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INSTITUTIONEN FÖR KEMI OCH MOLEKYLÄRBIOLOGI

Structure-based drug design applied to the antibacterial target MraY

On the route to novel antibiotics

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Abstract

Antibiotic resistance is one of the biggest threats to human health of our time. We are being warned of a so-called post-antibiotic era, where a simple surgery or bacterial infection could kill human beings. Without the rapid development of novel antibiotics, the continued growth of antibiotic resistance will put our society in a crisis of unprecedented scale.

The bacterial cell wall resembles a protective barrier and is crucial for bacterial survival. Hence, disruption of the cell wall synthesis will lead to cell death. The bacterial membrane protein MraY is involved in the peptidoglycan synthesis, which is a component of the bacterial cell wall, by catalysing the synthesis of lipid I - a peptidoglycan precursor. In this thesis, functional and structural studies of MraY with inhibitors were performed with the future aim of designing novel antibiotics. We solved the crystal structure of MraY from the Gram-positive pathogen *Clostridium bolteae* in complex with the natural product inhibitor tunicamycin at 2.6 Å resolution and provided a biophysical characterisation of the binding mode of tunicamycin. A structural comparison between MraY and its human homolgue GPT identified regions to modify tunicamycin to selectively target MraY. We modified and purified tunicamycins to explore their inhibitory effect and potency towards MraY and identified potent MraY inhibitors with reduced eukaryotic toxicity. Finally, we optimised the purification protocol for MraY for future biophysical and structural studies and developed a novel method using teabags for membrane protein purification.