Cationic host defence (antimicrobial) peptides are produced by virtually all organisms, ranging from plants and insects to humans, as a major part of their immediately-effective, non-specific, innate defence against infections. Their activities range from modulation of immunity to broad spectrum antimicrobial action. Natural peptides vary in length from 12 to around 50 residues and have a net positive charge conferred by lysine and arginine residues and usually greater than 50% amino acid residues. Biochemical and animal model studies demonstrate that the directly antimicrobial peptides have potential as stand-alone, broad-spectrum antibiotics, and clinical trials of efficacy of topically applied peptides against infections were recently completed. Similarly immunomodulatory peptides are able to act as broad spectrum anti-infectives by virtue of their ability to selectively modulate innate immunity and Phase I clinical trials were recently completed.

The initial sites of interaction are with cellular membranes. Although dogma suggests that their lethal action involves disruption of the bacterial cytoplasmic membranes, a number of cationic peptides can freely traverse both prokaryotic and eukaryotic membranes to interact with internal targets, and indeed they have the properties of so-called “cell penetrating peptides”. We have studied this in detail using a wide variety of assays of peptide interaction with membranes, including fluorescence tagging, planar bilayer, monolayer, and liposome (calcein release, lipid flip-flop, trp fluorescence enhancement and translocation) assays. Based on these investigations we have proposed models to explain how amphiphilic peptides as short as 12 amino acids can interact with the cytoplasmic membranes leading to translocation.

To develop improved molecules, cationic peptides from all four known structural classes have been used as templates using NMR-determined structures and/or molecular modelling to assist in design. Recently we have utilized random robotic-directed synthesis on cellulose sheets (peptide arrays) to more thoroughly determine structure activity relationships, and the ability to examine thousands of sequences has permitted for the first time QSAR analysis and computational prediction of optimized sequences.