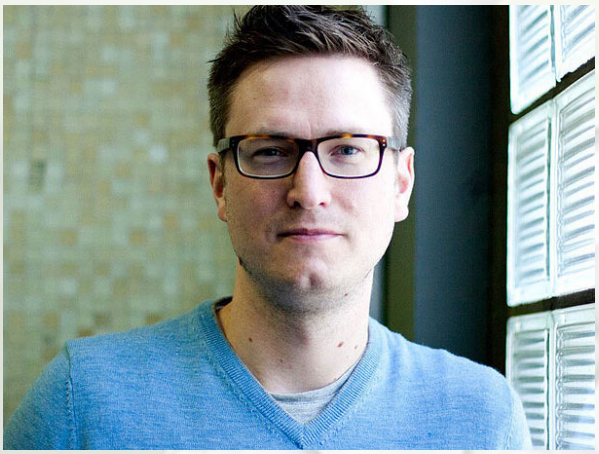
BIOMOL STRUCT

GUEST LECTURE SERIES

C-TYPE LECTINS AS CELL-TYPE SPECIFIC RECEPTORS FOR TARGETED DELIVERY



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Thursday, 02.03.2023, 15:00
Seminar Room MC1.F.05.017, MED Campus (F, 5th floor)

Abstract

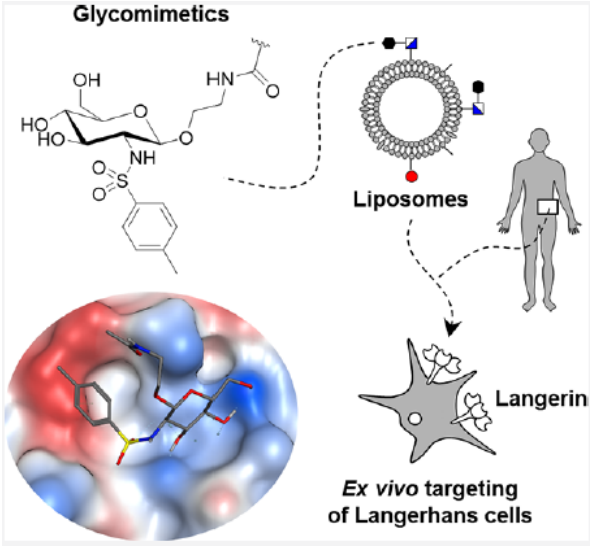
C-type lectins resemble the largest and most complex family of mammalian carbohydrate-binding proteins with a distinct expression pattern on defined cellular subsets. These patterns have led to significant interest in targeting C-type lectins for many decades. The asialoglycoprotein receptor (ASGPR) is a prime example with respect targeted delivery approaches and has been utilized as hepatic receptor to enable specific delivery of therapeutic siRNAs to the liver. The ASGPR recognizes carbohydrates conjugated to RNA and promotes endocytosis. Taking this principle, other members of the C-type lectin family have been explored for other indications since they are associated with cells of the innate immune system. These cell surface receptors often promote pathogen recognition leading to immune cell activation and/or endocytosis, finally fostering antigen presentation. Overall, having a defined expression pattern and triggering an immune response, render C-type lectin receptors excellent drug targets for immunomodulation.

Here, I will summarize our attempts to develop small molecule modulators of C-type lectins. For this the structural plasticity of these lectins played an important role. We found that besides the shallow and featureless carbohydrate recognition site, several secondary sites exist that are partially druggable and offer possibilities for inhibitor design against C-type lectins[1]. Complemented by our studies into the receptor flexibility using protein NMR in combination with molecular dynamics simulations, we revealed an allosteric network of communicating amino acid sidechains that could be used for targeting ligand design. To showcase the application of our C-type lectin ligands, I will present some of your latest work on the targeted delivery of therapeutics to Langerhans cell in the human skin via targeting of langerin[2,3].

[1] Wawrzinek R, Wamhoff EC, Lefebre J, Rentzsch M, Bachem G, Domeniconi G,Schulze J, Fuchsberger FF, Zhang H, Modenutti C, Schnirch L, Marti MA, Schwardt O, Bräutigam M, Hauck D, Seeberger PH, Seitz O, Titz A, Ernst B, Rademacher C. (2021) A Remote Secondary Binding Pocket Promotes Heteromultivalent Targeting of DC-SIGN, J Am Chem Soc, 143, 18977-18988

[2] Wamhoff EC, Schulze J, Bellmann L, Rentzsch M, Bachem G, Fuchsberger FF, Rademacher J, Hermann M, Del Frari B, van Dalen R, Hartmann D, van Sorge NM, Seitz O, Stoitzner P, Rademacher C. (2019) A Specific, Glycomimetic Langerin Ligand for Human Langerhans Cell Targeting, ACS Cent Sci 5, 808-820

[3] Rentzsch M, Wawrzinek R, Zelle-Rieser C, Bellmann L, Fuchsberger FF, Schulze J, Busmann J, Rademacher J, Sigl S, Del Frari B, Stoitzner P, Rademacher C. (2021) Specific Protein Antigen Delivery to Human Langerhans Cells in Intact Skin, Front Immunol, 12:732298



Graphical Abstract[2]