Chiral mass spectrometry analysis for metabolomics

C. Cao[1)], JC. Tabet[1),2)], S. Alves[2)], C. Chalet[2)], E. Darii[3)], E. Rathahao-Paris[2)], D. Lesage[2)], Y. Gimbert[2)], A. Perret[3)], F. Fenaille[1)], C. Junot[1)], A. Damont[1)]

1) Département Médicaments et Technologies pour la Santé (DMTS), MetaboHUB, Université Paris-Saclay, CEA, INRAE, Gif-sur-Yvette, France;
2) Faculté des Sciences et de l'Ingénierie,Institut Parisien de Chimie Moléculaire (IPCM), Sorbonne Université, Paris, France;
3) Génomique Métabolique, Genoscope, Institut François Jacob, CEA CNRS, Univ Evry, Université Paris-Saclay, 91057 Evry, France.

Chirality presents a unique challenge in life science domain since individual enantiomer may exhibit different biological activities and be involved in different biological pathways. In the field of metabolomics, chiral recognition may be a key to highlight specific disease biomarkers. Today, absolute stereochemical determination remains largely unexplored and extremely challenging in large scale metabolomics studies due to the complexity of biological samples and the structural chemical variety of molecules constituting the metabolome. Therefore, there is still a need to explore and develop efficient chiral analytical methods applicable to the untargeted profiling of biological samples. As high-resolution mass spectrometry (HRMS) is the most frequently used analytical platform to explore the metabolome, the development of gas-phase chiral recognition methods are of particular interest.

In this context, we aimed to develop an innovative method for fast and sensitive chiral analysis based on mass spectrometry and its application in metabolomics. The key issue is based on chiral recognition through the formation of non covalent diastereoisomeric multimer ions displaying specific gas phase behaviors. For this, a chiral reference (R) displaying specific gas phase behavior towards an enantiomer (E) of interest has to be employed in combination with a metal (M) ion (e.g., Cu2+, Fe2+ and others).

The approach for the search of R on the one hand and promising M on the other hand to the development of an enantioselective method will be presented. The optimal conditions for the implementation of a sufficiently sensitive chiral analysis on an Orbitrap instrument (Fusion, Thermo Scientific) will also be discussed. Finally, the first results of chiral analysis through the study of the fragmentation of non-covalent diastereomeric ions formed to differentiate L- and D-glutamine, as well as cis-hydroxy-L- and D-proline, will be introduced. In particular, the implementation of calibration ranges for determining enantiomeric excess (ee) in the buffer with ions of the type $[E+R-H+M^{2+}]^{+}$ will be demonstrated. The approach that will be detailed here is currently under development for the analysis of enantiomeric mixtures in the biological matrix.