Target Identification of Cysteine-directed Covalent Inhibitors in Pathogenic Bacteria

Authors

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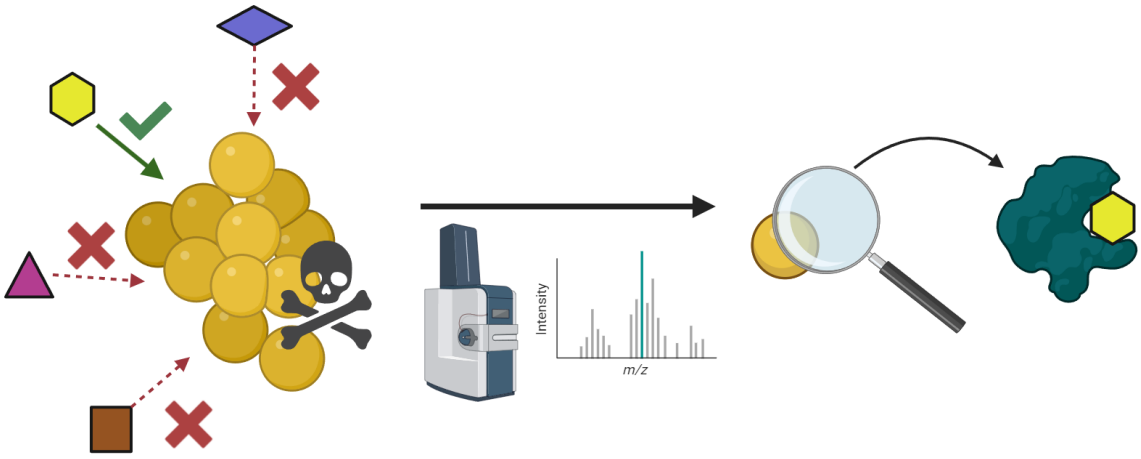
Abstract oral presentation

The worldwide emergence of antimicrobial resistance (AMR) has been recognized by the World Health Organization (WHO) as a top ten threat to global health.[1] Since clinically approved antibiotics target a limited set of molecular pathways, there is an urgent need to develop antibiotics with novel modes-of-action. In this context, covalent inhibitors that form a permanent bond with amino acid residues in proteins can have many advantages.[2] Especially the amino acid cysteine is an ideal target due to its nucleophilicity and unique role in bioprocesses.[2] We have screened a library of 10,000 covalent compounds of ~60 chemotypes for antibacterial activity against Gram-positive methicillin resistant *Staphylococcus aureus* (*S. aureus*) (MRSA) and Gram-negative Neisseria gonorrhoeae (*N. gonorrhoeae*) and performed additional studies to profile the hits. Isotopically labeled desthiobiotin – Activity Based Protein Profiling (isoDTB-ABPP)[3] was performed to reveal more than 2000 unique cysteines found in MRSA and around 3000 cysteines in *N. gonorrhoeae*. This corresponds to 42% and 46% of the total cysteinome, respectively. In both bacteria, 72% of cysteines in essential proteins were detected via this method. The protein targets of the determined hits were assessed and a selection was made for future studies. This research provides many new points of engagement towards the development of new antibiotics.



References

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3. Zanon, P. R. A., et al., *Isotopically Labeled Desthiobiotin Azide (isoDTB) Tags Enable Global Profiling of the Bacterial Cysteinome*. Angew. Chem. Int. Ed., 2020, **59**: p. 2829-2836.