FROM A UNIQUE TETRASACCHARIDE SCAFFOLD TO A BROAD SEROTYPE COVERAGE *SHIGELLA FLEXNERI* VACCINE CANDIDATE

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Shigella flexneri are Gram-negative enterobacteria and the main causative agent of endemic shigellosis, a major diarrheal disease especially in children under five from low- and middle-income countries. Disease burden calls for a *Shigella* vaccine that would induce broad serotype protection in the population most at risk. Protective immunity is believed to be achieved to a large extent by antibodies directed at the *Shigella* O-antigen (O-Ag), making it a prime target for vaccine development. Most *S. flexneri* serotypes exhibit closely related O-Ags built from the same backbone. Structural diversity reflecting serotype specificity derives from site-selective substitutions on a tetrasaccharide core (Figure 1) [1].

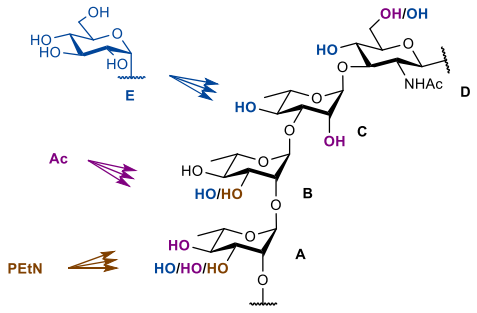

Figure 1. Backbone repeating unit (RU) from most *S. flexneri* O-Ags and type-specific substitutions thereof [1].

A semi-synthetic glycoconjugate was designed to help protect against *S. flexneri* serotype 2a. Promising data in phase 1 and phase 2a clinical trials support the development of novel strategies enabling serotype broadening to answer the need in the field [2,3].
This presentation illustrates the concept of synthetic glycan-based vaccines in the context of *S. flexneri*. Focus is on the design of functional oligosaccharide mimics of O-Ags representing the most prevalent serotypes. Going beyond original achievement [2,3], we report a concept whereby key RU building blocks featuring type-specific substitutions are built from a single fine-tuned tetrasaccharide scaffold by means of controlled 1,2-*cis* glucosylation of suitable acceptors. Chain elongation at either end of the glucosylated bricks and full deprotection delivered the required panel of linker-equipped type-specific oligosaccharides. The subsequent conjugation of the latter onto a protein carrier provided sets of potential immunogens representative of three different *S. flexneri* serotypes.
Immunogenicity data in mice will be discussed. The proof-of-concept for a broad coverage synthetic glycan-based *S. flexneri* conjugate vaccine will be illustrated.

References:
1. A. V. Perepelov AV et al, *FEMS Immunol. Med. Microbiol.* **2012**, *66*, 201.
2. D. Cohen et al, *Lancet Infect. Dis.* **2021**, *21*, 546.
3. A. Phalipon, L. A. Mulard, *NPJ Vaccines*, **2022**, *10*, 403.