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Opportunities in Bacterial Cell Wall Biogenesis

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One of the foremost challenges in the management of infectious diseases is antimicrobial resistance. The manifestation of multidrug resistance in bacteria, over the past several decades has resulted in one of the most pressing clinical problems in modern medicine. The Infectious Disease Society of America has identified a number of Gram-positive and Gram-negative human pathogens that pose a significant challenge in infectious disease management [1]. In recent years, there has been a global emergence of bacteria that are resistant to most or all of the currently available antibiotics, complicating treatment options for infected patients [2]. If the drug-discovery pipeline fails to produce new antibiotics to tackle this problem, clinical options for treating infections caused by these pathogens will be very limited, adding to the economic burdens caused by these infections on the health care system. Part of the approach to combating this daunting problem will require new chemical entities with antibiotic properties, to fill the antibiotic pipeline [3]. The genomics revolution has provided a wealth of sequence data for bacteria, allowing for the exploration and identification of potential new targets for antimicrobial development. With this information at hand, one can look at traditional antibacterial targets with new eyes or target bacterial virulence and block infection. The microbial glycome in particular, contains numerous attractive targets for antibiotic discovery [4]. Bacterial glycans and polysaccharides are involved in a myriad of biological processes, from structural (peptidoglycan) to host-pathogen interaction and virulence (lipopolysaccharides, teichoic acid), that could potentially serve as new targets for antibacterial drug development. In addition, many bacterial polysaccharides are assembled on polyisoprenyl-phosphates. As a result, inhibition of polyisoprene biosynthesis in bacteria could also be a promising route to antimicrobial development.

The bacterial cell wall, and in particular, peptidoglycan (PG) (Figure 1A), has served as the target of many of our traditional antibiotics (Table 1). To date, the most successful and currently available antibiotics that target PG, including the ß-lactams and vancomycin, focus on the highly-variable stem peptide. Use of both these classes of antibiotics is hampered clinically, due to a high degree of resistance. While there appears to be extensive chemical variation of the stem peptides [5,6], there is little variation in the chemical structure of the glycan chains in PG. It is this lack of variation in the glycan chain that makes it an attractive target for antimicrobial development. Both Gram-positive and Gram-negative bacteria produce a wide variety of enzymes that synthesize and degrade peptidoglycan [7]. By targeting enzymes that act on the highly conserved glycan backbone of PG, it may be possible to develop a new class of antibiotics that have a lower rate of resistance development. The idea of targeting enzymes that act on the glycan backbone is gaining favor, particularly in the creation of inhibitors that mimic the oxazoline intermediate of lytic transglycosylases (LTs) (Figure 1B), and the high molecular weight penicillin-binding proteins (HMW PBPs) involved in polymer extension [8-10]. The main challenge in this approach lies in the detailed biochemical characterization of these enzymes. The fact that these enzymes work on an insoluble heteropolymer, makes studies of protein-ligand binding and kinetic analysis difficult. In order to facilitate high-throughput screening (HTS) approaches to identifying inhibitors of LTs and HMW PBPs, the development of assays amenable to the constraints of HTS are required. Most of the literature regarding inhibition of these enzymes focuses on mimicking the proposed oxazoline intermediate,

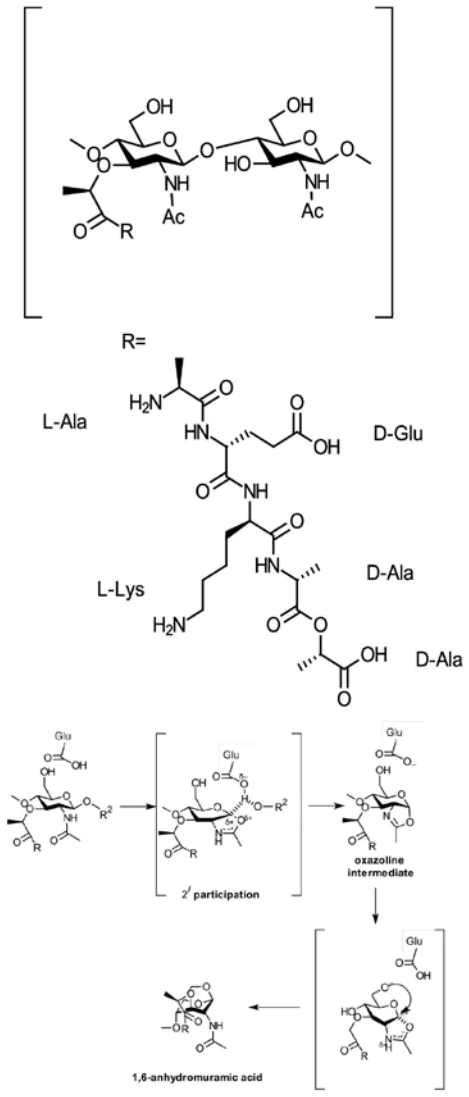

Figure1: (A) Structure of the peptidoglycan repeat unit composed of N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc) linked via a β-1,4 glycosidic linkage. Off of the C-3 lactyl moiety of MurNAc is attached a pentapeptide which is involved in cross-linking adjacent peptidoglycan strands. **(B)** Proposed mechanism of action of lytic transglycosylases.

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Antibiotic Class	Representative Compounds	Target-mode of action
β-Lactams	Penicillin Cephalosporin Monobactams carbapenems	Penicillin-binding proteins (PBPs)-inhibition of transpeptidation
Ribosomally made peptides	Lantibiotics (ex nisin) Defensins (ex plectasin)	Lipid II-pore formation Lipid II
Glycopeptides	Vancomycin Teicoplanin Telavancin Dalbavancin Oritavancin	Lipid II-(D-Ala-D-Ala)
Cyclic lipo(depsi-)peptides	Ramoplanin Katanosin B Bacitracin	Lipid II C_{55}-PP
Amino acid analogs	D-cycloserine Fosfomycin	DdlA MurA
Sugar substrate analogs	Tunicamycin moenomycin	MraY PBPs-inhibition of transglycosylation

Table1: Antibiotics inhibiting bacterial cell wall biosynthesis.

that stabilizes the oxocarbenium ion upon cleavage of the glycosidic bond (LTs), or transfer of the peptidoglycan repeat to a growing PG strand (HMW PBPs). With this approach, the main stumbling block to the creation of oxazoline-intermediate mimics of these enzymes lies with the preparation of adequate yields of muramyl-oxazoline analogs, for biological testing [11]. These obstacles could be overcome by the use of peptides to mimic the oxazoline intermediate [12,13], or by using the strategy of aglycone profiling to develop inhibitors that are specific to these proteins [14].

While targeting the enzymes involved in the polymerization and degradation of the glycan backbone is one avenue for new antimicrobial development, the biosynthesis of undecaprenyl phosphate (Und-P), the polyprenyl carrier for assembly of the PG repeat unit, is an untapped resource of antibiotic targets [15]. Currently, our list of antibiotics that target the lipid intermediate steps of peptidoglycan biosynthesis lies with the lantibiotics, glycopeptides and cyclic depsipeptides (Table 1). In all cases, inhibition is through interaction with undecaprenyl pyrophosphate (Und-PP) or lipid II. Polyisoprenols as membrane constituents and polyprenyl phosphates as preferred glycan carriers in biosynthetic processes are poorly understood [16]. A targetted lipidomics approach to unraveling the biosynthetic processes of this essential molecule, for the synthesis of many bacterial polysaccharides could yield a wealth of new antimicrobial targets. Unfortunately, the tools currently available for studying bacterial glycolipidomics are weak, as many of the analytical tools at disposal for eukaryotic glycolipidomics studies, are not amenable to bacteria.

Given these complications, the task to find new and effective antimicrobials before our current repertoire of clinically effective treatments is depleted, will be a challenging one. However, there is reason for optimism. Over the past decade, there has been a renaissance in bacterial cell wall biology with the identification of new targets and chemical entities [17]. Recent advances in the structural biology of many peptidoglycan biosynthetic [18] and degrading enzymes [19], and the development of screening assays for these enzymes [20] will form the foundation for new antimicrobial discovery.

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