Rational drug design of ligands for MD2/TLR4/CD14 signalling cascade as perspective adjuvants of anti-bacterial vaccines

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Modern vaccines typically consist of agents resembling external parts of pathogens and various adjuvants, which are designed to strengthen the work of cellular immunity. For instance, the basic component of anti-bacterial vaccines for a wide range of spread inflectional diseases (pneumonia, bronchitis, rhinitis and many others) is lipopolysaccharide (LPS) - major element of the bacterial outer membrane, which activates the innate immunity system and induces production of inflammatory mediators [1,2,3]. LPS recognition organized by the cascade of proteins: LPS binding protein (LBP), CD14 and Toll-like receptor 4 (TLR4)–MD-2 complex [3,4,5]. Unfortunately, in many situations LPS from vaccine cannot activate this immune cascade in effective manner (for example, in case of little children delicate immunity), and the design of effective adjuvants for additional activation of this cascade is the challenging question [6]. In our study we have conducted rational design of low-molecular ligands for MD2, CD14 and LBP proteins, using molecular docking modelling. Selected compounds are expected to change the activity of the immune cascade and its sensitivity to LPS, so they are likely to be used as effective adjuvants in anti-bacterial vaccines. Bioactivity of these compounds will soon be checked experimentally.

1. Rietschel ET, Brade H, Brade L, Kaca W, Kawahara K, Lindner B, Luderitz T, Tomita T, Schade U, Seydel U (1985) Newer aspects of the chemical structure and biological activity of bacterial endotoxins, *Progress in clinical and biological research*, **189**:31–51.

2. Medzhitov R, Janeway CJr. (2000) Innate immune recognition: mechanisms and pathways, *Immunological Reviews*, **173**: 89–97.

3. Raetz CR, Whitfield C. (2002) Lipopolysaccharide endotoxins, *Annual Review of Biochemistry*, **71**: 635–700.

4. Wright SD, Ramos RA, Tobias PS, Ulevitch RJ, Mathison JC. (1990) CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein, Sc*ience* **249**:1431–1433.

5. Chow JC, Young DW, Golenbock DT, Christ WJ, Gusovsky F. (1999) Toll-like receptor-4 mediates lipopolysaccharide-induced signal transduction, *The Journal of Biological Chemistry*, **274**: 10689–10692.

6. Marciani DJ. (2003) Vaccine adjuvants: role and mechanisms of action in vaccine immunogenicity, *Drug Discovery Today*, **8(20)**: 934-43.