Antimicrobial Resistance is a global threat that requires urgent solutions. Our research focuses on investigating virulence proteins, the molecular weaponry bacteria deploy to cause disease. Combining X-ray crystallography with molecular and biochemical studies, we dissect the mechanism of action of key bacterial virulence factors. We then apply the gained knowledge for developing antimicrobials that “disarm rather than kill bacteria”, a novel approach that promises to reduce resistance development.

Central to bacterial virulence potential are autotransporters, the largest group of secreted and surface proteins in Gram-negative bacteria [1-2]. Autotransporters allow bacteria to aggregate, adhere to human cells, and form biofilms, all key facilitators of pathogenesis. We recently constructed a much-needed update to autotransporter phylogeny through combining extensive sequence and published experimental data, to reveal new important functional relationships and divisions within this diverse protein family [2]. This phylogeny has revealed significant knowledge gaps within new and existing groups that we are addressing. For example, using our multidisciplinary approach, we have comprehensively characterised different autotransporter adhesins including Ag43, TibA and UpaB from Escherichia coli pathotypes [3-5]. We have shown that heat-to-tail associations between autotransporter proteins in adjacent cells leads to bacterial clumping. Our data to date demonstrates that this is a universally conserved mechanism for autotransporter mediated aggregation and biofilm formation. We have also elucidated the structure-function characterisation of EspC, an autotransporter cytotoxin from enteropathogenic E. coli. Most critically, we have determined the structure and mechanism of a subtilase autotransporter from Serratia marcescens, the first member from this large relatively unknown group of autotransporters. Finally, we are using these findings to develop specific autotransporter inhibitors such as our recently patented biofilm blocker [6].

Keywords: Bacterial infection, Autotransporters, Antimicrobials