Antimicrobial resistance (AMR) has become one of the biggest health challenges of this era, causing yearly millions of deaths worldwide. However, there has been a sharp decline in antibiotic development despite the critical need for novel therapies. In our work, we propose multiple methodologies for the discovery and design of peptidic compounds with antibacterial activities, ranging from natural products to inhibitor design. In this talk, we focus on the progress we have made in the development of nature-derived antimicrobial peptides (AMP). Lactomodulin, a 53-amino acid long microbiome-derived AMP, has both antibiotic and anti-inflammatory activity. We have analyzed the composition and structure of the parent peptide and generated shorter truncated versions analyzed based on AMP potential, helical propensity, and toxicity predictions. Out of 13 derivatives, one 15-mer LSKISGGIGPLVIPV-NH_2 and its cyclic versions have shown improved activity against Gram-positive (MIC 0.8–2.3 μM), including resistant strains, and Gram-negative bacteria (MIC 8–9.3 μM). Time killing assays further showed a fast bactericidal activity and TEM studies indicated a membrane-targeting mode of action. Interestingly, other peptides from the initial library also showed a retention of anti-inflammatory activity. These results pave the way for the development of unique peptides with Gram-positive, Gram-negative, and anti-inflammatory activities.