

# Teixobactin: A powerful antibiotic from natural resource

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## ABSTRACT

Antibiotics have been introduced and employed as therapeutic agents against bacteria since 1930s. However, most bacterial strains resistant to a particular antibiotic have emerged a few years after its discovery. Therefore, after 1960s, new antibiotics have rarely been introduced. At present, drug resistance has become a major global concern urging many countries to conscientiously enforce antibiotics policies and regulations to control the drug resistance problems. In the midst of hopelessness about antibiotics, a new antibiotic from a soil bacterium, teixobactin, has recently been discovered and claimed not to produce drug resistance in bacteria. In this review, some interesting aspects of teixobactin are discussed including isolation method, structure, mechanism of action and challenges for further development. If the technical problems about teixobactin analogs synthesis and a huge clinical trials expense are solved, it might be a new magic bullet to fight with drug resistant bacteria.

*Key words* : Antibiotics, Drug resistance, Natural resource, Soil bacteria, Teixobactin

## Introduction

Bacteria are ubiquitous minuscule creatures on earth. Although they are notorious for their disease causing properties, many of them are harmless or even healthful. Some bacterial species have both pathogenic (disease causing) and nonpathogenic (harmless) strains. For example, *Escherichia coli* K12 naturally inhabits human and other warm-blooded mammals' guts and prevents the settlement of pathogenic bacteria in the guts (Hudault *et al.*, 2001) while *E. coli* O157:H7 causes severe, even lethal infection (Lim *et al.*, 2010). Some bacterial species are considered to be pathogens only when they are present at particular parts of the body. For example, *Staphylococcus aureus*, when present on healthy skin, is an indigenous bacterial species and does not cause infection. However, when *S. aureus* intestinal coloni-

zation occurs, it usually results in severe illness (Myles and Datta, 2012). Some bacterial species are strictly pathogenic, normally not found in the healthy body. *Mycobacterium tuberculosis* is an example of human pathogen causing a serious disease called tuberculosis (Delogu *et al.*, 2013). Infections causing by all kinds of pathogenic bacteria have been a global health problem for a long time. They negatively affect population welfare and also nation's economy. Antibiotics are the most common antibacterial agents used due to its effectiveness and availability. There have been a wide variety of antibiotics to choose for controlling an enormous number of bacterial infections. Some antibiotics are called bactericidal antibiotics as they kill or eradicate bacteria while the others are called bacteriostatic antibiotics because they just suppress the growth of bacteria and let the body's immunity do the rest of

the killing process. However, at present, antibiotics are almost defeated by bacteria due to the development and spread of antibiotic resistance. Most of them are less effective or even ineffective against drug resistant species. Therefore, health organizations around the world now try hard to cope with such problem. Currently, many countries have strengthened enforcement of antibiotics policies and regulations to control indiscriminate use and unrestricted access which plays an important role in the development of bacterial resistance.

### Rise and fall of antibiotic age

The use of antibiotics to fight bacteria was first reported in 1930s (Fig. 1) (Lee *et al.*, 2013). Prontosil, a sulfonamide, was the first commercially available antibiotic. It was synthesized by Bayer chemists Josef Klarer and Fritz Mietzsch and then tested for its antibacterial activity by Gerhard Domagk. It was released onto the pharmaceutical market in 1935 (Aminov *et al.*, 2010). Penicillin was considered to be the first natural antibiotic synthesized by a fungus *Penicillium chrysogenum*. Although it was first found in 1928 by Sir Alexander Fleming, it was introduced on sizable amount for therapeutic uses in 1942 (Aminov *et al.*, 2010) when the “golden age” of antibiotics was considered to begin and last until 1960s. The word “golden age” reflects prosperous time of the discovery of most antibiotics still used as therapeutic agents at present. The reason behind the popularity of antibiotics at that time is that they were believed to be magic bullets effectively kill spe-

cific pathogenic microorganisms. However, not long after each antibiotic was discovered, microorganisms resistant to the corresponding drug were emerged (Fig. 2) (Annunziato, 2019; Kaur, 2016). The development of antibiotic resistance has downgraded the effectiveness of bacterial infections treatment by antibiotics. The most common mechanisms which bacteria use to escape from the lethal effects of antibiotics are enzymatic degradation, target alteration, decreased uptake and overexpression of efflux pump proteins. The ongoing problems on drug resistance lead to the down side of new antibiotic discovery and development which is called the “innovation gap” or the “lean years” of antibiotic discovery (Davies and Davies, 2010). During this time newly emerged drug resistant bacteria were continuously increasing and outfought most available antibiotics. This gap lasts until the early 2000s when scientists come back for more attempt to find the new antibiotics to fight against drug resistant bacteria (Fig. 1). However, they have faced the same problem of antibiotic resistance. In the present day, alternative agents such as bacteriophages and herbs become candidates as antagonistic agents against drug resistant bacteria (Jassim and Limoges, 2014; Mundy *et al.*, 2016).

### Teixobactin: Isolation method

In the midst of hopelessness about antibiotics, a group of scientists at Northeastern University, Massachusetts, USA reported in 2015 a new antibiotic, teixobactin, claimed to kill pathogenic bacteria with-

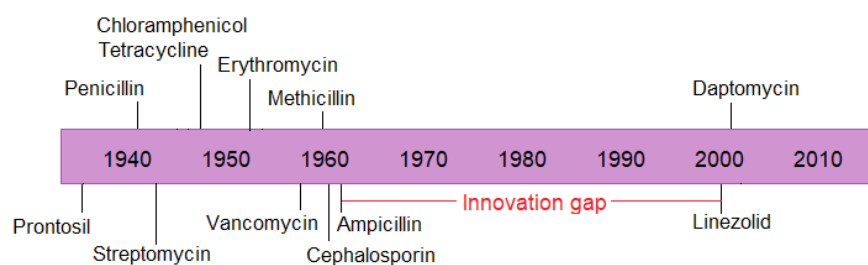


Fig. 1. Timeline of the availability of antibiotics

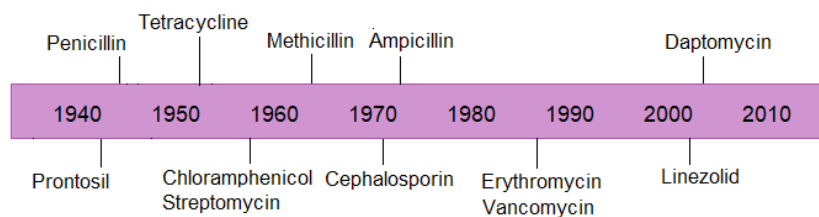


Fig. 2. Timelines of the emergence of antibiotic resistance

out detectable resistance (Ling *et al.*, 2015; Piddock, 2015). The result that they found is as interesting as the isolation method they used. They used a device called isolation chip or “iChip” that is an assembly of flat plates containing of multiple tiny wells (Fig. 3) (Nichols *et al.*, 2010; Sagar *et al.*, 2017). They used the device to culture bacteria isolated from soil samples in their natural environment instead of on petri dishes where only about 1% of bacteria in soil samples can be culturable. The iChip increases the survival rate of the bacteria up to 50% (Wright, 2015).

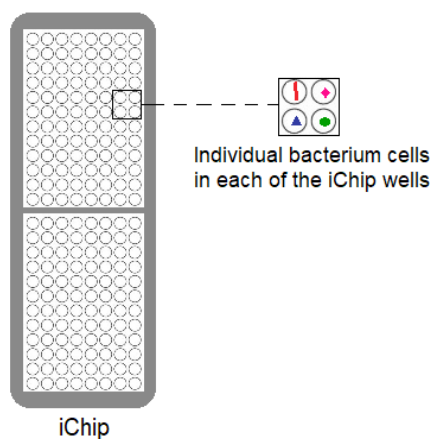


Fig. 3. Diagrammatic representation of the isolation of soil bacteria by iChip

The multi-channel device, called iChip, was initially developed to improve ability to isolate and cultivate bacteria in soil, one of the best resources of antibiotic producing bacteria. To isolate bacteria and cultivate bacteria which, in principle, are rarely cultivated on petri dishes, iChip was placed in a diluted soil sample to capture one bacterium or a few bacteria into one of the channels (wells) of iChip. The filled device was then wrapped in two semipermeable membranes, and was then placed back into the same environment sample where the bacteria are isolated. By this way, the bacteria had access to nutrient making it possible for them to grow in their natural environment in order to form a sufficiently large colony to make an *in vitro* culture possible. Theoretically, with this approach, about 50% of all soil bacteria can be isolated, while less than 1% would be isolated by using the traditional culturing methods (Ling *et al.*, 2015).

By using the iChip technique, more than 10,000 bacterial isolates were obtained. When they were

tested for their antimicrobial activity against *Staphylococcus aureus*, it was found that a gram negative bacterial strain, identified later as *Eleftheria terrae*, demonstrated exceptional antimicrobial activity (Ling *et al.*, 2015). Surprisingly, the genus *Eleftheria* has never been reported as a source of antibiotics before. The antibiotic produced by *E. terrae* was named as “teixobactin” after its ability to interfere with teichoic acid, an important component found within the cell wall of most gram positive bacteria.

#### Teixobactin: Structure and mechanism of action

Teixobactin, a newly discovered antibiotic, is a nonribosomal synthesized peptide produced by a gram negative bacteria *Eleftheria terrae*. It has a molecular mass of 1,242 daltons and consists of 11 amino acids with a lactone ring at the C-terminus. Among the amino acid components, there are 6 unusual (nonstandard) amino acids including D-phenylalanine, D-glutamine, D-isoleucine, D-threonine, methylated phenylalanine and L-*allo*-enduracididine (Fig. 4) (Rawal and Butani, 2016).

Teixobactin exerts bactericidal activity with cell lysis against its sensitive bacteria. Its mechanism of action is inhibition of bacterial cell wall synthesis by binding to lipid II and lipid III, a precursor of peptidoglycan and cell wall teichoic acid, respectively (Ling *et al.*, 2015). Since the target molecules of the drug do not exist in human and animals, it is harmless to these organisms. The synergistic inhibition of both peptidoglycan and teichoic acid biosynthesis of teixobactin makes it superior to other cell wall acting antibiotics such as beta lactams and vancomycin which inhibit only peptidoglycan biosynthesis. The drug not only kills MRSA (methicillin resistant *Staphylococcus aureus*), VISA (vancomycin intermediate *Staphylococcus aureus*) and *Mycobacterium tuberculosis in vitro* but also MRSA in mice. However, teixobactin is not active against gram negative bacteria because they have outer membrane to protect themselves from being attacked by the drug. Another interesting thing about teixobactin is that it produces no resistant mutant of *S. aureus* during the serial passage of the bacterium in the presence of sub-MIC levels of the drug over a period of 27 days (Ling *et al.*, 2015). The target molecules of teixobactin may play an important role for the difficulty to develop drug resistance. Lipids, targets of teixobactin, are more resistant to conformational changes or mutations than proteins, targets of most antibiotics, due to the fact that they are encoded by genes and

synthesized from genes that are vulnerable to mutations (Faron *et al.*, 2016; Shivaramaiah *et al.*, 2018). Furthermore, teixobactin simultaneously attacks two target sites, lipid II and lipid III, inside bacteria instead of one target site as other commonly used antibiotics do. Therefore, bacteria need to alter both target sites to become resistance to teixobactin. This may in part contribute to a very low rate of resistance development to teixobactin.

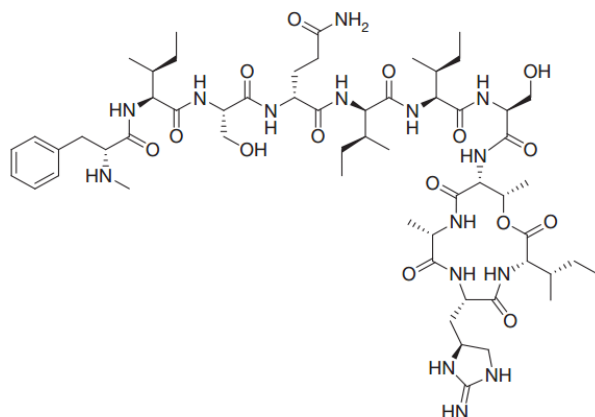


Fig. 4. Structure of teixobactin (Rawal and Butani, 2016)

Ability to inhibit drug resistant bacteria depends on several characteristics of teixobactin. It can inhibit MRSA because target sites of teixobactin and beta lactam (including methicillin) are different. Teixobactin acts on lipid II and lipid III while beta lactams acts on penicillin-binding protein 2 (PBP2) (Homma *et al.*, 2016). Upon the resistance development, MRSA strains reduce the affinity of PBP2 for beta lactams which has no effect on teixobactin inhibitory activity. For VISA strains, they develop thicker peptidoglycan layer to protect themselves from antibiotics. Vancomycin, capable of binding to mature peptidoglycan, is usually trapped in the VISA cell walls. In contrast teixobactin does not bind and hence is not antagonized by mature peptidoglycan. Therefore, it can inhibit VISA strains (Homma *et al.*, 2016).

### Challenges for future development

There are at least two major challenges associated with future development of teixobactin which are the synthesis of teixobactin analogs and the introduction of teixobactin into the market.

Currently, there is no ideal synthetic route for teixobactin analogs containing the unusual amino

acid *L*-allo-enduracididine which is not commercially available. This amino acid is essential for antimicrobial activity of teixobactin. The synthesis of such an unusual amino acid has many difficulties that can be a bottleneck in the development of teixobactin analogs (Jin *et al.*, 2016).

The biggest challenge to introduce teixobactin into the market deals with a huge expense. It is estimated that phase 2 and phase 3 trials of the drug can cost more than 50,000,000 US (McCarthy, 2019). This amount of money may limit the use of the drug although it is the most promising antibiotic. Without robust funding, it hardly to progress through the regulatory hurdles associated with FDA approval.

### Conclusion

Teixobactin is a novel promising antibiotic to inhibit gram positive bacteria and drug resistant bacteria including MRSA and VISA. However, it is too early to tell if teixobactin will be the new magic bullet to solve the drug resistance concern because it will take quite some times for mass production, clinical trials and marketing. If the technical problems in teixobactin analogs synthesis are solved and its clinical trials are funded, it will be commercially available a novel anti-drug resistant drug.

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