^{12} ions.cm^{-2}



- Detection of very intense Ga_2 et Gb_3 signals
- Possible to localize a single species with a micrometer resolution
- Colocalization with vitamin E, cholesterol and cholesterol sulfate

D. Touboul et al., ***Int. J. Mass Spectrom. 2007***, *260, 158-165*

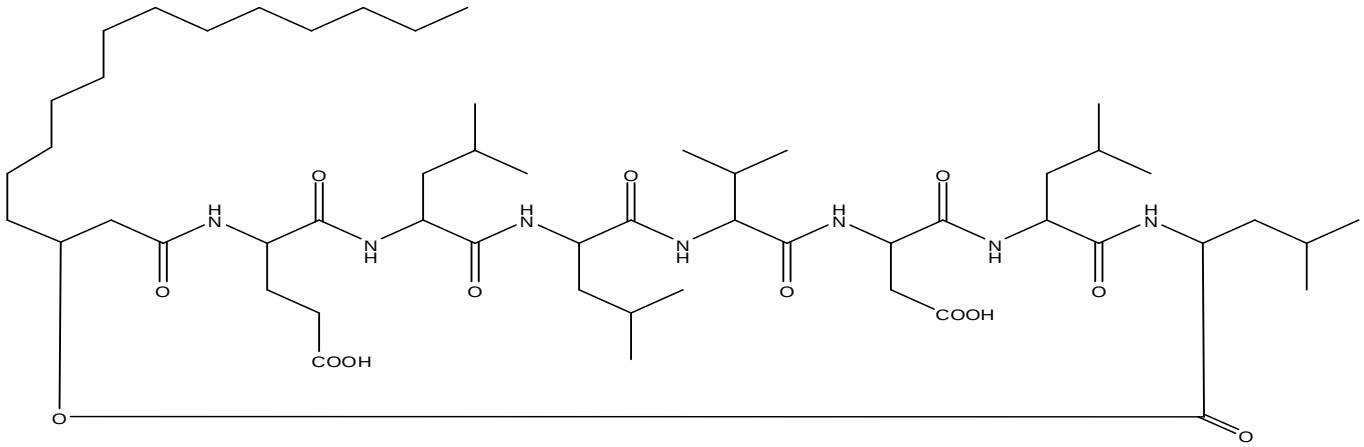
Surfactines from Bacillus subtilis strains

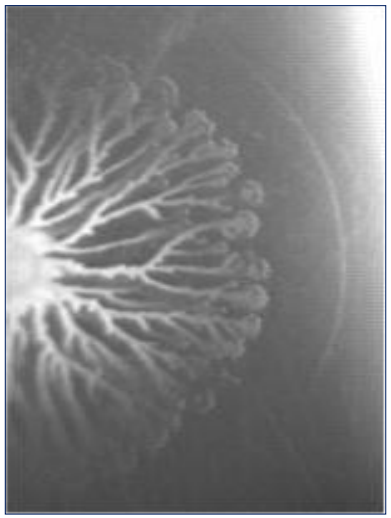
Introduction

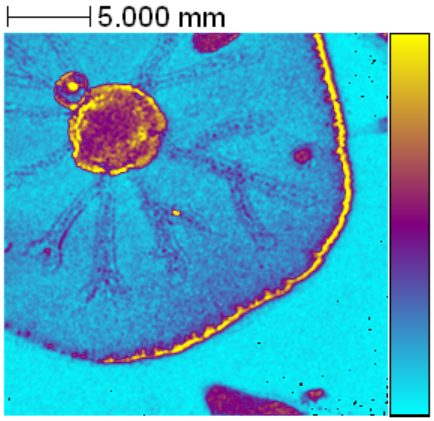
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Sum of surfactin ions
mc:50 tc:7.077e+5

Surfactines from Bacillus subtilis strains

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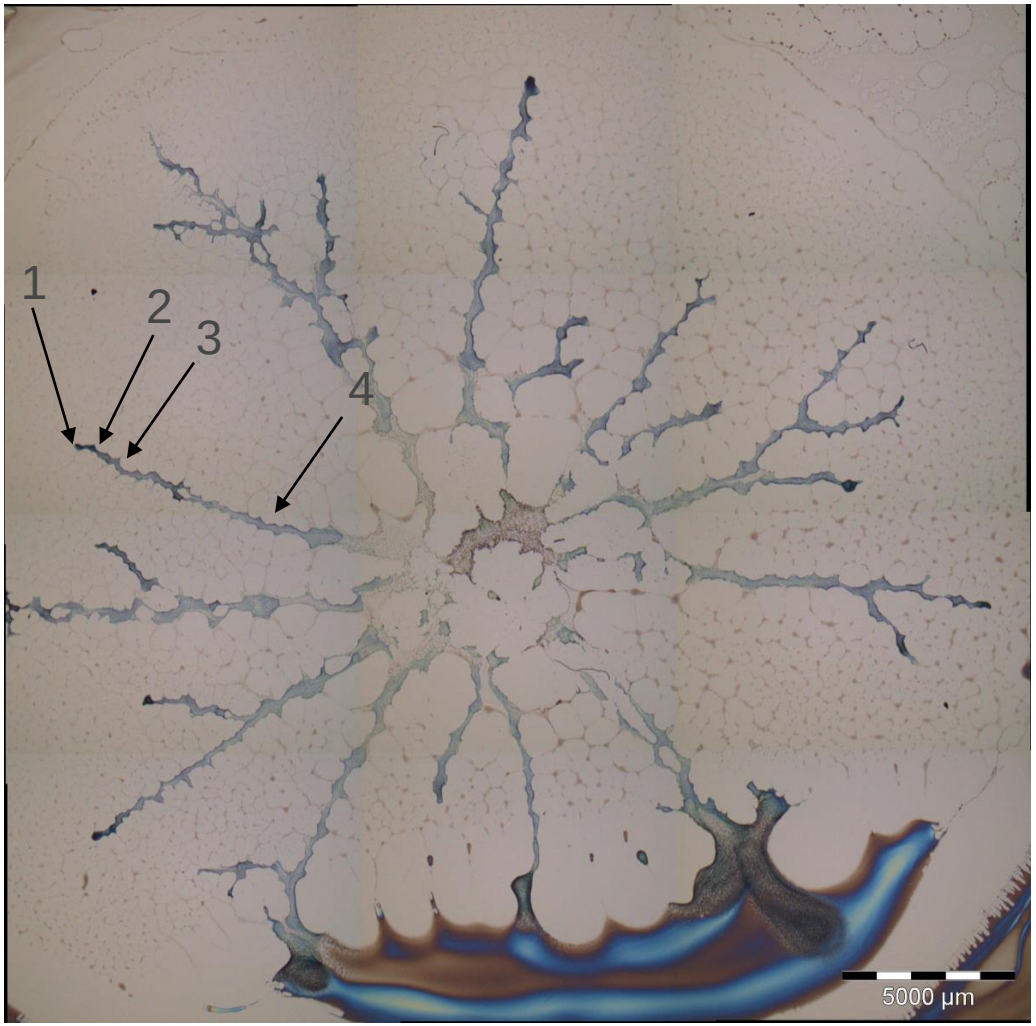


Image size: 500x500 µm²

Primary ions: Bi_3^+, 25 keV

Negative ion mode

PIDD: 5.10^{11} ions.cm^{-2}

Pixel size: 2x2 µm²

Acquisition time: 30 min

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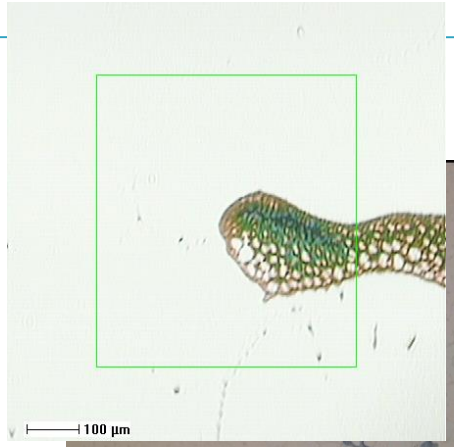
Surfactines from Bacillus subtilis strains

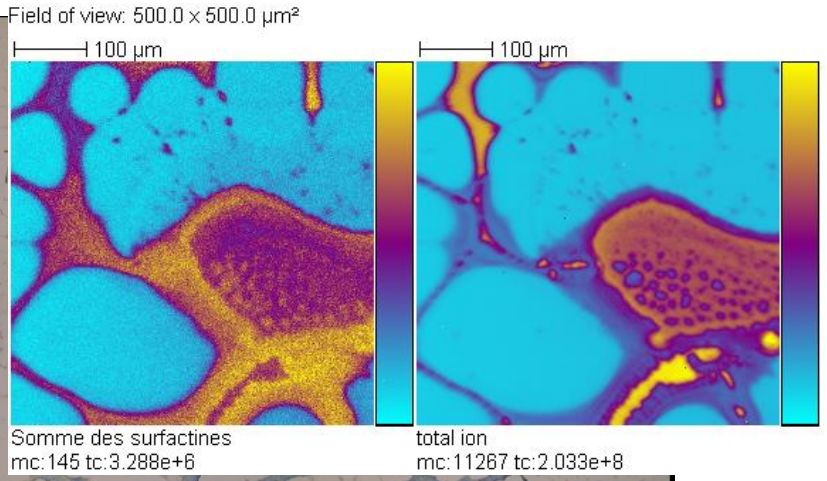
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Surfactines from Bacillus subtilis strains

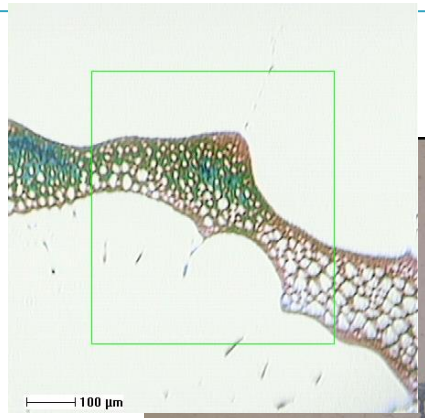
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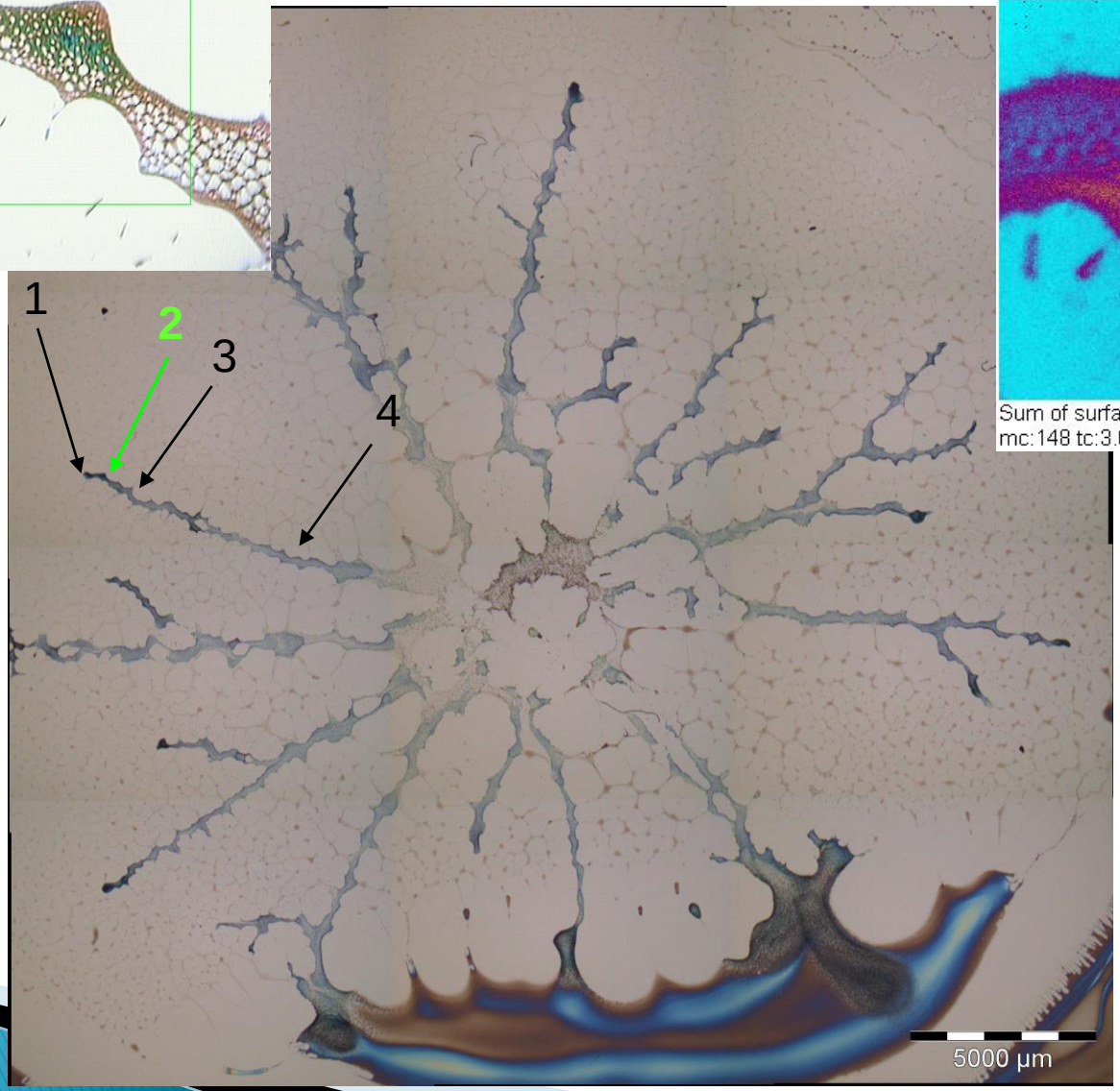
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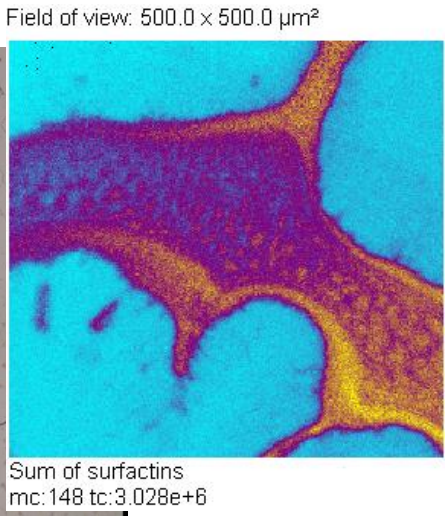
Special lipids
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Artwork analysis
- Dogon art
- Rembrandt
- Grünewald







Cholesterol distribution in the cortex of Alzheimer disease patients

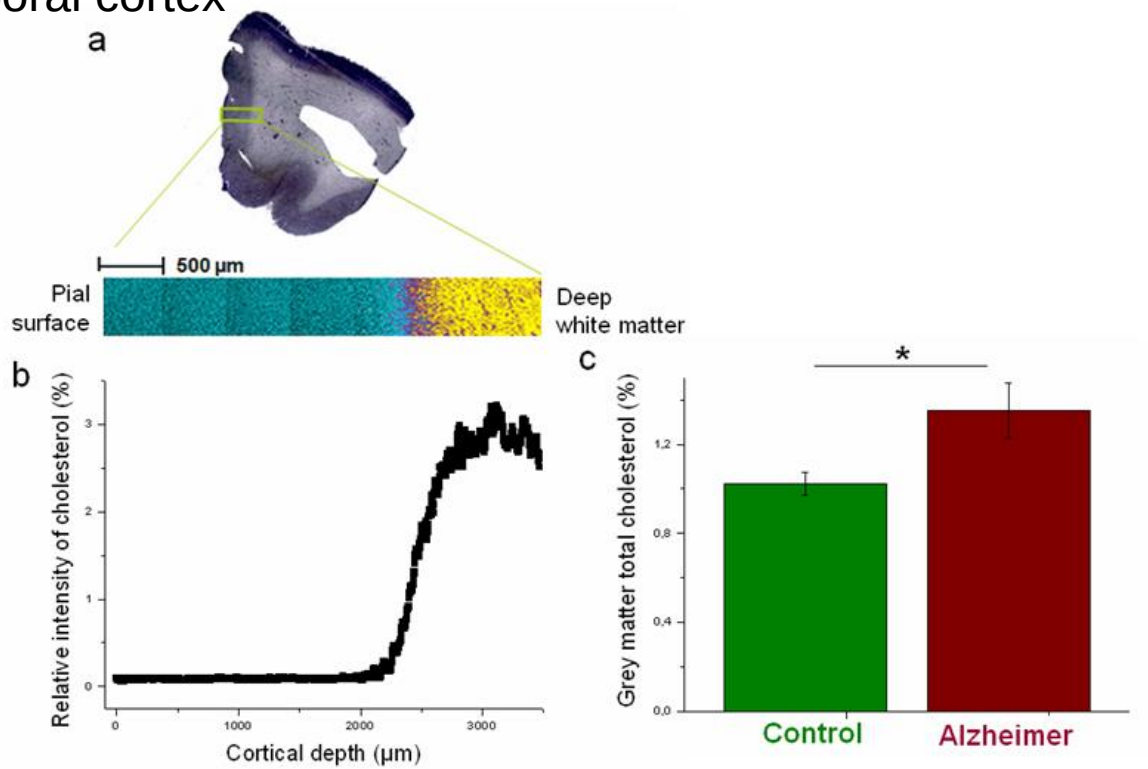
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Temporal cortex



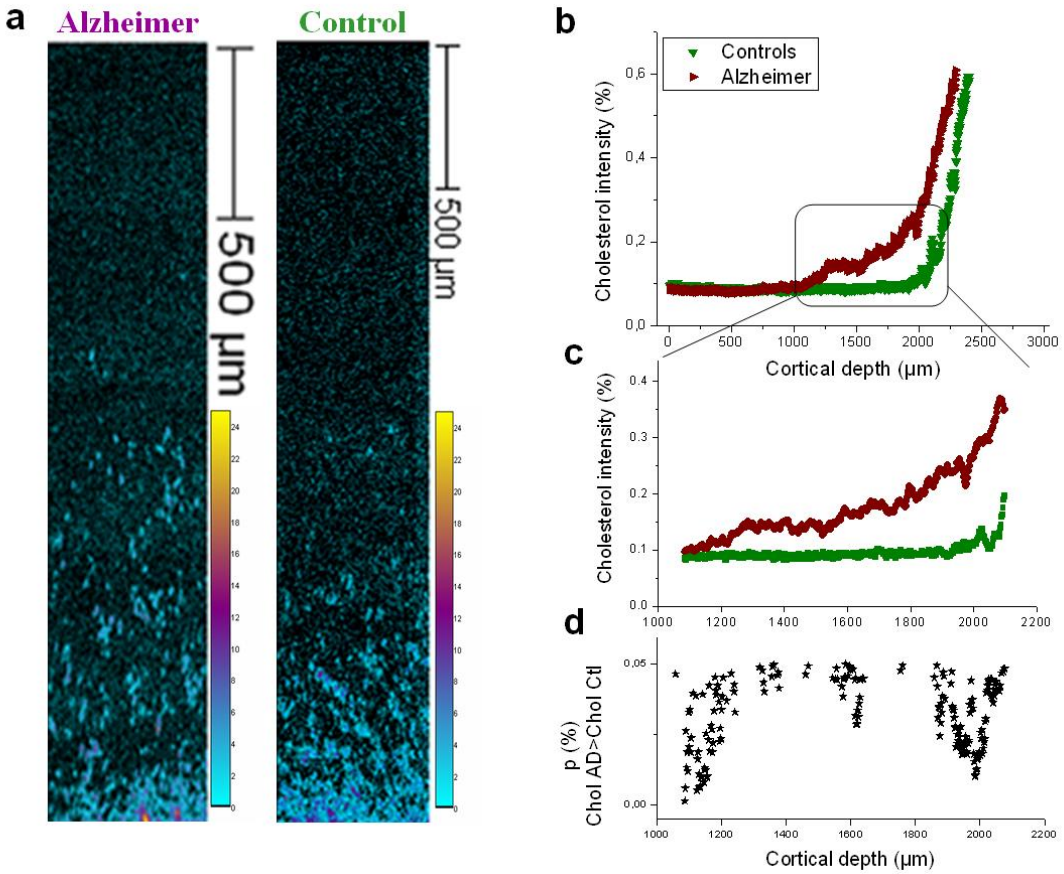
Cholesterol distribution in the cortex of Alzheimer disease patients

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Variation of cholesterol distribution along the cortex *(Alzheimer n=6, Controls n=4)*

A. N. Lazar *et al. Acta Neuropathologica,* **125**, 133-144 (2013)

Deca-bromodiphenyl ethers

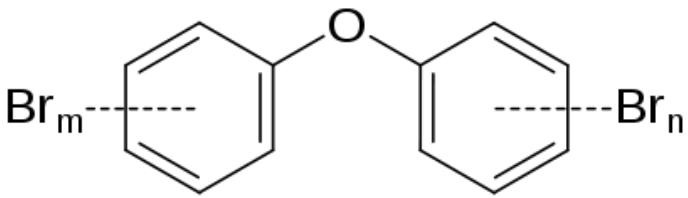
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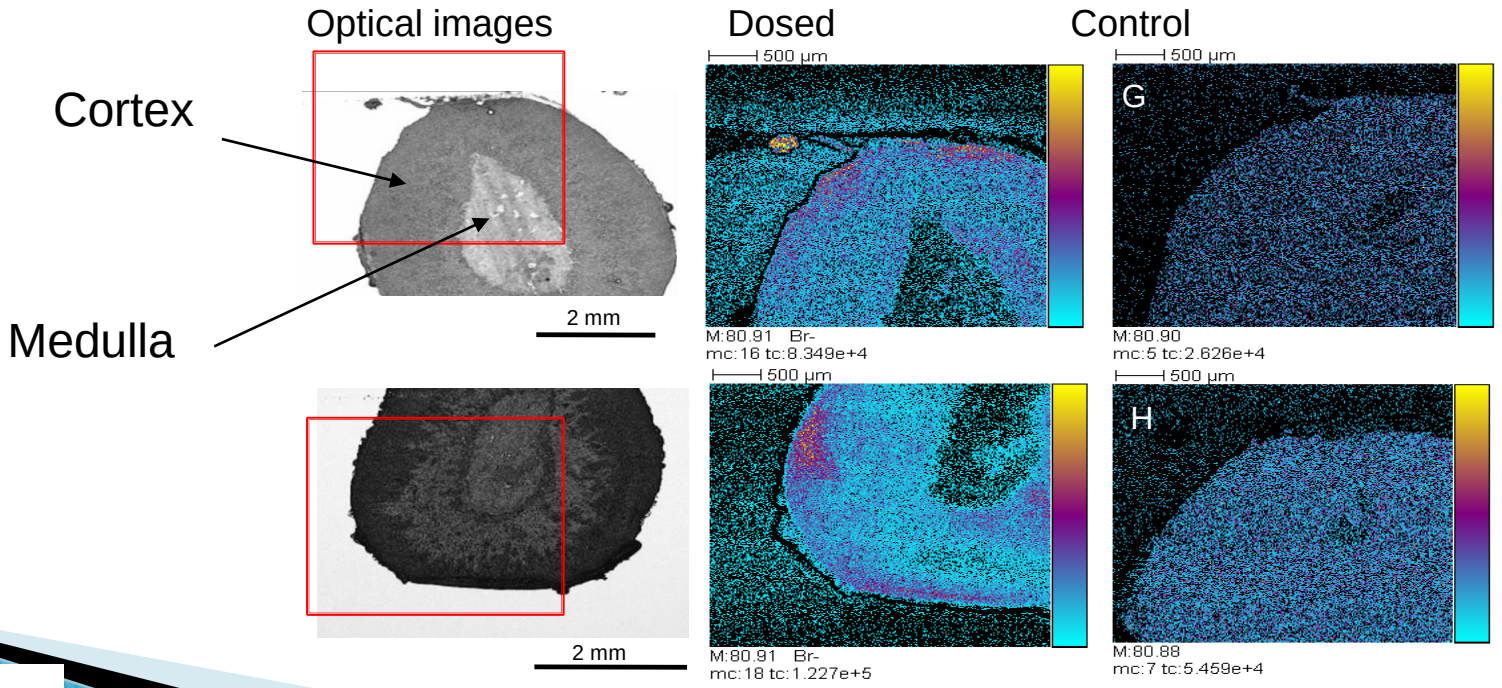
Xenobiotics
- Environmental pollutant
- Preservative
- Anti-acne drug

- Polybrominated flame retardants
- Endocrine disruptive chemicals



Imaging of DBDE in organs of dosed rats *vs.* control

ADRENALS



A. Seyer*J. Am. Soc. Mass Spectrom.* **21**, 1836-1845 (2010),

Deca-bromodiphenyl ethers

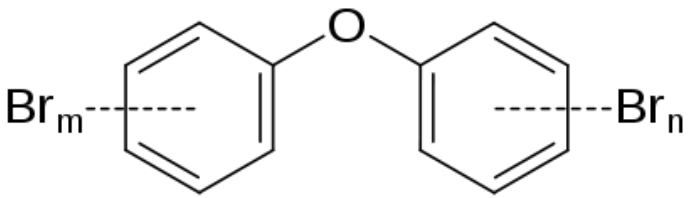
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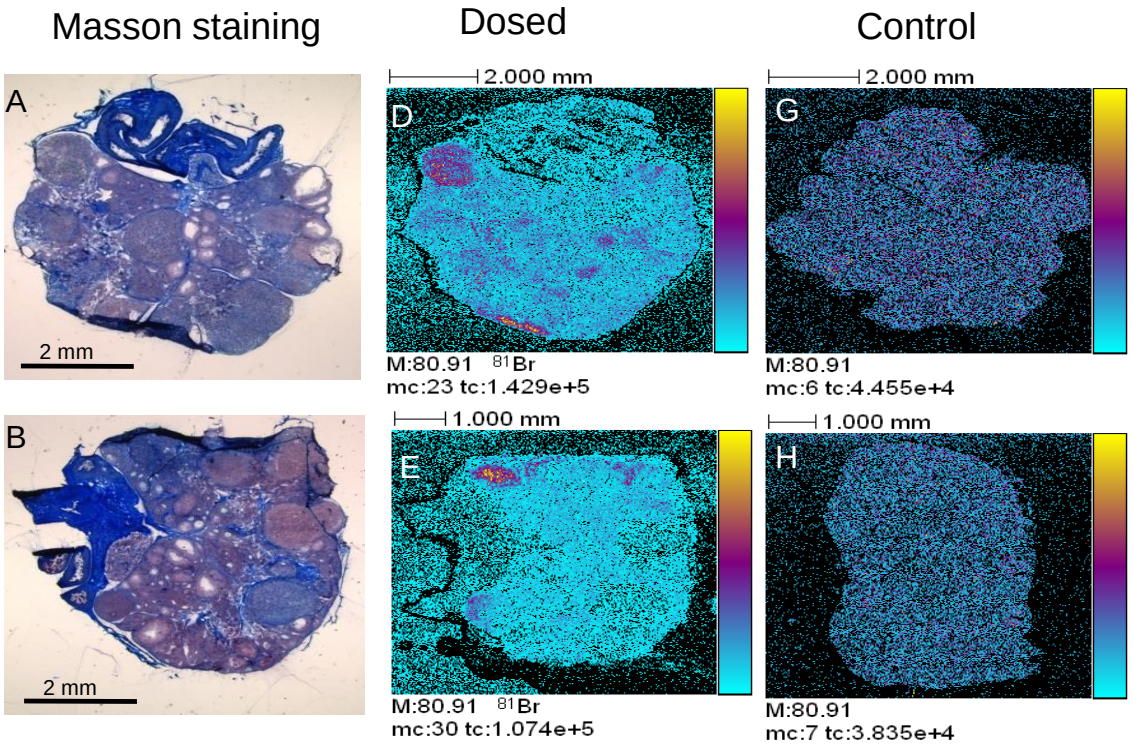
Xenobiotics
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- Polybrominated flame retardants
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Imaging of DBDE in organs of dosed rats *vs.* control

OVARIES



-Accumulation in some of the numerous corpora lutea
-Dependant on the corpus luteum's stage in the estrous cycle (?)

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Benzalkonium chloride

Introduction

Localized lipidomics
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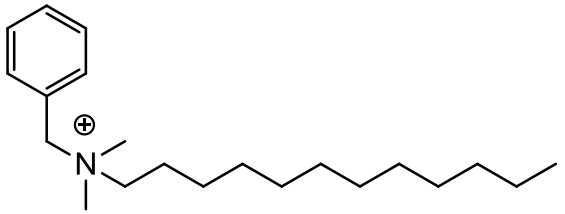
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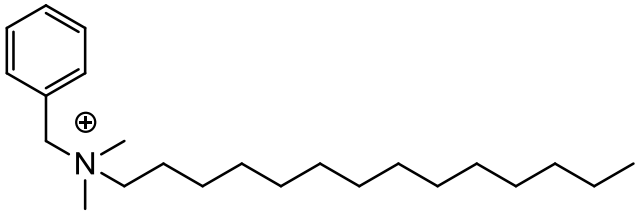
Used as preservative in eye drops of prostaglandin derivatives and betablockers as first line therapy for glaucoma

- But it is toxic:

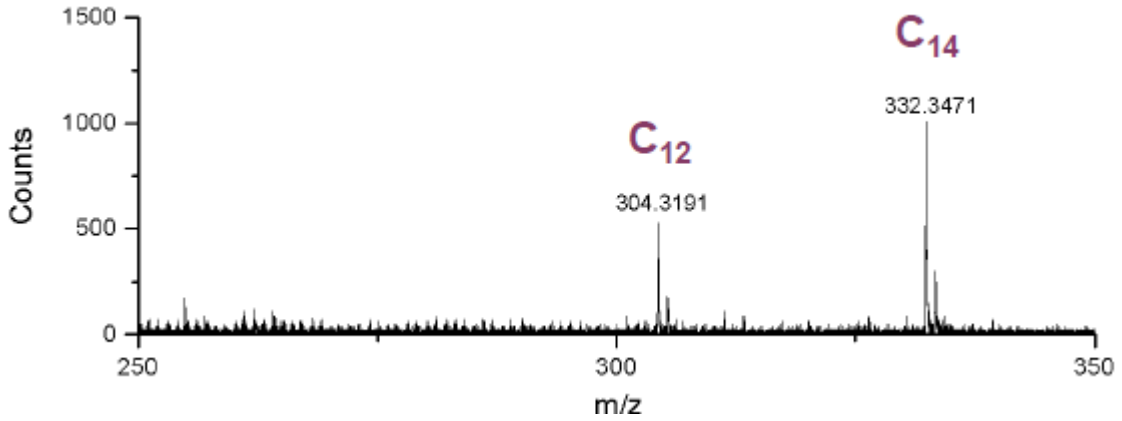
→ Damage of tissues due to oxidative stress
→Apoptosis



Benzododecinium ion (BAK C_{12})



Myristalkonium ion (BAK C_{14})



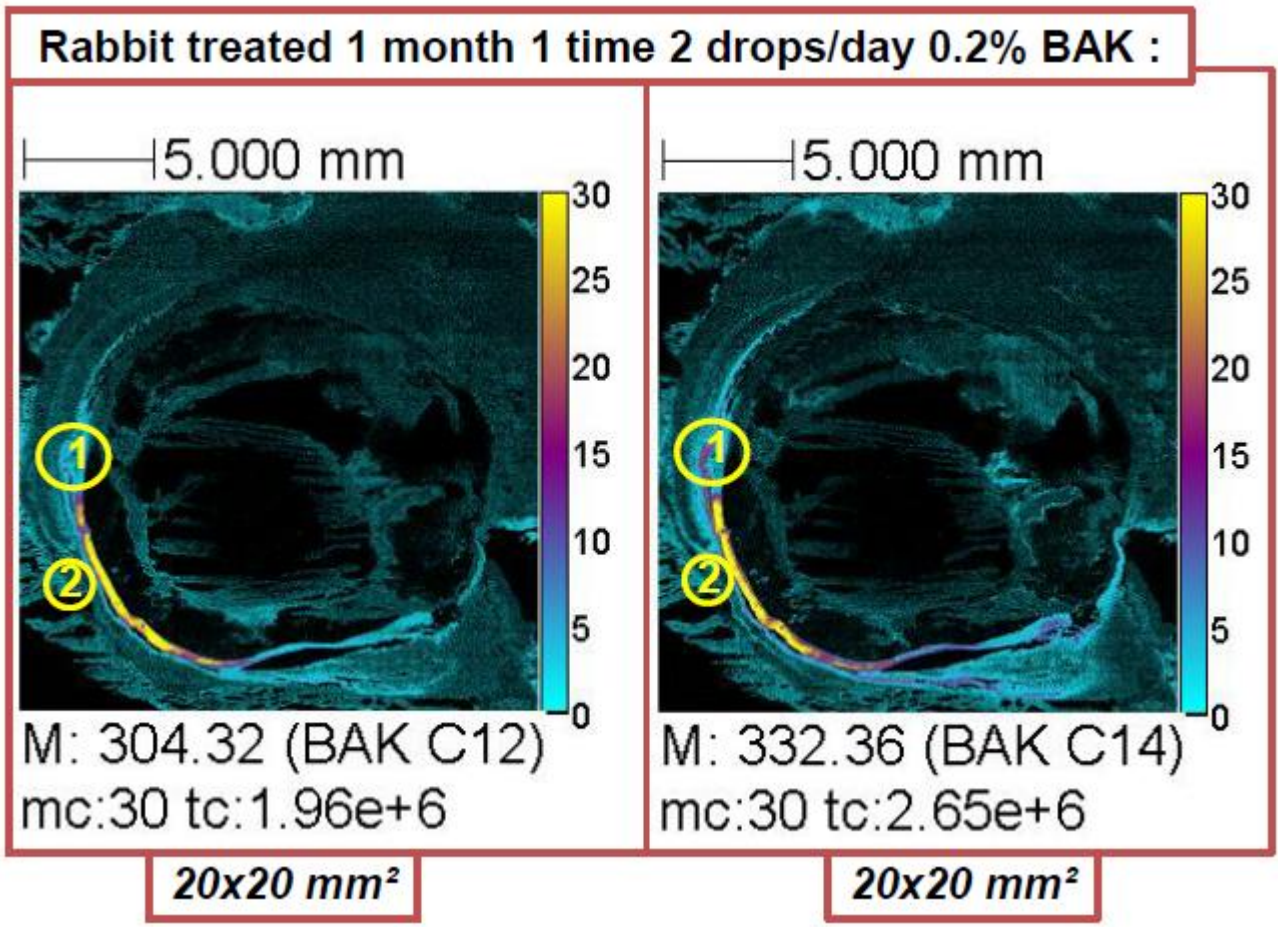
Benzalkonium chloride

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Benzalkonium chloride

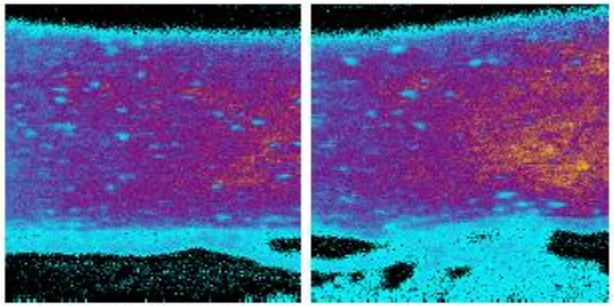
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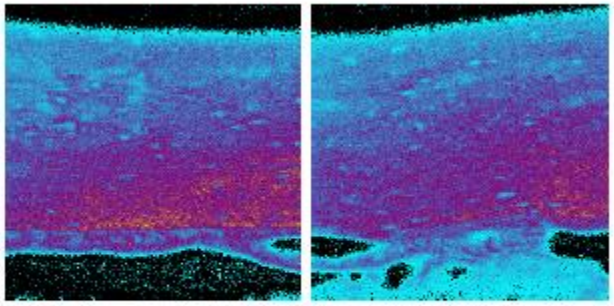
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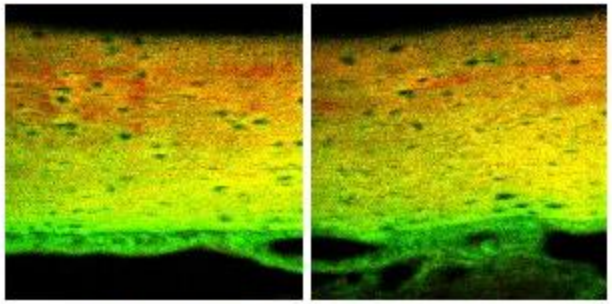
CORNEA



M: 304.32 (BAK C12)
mc : 60



m/z 332.36 (BAK C14)
mc : 57



M: 304.32 (BAK C12) Red
M: 332.36 (BAK C14) Green

overlay

N. Desbenoit *et al. Anal. Bioanal. Chem.*, **405**, 4039–4049 (2013)

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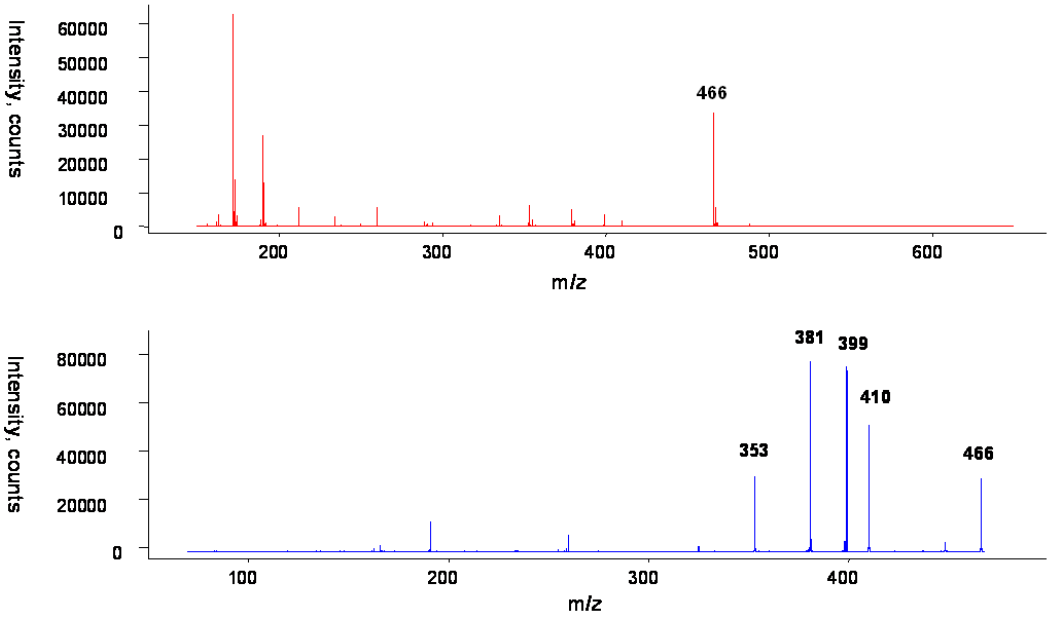
Anti-acne drug (collaboration: M. Stoeckli)

Introduction

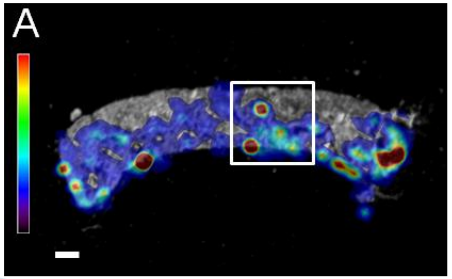
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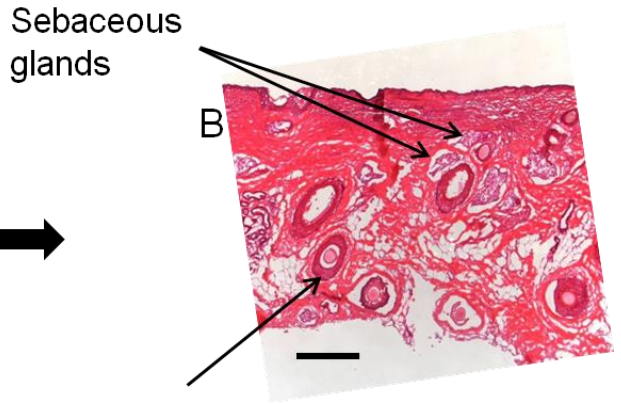
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MALDI Imaging





Anti-acne drug (collaboration: M. Stoeckli)

Introduction

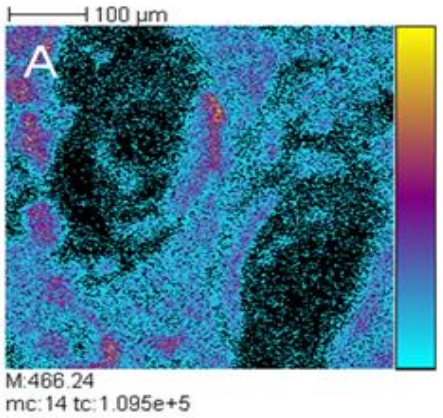
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- Cystic fibrosis

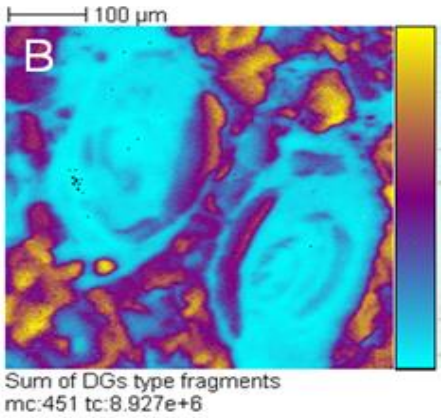
Special lipids
- Fabry disease
- Peptidolipids
- Cholesterol

Xenobiotics
- Environmental pollutant
- Preservative
- Anti-acne drug

TOF-SIMS Imaging

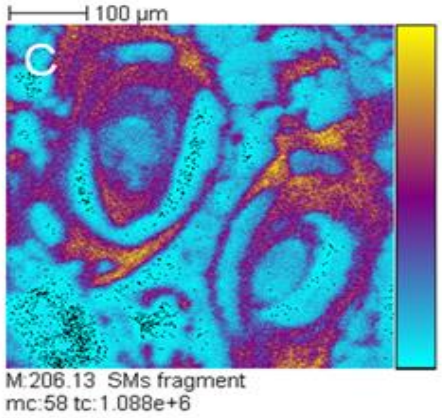
Drug

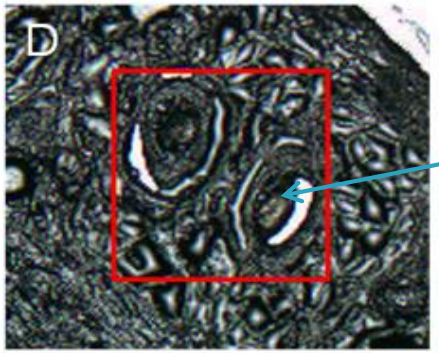




Diglycerides

Sphingomyelin





Hair follicle

→ colocalisation of the drug with the diglycerides around the hair follicles

TOF-SIMS analysis of a Rembrandt painting

Introduction

Localized lipidomics
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Artwork analysis
Rembrandt



Portrait of Nicolaes van Bambeeck

Rembrandt van Rijn, 1641

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TOF-SIMS analysis of a Rembrandt painting

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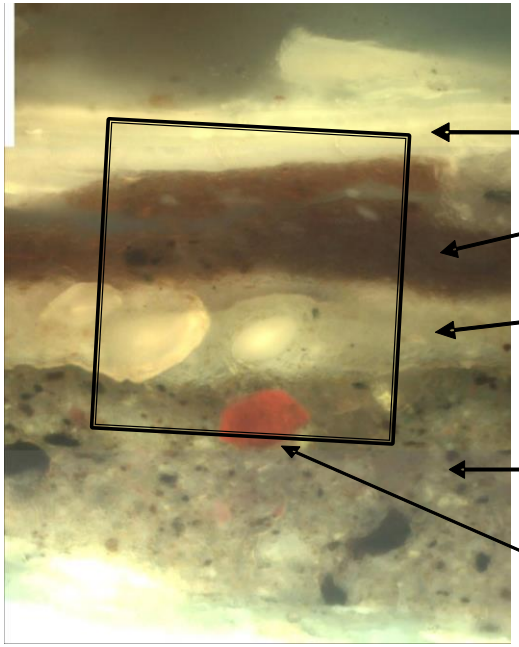
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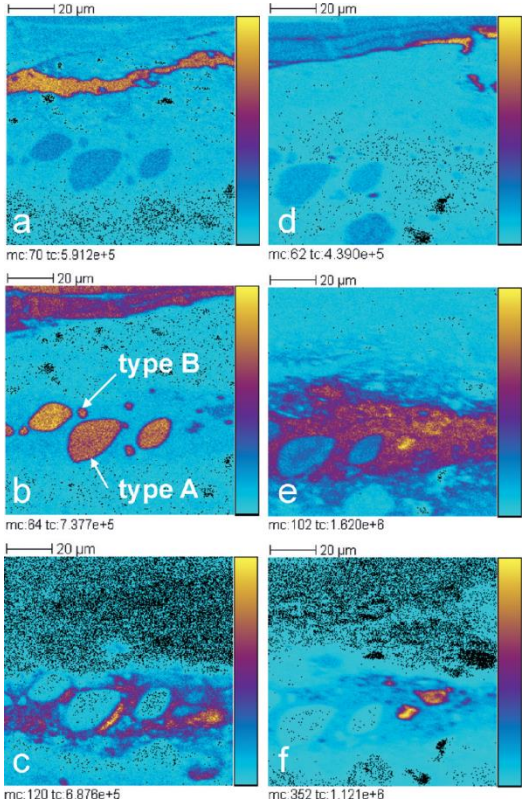
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Artwork analysis
Rembrandt



1500 µm long





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TOF-SIMS analysis of a Rembrandt painting

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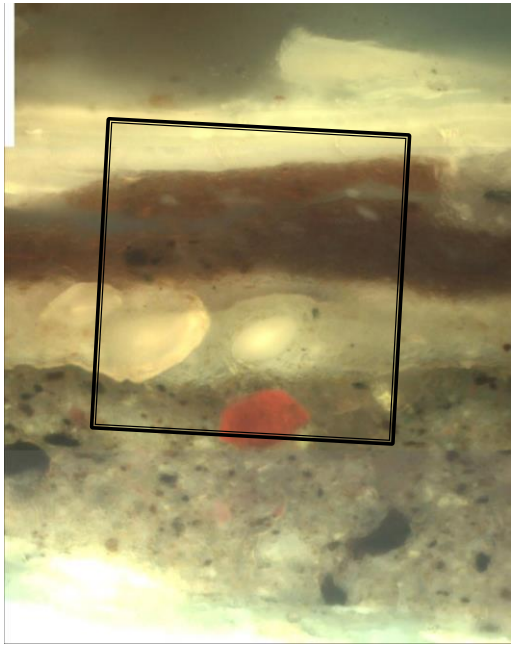
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Rembrandt



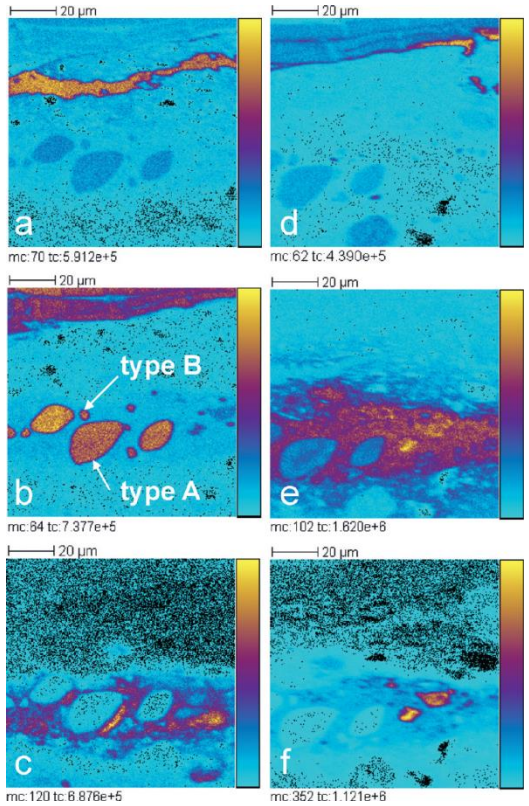
1500 µm long



m/z 85 (resin)

m/z 59 (saccharide fragment: starch)

Lipid ions



Amino acids

Pb^{+}
Pb^{2+}
Pb^{3+}

Lead white

TOF-SIMS analysis of a Rembrandt painting

Introduction

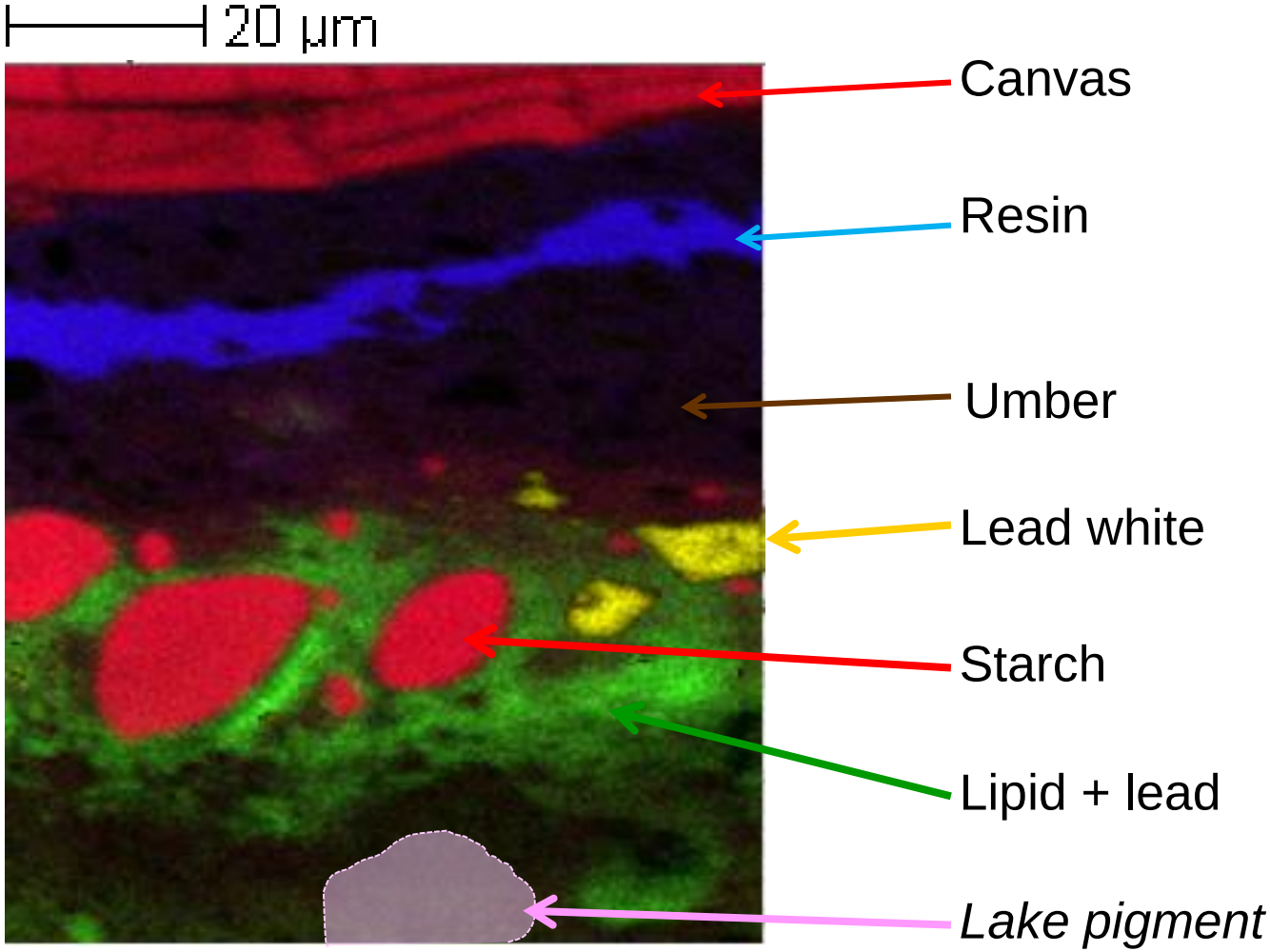
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Artwork analysis
Rembrandt

STRATIGRAPHY OF THE SAMPLE



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The Issenheim Altarpiece (Matthias Grünewald, 1561)

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Conclusion

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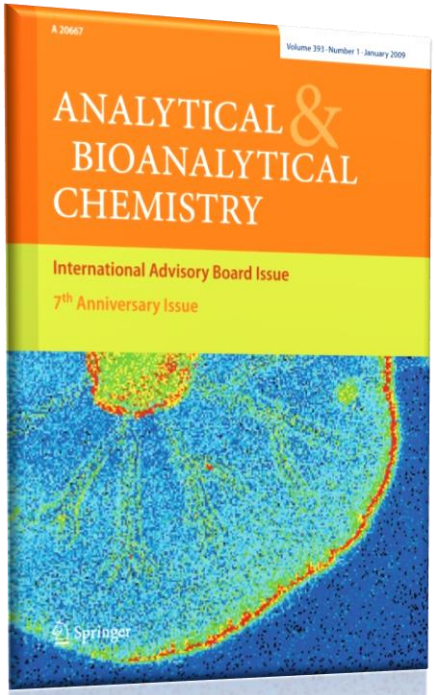
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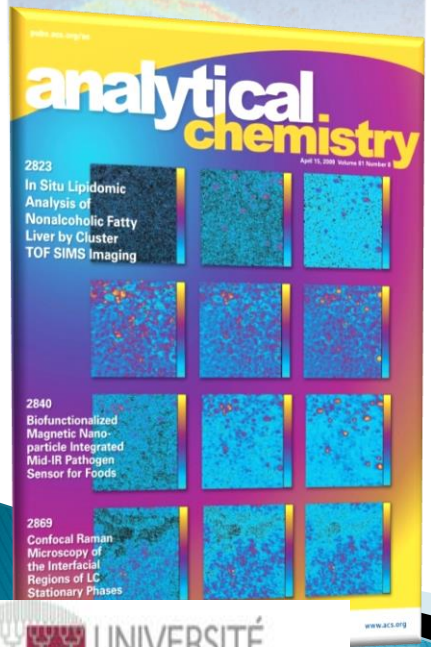
Xenobiotics
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Artwork analysis
- Rembrandt
- Grunewald

- For tissue imaging, the micrometer lateral resolution is enough in many cases (SIMS)
- The mass resolution and mass accuracy should be as high as possible
- Many organic ions can be identified by their co-localization with specific fragments (SIMS) or by MS/MS (MALDI). Don't forget the gas phase dissociation chemistry !
- Identification by spectral comparisons with standard compounds is always useful
- The targeted compounds must be highly concentrated in well-defined areas to be imaged.
- In biology, the expertise of histologists and/or collaboration with clinicians is mandatory.
- In SIMS *In situ* identification by MS/MS is lacking ➔ complementarity with MALDI-MSMS.

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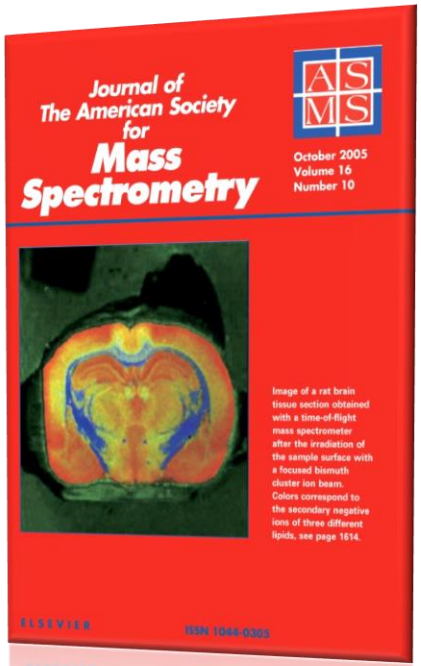
Grants:

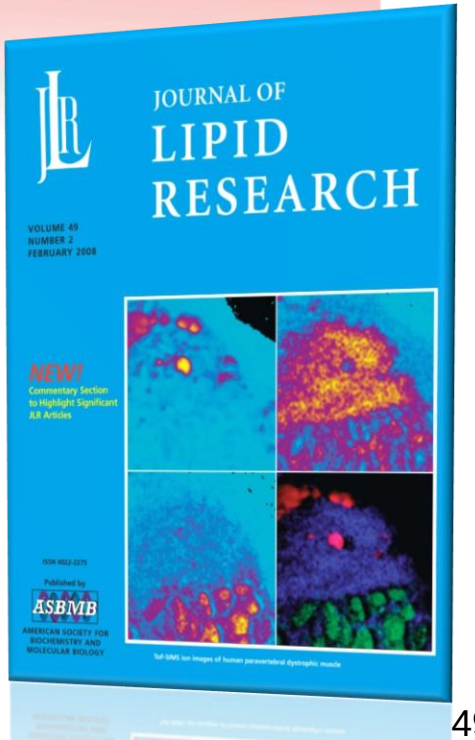
Agence Nationale de la Recherche Scientifique (ANR)

European Union (FP6 STREP Program)

Institut de Chimie des Substances Naturelles (ICSN)

Centre National de la Recherche Scientifique (CNRS)





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Alain Brunelle



David Touboul



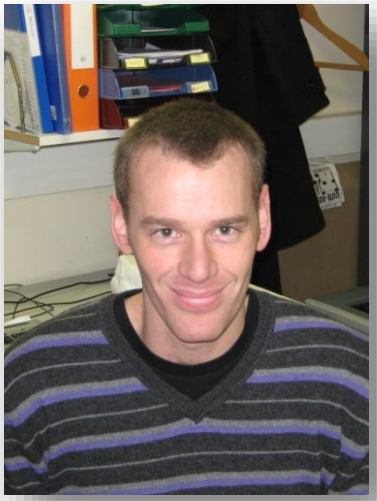
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Post-doc



Nicolas Desbenoit
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Alexandre Seyer
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Farida Messouaf
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