Synthetic carbohydrate-based vaccines: from concept to clinic

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Shigellosis, or bacillary dysentery, caused by the enteroinvasive bacteria *Shigella*, remains one of the top four diarrheal diseases in children under five.[1] Species and serotype diversity, added to their geographical distribution, strongly support the need for a multivalent vaccine. Protection against re-infection is thought to be achieved, to a large extent, by antibodies specific for the O-antigen moiety of the bacterial lipopolysaccharide. In this context, a multidisciplinary strategy toward vaccine candidates encompassing synthetic oligosaccharides mimicking the "protective" determinants carried by the O-antigen of selected serotypes was undertaken in the laboratory. The two-step process under development aims first at identifying sets of "protective" epitopes, and second at designing conjugates thereof acting as strong immunogens.

This presentation highlights the development of a monovalent *Shigella flexneri* 2a glycovaccine candidate ongoing a phase I clinical trial.[2,3] It also addresses our strategy for broadening species and serotype coverage. Interestingly, most known repeating units from *S. flexneri* O-antigens comprise a common tetrasaccharide backbone. Diversity and serotype specificity are related to the occurrence of α-D-glucosylation and/or O-acetylation of the basic tetrasaccharide, itself a linear combination of three L-rhamnose residues and a *N*-acetyl-D-glucosamine.[4] The possible impact of these substitutions on vaccine development is discussed, while their influence on hapten synthesis is exemplified. In particular, we illustrate the multidisciplinary strategy that we have implemented to identify promising well-defined mimics of the O-antigen from *S. flexneri* 3a, another prevalent serotype. We report a detailed investigation of the immunodominant role of O-antigen stoichiometric O-acetylation as revealed by chemical synthesis, immunochemistry, physical chemistry, NMR, and X-ray crystallography studies. Next, we describe the rational design, synthesis, and immunogenicity data of the first synthetic carbohydrate-based vaccine candidate against this serotype, on the way to a bivalent *S. flexneri* vaccine.

[1] K. L. Kotloff *et al, Lancet* **2013**, *382*, 209.
[2] F. Bélot *et al*, *Chem. Eur. J.* **2005**, *11*, 1625
[3] R. van der Put *et al*, *Bioconjugate Chem.*, **2016**, *27*, 883.
[4] A. V. Perepelov *et al*, *FEMS Immunol. Med. Microbiol.*, **2012**, *66*, 201.
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