AAP China Scholarship Council - CSC 2023

PROJET DE RECHERCHE DOCTORALE (PRD)

Titre du PRD : High-throughput and large-scale IM-MS approach for the characterization of oligosaccharides in breast milks

DIRECTION de THESE

Porteuse ou porteur du projet (***doit être titulaire de l'HDR***) :

NOM : ALVES

Prénom : Sandra

Titre : MCU ou Autre :

Section CNU : 32

Email : sandra.alves@sorbonne-universite.fr

Unité de recherche : Code (ex. UMR xxx) et Intitulé : IPCM UMR8232

Ecole doctorale de rattachement : ED406 - Chimie moléculaire de Paris Centre

Nombre de doctorants actuellement encadrés : aucun

CO-DIRECTION de THESE (HDR) ou CO-ENCADREMENT (Non HDR) :

NOM : Rathahao-Paris

Prénom : Estelle

Titre : Sélectionner ou Autre : IR1 (HDR)

Section CNU : 31

Email : estelle.paris@inrae.fr

Unité de recherche : Code (ex. UMR xxx) et Intitulé : UMR 0496 MTS

Ecole doctorale de rattachement : Sélectionner ED 563 MTCI

Nombre de doctorants actuellement encadrés : 1

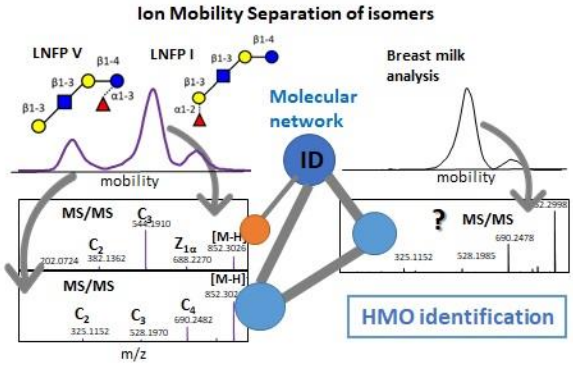
CO-TUTELLE INTERNATIONALE envisagée : ☐ OUI ☒ NON

DESCRIPTIF du PRD :

*Ce texte sera affiché en ligne à destination des candidates et candidats chinois : il ne doit pas excéder **2 pages** doit être rédigé en **ANGLAIS***

1. Context and objectives: Breast milk is the main source of nutrition for newborns and its characterization is therefore important in the field of nutrition (1). Indeed, milk is composed mainly of oligosaccharides, lipids, proteins and micronutrients, its composition varies between individuals and evolves during breastfeeding. Among these constituents, human milk oligosaccharides (HMOs) have been recently shown by experimental evidences not only to be substrates for microbiota bacteria but to be involved in the development of the immune system of newborns. Various analytical methods essentially based on mass spectrometry coupled with liquid chromatography (LC/MS) have been developed for oligosaccharide mixture analysis. Currently, about 200 different structures of HMOs have been identified in human population. Nevertheless, the identification of HMOs constitutes a great analytical challenge due to their structural diversity and in particular the existence of a large number of isomers. Thus, gas phase fragmentation analysis by tandem mass spectrometry (MS/MS) are essential to finely determine their structures (2). However, the analysis of highly complex HMO mixture poses two major challenges: on the one hand, the implementation of sensitive analytical techniques for high-speed acquisition of spectral fingerprints from complex milk samples and, on the other hand, the processing of such large data sets. The biggest challenge remains the identification of unknown HMOs for which no standard compound is available.

This project proposes the development of high-throughput approach for the exhaustive detection and identification without a priori of HMOs and on a large-scale using the complementarity of ion mobility separation, tandem mass spectrometry and the construction of molecular networks. Ion mobility spectrometry based on the gas phase separation has the main advantages of rapid analysis (millisec. scale) and isomer separation. Its efficiency to distinguish HMO isomers has been demonstrated in our previous work (3,4). Another aspect of the doctoral project is the construction of molecular networks specific to HMOs. By identifying similarities between MS/MS spectra, molecular network ("molecular networking") enables the organization and visualization of complex data from MS/MS. Such molecular networks should facilitate the overall interpretation of the data produced, in particular the annotation of all related HMOs even the unknown ones.



Scheme of an approach coupling tandem mass spectrometry with molecular networks for the rapid identification of HMOs

2. Methodology and relevance of expected results: Two complementary methods will be used: 1) analytical approach using high resolution mass spectrometry (Q/TOF instrument) to produce "MS/MS fragmentation fingerprints" after fast ion mobility separation, and 2) computational tools within the Global Natural Products Social platform (GNPS) to build molecular networks. Original results are expected as the creation of a spectral database of HMOs, the construction of molecular networks characteristics of various HMO structures, useful for structural confirmation but also to

identify unknown/new HMOs detected in milk. The results obtained will constitute the proof of concept of our strategy for the characterization without a priori of HMOs.

The PhD student will acquire advanced knowledge on mass spectrometry and ion mobility techniques, as well as on dedicated computional tools and their use for the field of health, food, and environment.

3. Benefit of collaboration between partners: This collaborative project proposes the development of an original approach implementing the complementarity of interdisciplinary skills in the fields of analytical chemistry, bioinformatics and biology. It implies two partners. More specifically, the sample preparation (standard HMOs and milk samples) as well as the construction of molecular networks will be carried out under the direction of Dr. E. Rathahao-Paris (INRAE) while the analytical methods will be developed at Sorbonne University under the direction of Dr. S. Alves (Sorbonne University). A fruitful collaboration between the two scientists (Drs. S. Alve and E. Rathahao-Paris) has been demonstrated though previous works as the two thesis projects (supervised by both) i) on the development of a high-throughput and high-resolution metabolomic approach (B. Habchi thesis, 2015-2017, DIMS Analytics funding (Ile-de-France region) 4 articles published (5, 6), thesis prize awarded in 2018 by the Francophone Network of Metabolomics and Fluxomics), and ii) on the characterization of isomers by mass spectrometry and ion mobility (PhD of A. Delvaux, 2020-2021, 4 articles published (3,4)).

Partner 1. Team of Structural Organic and Biological Chemistry (CSOB team) belong to Parisian Institute of Molecular Chemistry (Institut Parisien de Chimie Moléculaire IPCM UMR 8232) at Sorbonne University (Paris, France). The CSOB team, internationally recognized for its expertise in mass spectrometry, possess varied and state-of-the-art instruments, including very high resolution instruments (FT-CR and Orbitrap) as well as an instrument equipped with ion mobility (TIMS-TOF). The team is a partner of national infrastructures such as MetaboHUB, dedicated to developments in metabolomics and fluxomics, as well as the FT-ICR research federation (FR 3624), whose mission is to offer the scientific community their expertise in FT technology. Applied researches and the development of innovative mass spectrometry-based methodologies constitute a major research axis of the thesis director Dr. S. Alves, who supervised 12 phD projects (2 as thesis director). For 10 years, research work has been carried mainly out in metabolomics and high throughput methods. In 2020, Dr.S. Alves obtained funding for a collaborative scientific project (ANR), named CHIRAMICS dedicated to the chiral analysis by coupling ion mobility and MS/MS techniques.

Partner 2. Food Immuno-Allergy Laboratory (LIAA) of the UMR CEA-INRAE Medicines and Technologies for Health (UMR MTS, CEA de Saclay): The research work carried out within LIAA is linked to the management the risk of food allergies. The laboratory is particularly interested in the characterization of perinatal matrices such as meconium and breast milk in order to associate early exposures with the development of food allergies in childhood. The thesis co-director, E. Rathahao-Paris, is a specialist in mass spectrometry applied to the field of analysis of xenobiotic residues and their metabolites in various matrices (food, plant and animal), she has also developed high-throughput metabolomic approaches and initiated mass filters based approaches for mining high resolution mass spectrometry data.

References: (1) J. Plaza-Díaz et al. Nutrients, (2018) 10(8):1038. DOI: 10.3390/nu10081038. (2) E. Mirgorodskaya et al. Journal of The American Society for Mass Spectrometry (2018) 29; 1065–1074. 10.1007/s13361-018-1912-3. (3) A. Delvaux et al. Acta Chimica Acta, (2021) 1180, 338878. https://doi.org/10.1016/j.aca.2021.338878. (4) E. Rathahao-Paris et al. J Mass Spectrom. 2022; 57:e4885. DOI: 10.1002/jms.4885. (5) B. Habchi et al. Metabolomics, 13: 45. (2017). doi:10.1007/s11306-017-1179-x. (6) B. Habchi et al. Analytical and Bioanalytical Chemistry (2017). https://doi.org/10.1007/s00216-017-0738-3.

AVIS de l'Ecole Doctorale :

Merci d'enregistrer votre fichier au format PDF sous la forme :
NOM Prénom_Projet CSC 2023.pdf

Fichier à envoyer par mail simultanément
à l'école doctorale de rattachement et à csc-su@listes.upmc.fr