The antibiotics of tomorrow: from enzyme Lego blocks to customized enzybiotics

Antibiotics play a key role in the treatment of bacterial infections and have saved millions of lives since their invention. Moreover, they allowed the development of complex surgeries and cancer treatments. However, already in 1945, after receiving the Noble Prize of medicine for the discovery of penicillin, Sir Alexander Fleming warned for antimicrobial resistance development due to the misuse and overconsumption of antibiotics, both in health-care and in agricultural settings. To date, antimicrobial resistance is transformed from a rarity to an everyday occurring event that affects all layers of society. At this moment, one person per minute dies of the consequences of antimicrobial resistance. Moreover, several reports by various global institutes indicate severe human and economic losses if we fail in finding new treatments, the so-called post-antibiotic era, where even routine surgery will become challenging again.

A promising new approach that is explored by protein engineers is the use of enzyme-based antibiotics, also called enzybiotics. Specifically, they focus on the use of endolysins. These proteins are derived from bacteria-eating-viruses or bacteriophages. Endolysins function as molecular scissors that cut open the bacterial cell wall from within to release the bacteriophage progeny at the end of the lytic cycle. The intimate co-evolution between bacteriophages and bacteria over millions of years has resulted in highly active and specific endolysins in contrast to antibiotics that are mostly broad-spectrum and cause extensive collateral damage to natural microbiota.

Endolysins consist of different parts, modules, separated by a linker to ensure that both the modules function autonomously. Each module has a dedicated function; in the case of endolysins there is a part responsible for cell wall recognition and binding and another part for degradation of the cell wall. Such a module can be represented by a Lego building block. Remarkably, when protein engineers exchange the Lego building blocks of different endolysins, the engineered endolysins gain new functions: they become more soluble, work better in difficult environments, get a higher activity or different specificity, etc. In fact, protein engineers can now produce customized endolysins. This is what we call the modularity principle, we can design an endolysin with a certain function by exchanging modules of different endolysins.

The modularity principle can also be used to create functions that are new to nature, for example Artilysin®s. Here, a new module from another origin, specifically an outer membrane permeabilizing peptide, is added to an endolysin. This modification allows endolysins to cross the outer membrane of Gram-negative bacteria and to kill them, which is not possible with normal endolysins. The same principle has been used to engineer endolysins that they can bind to gauze to use them in wound dressings.

In a recent comparative study by Czaplewski and colleagues (Czaplewski et al., 2016, Lancet Infect Dis.), enzybiotics were rated as the most promising alternative class of antibacterials with

overall greatest clinical impact and technical feasibility. Indeed, the rapid mode-of-action and proteinaceous nature of endolysins and their derivatives differentiates them from any other class of antibiotics. They have recently entered (pre)clinical phases. Nevertheless, the first completely approved endolysin is not expected to reach the market before 2023.

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Publication

Synthetic biology of modular endolysins.
Gerstmans H, Criel B, Briers Y
Biotechnol Adv. 2018 May - Jun