I will present our research in collaboration with the group of professor Robert Ernst at U. of Maryland in which we elucidate the molecular basis by which gram-negative bacteria modify the lipid A component of lipopolysaccharide (LPS) and how these alterations affect or circumvent normal host innate immune system responses in order to develop a lipid A structure-activity relationship (SAR) library alluding to potential translation outcomes. Having a better understanding of the lipid A the SAR approach will allow us to design novel lipid A structures showing distinct functions that are antagonistic or agonistic toward the MD2/TLR4 receptor complex. Our approach to elucidate the lipid A SAR involves profiling the molecular structure via mass spectrometry and in some cases use of a novel ion mobility QE, and function as *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 topdown 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*.