Fondation Bordeaux Université

SOLVAY

Bordeaux INP AQUITAINE

université de BORDEAUX

Chair on "chemistry & Self-Assembly"

Master Internship

"Magnetic triggered drug delivery from hybrid Polymer/lipid vesicles" at LCPO U Bordeaux Pls: J-F Le Meins & O.Sandre

The topic of the internship consists in developing bioinspired and biocompatible self-assembled vesicles whose membrane permeability could be controlled ***via*** the association in a single membrane of polymer chains, phospholipids (so called **hybrid polymer lipid vesicles**) and magnetic nanoparticles. Hybrid vesicles are recent structures that ideally could present biocompatibility and biofunctionality of liposomes (lipid vesicles) and robustness and low permeability of polymersomes (polymer vesicles). The idea is to reach **a control of the release of encapsulated species** by increasing locally the temperature in the membrane**, *via* magnetic hyperthermia** above the melting temperature of the phospholipids, inducing a gel to fluid phase transition during which the permeability of lipid membrane goes through a maximum. (Figure 1)

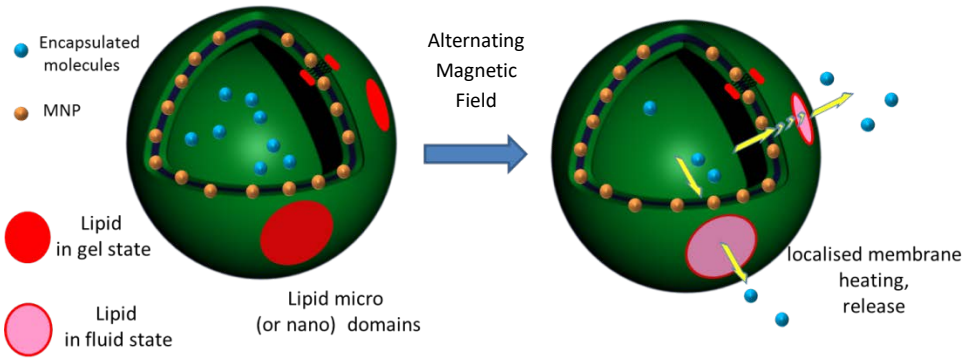

Figure 1: Release induced by localised membrane heating, under AMF, from hybrid polymer/lipid vesicles loaded with magnetic nanoparticles (MNPs).

Team "Polymer Self-Assembly & Life Sciences" from LCPO is one of the pioneering lab in the field of hybrid polymer/lipid vesicles.[1] Hybrid polymer lipid membrane can be obtained in vesicular form at the microscale (Giant Hybrid Unilamellar Vesicle, GHUV) and nanoscale (Large Hybrid Unilamellar Vesicle, LHUV), and it has been shown that membrane structuration (presence of micro- or nano-domains) could be tuned by the copolymer/lipid /composition, the copolymer architecture (block, grafted) and molar mass. In addition the team was pioneer in the development of magnetic polymersomes which could be deformed under magnetic field using Poly(butadiene)-*b*-Poly(glutamic acid) (Pbut-*b*-PGA),[2] Poly(butadiene)-b-Poly(ethylene oxide) (Pbut-*b*-PEO)[3] and maghemite (γ-Fe_2O_3) iron oxide nanoparticles made hydrophobic with a proper surfactant coating.

We propose to formulate hybrid-vesicles using copolymers based on Polydimethylsiloxane (PDMS) as hydrophobic block, Poly(ethylene oxide) (PEO) as hydrophilic block and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) as lipid as it presents a melting temperature of 41°C. PDMS is of great interest because it is expected that the high fluidity of the PDMS chain allows conformational adaptation to let hydrophobic mismatch at the lipid polymer boundaries, whereas PEO chains are interesting because of their stealthiness character. It is worth noting that a graft and triblock copolymer based on PDMS and PEO has been successfully mixed with different phospholipids to design hybrid polymer/lipid vesicles in LCPO.[4, 5] Also the team has developed recently a method to incorporate maghemite nanoparticles synthesized in the Lab using Massart's coprecipitation process, in PDMS-*b*-PEO giant polymersomes (Master 2 internship, Guillaume Galaud). Particles from 6 nm to 10 nm diameter could be incorporated depending on the membrane thickness of the polymer membrane (molar mass of the hydrophobic block).

Methodology

Diblock copolymers PDMS-*b*-PEO will be provided to the intern. They were synthesized by ring opening polymerization of hexamethylcyclo-trisiloxane (D3) cyclic monomer, end functionalization with azide group and further coupling with alkyne end-functionalized PEG by "click" chemistry. Molar masses and hydrophilic fractions have already been screened in order to obtain vesicular structure. Self-assembled nanostructures will be obtained through different techniques well known in the lab: Film hydration and extrusion, nanoprecipitation (solvent displacement method). The vesicle structure will be probed by different techniques like dynamic, static light scattering and small angle neutron scattering, TEM. Vesicles of ~100-150 nm diameters are required for parenteral or intravenous administration.

The hybrid vesicles will be obtained using the previous methodologies, using polymer lipid mixtures and characterized with the same techniques. Fluorescence resonance energy transfer (FRET) will be also used to probe the membrane at the nanoscale (presence of nanodomains), using a small amount in the formulation of fluorescently tagged polymer as a donor probe and lipid as acceptor probe (*e.g.* PDMS-*b*-PEO-NBD and 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-(lissamine rhodamineB sulfonyl) (DOPE-Rhod). On the other hand, magnetic iron oxide nanoparticles (from 6 to 10 nm range) synthesized using either coprecipitation or polyol synthesis[6] will be coated with poly(aminopropylmethylsiloxane-*co*-dimethylsiloxane) PDMS-*co*-APMS to insure compatibility with the PDMS membrane core of the vesicle. MNPs will be incorporated in membranes during the self-assembly process either from a film or by nanoprecipitation. Fluorescence microscopy measurements of m-GHVs (formulated this time as giant unilamellar vesicles *i.e.* several tens of µm by electroformation, or emulsion sedimentation) will be also using dyes in the magnetic, lipidic and polymeric components. Besides structural information, dynamic properties will also be evaluated through collaboration with the loboratory of Pr Dermot Brougham at University College Dublin using NMR relaxometry and neutron spin-echo experiments.

Finally the effect of localized membrane heating under an alternating magnetic field (AMF) on the vesicle structure and the release of encapsulated species will be assessed using a radiofrequency a Seit Elettronica Junior™ induction machine combined with *in situ* dynamic light scattering measurements during the magnetic field application using the VASCO Flex™ remote-head DLS instrument developed by Cordouan Technologies.[7] UV and fluorescence measurement will be also performed (off-line). In that case calcein will be used as model hydrophilic drug and loaded in vesicles at its self-quench concentration. Calcein in excess will be removed by size exclusion chromatography. An increase of the fluorescence signal, due to a dilution effect of the probe outside the vesicle, is expected under AMF application due to local heating and melting of the DPPC gel phase lipid. To sum up, the aim of the internship is to establish structure-function relationship between membrane structure (*e.g.* lipid nanodomains), loading content in MNPs, and drug release properties under AMF.

1. M. Chemin, P. M. Brun, S. Lecommandoux, O. Sandre and J. F. Le Meins, *Soft Matter*, 2012, **8**, 2867-2874.
2. S. Lecommandoux, O. Sandre, F. Checot, J. Rodriguez-Hernandez and R. Perzynski, *Advanced Materials*, 2005, **17**, 712-718.
3. D. Habault, A. DÃ©ry, J. Leng, S. Lecommandoux, J. F. Le Meins and O. Sandre, *IEEE Transactions on Magnetics*, 2013, **49**, 182-190.
4. T. P. T. Dao, F. Fernandes, M. Er-Rafik, R. Salva, M. Schmutz, A. Brulet, M. Prieto, O. Sandre and J. F. Le Meins, *ACS Macro Letters*, 2015, **4**, 182-186.
5. T. P. T. Dao, F. Fernandes, E. Ibarboure, K. Ferji, M. Prieto, O. Sandre and J.-F. Le Meins, *Soft Matter*, 2017, **13**, 627-637.
6. G. Hemery, A. C. Keyes, E. Garaio, I. Rodrigo, J. A. Garcia, F. Plazaola, E. Garanger and O. Sandre, *Inorganic Chemistry*, 2017, **56**, 8232-8243.
7. G. Hemery, E. Garanger, S. Lecommandoux, A. D. Wong, E. R. Gillies, B. Pedrono, T. Bayle, D. Jacob and O. Sandre, *Journal of Physics D: Applied Physics*, 2015, **48**, 494001.

MSc. internship: Magnetic triggered drug delivery from hybrid Polymer/lipid vesicles

Laboratory : Laboratoire de Chimie des Polymères Organiques, Laboratoire de Chimie des Polymères Organiques, LCPO UMR5620 CNRS / Université de Bordeaux / Bordeaux INP

Address: ENSCBP, LCPO, 16 Avenue Pey Berland 33607 PESSAC cedex

Director of laboratory: Pr. Sébastien Lecommandoux

Research Team: Polymer Self-Assembly and Life Sciences

Team leader: Pr. Sébastien Lecommandoux

Principal investigators: Dr. Olivier Sandre (+33-5-4000-3695) and Dr. Jean-François Le Meins (+33 5-4000-3696), including on-going collaboration with Pr. Dermot Brougham (UCD, Dublin)

Email addresses: olivier.sandre@enscbp.fr / lemeins@enscbp.fr

Graduate (Doctoral) School associated: ED 40 Sciences Chimiques (Bordeaux)

Profile looked for: Physico-chemist / Material scientist / Membrane Biophysicist

6-month fellowship funded by SOLVAY Char on "Chemistry and Self-Assembly" of the Foundation of the Univ. Bordeaux