23.1.3 Bacteria and the Need for New Drugs

Antibiotic resistance crept along ever since the wide and successful use of antibiotics. The WHO identified antibiotic resistance as one of the three greatest threats to human health.* Nosocomial (i.e., hospital-acquired) infections caused by multi- or pan-drug-resistant (Box 23.1) pathogens (e.g., *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa*) are of serious concern; so is the emergence of extensively drug-resistant *Mycobacterium tuberculosis* strains.

23.2 ANTIBIOTICS IN CLINIC

From 1938 to 2013, the FDA had approved 155 antibacterial new molecular entities, but less than 62% of them are used today (Figure 23.1). Most antibiotics introduced in the past 30 years are semi-synthetic or synthetic natural product derivatives of previously approved antibiotics.

Currently, all the approved antibiotic classes target one of the five essential bacterial processes (Figure 23.1). As the time between the introduction of a new antibiotic into the clinic to the time when resistance is first observed is getting alarmingly short, there is a dire need for new antibiotics.

Usable antibiotics act on targets that are either absent or differ significantly from their eukaryotic counterparts. While the direct effect of the drug–target interaction is known, the associated cellular response mechanisms that contribute to the death of bacterial cells is a subject of ongoing research.

23.3 ANTIBIOTICS AFFECTING BACTERIAL CELL WALL FORMATION

Most prokaryotic cells are surrounded by a cell wall, responsible for their shape and their ability to survive in hypotonic environments. $Gram^+$ bacteria are surrounded by a plasma membrane and a thick cell wall consisting of peptidoglycan to which teichoic acids (polyol phosphate polymers) are linked. $Gram^-$ bacteria have a much thinner cell wall and an outer membrane comprising lipid, lipopolysaccharide, and protein (Figure 23.2). Mycobacterial cell wall is unique, more complex, and a formidable barrier to antibiotics.

The bacterial cell wall is a good target because it is an essential component, structurally and functionally conserved across bacterial species, absent from humans (no adverse effects), and is readily accessible to exogenously added compounds. Many of the antibiotics targeting the cell wall act by inhibiting enzymes or sequestering the substrates involved in peptidoglycan assembly and crosslinking.

Peptidoglycan forms an extensive polymer, also called "murein sacculus" (Latin murus: wall) which surrounds the entire cell. Peptidoglycan is a polymer of alternating *N*-acetylglucosamine (GlcNAc) and *N*-acetylmuramic acid (MurNAc), crosslinked by a short peptide bridge. MurNAc is the 3-*O*-D-lactylether of *N*-acetylglucosamine. GlcNAc and MurNAc are linked by β-(1,4) glycosidic bonds and form a linear structure. The carboxyl group of MurNAc is linked to a short peptide which forms a bridge with another GlcNAc-MurNAc strand (Figure 23.3).

23.3.1 β-Lactam Antibiotics

This class of antibiotics is the biggest (in terms of FDA-approved members as well as market sales), safe, and time-tested as reflected by widespread use for almost seven decades. Members of this class share the common β-lactam (four-membered cyclic amide) ring structure (Table 23.1) which is the active pharmacophore. Their mode of action is indicated in Table 23.2.

* http://www.who.int/medicines/areas/priority_medicines/BP6_1AMR.pdf.