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A structure-function approach to rational adjuvant design

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The recognition of microbe associated molecular patterns (MAMPs) by the innate immune system is mediated by classes of receptors that combine two disparate features: Recognition of a broad array of molecules of a single class and narrow recognition of just that class of molecules. An example of this is the multitude of forms of lipopolysaccharides that are recognized by TLR4: They vary by the carbohydrate head groups, the number, position and length of lipid chains attached to the disaccharide core as well as the charge imparted by the 1 and/or 4' phosphate groups. It is known that different TLR4 ligands can stimulate different profiles of cytokine response and it is attractive to speculate that nature has built an elegant, but subtle, discriminatory system that not only relies on binary on/off binding to TLR4 to determine the signaling outcome, but additionally senses how the ligand is bound. This would make sense for pathogen associated molecular pattern (PAMP) recognition since it could well be beneficial to the host to respond differently to various microorganisms expressing a class of MAMPs. For example, if the host could respond with little inflammatory signal to a TLR4 ligand produced by a commensal bacterium while maintaining full inflammatory responses to TLR4 ligands from pathogenic gram negatives, the innate responses could select between "good" and "bad" Gram negatives. By leveraging this non-binary, "fuzzy" receptor/ligand response pattern one should be able to design stimulatory adjuvant molecules that induce more of the type of immunity desired while separating that activity from the induction of pyrogenic and inflammatory responses as reported here. Leveraging this discerning ability, we subtly altered a synthetic MPLA structure resulting in SLA, a designer TLR4 ligand that has a number of desirable adjuvant effects: The SLA molecule stimulates human TLR4 and induces Th1 biasing cytokines and chemokines. On human cells, the activity of SLA plateaus at lower concentrations than a synthetic MPLA comparator and induces distinct cytokine profiles from other TLR4 agonists, including notably fewer inflammatory cytokines while maintaining high levels of induced interferons. The new molecule has adjuvant properties in animal models and was tested in human clinical trials. The results that will be presented indicate that SLA is a potent candidate for developing human Th1 biasing adjuvants and demonstrate the potency of using structural biology in adjuvant design.