13.7 Other Approaches to Overcome Bacterial Resistance

The outer membrane is one of the main hurdles for antibiotics overcome to reach targets in Gram-negative bacteria. The hijacking the nutrient-import transporters is one of a possible route for overcoming the impenetrability of this cell wall. The bacterial iron transport system is often targeted by conjugating antibiotics to siderophores, small molecules that bacteria use to transport iron (Schalk 2018). Siderophore conjugated to an antibiotic should still be recognized by the mechanism of siderophore recognition, with a suitable linker being stable in the extracellular environment and allowing the intracellular release of the antibiotic by enzyme action (Figure 13.1g). The 3D structures of siderophore receptors that are available in the Protein Data Bank should be utilized to design conjugates that have siderophore recognition motif accessible, but the features of recognized by efflux pumps should be masked or designed out.

Furthermore, quorum sensing, a regulation mechanism in bacteria that allows coordination of population density, relies on release and accumulation of signaling molecules in the environment. These signaling molecules interact with their target protein, which depends on the type and strain of the bacteria. The interactions that occur within quorum-sensing communication are similar to ligand–receptor interactions, suggesting that anti-quorum-sensing, antibiofilm antibiotics could be designed using current standard pharmacologic principles (Raffa et al. 2005).

Such quorum-sensing inhibitors (QSIs) can effectively block QS and not only attenuate the virulence of *P. aeruginosa*, but it can also increase its susceptibility to both antibiotics and the immune system. Quorum-sensing receptor LasR (PDB entry: 2UV0) was considered as a target for an SVBS approach. A set of 3040 compounds were docked, resulting in a selection of 22 QSI candidates based on their docking scores and molecular masses. Five compounds were found to be able to inhibit QS-regulated gene expression in *P. aeruginosa* in a dose-dependent manner (Tan et al. 2013). Conversely to the structure-based approach, the search for an inhibitor of pqs quorum-sensing communication system characteristic for *P. aeruginosa* that controls virulence factor production and is involved in biofilm formation, an LBDD approach. A series of compounds targeting pqsR, the receptor of the pqs system, was designed by modifications of 2-heptyl-4-hydroxyquinoline. The testing of these compounds showed the reduction of virulence factor pyocyanin, but without reducing the viability of *P. aeruginosa*; therefore, they should not induce natural selection pressure and result in antibiotic resistance (Lu et al. 2012). These approaches can result in compounds that overcome the shortcomings of traditional antibiotics and may open new avenues for addressing the issue of antibiotic resistance (Kalia et al. 2019).

The impact of the infection can also be modulated by affecting the host signaling enzymes that are exploited by bacteria for their invasion, replication,