MAGNETIC POLYMER 'NANOPILLS'

With specialist knowledge of polymer-based, self-assembled nanoparticles, the Laboratoire de Chimie des Polymères Organiques shares developments in polymer synthesis and polymer materials

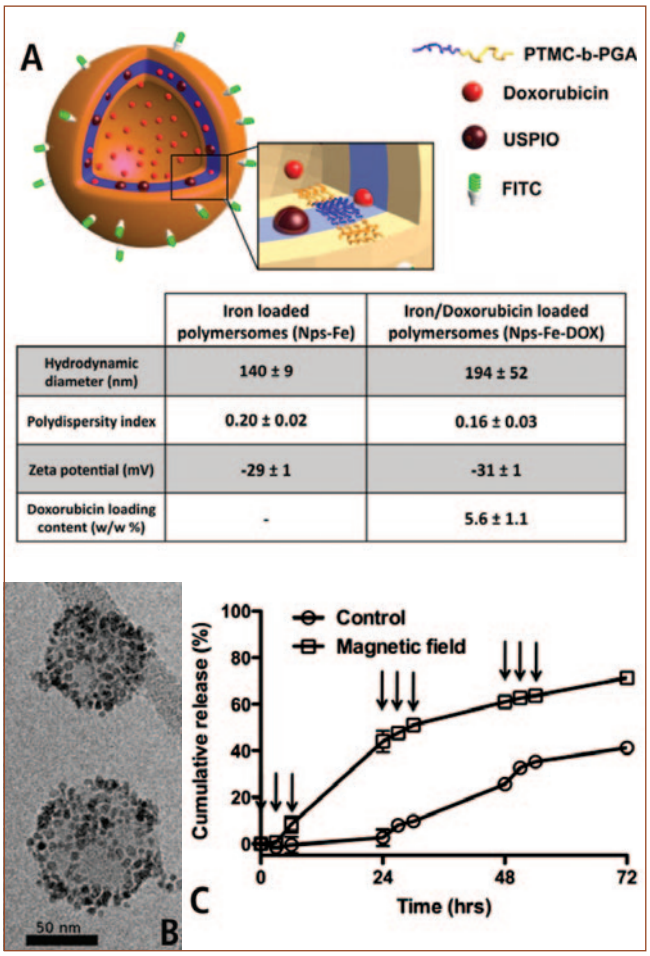
WE are a group of five tenured academic researchers and about 15 non-permanent researchers in the Laboratoire de Chimie des Polymères Organiques, a joint research unit of CNRS, University of Bordeaux, and Bordeaux National Polytechnic Institute, dedicated to polymer synthesis and polymer materials. More precisely, our group develops polymer-based, self-assembled nanoparticles with high loading rates of active pharmaceutical ingredients (anticancer drugs, peptides, proteins etc.), multi-modal labelling (MRI, NIR etc.) and targeting (e.g. mAb). Our knowhow includes the synthesis of biocompatible polymers such as polypeptides (by chemical synthesis or recombinant route), polysaccharides and their combination as copolymers. We have more than a decade of experience in the design of multifunctional polymer vesicles called 'polymersomes', loaded with drugs, iron oxide nanoparticles and grafted to antibodies, and several patents, including one licensed to a pharmaceutical company located in Lyon (Adocia). We have experience in participating in European projects, including an FP7 large NMP project (NANOTHER), which led to very promising results and productive interactions with biomedical companies, and we are now seeking to be active partners in a new H2020 project on nanomedicine.

Our research group is entitled 'polymer self-assembly and life sciences.' We have developed a fundamental approach to mimicking complex mechanisms or interactions of biological cells or viruses by reproducing simplified mechanisms (e.g. endocytosis of nanoparticles in cells or enzymatic reactions) in self-assembled systems. In parallel, we are addressing several issues of nanomedicine such as the development of multimodal, multifunctional and theranostic nano-carriers. Through collaborative projects with biologists, pharmacists, medical doctors and companies, we have developed a variety of polymersomes to convey different therapeutic payloads, such as chemotherapeutics (e.g. doxorubicin, paclitaxel) or biomolecules (siRNAs, peptides, proteins), while extensively testing their *in vitro* cytotoxicity and *in vivo* biodistribution. The formulations also include one bio-imaging modality (e.g. visible or near-infrared fluorescence, MRI contrast agents) and grafting of specific surface ligands (e.g. small molecules, peptides, antibodies).

Magnetic polymersomes for theranostics.

Our team was a pioneer in the development of magnetochemotoxicity, which consists of the enhanced delivery of a chemotoxic drug by an applied radiofrequency magnetic field.[1,2]

The RF magnetic field induces fast relaxation of the magnetic moments of the nanoparticles embedded in the membrane. This local heating causes an increase of the polymer permeability, promoting a faster release of the drug into the medium. Once these magnetic polymer vesicles were injected into the blood circulation of mice, their biodistribution and pharmacokinetics were monitored non-invasively by MRI. This enabled us to evidence the targeting of an orthotopic model of bone metastases of breast cancer by magnetic polymersomes grafted by, on average,~30 monoclonal antibodies against the human endothelial receptor (HER2).[3]



	Iron loaded polymersomes (Nps-Fe)	Iron/Doxorubicin loaded polymersomes (Nps-Fe-DOX)
Hydrodynamic diameter (nm)	140 ± 9	194 ± 52
Polydispersity index	0.20 ± 0.02	0.16 ± 0.03
Zeta potential (mV)	-29 ± 1	-31 ± 1
Doxorubicin loading content (w/w %)	-	5.6 ± 1.1

Fig. 1 A) Scheme of dual-loaded polymersomes with iron oxide nanoparticles and doxorubicin in their membrane; B) CryoTEM image; C) Release curve of doxorubicin under a radiofrequency magnetic field (14mT at 755kHz) Copyright 2012 Elsevier (ref 2)

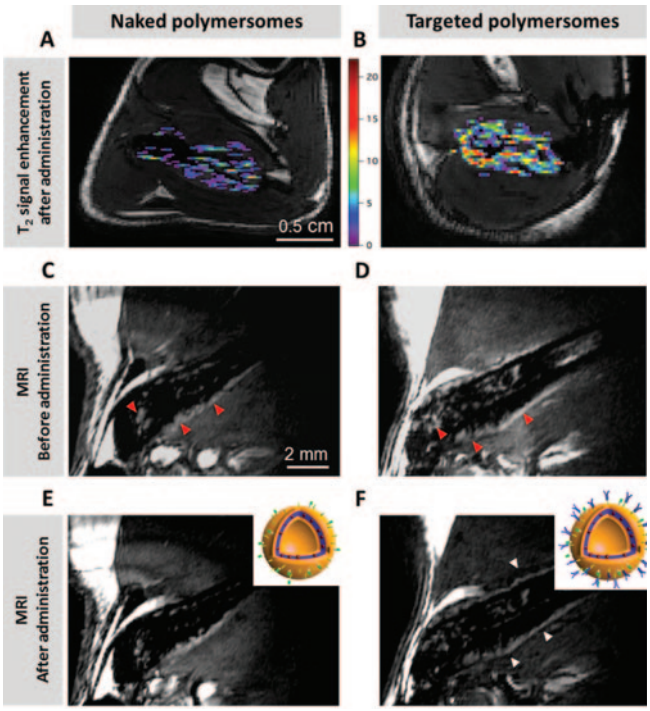


Fig.2 A, C, and E) Passive Targeting; 8, D, and F) Active Targeting in an orthotopic tumour (metastases of breast cancer in a mouse femur) Copyright 2013 Wiley (ref 3)

Magnetic polymer nanoparticles for MRI contrast

Each year, dozens of articles report the synthesis of new biocompatible magnetic nanoparticles for potential use as MRI contrast agents. But only a few of them are designed – before the synthesis – for a maximal 'relaxivity', i.e. an optimal ratio between the 1/T1 and 1/T2 relaxation rates of water protons and the concentration of magnetic compounds. In collaboration with colleagues at Mons in Belgium[4] and Milan in Italy,[5] both specialists in NMR, we rationalised the design of self-assembled clusters of magnetic nanoparticles and polymers to optimise the MRI contrasting properties. Only three parameters enable the tuning of the T2 relaxivity: the particle's magnetisation and 'relaxometric' size and the internal volume fraction of magnetic material in it. In our on-going research, we are studying the effect of a polymer shell surrounding the magnetic cores that can switch, by raising temperature, from a swollen hydrophilic brush to a collapsed state impermeable to water protons, enabling a new method of thermometry by MRI.

Self-targeting micelles and polymersomes

The self-targeting of micelles and polymersomes towards tumours expressing the CD44 receptor with polypeptide-block-polysaccharide copolymers such as PBLG-b-hyaluronan was reported by the team.[6,7,8] We proved the concept of self-targeting polymersomes, with hyaluronan playing two roles: first, as a hydrophilic block bringing colloidal stability; and then, as the bioactive moiety allowing interaction with CD44 receptors. *In vitro* and *in vivo* experiments were conducted on breast and lung cancer models in collaboration with biologists. This original concept was patented and licensed to two companies – one in the area of cosmetics, the other for anticancer nanomedecine.

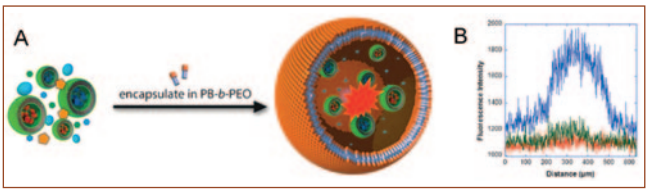


Fig.3 Multi-compartmentalised polymersomes or 'plastic cells' as enzymatic micro-reactors. A) Graphical depiction of the system; B) Plot profiles of the fluorescence cross-section for different time points showing the increase of fluorescence. Copyright 2014 Wiley (ref 9)

Compartmentalised polymersomes as bioreactors

Compartmented vesicles such as polymersomes-in-polymersomes or liposomes-in-polymersomes were designed to host simple enzymatic or photocatalysed reactions. These constructs can be seen as layman models to reproduce the complex intracellular machinery (photosynthesis, protein synthesis etc.), with possible outcomes in synthetic biology or in autonomous implanted biosensors or bioactuators.[9] Also named 'plastic cells', these systems are the most recent and yet highly promising projects currently under development in our team.

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