



Nestlé Skin Health

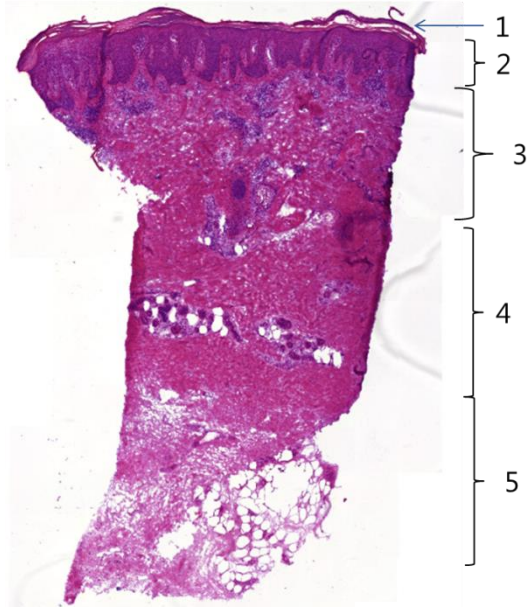


MALDI imaging a new quantitative methodology
approach for understanding drug distribution in skin

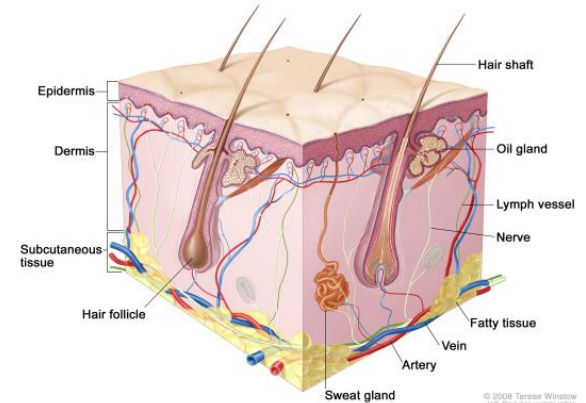
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delphine.maux@galderma.com

Dermatology

- In dermatology the efficacy of a topical drug may be related to its concentration and distribution within the skin.



- 1- Stratum corneum
- 2- Epidermis (100-280 μ m)
- 3- Dermis (1200 μ m)
- 4- Deep dermis (1200 μ m)
- 5- Hypodermis

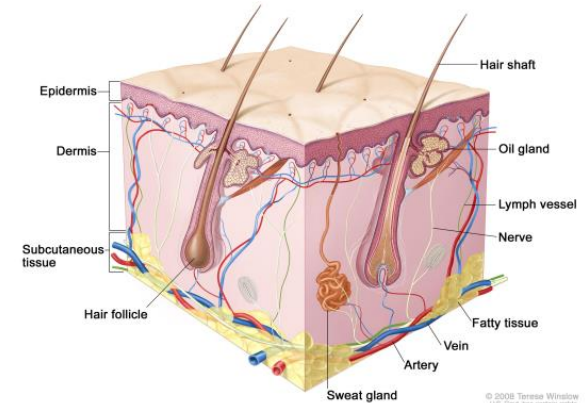


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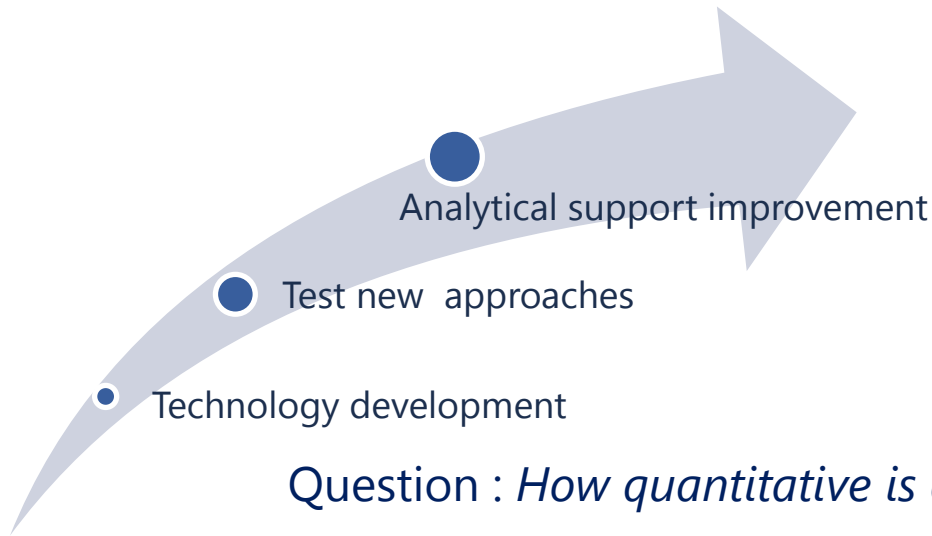
Dermatology

- In dermatology the efficacy of a topical drug may be related to its concentration and distribution within the skin.
- Key questions :
 - Does the drug reach the target in the skin ?
 - To what extent does the drug reach the target
 - How long does it stay there ?
- Approach :
 - Up to now LC-MS-MS analysis (gold standard method) was used to determine the concentration of drug in the different compartments of the skin (stratum corneum, epidermis, dermis,)



Bioanalytical support

- Bioanalytical support, a continuous improvement journey

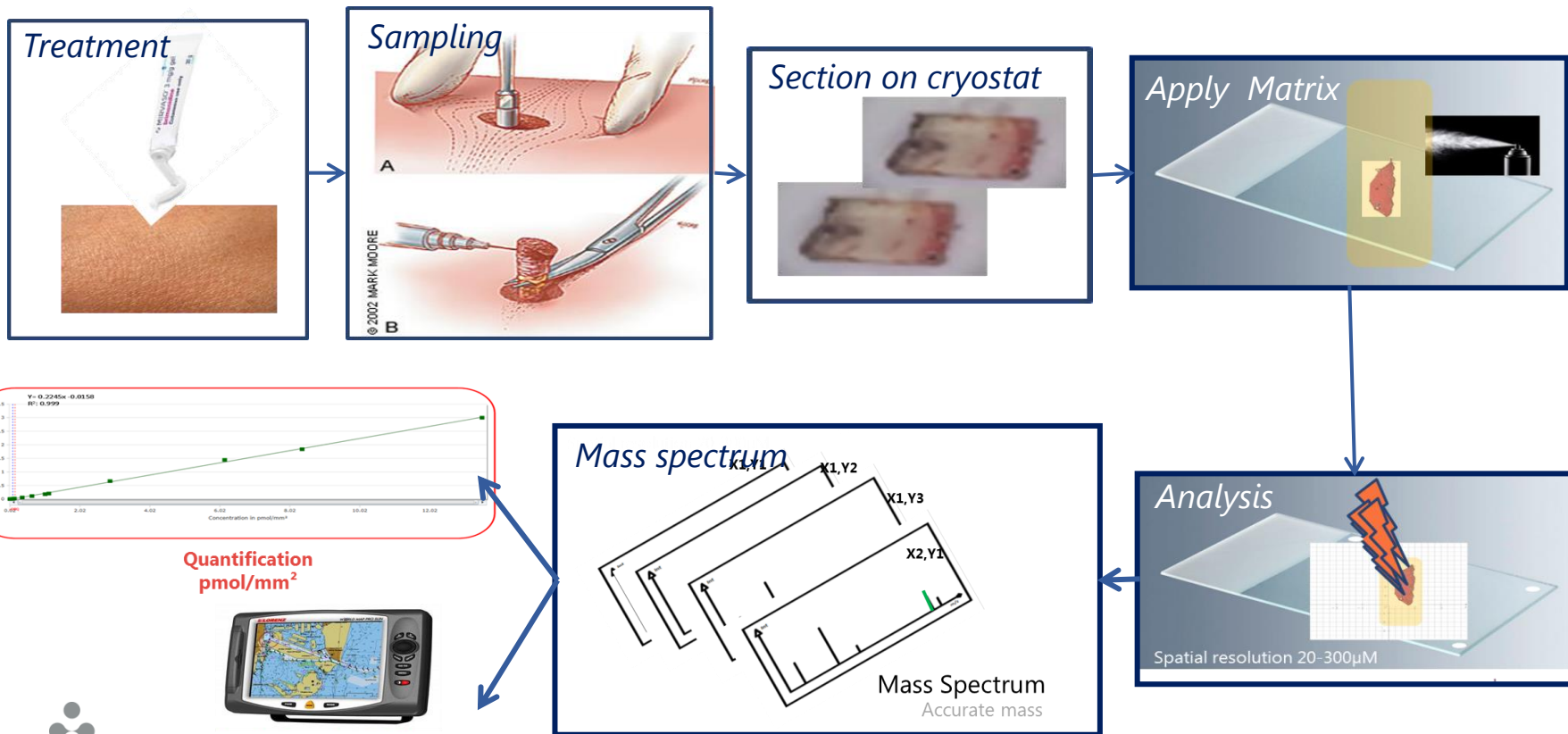


Question : *How quantitative is quantitation using imaging technology ?*

- Few examples of one technology, MALDI-FT-ICR

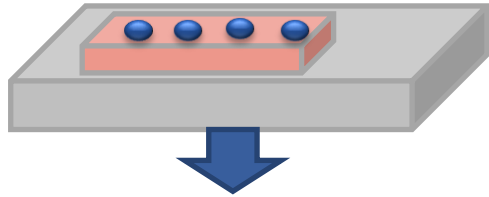


Skin samples analysed by MALDI-FT-ICR MS



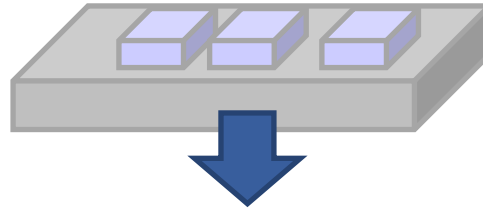
Calibration curve approach

- Few approaches regarding calibration (calibration curve)



On tissue dilution range

- ☺ Ion suppression
- ☹ Skin area specific (normalised by pseudo IS)

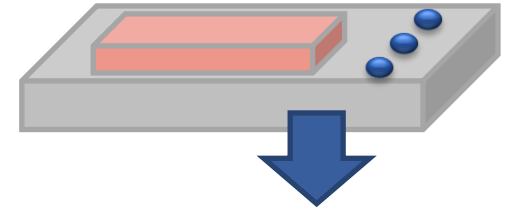


Mimetic tissue dilution range

- ☺ Ion suppression
- ☹ Skin compartment specific

Mixed, spiked & reconstituted tissue

Patent FR1154731
US Patent pending



In-solution dilution range

- ☺ Multi organ analysis
- ☹ Ion suppression

Tissue Extinction Coefficient calculation

Patent FR1152334
US Patent pending



Example : formulation choice

- Context



Formulation 2
0,2% solution



Formulation 3
0,5 % gel



Deep Dermis



Which is the best formulation

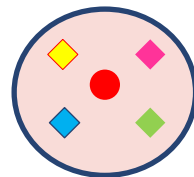
- Study

- In vitro skin penetration study performed (Franz cell)

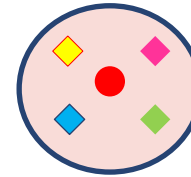
- Area treatment = 2 cm²
- Biopsy punch size = 3.5 mm

- Quantification performed by :

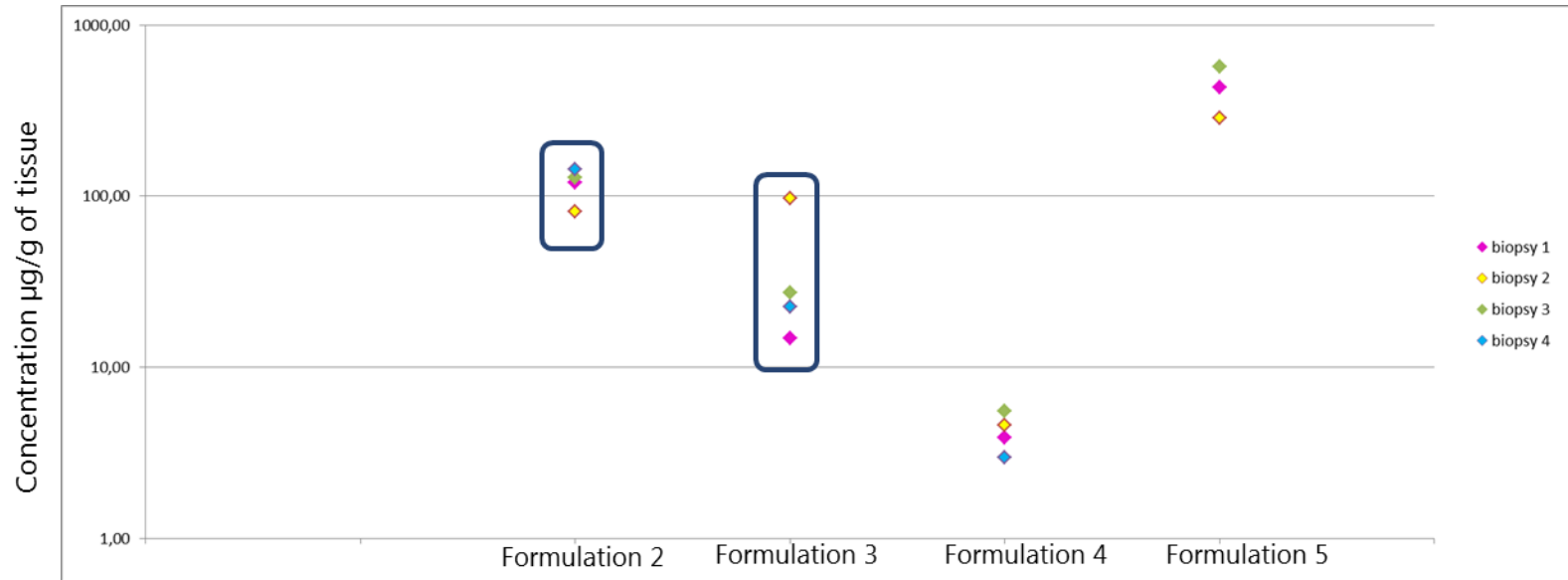
- LC-MS-MS 
- MALDI FT-ICR-MS 



Example : formulation choice

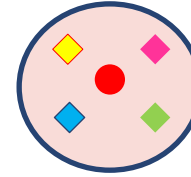


- LC-MS-MS analysis results

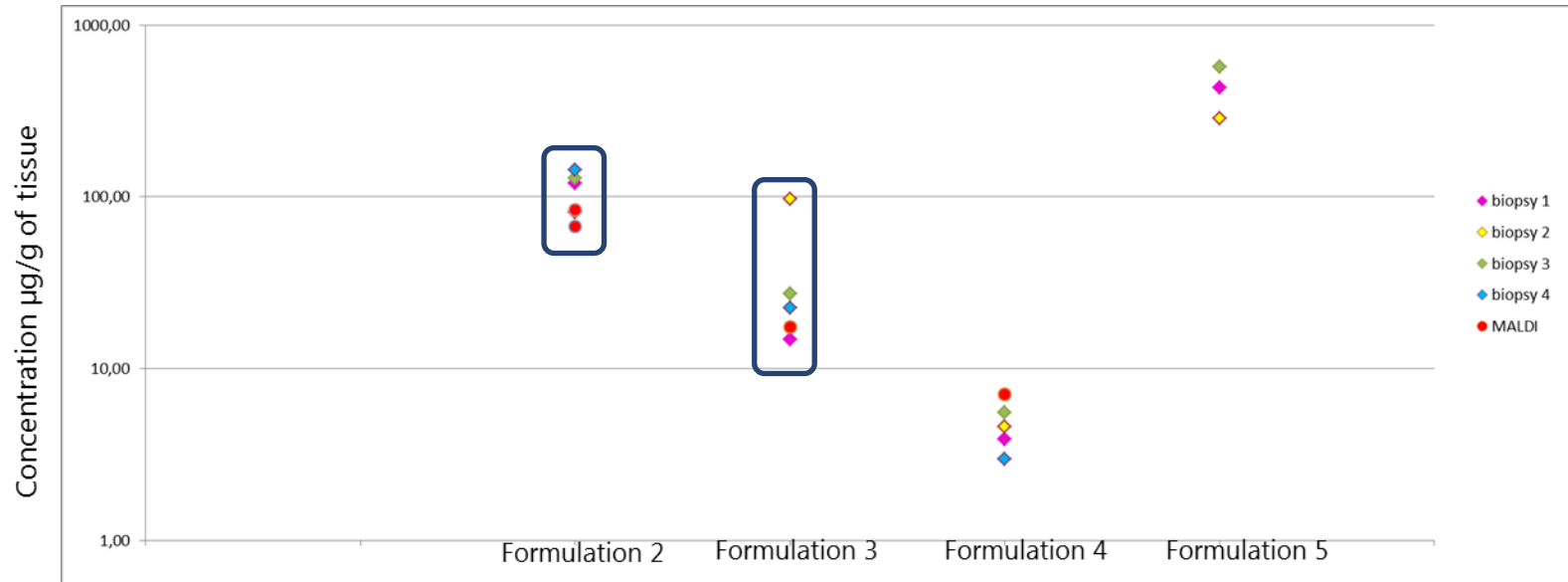


➤ Formulation 2 appears to be better than 3

Example : formulation choice



- MALDI-FT-ICR MS results



Example : formulation choice

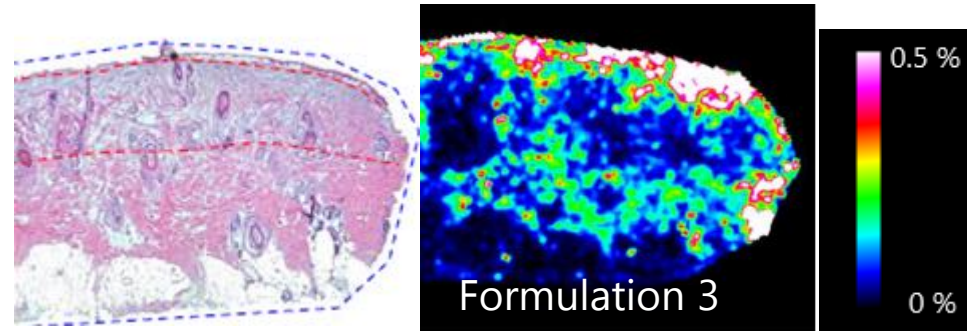
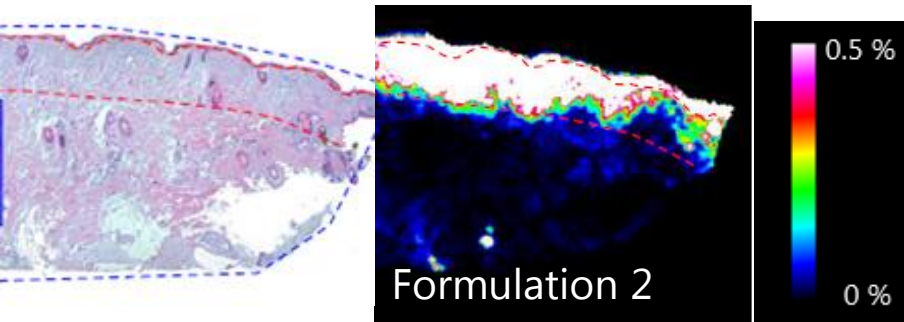
- Added value of image



Deep Dermis



Which is the best formulation



- Formulation 3 is able to reach the deep target
- The best formulation is number 3

Example : exposure at site of action

- Context



Formulation 1



Dermis



Does the formulation provide the right exposure at the target

- Study

- Treatment :

- Area = large surface
- Repeated application (3 weeks , one application per day)
- Biopsy punch size = 3.5 mm

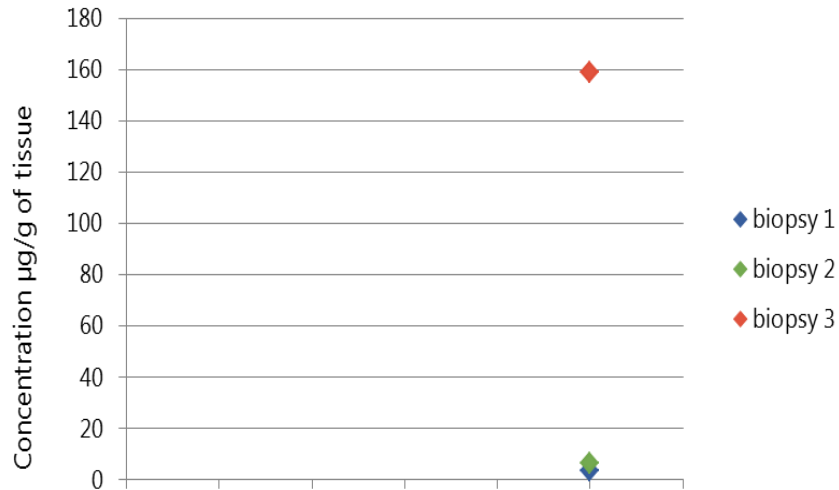
- Quantification performed by :

- LC-MS-MS 
- MALDI FT-ICR-MS 



Example : exposure at site of action

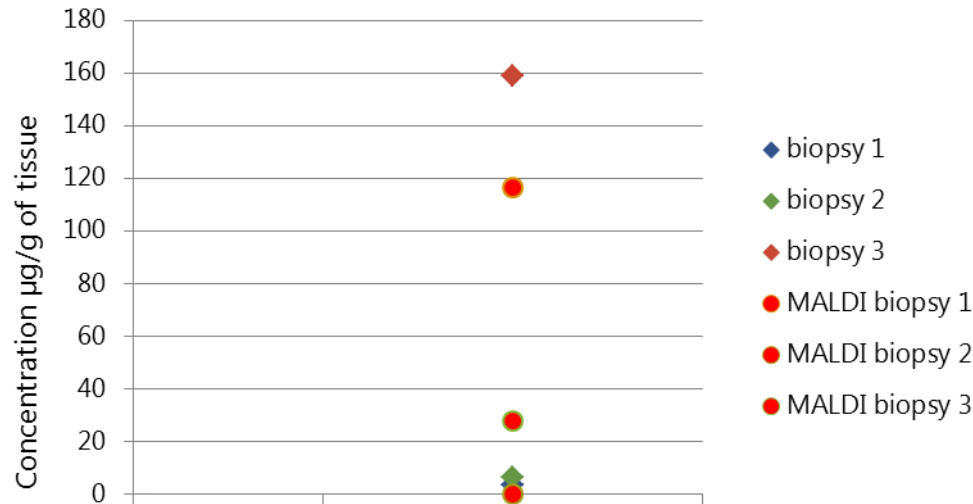
- LC-MS-MS analysis results



- High level of exposure using LC-MS-MS, but highly variable !!!!
- Quantification level seems enough regarding EC₅₀

Example : exposure at site of action

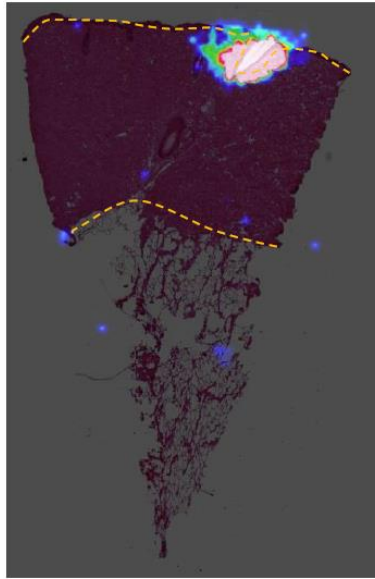
- MALDI-FT-ICR MS results



- Similar level of exposure using MALDI-FT-ICR MS
- Exposure highly variable too !!!!

Example : exposure at site of action

- Added value of image



Dermis



Does the formulation provide the right exposure at the target

- Localized "only" in the hair follicle area
- Exposure is directly linked to the number of hair follicles in the biopsy
- Not enough exposure at the target !!!!



Quantification by MALDI FT-ICR-MS versus LC-MS-MS

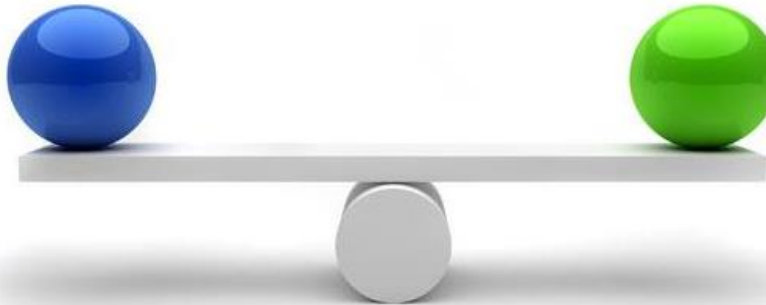
- Overview of internal correlation
 - 200 < compound MW < 700
 - Skin samples

Works on all compounds tested / all skin matrix tested



Quantification
by LC-MS-MS

Quantification
By MALDI FT-ICR-MS
(3 sections per biopsy)



Quantification using MALDI FT-ICR-MS versus LC-MS-MS

- Overview of internal correlation
 - 200 < compound MW < 700
 - Skin samples

Quantification
by LC-MS-MS



Quantification
By MALDI FT-ICR-MS
(3 sections per biopsy)

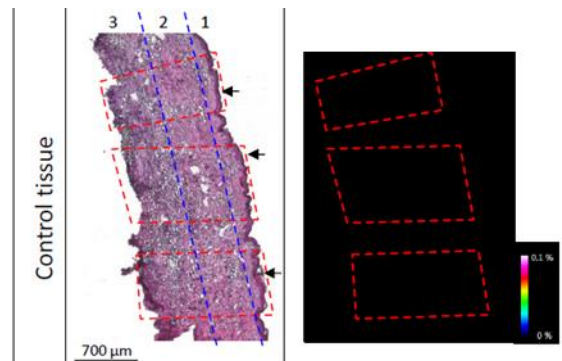
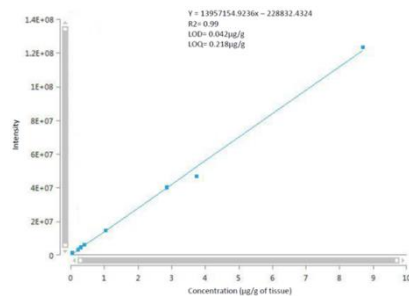
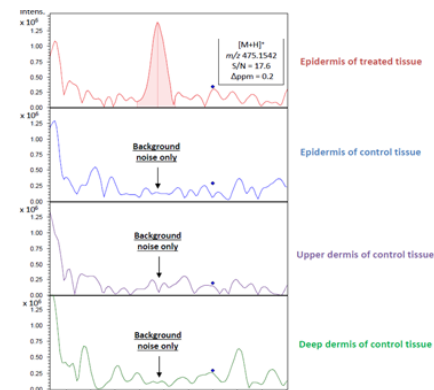


Should we use MALDI-FT-ICR to quantify compounds in tissue? Can we validate the analytical method and workflow?



Scientific “validation” approach using MALDI FT-ICR-MS

- Based on previous results : Why not ?
 - Key points should be verified:
 - Specificity regarding compound response
 - Matrix effect (calibration approach)
 - Reproducibility
 - Accuracy
 - Drug stability in tissue during sampling, storage, and analytical workflow



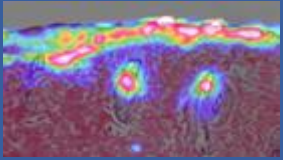
Summary of using MALDI FT-ICR-MS

- MALDI FT-ICR-MS shows similar quantitation compared to the “gold standard” LC-MS-MS approach
- The added value of using this technique is the image produced
- The image shows the extent of exposure at the target site (e.g. dermis)
- By using MALDI FT-ICR-MS we can answer the key questions :
 - Does the drug reach the target in the skin ?
 - To what extent does the drug reach the target ?
 - How long does it stay there ?

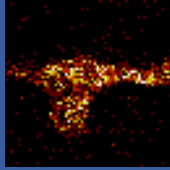


And???

MALDI
Matrix Assisted
Laser Desorption
Ionization,
(Imabiotech, Lille)



SIMS
Secondary Ion
Mass
Spectrometry
Imaging



DESI
Desorption
Electrospray
Ionization Imaging

Infra-red
spectroscopy :
Quantum cascade
lasers imaging
(QLR-IR with Daylight
solution, US)
Coherent Anti-
Stokes Raman
Scattering (CARS)
microscopy
imaging. (Fresnel
Institute, Marseille).

Laser Micro
Dissection Liquid
Vortex Capture
ESI-MS
(Oak Ridge
National
Laboratory)



Thanks



DMPK team

MALDI imaging : collaboration with Imabiotech
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