Exploiting Inflammatory Processes: Design, Synthesis and Biological Characterization of New Modulators of Toll-Like Receptor 4 (TLR4)

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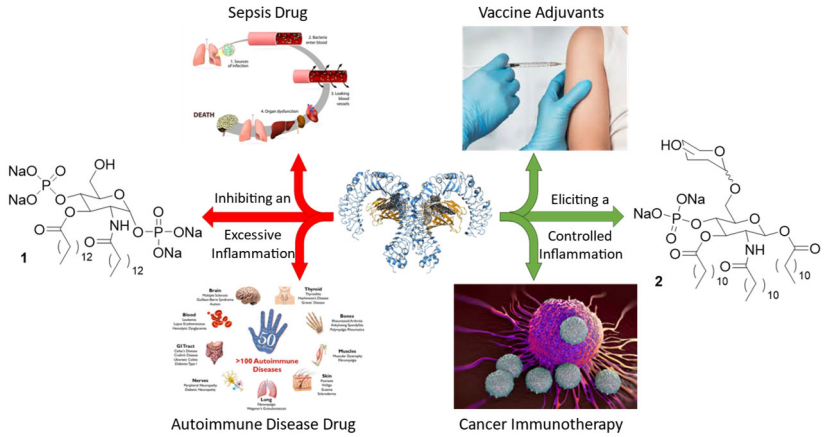
Abstract:

Innate Immunity is the first defense line in multicellular organisms against internal of external threats. Toll-Like Receptor 4 (TLR4) is a pivotal protein in innate immunity: after binding its natural ligand, gram-negative bacteria lipopolysaccharide (LPS), TLR4 kickstarts inflammation.[1]

TLR4 modulation is recognized as a therapeutic approach in several clinical settings. TLR4 inhibition has a potent anti-inflammatory effect, useful against sepsis or autoimmune diseases. On the other hand, a mild activation of TLR4 can be used to stimulate immunity, useful in vaccine adjuvants or cancer immunotherapeutic drugs.[2,3]

We present rationally designed lipid A analogues based on a monosaccharide structure that are active in binding TLR4 and its coreceptor MD2, thus activating or inhibiting TLR4 signalling. We also present synthesis optimization of TLR4 modulators, which is being applied for the industrial scale-up and future commercial application of such compounds.



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