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TITLE: ***"Lipid A as Diagnostic and Therapeutic"***

ABSTRACT: We will discuss our efforts with the Ernst laboratory, with whom we have collaborated for nearly twenty years, to develop lipid A as both a diagnostic and therapeutic agent. The latter revolves around development of a structure-activity relationship (SAR) library for lipid A. Having a better understanding of the lipid A SAR will allow us to design novel lipid A structures/functions that are antagonistic or agonistic toward the MD2/TLR4 receptor complex. Our approach to elucidate the lipid A SAR involves profiling the structure (via mass spectrometry and in some cases use of a novel ion mobility QE instrument) and function (i.e. *in vitro* and *in vivo* cytokine activity) of novel lipid A molecules from marine and extremophile sources as well as mapping by tissue imaging the true *in vivo* structural variant populations of lipid A in ways never before possible. We will also provide an update on the use of surface acoustic wave nebulization (SAWN) coupled to mass spectrometry for the purpose of facile lipid A analysis as well as the use of top-down proteomics to understand glycoforms of MD2 and how this affects function and the use of bottom-up proteomics to define macrophage proteomes as a function of stimulation with select lipid A molecules. Our approach when realized will result in a definitive description of the agonism/antagonism structural switch of lipid A binding to MD2/TLR4 and will be the basis for further understanding of lipid A modifications *in vivo*. With regard to diagnostics we are constructing a library of bacterial and fungal glycolipid mass spectra from which bacteria and fungi may be identified direct from specimen without culture from in vitro sources but also clinical specimens. This latter effort is being commercialized by a Baltimore-based startup company, Pataigin, but both efforts are supported by two NIH MPI RO1 awards.