PhD Position

Chemical tools to identify the Lysosomal Oligosaccharide Transporter (LOST)

An FRM-funded PhD position is available in the lab of Dr. Stuart Moore at INSERM Unit 1149/Université Denis Diderot, Faculté de Medicine Xavier Bichat, 75018 Paris. Our laboratory is interested in fundamental aspects of protein N-glycosylation. In collaboration with chemists Dr. Christine Gravier Pelletier (CICB-Paris, CNRS UMR8601, Université Paris Descartes, Paris, France) and Sébastien Fort (CERMAV-CNRS UPR 5301, Grenoble, France), we are characterising and identifying proteins required for the generation and intracellular trafficking of free oligosaccharides (fOS) that are generated during the biosynthesis of glycoproteins (1-3). Under certain circumstances partially demannosylated fOS are known to be proinflammatory, but how and where these proinflammatory fOS are demannosylated remains unknown (4). Several years ago, our laboratory demonstrated that, after fOS transport out of the ER into the cytoplasm (5,8), a cytoplasm-to-lysosome transport process (LOST; for Lysosomal OligoSaccharide Transport) assures lysosomal demannosylation of fOS (6-8). Therefore, the lysosome may be involved in processing ER derived fOS into proinflammatory mediators. LOST appears to be mechanistically distinct from classical autophagy pathways that are responsible for the transfer of cytoplasmic material (eg glycogen, proteins, organelles) into lysosomes, and the proteins/genes responsible for LOST have yet to be identified. we are developing fluorescent substrates and cross-linking reagents to characterise, purify and identify LOST proteins. With the aid of these tools we aim to identify LOST proteins using quantitative proteomics. Identification of the corresponding genes will allow us to test the role of “hit proteins” in lysosomal fOS transport using RNAi approaches and test the hypothesis that LOST is required for the generation of proinflammatory oligosaccharides.

(1) Massarweh A, et al. J Lipid Res (2017) 57:1029-42
(2) Massarweh A, et al. J Lipid Res (2017) 57:1477-91
(3) Bosco M, et al. Eur J Med Chem (2018) 125: 952-64
(4) Hasan M, et al. Immunity (2015) 43: 463-74
(5) Moore SEH, et al. EMBO J (1995) 14: 6034-42
(6) Saint-Pol A, et al. J Cell Biol (1997) 136: 45-59.
(7) Saint-Pol A, et al. J Biol Chem (1999) 274:13547-55.
(8) Moore SEH. Trends Cell Biol (1999) 9: 441-6.

The applicant should be interested in developing approaches at the interface of chemistry and biology for the study of pathophysiological processes. Expertise/knowledge of glycobiology is not essential. The position is funded for 3 years and will start after 07-01-2019.

Interested applicants should send a motivation letter, curriculum vitae and the names and contact details of two referees to Dr. Stuart Moore (stuart.moore@inserm.fr).