Sugar-mimetics as inhibitors of host-pathogen interaction : the case study of C-type Lectin targeted compounds

Ieva Sutkeviciute[1], Vanessa Porkolab[1], Norbert Varga[2], Michel Thépaut[1], Javier Rojo[3], Sara Satin[2], Angela Berzi[2], Ali amara[4], Mario Clerici[2], Anna Bernardi[2], **Franck Fieschi[1]**

[1]*Institut de Biologie structurale, UMR 5075 CEA/CNRS/UJF. 38027 Grenoble.*
[2]*Università degli Studi di Milano, 20157 Milano, Italy*
[3]*Instituto de Investigaciones Químicas (IIQ), CSIC e Universidad de Sevilla, Spain.*
[4]*INSERM U944, Laboratoire de Pathologie et Virologie Moléculaire, Hôpital Saint-Louis, Paris, France.*

DC-SIGN is a C-type lectin receptor (CLR) specifically expressed on dendritic cell surface. It recognizes highly glycosylated proteins expressed on the surfaces of various pathogens and is implicated in the early stages of many viral infections, which makes it an interesting target for therapeutic intervention (1). Thus DC-SIGN has been widely described as an HIV attachment receptor, at the level of genital mucosa, and as playing a role in viral transmission to T lymphocytes. On the opposite, Langerin, a CLR of the same family, could contribute to viral clearance. Some microbicidal strategies aiming to block initial mucosal HIV capture after sexual intercourse, could target DC-SIGN but without a simultaneous inhibition of Langerin. This last considerations represent in itself a challenging task since both receptors have overlapping recognition specificities.

Over the last year we have developed inhibitory strategies trying to address the specifications described above. The synthetic carbohydrate molecules are good drug candidates for DC-SIGN inhibition due to their high solubility, resistance to glycosidases and non-toxicity. Indeed, a first molecule has been shown as efficient to inhibit DC-SIGN-mediated HIV infection (2). From that point, X-ray structure of this glycomimetic within the DC-SIGN binding site allowed us to identify part of it that could be chemical optimized in order to improved its inhibitory efficiency in term of affinity and selectivity to DC-SIGN (3). We went through a second and a third round of ligand optimization we have now in hands, glycomimetic ligands totally specific for DC-SIGN with respect to Langerin. Using dendrimeric scaffold for ligands presentation we have been able to show that our compounds are able to inhibit HIV infection in human cervical explant (4). Finally, since DC-SIGN can be also used by Dengue viruses, we have done some preliminary experiment in a dengue virus infection test (5). Again, it shows some promising inhibition potency of our multivalent inhibitors.

References :

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