PhD thesis: Glycodots

Mechanical force-triggered drug delivery systems combining polysaccharides and Lipidots

Co-directed by:
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Location:
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Grant: from the Glyco@Alps cross disciplinary program (October 2017 – September 2020)

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Context:
The PhD project is inscribed in the UGA IDEX GlycoAlps devoted to explore the potential of carbohydrates notably in materials and health sciences. The design of new medical devices or drug delivery systems demands the use of innovative smart biomaterials. Polysaccharides are biopolymers of choice for these applications thanks to their biocompatibility and the tuneability of their structure and functions that can be achieved through chemical modifications. LETI-Health has recently developed know-how on processing of biomaterials through a wide panel of techniques (freeze-drying, electrospinning...). Cermav has expertise in the controlled chemical modification of polysaccharides and their assembly in functional materials.

PhD project:
The project challenge is the design, synthesis, and characterization of innovative materials combining polysaccharides and lipid nanoparticles, for the spatial and temporal control of drug release through a mechanical force-based stimulus (compressive or tensile force). Our motivation for designing mechanical stimuli-responsive medical devices is that mechanical force is ubiquitously achieved in the body or easily applied externally. Our 2 research groups previously developed hybrid lipid nanoparticle/polysaccharide materials enabling the controlled release of lipophilic drugs from a porous hydrophilic polysaccharide matrix.\textsuperscript{1} We now wish to implement mechanical stimuli-

\textsuperscript{1} L. Racine, A. Guliyeva, I. Wang, V. Larreta-Garde, R. Auzély-Velty, I. Texier, Time-controllable lipophilic-drug release system designed by loading lipid nanoparticles into polysaccharide hydrogels, Macromolecular Bioscience, submitted; L. Racine PhD thesis, defended on November 22\textsuperscript{nd} 2016.
responsive properties to the materials in order to control the delivery of drugs on demand by compression/stretching via joint movements or a force applied through the skin (Fig. 1).²

To produce stretch-induced and/or compressive force-sensitive drug delivery systems, 2 mains strategies will be investigated. The first one lies in the conception of interpenetrating polymer networks (IPN) (Fig. 2A). Preliminary experiments demonstrated that this strategy yields highly porous materials for easy drug-loaded nanoparticle diffusion, whereas maintaining high resistance to elongation.³ A second approach based on the reinforcement of the polymer matrix by nanocellulose crystals or fibers to achieve the targeted mechanical properties (Fig. 2B) will also be explored in collaboration with the group of Julien Bras (LGP2, Grenoble University Campus, GlycoAlps).

The working program of the PhD will be composed of three main tasks (Fig. 3):

1) Chemical modification of polysaccharide building blocks and design of lipid nanoparticles. Polysaccharides will be selected for their biocompatibility and biological properties (mainly hyaluronic acid, dextran, chitosan, cellulose). Lipid nanoparticles with different size and surface coating for tunable interactions with the polymer matrix will be designed. They will be loaded with a fluorescent dye as drug model during process development, and finally with an anti-inflammatory drug as a demonstrator.

2) Optimization of material fabrication process. Material processing steps (polymer cross-linking, particle loading, drying...) will be optimized to yield easy-to-handle materials for final applications.

3) Characterization of the new materials in their medical use context. In particular structural and mechanical properties of the biomaterials will be investigated, as well as their safety, their shelf lifetime and the kinetics of drug release in fluids by compression/stretching. Evaluation of materials for improved transcutaneous delivery of a model drug will be performed in collaboration with Prof. R. Fonseca Vianna Lopez, USP, Brasil, Ribeiro Preto).

Expected results/Integration in the Glyco@Alps program:

In the frame of the GlycoAlps project, the aim of the proposed PhD is to promote the use of polysaccharides in high added-value functional materials. The expected outcome is the design of a new family of hybrid polysaccharide/lipid materials with mechanical-force triggered delivery abilities that could be valuable as material dressings, implant coatings (prosthesis) or implanted drug delivery systems.

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systems. To take full benefit of the GlycoAlps consortium, an enlarged PhD committee will be established for regular result discussion, with participation of other groups working notably on nanocellulose (LGP2) or polysaccharide mechanical characterization (3SR).

**Keywords:** Polysaccharides, nanoparticles, drug delivery systems, medical devices.

**Candidate profile:**
FR: Le(la) candidat(e) doit être titulaire d’un master Chimie ou d’un diplôme d’ingénieur en Chimie et doit posséder de solides connaissances en sciences des polymères. Une expérience dans les techniques de caractérisation suivantes est indispensable: rhéologie des interfaces et caractérisation physicochimique des polymères (GPC, RMN, DLS, etc.). Une expérience antérieure dans le domaine des polysaccharides sera appréciée. Le(la) candidat(e) devra s’adapter à un environnement interdisciplinaire en relation avec des chimistes, des biologistes, et potentiellement des industriels et des cliniciens. De solides compétences en anglais sont également nécessaires.

EN: Applicants should hold a Master in Polymer Science with strong background in characterization: rheology of interfaces and physicochemical characterizations of polymers (GPC, NMR, DLS, etc.). A background in polysaccharides will be appreciated. Ability to work in a cross-disciplinary environment in connection with chemists, biologists, and potentially industrial partners and, clinicians is absolutely required. Good skills in English are also required.