SYNTHETIC PYROPHOSPHATE - CONTAINING ZWITTERIONIC LPS/LIPID A VARIANTS

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Gram-negative bacteria exploit various mechanisms to adapt their cell wall membranes by altering LPS composition to evade the host immune responses. Bacterial LPS-remodelling, modulated by the PhoP-PhoQ regulatory system and the activation of PmrA-PmrB leads to the decoration of the lipid A phosphate groups with amino group–containing appendages (i.e., ethanolamine, phosphoethanolamine or β-L-Ara4N) which are essential for LPS/lipid A recognition by the mammalian innate immune receptors. On the other hand, modifications of the LPS phosphate groups can shield bacteria from recognition by host cationic antimicrobial peptides, contributing to bacterial virulence. Due to intrinsic microheterogeneity and inherent instability of glycosyl phosphodiester and pyrophosphate modifications in LPS, LPS preparations from bacterial cultures exhibit significant structural variability making a consistent immunobiological assessment of the consequences of LPS remodelling difficult.
To study the impact of LPS phosphate groups modification on the host innate immune responses and on the LPS-protein interactions, we synthesised a collection of immunomodulatory LPS/lipid A motifs possessing various appendages on their phosphate groups. We developed an efficient and robust methodology to synthesize phosphoethanolamine (PE)-modified lipid A variants, comparing the use of phosphoramidite and H-phosphonate chemistries. As regarding to the synthesis of glycosyl pyrophosphodiesters, as found in the LPS of several bacterial species such *Salmonella* or *Neisseria,* this is challenged by the intrinsic instability of glycosyl pyrophosphates under different conditions, as well by the complex control of stereoselectivity required. To tackle this challenge, we exploited the application of P(V)-P(III) coupling which provided a more efficient and rapid coupling step in comparison to the classical P(V)-P(V) approaches.

References:

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