Synthetic glycan-based vaccines to combat bacterial diseases: from concept to immunogenicity in human

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Pathogens often express unique surface glycans, which contribute to their survival in the host and represent potential targets for vaccine development. Several polysaccharides and polysaccharide-protein conjugates are now licensed for routine vaccination and others are being developed. Otherwise, synthetic glycan-based conjugate vaccines are gaining increasing interest as attractive substitutes to the use of polysaccharide antigens of biological origin.[1]

Shigellosis, or bacillary dysentery, caused by the enteroinvasive bacteria *Shigella*, was identified as one of the main diarrheal diseases in children under five.[2] Species/serotype diversity and geographical distribution strongly support the need for a broad serotype coverage vaccine.
Using the *Shigella* context and the need for a highly immunogenic vaccine able to generate protective immunity in young children, we will address cutting-edge strategies for the design of the next generation glycoconjugate vaccines against infectious diseases.[3]

Interfacing chemical biology and structure-based vaccinology, we have developed vaccine candidates consisting of synthetic fragments of selected *Shigella* surface polysaccharides (Figure) covalently linked *via* single point attachment to protein carriers. SF2a-TT15,[4] a conjugate featuring a 15mer oligosaccharide hapten was shown to be strongly immunogenic in human volunteers.

With SF2a-TT15 as a model, the presentation will discuss oligosaccharide selection, vaccine design, synthesis, and properties thereof. Shedding light on the input of organic chemistry in the context of vaccine development, the path forward to a broad coverage *Shigella* vaccine will also be exemplified for *S. flexneri* 3a and *S. sonnei*, two other prevalent *Shigella* serotypes. Emphasis will be on the importance of site-selective *O*-acetylation and on the challenge of zwitterionic oligosaccharide synthesis.[5]

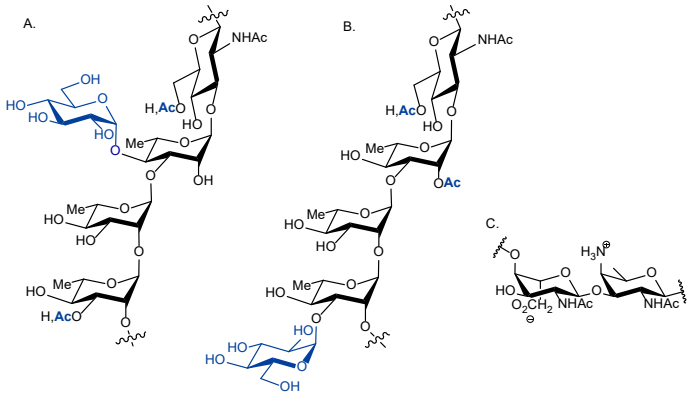

Figure: Repeating unit of the specific polysaccharides from *S. flexneri* 2a (A), *S. flexneri* 3a (B) and *S. sonnei* (C).

[1] R. Adamo, *Acc. Chem. Res.* **2017**, *50*, 1270-1279.
[2] J. Liu, J. A. Platts-Mills, J. Juma *et al*, *Lancet* **2016**, *388*, 1291-1301.
[3] L. A. Barel, L. A. Mulard, *Hum. Vaccin. Immunother.* **2019**, *15*, 1338-1356.
[4] R. M. F. van der Put, C. Smitsman, A. de Haan *et al*, *ACS Cent. Sci.* **2022**, *8*, 449-460.
[5] D. Dhara, L. A. Mulard, *Chem. Eur. J.* **2021**, *27*, 5694-5711.