The human innate immune system is tuned to recognize specific threats of infection and respond to infectious agents with lethal force. Recognition and response occur at the molecular level, and it is possible to influence and mimic recognition and response with small molecules. One aspect of recognition involves surveillance by natural killer T (NKT) cells for signs of bacterial infection. NKT cells regulate immune reactions to infection and influence disease states ranging from tumor rejection to autoimmunity. Glycolipids from specific classes of bacteria trigger NKT cell responses, which can lead to beneficial or deleterious effects. An understanding of how NKT cells are stimulated by glycolipids is essential to the control of their behavior. Our collaborative group has discovered many of the types of glycolipids that stimulate NKT cell responses, and we have optimized the structures of synthetic molecules that elicit responses from NKT cells at very low concentrations.

Many vaccines have been developed that are well designed but lack the ability to generate a protective response in humans. The primary reason that protective responses are not generated is that the body does not view the vaccine as foreign and an immune response is not triggered. Stimulation of NKT cells provides the inflammatory signals necessary to aid the adaptive immune system in generating protection against antigens in vaccines and the corresponding diseases. We have demonstrated that NKT cells are uniquely suited for aiding vaccines, and the addition of glycolipids as vaccine adjuvants increases the effectiveness of vaccines dramatically. A compound that has been optimized for NKT cell stimulating properties will enter human clinical trials this year.

A response element of innate immunity is the action of endogenous antimicrobial peptides (AMPs). AMPs are required to control bacterial growth in many tissue types, and deficiencies in AMPs have been correlated with persistent skin infections, periodontal disease, urinary tract infections, and blood stream infections associated with medical devices. AMPs are found in organisms ranging from mammals to insects to amphibians to plants. Their ubiquity argues that they have exerted their protective effects for eons. Consequently, it is expected that they will not readily engender resistance. This observation has lead to considerable work to develop AMPs for clinical use. However, peptide therapeutics are relatively expensive to prepare at large scale, and because AMPs are generally linear peptides, they are quickly degraded in vivo by proteases.

We have developed a class of compounds that mimics the antibacterial activity of AMPs but is not peptide based. These compounds selectively target bacterial membranes and are rapidly bactericidal. They are relatively simple to prepare and are stable under most conditions. These compounds appear to be well suited for augmenting and/or replacing the activities of AMPs in a number of different applications. These include decolonization of the gastrointestinal tract, treatment of skin infections, and prevention of bacterial colonization of medical devices. These AMP mimics are in small and large animal studies, and it is anticipated that they will begin trials in humans in the near future.