# Antibiotic Resistance in Enterococcus faecalis: Influences from a Serine/Threonine Kinase

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The regulatory control of gene expression by external stimuli in bacteria is poorly understood but is fundamental to bacterial signaling, environmental response and antibiotic resistance. It has been known for sometime that almost all bacteria use multiple membrane bound histidine kinases and cytoplasmic response regulator proteins to form two-component systems (2CS) to respond to external stimuli. However, the nature of these protein-ligand interactions and how that interaction is transmitted through the membrane is still largely unexplored. It is becoming increasing clear that many bacterial also contain single Serine-Threonine kinase (STK) proteins (Figure 1), similar to those found in eukaryotes, which are responsible for more global extracellular signal responses.

Between groups at Columbia (USA) and Warwick (UK), we have identified IreK as a unique STK in pathogenic Enterococci that appears to have a highly significant role in peptidoglycan and related antibiotic resistance. The aim of this project is to dissect the molecular architecture and interaction of the Enterococcal IreK. We have already assembled a molecular tool kit of proteins, ligands and chemical probes to explore this system. We are interrogating IreK extracellular domain ligand interactions using SPR and NMR structural characterization of these domains to monitor the ligand interaction. We aim to describe IreK ligand recognition to intracellular signaling and its relationship to antibiotic resistance.

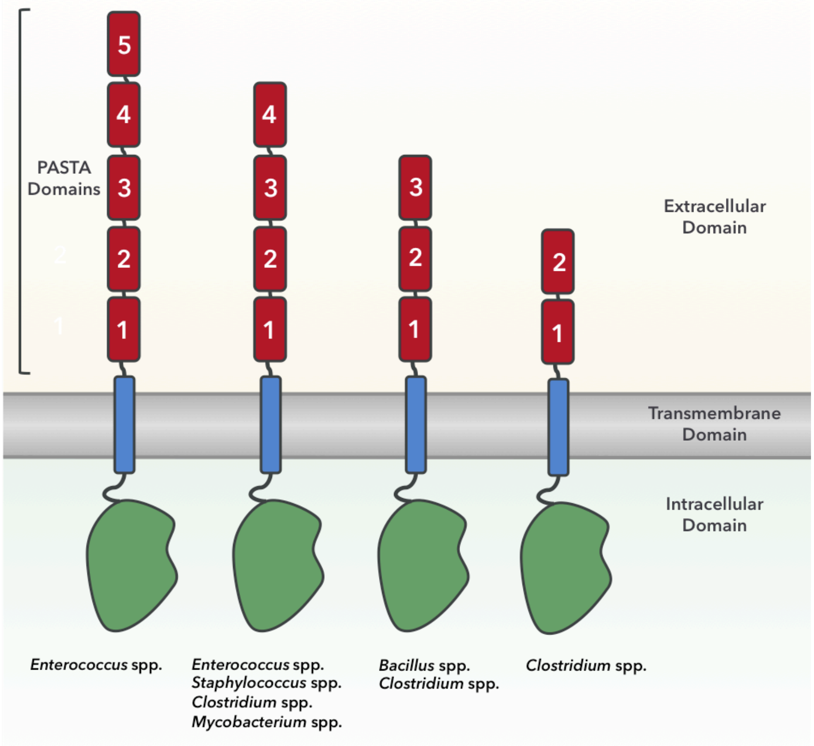

**Figure 1 -** Schematic demonstrating the diversity of Prokaryotic STK. The Intracellular Kinase domain is generally conserved between species and the Transmembrane domain is generally variable, but the PASTA domains have a lower order of homology in terms of conserved sequences and length.