Université de technologie de Compiègne - Proposition de thèse

1re partie : Fiche scientifique	
Intitulé de la thèse	**Dyna-MIPs: Synthesis of light-responsive, dynamic molecularly imprinted polymers for specificity modulation**
Type de financement	Contrat doctoral sur allocation MESRI
Laboratoire d'accueil	UMR CNRS 7025 Génie Enzymatique et Cellulaire Thème Métabolisme Végétal et Bioressources http://www.umr7025-gec.fr/
Directeur(s) de thèse	Carlo GONZATO
Domaines de compétence	Synthèse organique – polymérisation – reconnaissance moléculaire
Description du sujet de thèse	**The Dyna-MIPs project proposes to use molecular biomimicry to develop a platform for raising highly specific "plastic antibodies", by simple contact of the antigen with generic polymer networks that change their conformation under irradiation with visible light.** **Context:** Current "plastic antibodies",[1] better known as molecularly imprinted polymers (MIPs), are obtained by introducing a templating species during their synthesis, which locally affects their primary structure and creates tailored binding sites featuring high affinity and selectivity. This process includes the self-organization of functional monomers around a template, and their subsequent reaction with an excess of cross-linker, which secures their position into a rigid matrix. Upon template removal, binding sites with size, shape and chemical complementarity to the template are thus revealed.[2] MIPs ability to bind to their target is often assessed by comparison with a non-imprinted polymer (NIP), which shares with the MIP the same monomer composition but lacks the binding sites as the template is absent during its synthesis. As a result, NIP's affinity and selectivity for the template are negligible compared to those of its respective MIP. Due to their functional similarity with biological entities such as antibodies, hormone receptors or enzymes, and superior physico-chemical properties, MIPs have important applications in fields involving molecular recognition, such as solid phase extraction, affinity chromatography, bio/chemo-sensing, (bio)imaging, cosmetics, drug delivery and therapy.[3] Built on commercial functional monomers, MIPs composition can easily be tuned. Similarly, their physical form can be modified to adapt to different targets and cover different applications. In this rich context, a recent trend in improving MIPs' versatility deals with the development of **strategies for the stimuli-responsive modulation of their binding properties** such as template release and uptake. [4-6] Among the different stimuli which have been studied (i.e. temperature, pH and light) the latter is regarded as an easy and friendly way to **spatiotemporally** control MIP's binding properties. Zhang and co-workers reported for instance on the use of azobenzene as a functional monomer to modulate the accessibility of the binding sites *via* its photo-regulated *trans-cis* isomerisation. Indeed, upon exposure to UV light, the functional monomer switches from trans to cis, which induces important geometrical and dipole changes resulting in a decreased affinity for the template, which ultimately gets released.[6] On the other hand, exposure to visible light, or keeping in the dark allows the azobenzene to regain its *trans* conformation, thus recovering the MIP's binding properties. Reports on photoreponsive MIPs are still scarce and they are all based on azobenzenes modified with different functional groups in order to interact with the template *via* acid-base interaction, hydrogen bonding, or π-π stacking, etc. Nevertheless, they all share an identical isomerisation behaviour upon UV-vis light irradiation, which only allows the binding site to turn "ON" or "OFF", thus to act on its affinity, without being able to switch the binding specificity/selectivity. **Scientific objectives:** The Dyna-MIPs project takes **the concept of light-modulated properties of MIPs from a rather different angle, aiming at**

controlling the binding specificity of a material rather than its affinity, by using a non–imprinted polymer (NIP) capable of reshuffling its structure upon an external stimulus and adapt it around a template introduced together with the stimulus.

Dissociation and re-formation of covalent bonds would provide a NIP with an unprecedented ability to re-shape its entire structure (i.e. reshuffling) including the possibility of forming **binding sites around a template,** *via* an innovative **post-polymerization imprinting process**. This would in practice **allow**

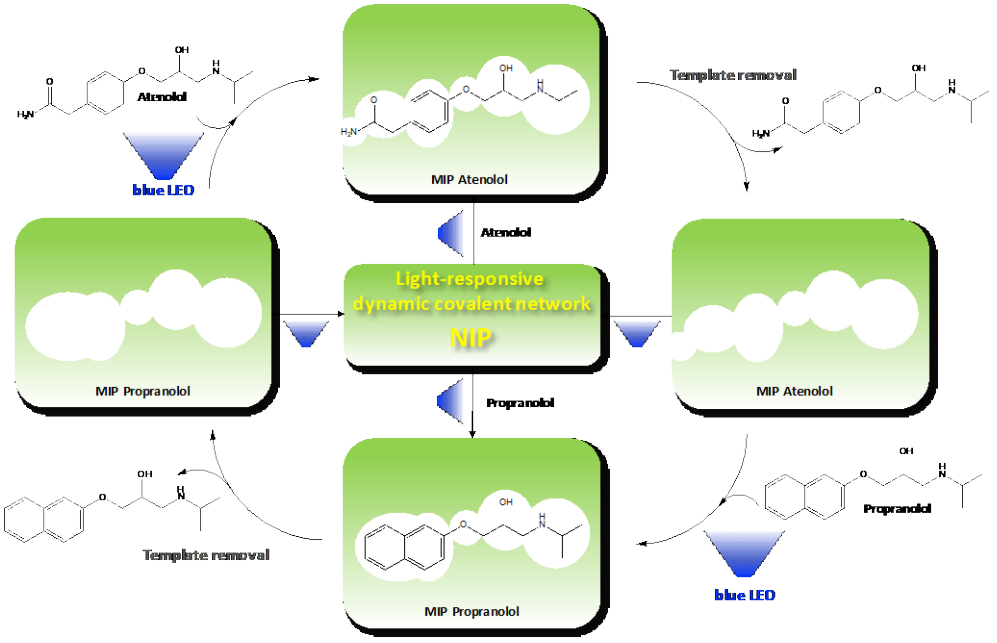

Figure 1: Schematic representation of the light-induce, sequential imprinting of a functional network (NIP) with respectively atenolol (MIP-atenolol) and propranolol (MIP-propranolol).

switching from a NIP to a MIP (and even to multiple MIPs) just upon reshuffling the polymer scaffold, without the need of a new synthesis (Figure 1). The Dyna-MIPs project aims at formulating dynamic networks based on the use of a trithiocarbonate (TTC)-based methacrylic cross-linker (Figure 2, inset). In order to make the imprinting process effective, the template should show some affinity for the network, which can be obtained by choosing a **functional comonomer to be included in the NIP** capable of **chemical complementarity to the template**.

When focusing on light as a stimulus, sulphur chemistry plays an important role in offering various possibilities for covalent exchange.[7] Dynamic exchanges involving allyl sulphides and thiols, or just disulfides, have been reported in literature, but these examples all require UV triggering[7] (in the MIP field visible light would be preferred to preserve template stability). Exchange based on trithiocarbonates has also been described, as reported for instance by Matyjaszewski and co-workers,[8,9] Ma and co-workers[10] or Ran and co-workers[11] who used respectively a radical source,[8] UV light,[9] and microwaves.[11] **However, to the best of my knowledge, no examples of dynamic exchange of trithiocarbonates triggered by visible light have been reported, nor has a similar principle ever been applied to the synthesis of dynamic MIPs.** TTCs are characterized by an *n to π** electronic transition with maximum wavelengths between roughly between 430 and 445 nm (i.e. blue region of the visible spectrum),[12] which can be triggered to reversibly dissociate the C-S bond.[13] This characteristic has recently allowed TTCs to be used as photoiniferters for the controlled synthesis of poly(meth)acrylates[14-17] and polyacrylamides[15] using low power LEDs as visible light sources. Indeed, upon blue light irradiation, these groups undergo a reversible homolytic cleavage of the C-S bond, which generates a reactive radical (initiating the polymerization) and a dormant radical capable of combining with propagating radicals for reversible termination. In absence of monomer feeding, the blue light irradiation of NIPs incorporating TTCs is then expected to promote the **reversible dissociation** and **reshuffling of their cross-linked structure** (Figure 2) making the polymer chains **creating *ex novo* binding sites to accommodate the template** and ultimately **modulating its binding specificity**. This feature represents an enormous opportunity for the development of an innovative product, as **it would make possible to commercialize libraries of NIPs compatible with different classes**

of templates (such as acidic, basic, hydrophobic etc.) by simply formulating NIPs with suitable

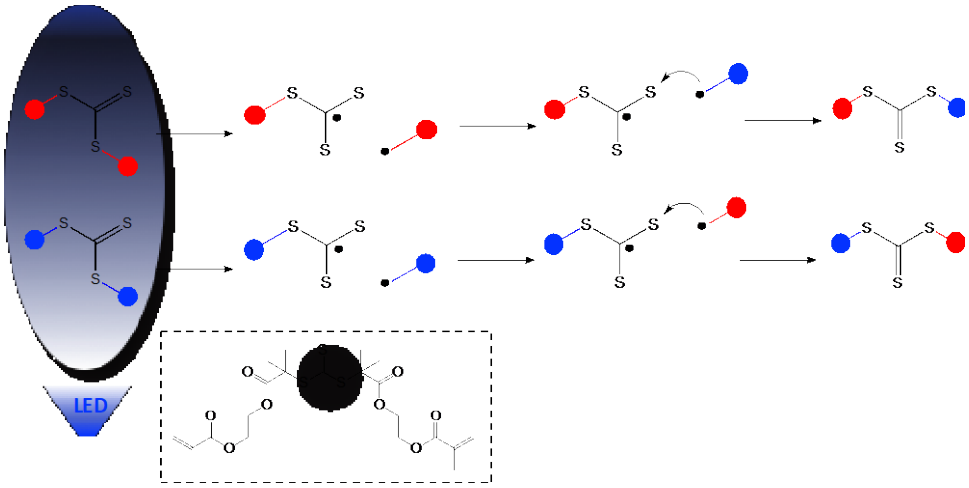

Figure 2: blue light promoted reversible dissociation of the TTC group allowing for re-shuffling the network structure. Inset: TTC (yellow circle)-based cross-linker used for synthesizing such dynamic scaffolds.

(i.e. chemically complementary) functional comonomers. Moreover, such "imprintable matrices" will also feature an unprecedented **re-cycling** ability, which will **improve their environmental impact**. In this perspective, one might think about the possibility of making **reusable sensors**, which would show recondition ability upon shining with light in presence of a new target analyte.

Methodology: The Dyna-MIPs project will be organized around two main axes:

(**1**) **synthesis and characterization of (TTC)-based polymer matrices.** This axis will include (**a**) synthesis of the TTC-based cross-linker according to literature.[8] (**b**) synthesis by radical polymerization of a model NIP based on such TTC cross-linker (TTC-NIP), using methacrylic acid (MAA) as a model acidic functional monomer and dimethyl sulfoxide (DMSO) as a solvent.[18] (**c**) physico-chemical characterization of the synthesized polymer (i.e. gravimetric yield, double bond conversion by FTIR, absorption spectrum and size by SEM). (**d**) Fluorescent binding tests to the determine the binding affinity with respect to two model molecules which have affinity for MAA and are well–established in the imprinting field: propranolol and atenolol (Figure 1).[19] Both compounds are intrinsically fluorescent and do not absorb blue light. (**d**) Synthesis of reference MIPs against propranolol and atenolol based on the widely used ethyleglycol dimethacrylate (EGDMA)[20] for comparing the binding properties of TTC-NIPs with traditional (i.e. reference) MIPs.

(2) post-polymerization imprinting *via* TTC-reshuffling in presence of templates. This axis will include: (**f**) Blue-light irradiation of TTC-NIP in presence of propranolol to create binding sites *via* TTCs' reshuffling. A 470 nm blue LED will be used, with intensities ≤ 1 mW/cm^2 (this value may require optimization) to avoid photobleaching on the TTCs. The successful imprinting will be verified through binding tests evaluating specificity and selectivity for respectively propranolol and atenolol (see above). (**g**) Blue-light irradiation of propranolol-TTC-MIP in absence of template; this should reshuffle the distribution of TTCs making the MIP losing its affinity for propranolol and regaining the TTC-NIP configuration. A binding test will then measure the affinity loss (i.e. **imprinting reversibility**). (**h**) Blue-light irradiation of TTC-NIP in presence of atenolol as a new template: this is expected to reshuffle the NIP structure in order to tailor the binding sites around this new template. A binding test will then determine new affinity values for atenolol and propranolol.

To validate the general applicability of the Dyna-MIPs approach, the same methodology will then be adapted to the case of a basic functional monomer, such as dimethylaminoethylmethacrylate, with respect to acid targets (e.g. trimesic acid).

References related to the project

1 K. Haupt, *Nature Materials*, 2010, **9**, 612–614.

2 B. Sellergren, Ed., *Molecularly Imprinted Polymers*, Elsevier, Amsterdam, 2001, vol. 23.

3 J. J. BelBruno, *Chem. Rev.*, 2019, **119**, 94–119.

	4 S. Xu, H. Lu, X. Zheng and L. Chen, *J. Mater. Chem. C*, 2013, **1**, 4406–4422. 5 G. Pan, Y. Zhang, X. Guo, C. Li and H. Zhang, *Biosensors and Bioelectronics*, 2010, **26**, 976–982. 6 L. Fang, S. Chen, Y. Zhang and H. Zhang, *J. Mater. Chem.*, 2011, **21**, 2320–2329. 7 L. Li, J. M. Scheiger and P. A. Levkin, *Adv. Mater.*, 2019, **31**, 1807333–17. 8 R. Nicolay, J. Kamada, A. Van Wassen and K. Matyjaszewski, *Macromolecules*, 2010, **43**, 4355–4361. 9 Y. Amamoto, J. Kamada, H. Otsuka, A. Takahara and K. Matyjaszewski, *Angew. Chem. Int. Ed.*, 2011, **50**, 1660–1663. 10 P. Dong, K. Cui, F. Xu, T. Jiang and Z. Ma, *Polym. Int.*, 2018, **67**, 868–873. 11 L.-X. Yu, D. Zhuo and R. Ran, *International Journal of Polymeric Materials and Polymeric Biomaterials*, 2013, **62**, 749–754. 12 K. Skrabania, A. Miasnikova, A. M. Bivigou-Koumba, D. Zehm and A. Laschewsky, *Polym. Chem.*, 2011, **2**, 2074–10. 13 T. G. McKenzie, L. P. da M. Costa, Q. Fu, D. E. Dunstan, G. G. Qiao, *Polym. Chem.*, 2016, **7**, 4246–4253. 14 J. Xu, S. Shanmugam, N. A. Corrigan and C. Boyer, in *Reversible Deactivation Radical Polymerization: Mechanisms and Synthetic Methodologies*, American Chemical Society, Washington, DC, 2015, vol. 1187, pp. 247–267. 15 T. G. McKenzie, Q. Fu, E. H. H. Wong, D. E. Dunstan and G. G. Qiao, *Macromolecules*, 2015, **48**, 3864–3872. 16 A. Bagheri, C. Bainbridge and J. Jin, *ACS Applied Polymer Materials*, 2019, **1**, 1896–1904. 17 M. J. Garcia-Soto, K. Haupt and C. Gonzato, *Polym. Chem.*, 2017, **8**, 4830–4834. 18 P. Çakir, A. Cutivet, M. Resmini, B. T. S. Bui and K. Haupt, *Adv. Mater.*, 2012, **25**, 1048–1051. 19 E. I. Paruli, T. Griesser, F. Merlier, C. Gonzato and K. Haupt, *Polym. Chem.*, 2019, **10**, 4732–4739. 20 C. Alexander, H. S. Andersson, L. I. Andersson, R. J. Ansell, N. Kirsch, I. A. Nicholls, J. O'Mahony and M. J. Whitcombe, *J. Mol. Recognit.*, 2006, **19**, 106–180. 21 S. Beyazit, B. T. S. Bui, K. Haupt and C. Gonzato, *Progress in Polymer Science*, 2016, **62**, 1–21. 22 V. Montagna, K. Haupt and C. Gonzato, *Polym. Chem.*, 2020, –. 23 P. Bonomi, M. D. Attieh, C. Gonzato and K. Haupt, *Chem. Eur. J.*, 2016, **22**, 10150–10154. 24 M. Bompart, A. Goto, O. Waittraint, C. Sarazin, Y. Tsujii, C. Gonzato and K. Haupt, *Polymer*, 2015, **78**, 31–36. 25 C. Gonzato, P. Pasetto, F. Bedoui, P.-E. Mazeran and K. Haupt, *Polym. Chem.*, 2014, **5**, 1313–1322.
Mots clés	Polymères à empreinte moléculaire – matériaux stimuli-responsive – photochimie.
Profil et compétences du candidat	Applicants should have a background in **polymer or materials** chemistry, with **excellent skills in organic chemistry**. An additional interest in physicochemical and nanometric characterization techniques will be a plus
Date de début de la thèse	Dès que possible
Lieu de travail de thèse	Centre de recherche UTC, laboratoire GEC

2e partie : Fiche de poste	
Durée	36 mois
Possibilité missions complémentaires	Une participation aux enseignements de l'UTC pourra être envisagée.
Laboratoire d'accueil	Les approches scientifiques développées au GEC répondent à trois grands concepts permettant des découvertes scientifiques et technologiques en lien avec la biologie : les bioressources, le biomimétisme et la bioinspiration.
Moyens matériels	Laboratoires et plateformes d'analyse permettant la synthèse et la caractérisation des matériaux synthétisés.
Moyens humains	Le GEC compte actuellement 57 membres dont 34 permanents (Enseignants chercheurs/chercheurs/personnels techniques) et 23 doctorants/post doctorants. Le laboratoire est bi-localisé à Compiègne (UTC) et à Amiens (UPJV).
Moyens financiers	Le fonctionnement serait finance avec les reliquats d'un projet industriel (SANOFI).
Modalités de travail	Le thésard effectuerait les différentes synthèses et caractérisations au sein des locaux du GEC. Il serait idéalement supporté par deux étudiants (master) lors des étapes d'optimisation des conditions d'irradiation des matrices synthétisées.
Projets de recherche liés à cette thèse	None :
Collaboration(s) nationale(s)	NO
Collaboration(s) internationale(s)	NO
Thèse en cotutelle internationale	NO
Coordonnées de la personne à contacter	carlo.gonzato@utc.fr

Contacter d'abord le directeur de thèse avant de renseigner
un dossier de candidature en ligne sur https://webapplis.utc.fr/admissions/doctorants/accueil.jsf