Innovative surfactants as stabilizers of membrane proteins for structural studies in solution

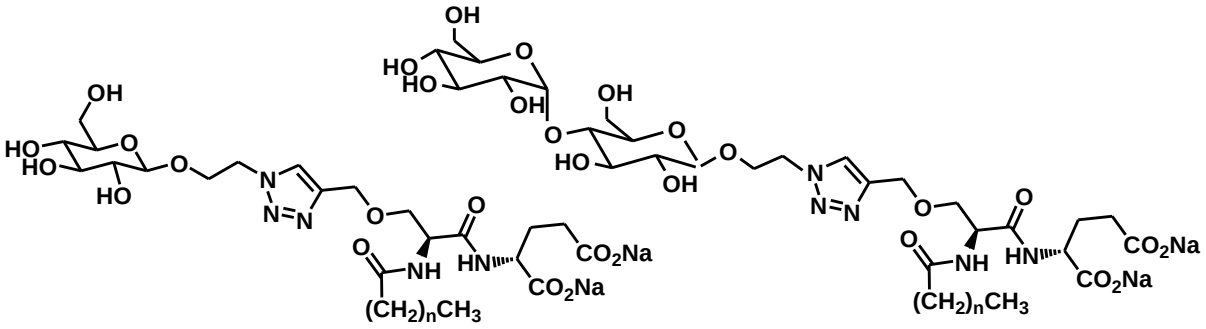
Ahcène BOUMENDJEL and Pierre FALSON
Département de Pharmacochimie Moléculaire
Faculty of Pharmacy
Université Grenoble Alpes/CNRS, 38041 Grenoble
ahcene.boumendjel@univ-grenoble-alpes.fr
https://dpm.ujf-grenoble.fr

Membrane proteins (MPs) account for 25-30% of proteomes and present over 70% of the pharmaceutical targets. MPs play key roles in the transport of a large panel of compounds through the cell membrane. The presence of MPs in the hydrophobic cell membrane makes them difficult to be isolated in their functional forms and to be crystallized for further steps to a 3D-structure resolution and ultimately to be used as targets in the structure-based drug design approaches. As a consequence, membranes proteins account for less than 5% of the 3D-structures resolved.

In this context, surfactants (detergents) are used as key components during the extraction and structural studies of MPs. Detergents are required for maintaining MPs in solution for crystallography needs. Unfortunately, major detergents tend to unfold these proteins as they are in fast-exchange equilibrium with micelles, weakening the compactness of the membrane region and leading to a partial-to-severe loss of functionality.

Based on the concept that the vast majority of membranes proteins share a net enrichment in basic residues at the interface between membrane and cytoplasm, a property known as the positive-inside rule, we conceived a new class of detergents based on this feature, which, in addition to their capacity to interact with membranes proteins through hydrophobic interactions, will have the additional capacity to generate a network of salt bridges around the membrane region with these basic residues.

Our main focus will deal with the design, the chemical synthesis and the outcome of new generation of detergents for the extraction, stabilization and crystallization of membrane proteins.[1]



1. Nguyen *et al*. *Angew. Chem*. **2018**, *57*, 2948-2952.