# LC-ESI-FTMS metabolomic analysis reveals molecular changes associated with the exposure of the blood-brain barrier to nano-$TiO_2$

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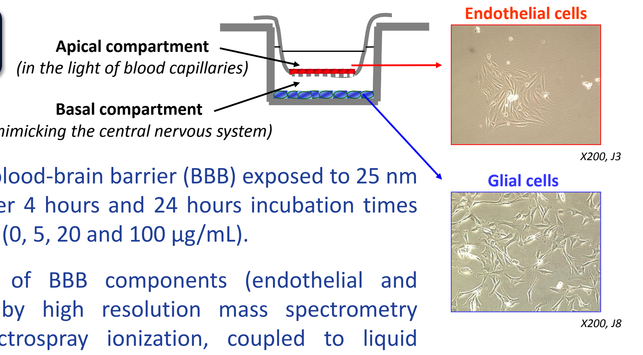
## INTRODUCTION

Among the wide diversity of nanomaterials, **titanium dioxide ($TiO_2$) nanoparticles** are produced on a large industrial scale and are found in numerous commercial products such as paints, food additives, cosmetics and environmental decontamination systems. While $TiO_2$ nanoparticles induced-toxicity is well established on various cell lines, very few studies were focused on the **central nervous system**. The ability of metabolomics to evidence acute and chronic toxicological effects of $TiO_2$ nanoparticles on blood-brain barrier and to identify putative biomarkers of toxicity was presently tested.

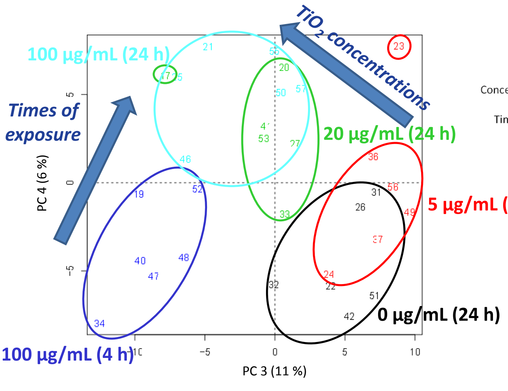
## MATERIAL & METHODS



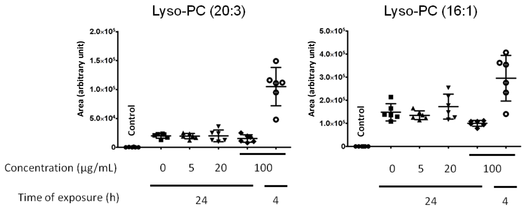

- The molecular responses of *in-vitro* blood-brain barrier (BBB) exposed to 25 nm $TiO_2$ nanoparticles were studied after 4 hours and 24 hours incubation times and for four different concentrations (0, 5, 20 and 100 µg/mL).
- Acquisition of **metabolic profiles** of BBB components (endothelial and astrocyte cells) were performed by high resolution mass spectrometry (Orbitrap™ technology) after electrospray ionization, coupled to liquid chromatography. Positive and negative datasets were obtained in full scan mode on the range m/z 75-1000.
- Data were processed by **XCMS**. Multivariate statistics (PCA, PLS) and ANOVA methods were performed to analyze the datasets and highlight relevant variables.

## RESULTS

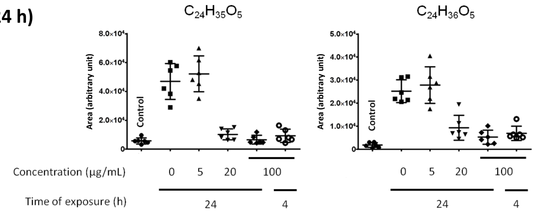
- Principal component analysis




- Time-dependant discriminant metabolites




- $TiO_2$ concentration-dependant discriminant metabolites




## CONCLUSION

- Metabolomics is suitable to evidence **toxicological effects** of **$TiO_2$ nanoparticles** on **BBB cells** and to highlight time and concentration effects. Multivariate statistical analyses showed a clusterization of **smaller concentrations** (0 and 5 µg/mL) *versus* **higher concentrations** (20 and 100 µg/mL) at 24 hours. A discrimination between 4 and 24 hours of exposure was also observed at 100 µg/mL.
- **Robust variables** were found to significantly discriminate between **concentration** and **time factors**. The characterization of the corresponding metabolites is under progress.

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