Development of highly functionalized lipid A for self-adjuvanting vaccines.

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Lipopolysaccharide (LPS), the outer membrane component of Gram-negative bacteria, has been known as a potent immunostimulator. Its terminal glycolipid moiety "lipid A" is an active principal of the LPS. Monophosphoryl lipid A derivative 3D-MPL (GlaxoSmithKline) has been practically used as a vaccine adjuvant.[1)] It has also been reported that a self-adjuvant vaccine composed of an antigen and an adjuvant can promote efficient antibody production.[2)] Meanwhile, the lipid A conjugation strategy maintaining its innate immunological function is still under developing. In this study, we investigated the lipid A conjugation method that enables highly functionalized lipid A for self-adjuvanting vaccines.

We developed self-adjuvanting vaccine **5** based on MPL504, attenuated lipid A developed by our group (Figure 1). We planned to introduce antigen moiety using hydrophilic (sugar mimic) linker at 6'-position of lipid A via an amide bond considering increased stability *in vivo* and linking of the polysaccharide moiety to 6'-position of lipid A in natural LPS. We previously found that the linker influenced the activity of lipid A, *i.e.*, polyethylene glycol linker significantly decreased the lipid A activity, whereas the more hydrophilic linkers maintained the activity.[3)] In this study, we designed and synthesized a novel hydrophilic sugar mimic linker **2** from D-mannitol. The disaccharide intermediate **1** was synthesized according to our previous report.[4)] Introduction of fatty acids and 6'-amination **3** afforded **3**. Coupling of **3** with the linker **2** afforded **4**. After the introduction of antigen moiety, all protecting groups were removed to afforded **5**.

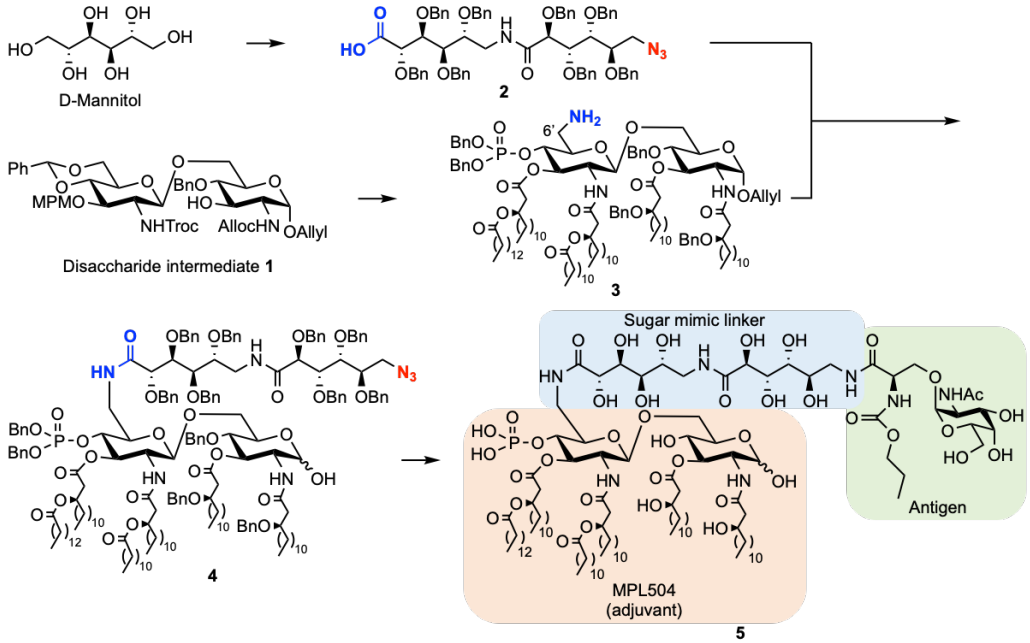

Figure 1. Synthesis of self-adjuvanting vaccine **5** based on MPL504

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