

SÉMINAIRES ET CONFÉRENCES



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« Fragment-based screening to identify inhibitors of bacterial type IV secretion systems »

The development of antimicrobial resistance (AMR) and the transfer of antibiotic resistance genes are big medical problems and novel treatment options are urgently needed. We study type IV secretion systems (T4SS) that are membrane-bound multiprotein complexes mediating the translocation of macromolecules (proteins, DNA or protein-DNA complexes) across the bacterial cell envelope. They are required for the virulence of many bacterial pathogens and for the transfer of antibiotic resistance genes between bacteria by conjugation. T4SS are interesting targets for the development of anti-virulence drugs and of inhibitors of plasmid conjugation. We study the mechanism and inhibition of T4SS using the mammalian pathogen *Helicobacter pylori* as well as the plasmid pKM101 conjugation system as models. T4SS contain eleven conserved VirB proteins and VirD4 that assemble into a transmembrane complex and surface-exposed pili. I will present our recent work on the VirB8 homolog TraE from pKM101 and on the VirB11 homolog Cag-alpha, an ATPase that is necessary for translocation of the CagA cytotoxin from *H. pylori* into mammalian cells. We conducted fragment-based screening using differential scanning fluorometry (DSF) to identify binding molecules. Next, we developed small-molecule inhibitors of the ATPase activity of Cag-alpha and of the dimerization of TraE. Analysis by X-ray crystallography showed that these inhibitors have novel binding sites and we also identified the mechanisms of inhibition of both proteins in vitro. The active molecules reduced T4SS functions in vivo, suggesting that they have potential for further development into more potent inhibitors. In our future work we will also identify additional molecules to conduct more detailed mechanistic studies and to develop inhibitors of bacterial virulence and of AMR gene transfer..



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