Ecole Nationale Supérieure de Chimie de Rennes

PhD thesis Fellowhip

(start from October 2019)

Studies and optimization of oligoglucans-receptors interactions thanks to multivalent grafting to trigger efficient immunostimulation

Context and objectives: Nowadays there is a rising demand to change the available adjuvant in vaccines because of their controversial reputation. An adjuvant aims at triggering a controlled inflammatory response in order to properly recruit immune cells. The aim is to compensate the rather low immunogenicity of the co-injected antigens. Thanks to the development of immunology and chemical biology, the crucial role of oligosaccharide grafted to the surface of bacteria or parasites in the immunological response was highlighted. In this context, the **β-(1,3)-glucans,** homopolymers of glucose was identified as Biological Response Modifier because they can positively influence the immune system. The COrInt team in Rennes also demonstrated that small oligomers of glucans, analogs to the native polysaccharide have similar activity than the natural compound. They are therefore good targets as new adjuvants for vaccine application.

In an ongoing program related to the synthesis and evaluation of neo β-(1,3)-glucans, we wish to cross the next step by conceiving a library of β-(1,3)-glucans analogs and graft them on a multimeric platform based on a cyclopeptidic core. The resulting glycodendrimers will be screened against their interactions with the receptors of the natural glucan Dectin-1 using a microarray technology and the ITC tools. They should exhibit higher activity than the combined effect of the single molecules thanks to the cluster effect.

Methodology: The different tasks of the PhD project will involve: i) the convergent synthesis of small oligosaccharides that mimic the β-(1,3)-glucanes ; ii) the grafting of the oligomers on a multimeric cyclopeptide and iii) the biological evaluation of the resulting glycoclusters. The aim would be to exacerbate the interaction with Dectin-1 in order to obtain a very powerful and innovative family of adjuvants. While the synthesis will be performed in the CorInt Team, the coupling to the multimeric scaffold as well as the evaluation will be done in the I2BM Team.

Scientific environment: The thesis proposed here is supported conjointly by the Brittany region and the University of Grenoble-Alpes. Therefor the PhD student will share his time between the two team's facilities.

In Rennes, Laurent Legentil, CNRS Researcher at the Rennes Institute of Chemistry, will assure the management of the project. He is specialized in the conception and synthesis of oligosaccharides with potential biological activities.

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In Grenoble, the supervision of the project will be dedicated to Olivier Renaudet, professor at the Grenoble-Alpes University. He owns a recognized expertise in the domain of glycoclusters with potent biological properties.

Candidat's profile: The applicant for this PhD thesis should possess a strong knowledge in organic chemistry and in particular in multi-step synthesis of natural compounds. A strong interest in projects at the interface between chemistry and biology will be an asset. In addition, the candidate should accept to work in two different locations during the three years of the project.

Key-words: beta-glucans, glycoclusters, adjuvant, vaccin.

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