Soutenance

THESE

Mardi 26 Juin 2018 à 09h

Salle des séminaires

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Recombinant C-type Lectin Receptors production and selective ligand identification: new tools towards immune system tailoring

Thèse de Doctorat de l'Université de Grenoble

C-type Lectin Receptors (CLRs) are carbohydrate-binding proteins mainly expressed on Antigen Presenting Cells (APCs), including Dendritic Cells (DCs), the sentinel of the innate immune system. The crucial role played by CLRs in the balance of immune responses offers to CLR-glycan interactions pharmaceutical applications. The long-term objective of the research project in which this PhD is included is to use these CLRs as modulators in order to tailor the immune system responses. To do so, neoglyco-conjugates selective to each individual CLR have to be developed.

Nine different CLRs were produced in this work: BDCA2, DC-SIGN, DC-SIGNR, dectin-1, dectin-2, langerin, LSECtin, MCL and Mincle.

Our collection of CLRs were used to screen glycan and glycomimetic arrays, highlighting context-dependent binding and identifying natural ligands or glycomimetics selective to each CLRs.

To guide the choice of the glycomimetics and estimate their optimisation, diverse biophysical studies were performed to evaluate the strength and specificity of the interaction. This enabled the development of an ultimate ligand selective towards DC-SIGN. A co-crystallised structure of the protein with this ligand revealed an interesting binding mode that also opens new questions.

Simultaneously to monovalent ligand optimization, a first step towards the design of a highly defined molecule for cancer vaccination by CLR targeting was made. SPR results revealed potential candidates to exploit and preliminary biological assays were performed. Finally, a strategy for tetrameric lectin engineering as been explored, termed TETRALEC. This tool for screening and lectin characterization, has been obtained with one the lectin of the study, DC-SIGNR, by a site-specific labelling of the lectin.