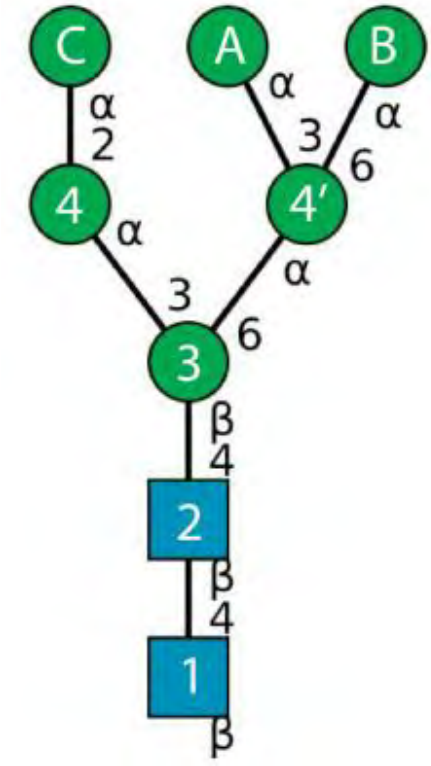
MS10-2-1 FimH bacterial lectin switches arms between monovalent and multivalent binding of N-glycans #MS10-2-1

J. De Ruyck [1], S. Semwal [1], J. Bouckaert [1]
[1]Unité de Glycobiologie Structurale et Fonctionnelle - Villeneuve d'Ascq (France)

Abstract
The lectin domain of the fimbrial adhesin FimH from *Escherichia coli* recognizes, with a similar high affinity (K_d < 20 nM) and in a monovalent fashion (1), oligomannoside-3 and -5 *N*-glycans, on the condition that these ligands are present in a molar excess. Oligomannose-6 is generated with the first transfer of a mannose in α1,2-linkage, to the mannose that is itself α1,3-linked to the common core of *N*-glycans (Fig. 1). This extra mannose, C, causes a 10-fold affinity loss compared to oligomannose-3 and -5 but permits divalent binding that is sustained beyond a molar excess of the ligand (2).
Oligomannose-6 co-crystals with FimH lectin occurred only at the surface of a large lithium sulfate crystal. In these crystals, oligomannose-6 is a divalent ligand bridging two FimH lectins (Fig. 2). Oligomannose-6 bound via two non-reducing mannosides, A and B, that sprout from the central mannose, 4' (Fig. 1), that is α1,6-linked to the common *N*-glycan trimannose core. In contrast, in the co-crystal structure of FimH lectin with core(α1,6)-fucosylated oligomannose-3, no change is observed in the monovalent capture of mannose 4 of oligomannose-3, or the precursor of arm C (Fig. 1).
We profiled the binding of the FimH lectin on a glycan microarray and measured the kinetics of FimH interactions with oligomannosidic *N*-glycans and glycoproteins. To transition to oligomannose-6, we measured the kinetics of FimH binding with Manα1,2Man, Manα1,3Man, Manα1,6Man and Manα1,4Man coupled with bovine serum albumin, and compared affinities with direct binding in a FimH Lectprofile assay. Both earlier studies (3), mixed interfaces of the three different non-reducing *N*-glycan dimannosides of oligomannose-6 (Fig. 1) and molecular dynamics simulations suggest a positive cooperativity in the simultaneous binding by FimH (Fig. 2) of Manα1,3Manα1 and Manα1,6Manα1 (Fig. 1) on arms A and B of oligomannose-6.

References
(1) Bouckaert, J., Mackenzie, J., de Paz, J. L., Chipwaza, B., Choudhury, D., Zavialov, A., Mannerstedt, K., Anderson, J., Pierard, D., Wyns, L., Seeberger, P. H., Oscarson, S., De Greve, H., Knight, S. D. (2006) The affinity of the FimH fimbrial adhesin is receptor-driven and quasi-independent of Escherichia coli pathotypes. Molecular Microbiology 61, 1556-1568
(2) Sauer, M. M., Jakob, R. P., Luber, T., Canonica, F., Navarra, G., Ernst, B., Maier, T., Glockshuber, R. (2019) Binding of the bacterial adhesin FimH to its natural, multivalent high-mannose type glycan targets. J Am Chem Soc 141, 936-944
(3) Dumych, T., Bridot, C., Gouin, S. G., Paryzhak, S., Szunerits, S., Bilyy, R., Bouckaert, J., (2018) A novel integrated way for deciphering the glycan code for the FimH lectin. Molecules 23, 2794

Oligomannose-6



Oligomannose-6 bridging two FimH lectins