Characterization of Chemical Probes for Therapeutic Intervention of Innate Immune Signaling

by

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The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.

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The innate immune system protects us from incessant attacks by microorganisms. However, immunity is a double-edged sword, and inflammation must be carefully regulated. Chemical biology offers a means to maintain healthy homeostasis by influencing the immune response. We have used small molecule and peptide chemistries to exploit Toll-like receptor, caspase, and antimicrobial peptide signaling for therapeutic purposes. These compounds may find applications treating sepsis and autoimmune disease, and can influence the design of next-generation antibiotics and vaccines.

Toll-like receptors are pattern recognition receptors that sense bacteria and viruses, and then induce inflammation to stave off infection. We have designed saccharin-derived small molecules capable of reducing inflammation by inhibiting JAK/STAT1 signaling. We have also explored Toll-like receptor specificity by designing TLR8-specific imidazole-derivatives that are promising immune-responsive vaccine adjuvants.

Caspases are proteases that control inflammation and cell death. Much is still unknown about the role of caspases as innate immune receptors, particularly lipopolysaccharide-sensing caspase-4. We have performed two small molecule screens to identify caspase-4 inhibitors for use as both therapeutics and signaling probes. From this, we have discovered a new role for non-steroidal anti-inflammatory drugs as multi-caspase inhibitors, which may shape patient applications of these essential drugs. We have also identified novel caspase-4 specific small molecules for sepsis treatment.

Antimicrobial peptides are small, amphipathic peptides able to both disrupt bacterial membranes and influence inflammation. We have designed a series of peptidomimetics able to mimic the properties of host-defense peptides. These peptidomimetics are active against a wide array of Gram-positive and Gram-negative pathogens, and reduce the inflammatory response. In an era of prevalent antibiotic resistance, peptidomimetics offer a path for the design of new antibiotics.