Tackling Antibiotic Resistance With Covalent Macrocycles

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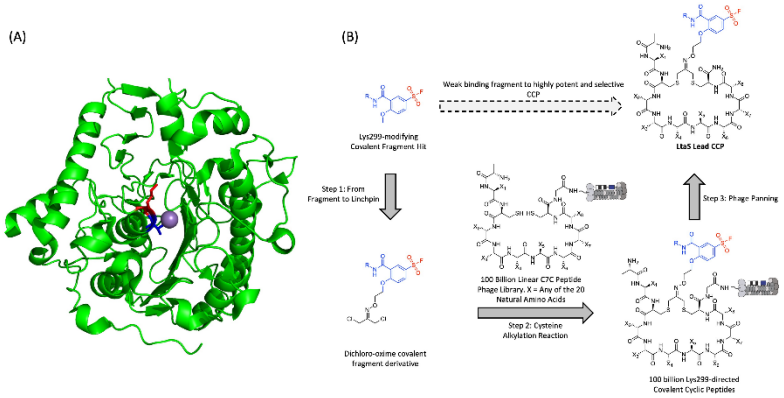

Figure 1: Strategy for identifying a CCP for LtaS. (**A**) Structure of LtaS with K299 shown in the active site in red, adjacent to the catalytic threonine (T300) shown in blue and the manganese ion shown in purple. PDB: 2W5Q. (**B**) The proposed workflow for transforming a weak binding covalent fragment (shown in blue with the electrophile in red) to a potent and selective CCP. Step 1: A linchpin derivative of the hit fragment is synthesised. Step 2: The linchpin is used to cyclise a linear peptide phage library by cysteine alkylation generating a 100 billion-membered CCP library. Step 3: The library is panned against LtaS to identify the most potent CCP antagonist.

Project description:

Infections with multidrug-resistant bacteria like methicillin-resistant Staphylococcus aureus (MRSA) are major threats to human health. Discovering novel druggable targets for antibiotic development is a pivotal task to guarantee effective treatment in the future. Lipoteichoic acid synthase (LtaS) catalyses the synthesis of lipoteichoic acid (LTA) from phosphatidylglycerol and is a key enzyme for S. aureus cell wall biosynthesis. LtaS is an attractive antimicrobial target as Gram-positive bacteria that lack LTA exhibit impaired cell division and growth defects.

In this PhD project, you will use a phage display approach, developed in the Lovell lab, to identify a potent and selective covalent cyclic peptide (CCP) antagonist for LtaS. You will screen in-house compound libraries to identify covalent fragments that modify Lys299 in the active site of LtaS (Fig. 1A). Hit fragments will be resynthesized as linchpin derivatives and grafted onto peptide phage display libraries to generate billions of Lys299- directed CCPs to screen against LtaS (Fig. 1B). You will carry out multiple rounds of phage panning and amplification and perform bioinformatic analyses to prioritize enriched CCPs for synthesis and testing in surface plasmon resonance binding studies. Working with the Spencer lab you will obtain co-crystal structures of hit CCPs bound to LtaS revealing critical interacting residues and enabling structure-guided optimization of key molecule parameters such as selectivity and proteolytic stability. You will validate the proteome-wide selectivity of CCPs using chemical proteomics approaches. Working with the Laabei and van den Elsen labs you will apply the lead CCP to a panel of MRSA isolates and assess changes in LTA biosynthesis and growth rate. Finally, you will assess the effects of inhibiting LtaS in vivo by incubating the lead CCP with Manduca Sexta Larvae challenged with S.aureus.

Your PhD research will validate LtaS as an actionable therapeutic target for the treatment of MRSA infections and will provide an optimized molecule for further pre-clinical assessment.

This truly interdisciplinary PhD project will provide you with a wealth of training and expertise in cutting-edge drug discovery and biotechnology, bioinformatics, chemical biology, structural biology, and infection biology. You will develop skills in peptide chemistry and phage display and will learn how to carry out bioinformatic analyses of deep sequencing data, perform X-ray crystallography studies and develop in vivo models of S. aureus infection. You will have the opportunity to communicate your research through publishing articles and presenting at national and international conferences.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.