SORBONNE UNIVERSITÉ

CHINA SCHOLARSHIP COUNCIL

Appel à projets
Campagne 2022
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Title of the research project :

Insertion of biological and synthetic nanopores into polymersomes and planar polymeric

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Research Unit

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Code *(ex. UMR xxxx)* :

UMR 8232

Doctorate School

Thesis supervisor's doctorate school (candidate's futur doctoral school) : ED397

PhD student currently supervised by the thesis supervisor (number, year of the first inscription) :

3 50%- 2019,2020

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Natural cells have many properties among them two are fundamental: compartmentalization and selective permeability. They are able to regulate the flow of ions and (macro)molecules through their membrane, thanks to biological channels. Since many years, one of the objectives of the scientific community (chemists, physicists, biologists) is to understand and mimick the functions of cells, to move towards biomimetism.

In terms of compartimentalization, liposomes were used as the simplest models for mimicking and understanding cells. Indeed, they are artificial vesicles composed of lipids, with a hydrophilic polar head and a hydrophobic apolar tail, forming bilayers. However, the mechanical stability of the membranes was found to be an issue for numerous applications and hampered some applications requiring high stresses or extreme conditions. That is one of the reasons why synthetic analogues of liposomes were developed, based on polymers. Polymersomes are vesicles formed from the self-assembly of amphiphilic block copolymers.[1] In full expansion since the late 1990s, such objects are found in many fields such as drug delivery, protein and DNA delivery, nanoreactors, artificial organelles.[2-8] While various applications are nowadays encountered, controlled mass transfer through their hydrophobic part of the membrane is a challenge. If we consider membrane permeability, there are different strategies to induce a permeabilization of the membrane: layer-by-layer self-assembly,[9] external stimuli-induced permeabilization,[10] biological nanopores, usually proteins.[8,11-13] Looking at the lipid technology, synthetic nanopores were demonstrated to elegantly allow the permeation of lipid bilayers, with a pretty high selectivity in some extent.[14,15] Surprisingly, well-defined synthetic nanopores have never been addressed to provide a controlled permeability of the polymeric membrane.

This project has the objective to develop a robust 'synthetic cell' composed of polymeric membranes and synthetic nanopores inserted into the polymeric membrane.

The benefit to use polymeric membranes is its longer stability and the possibility to tune the membrane thickness to modulate the membrane performances,[16] thanks to the change of the molar mass of the polymer blocks, with a suitable weight fraction of the blocks. The nature of the polymer and the hydrophilic/hydrophobic ratio will determine the morphology of the self-assembly (micelles, cylinders, polymersomes). An appropriate agreement between molar mass and mass fraction of the blocks permits to stick to the polymersome assemblies part of the phase diagram, with the thickness membrane modulation.[1,16] We have already demonstrated that polyglycidol-*b*-poly(butylene oxide) and polyglycidol-*b*-poly(butylene oxide)-*b*-polyglycidol copolymers, obtained by sequential anionic ring-opening polymerization of butylene oxide and

ethoxyethylglycidylether, followed by a deprotection step, could allow the formation of polymersomes with a size range from of 80 nm to 125 nm, characterized by DLS, SLS, SAXS and cryo-TEM.[17] Competitive results were also provided by Meier *et al*.[18] and both our obtained results allowed to draw the draft of a phase diagram of this system. A systematic study is however needed in terms of packing parameter, weight fractions of the hydrophilic and the hydrophobic blocks, molar masses of the copolymers, in order to have a complete view of the obtained morphologies, and to define the boundaries that can be achieved concerning the self-assemblies in terms of size of the vesicles, thicknesses of the hydrophobic part of the membranes and the membrane permeability towards various analytes.

Addressing the membrane permeability will be a next target of the project. Using synthetic nanopores, presenting functional and structural characteristics,[14,19-20] seems to be interesting, considering the limitations of biological nanopores. Indeed, the handling of such biological tools is difficult; those systems present a quite low stability and no versatility. The fitting between the dimension of the protein and the thickness of the polymersome membrane is not guaranted, such as the favorable interactions between polymersome membrane and biological nanopores. The strategy we have first chosen is to use β-cyclodextrin-based star copolymers or macrocycle-based star copolymers, having a similar chemical structure than the one of the polymersome membrane. We have already demonstrated that β-cyclodextrin-based star copolymers are able to insert into lipid membranes.[21-24] By setting the chemical structures and the hydrophilic-hydrophobic dimensions of the synthetic nanopores to the one of the polymersome membranes, we assume that the insertion of the objects into the polymeric membrane will be ensured, even if the polymeric fluidity and dynamics are less important than the ones of lipid bilayers. Nanopore insertion in amphiphilic copolymer membrane will be investigated by fluorescence and electrical detection, thanks to the building of a home-made set-up. Selectivity of the nanopores will be demonstrated, and the contribution of synthetic nanopores will be compared to the various strategy used to allow polymer membrane permeability.

Different steps will then be necessary for this project:

- To synthesize and characterize amphiphilic triblock and diblock copolymers (NMR, SEC)
- To build and characterize the polymersomes, thanks to DLS, SLS, cryo-TEM, SAXS-analysis

- To study the permeability of membranes, by fluorescence spectrometry and NMR (pulsed-field gradient NMR spectroscopy),
- To study the ability to go from polymersomes to planar polymeric membranes, by using black-lipid membrane – type technique.
- To insert biological nanopores, in a first attempt, and, finally, synthetic nanopores into polymeric membranes and to study the potential permeability.

The PhD student will have a project at the interface of organic chemistry, polymer chemistry and physico-chemistry and biophysics.

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