

## Developing New Toll-Like Receptor 4 (TLR4) Modulators As Innovative And Inexpensive Vaccine Adjuvants

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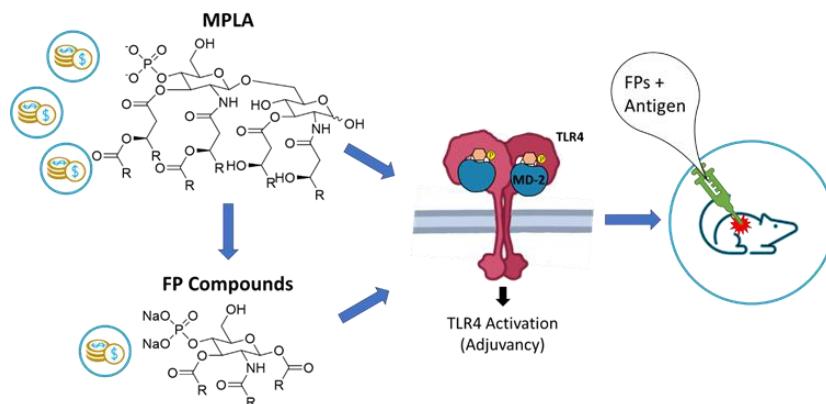
### Abstract:

Vaccines have been a breakthrough in medicine: they saved millions, reduced the incidence and morbidity of diseases such as polio, measles and tetanus and caused smallpox eradication.<sup>1</sup>

Modern subunit-based and nucleic acid-based vaccines are safer and easier to produce than inactivated pathogen-based ones, but require vaccine adjuvants to achieve a proper immunization.<sup>2</sup>

A vaccine adjuvant is any entity that enhances a vaccine efficacy. For 70 years, Alum® has been the only licensed adjuvant: only recently few new adjuvants have been approved.<sup>3</sup> The most prominent example is Monophosphoryl lipid A (MPLA), an agonist of Toll-like Receptor 4 (TLR4). MPLA is commercialized by Croda International PLC and is employed in several vaccines.<sup>3</sup> However, MPLA is complex, its synthesis is long (>25 reactions) and the final cost high (~230 USD/mg).<sup>4</sup>

We present here a series of simplified, rationally designed MPLA analogues called FP compounds. FPs show a similar or better TLR4 agonists activity than MPLA, thus being promising vaccine adjuvant. As FPs are much easier to synthesize, they are currently being preclinically developed in collaboration with Croda International PLC as innovative and inexpensive vaccine adjuvants.<sup>5–7</sup>



### References:

- [1] Kayser, V.; Ramzan, I. *Hum. Vaccines Immunother.* 2021, 17 (12), 5255–5268.
- [2] Vetter, V.; Denizer, G.; Friedland, L. R.; Krishnan, J.; Shapiro, M. *Ann. Med.* 2018, 50 (2), 110–120.
- [3] O'Hagan, D. T.; Lodaya, R. N.; Lofano, G. *Semin. Immunol.* 2020, 50, 101426.
- [4] Shaw, W. A.; Burgess, S. W.; et al. *Disaccharide Synthetic Lipid Compounds and Uses Thereof*, 2016.
- [5] Facchini, F. A.; Minotti, A.; et al. *J. Med. Chem.* 2021, 64, 12261–12272.
- [6] Romerio, A.; Gotri, N.; Franco, A. R.; et al. *J. Med. Chem.* 2023, 66 (4), 3010–3029.
- [7] Romerio, A.; et al. *ACS Omega* 2023, 8 (39), 36412–36417.