**Teixobactin, the first of a new class of antibiotics discovered by iChip technology**

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**Synopsis**

Teixobactin is a recently described antibiotic of a new class produced by a hitherto undescribed soil microorganism. It was isolated with a new tool, the iChip, that allowed the environmental bacterium to grow and for the antibiotic it produced to be isolated and subsequently identified. Teixobactin has activity for Gram-positive (but not Gram-negative) organisms and Mycobacteria and a novel mode of action inhibiting peptidoglycan biosynthesis. *In vitro* no teixobactin-resistant *Staphylococcus aureus* or *M. tuberculosis* were selected. In experimental infections of MRSA and *S. pneumoniae* in mice, teixobactin was effective at reducing the bacterial load. Whether teixobactin is developed into a new drug to treat infections in patients remains to be seen.

**Introduction**

There has been a great interest from scientists, doctors and the public about a new agent from a new class of natural product antibiotics, teixobactin, discovered by Ling *et al*.1 using a new technology, the iChip. Ling *et al.* were able to isolate teixobactin by using a new tool, the iChip,1 which was used to screen for compounds from antibiotic-producing soil microorganisms with activity for *S. aureus*. This not only yielded a new natural product but also allowed isolation of the unculturable microorganism. It is estimated that <1% of micro-organisms from soil are grown by conventional microbiological approaches,2 so the iChip offers a significant advance in sensitivity. The iChip is an assembly of plastic plates and membranes to capture environmental microorganisms that produce antimicrobial compounds. In essence, it comprises plastic plates, which contain hundreds of holes each forming a very small diffusion chamber. Each chamber allows the growth of only one microorganism. One plate is dipped in a dilution of an environmental sample, such as a soil suspension. This plate is clamped to membranes and a top and bottom plastic plate to allow growth of the producing microorganisms as well as diffusion of any antimicrobial compounds (see Figure 1 in reference 3). This method of screening will greatly facilitate the discovery of new antibiotics as it allows compounds to be isolated from environmental micro-organisms that do not grow under normal laboratory conditions. Although teixobactin has mostly anti-Gram positive activity, it is possible that other natural products isolated with the iChip will be active against Gram-negative bacteria.

**Teixobactin: Spectrum of activity, mode of action and development of resistance**

This new antibiotic is produced by a new species of β-proteobacteria provisionally named *Eleftheria terrae,* which belongs to a new genus related to *Aquabacteria*. The authors showed that teixobactin was able to kill representative strains of bacteria that cause wound and invasive infections such as *Staphylococcus aureus* including MRSA, those that cause pneumonia (*Streptococcus pneumoniae*) and *Mycobacterium tuberculosis*. It also showed good activity for *Clostridium difficile* and *Bacillus anthracis*. Teixobactin was also effective in single dose in significantly reducing bacterial numbers in experimental infections in a septacaemic protection mouse model of MRSA and in an immunocompetent lung infection model of *S. pneumoniae* in mice.

From the culture supernatant of *E. terrae* a partially purified active fraction was obtained and shown to contain a compound, teixobactin. It is an unusual depsipeptide containing enduracididine, methylphenylalanine and four D-amino acids. The biosynthetic pathway of teixobactin was identified by genome sequencing of *E. terrae* and homology searches.

Teixobactin has a different mode of action to other antibiotics currently used to treat bacterial infections in people (and animals). Ling *et al*. showed that teixobactin inhibits peptidoglycan biosynthesis in *S. aureus* by binding to a highly conserved motif of lipid II (a precursor of peptidoglycan) and lipid III (a precursor of teichoic acid). No teixobactin-resistant *S. aureus* or *M. tuberculosis* were isolated at four times the MIC. Furthermore, no resistant *S. aureus* were obtained after serial passage in sub-inhibitory concentrations of teixobactin. This led the authors to suggest that it will be difficult for bacteria that cause infections in people to become resistant to teixobactin. However, teixobactin is a natural product from a microorganism that lives in the soil. Many antibiotics have been discovered from the natural environment, and the microorganism that produces the antibiotic, and sometimes its close microbial neighbours, are resistant to the antibiotic.4-6 For the producing microorganism, resistance is essential otherwise production of its own antibiotic would cause the microorganism to kill itself. Likewise, close neighbour environmental microorganisms can be resistant so that they can survive in the same environment as the producing microorganism. ‘Natural’ antibiotic resistance genes can be transferred into pathogenic bacteria.7 Indeed, the gene encoding one of the most common mechanisms of antibiotic resistance, extended spectrum β-lactamases, was acquired from an environmental bacterium.8 This is the most likely route of any resistance, should it occur, to teixobactin. However, this could be a very rare occurrence because the bacterial strains that cause infection in people would need to have mixed with the teixobactin-resistant soil bacteria. Nonetheless, to be sure that resistance to teixobactin is unlikely to occur when used in human medicine, bacteria isolated from the same environmental niche as the teixobactin-producing organism should be screened for teixobactin-resistance conferring genes.

**Activity against Gram-negative bacteria**

According to the World Health Organization’s report in April 2014,9 one of the major global concerns of physicians is antibiotic resistance in Gram-negative bacteria such as *Escherichia coli* and *Klebsiella spp.*  The Gram-negative bacterial cell envelope structure makes it difficult for many antibiotics to gain entry into the bacterium and once inside many antibiotics are exported by multi-drug efflux pumps.10 Ling *et al*. showed that teixobactin had no activity for *E. coli¸* suggesting that *E. coli* are impermeable to this agent or it is effluxed (or both). Either way teixobactin does not inhibit *E. coli* and so is unlikely to be effective against other Gram-negative bacteria.

**Will teixobactin be developed into a new drug?**

For teixobactin (and any new compound with antimicrobial activity) to become a drug to treat infections in people, clinical trials will need to be carried out to make sure that the drug is safe, well tolerated and is efficacious in patients. To do this, teixobactin will need to be formulated so that the antibiotic remains active *in vivo* at clinically relevant sites of infection. Full toxicology tests will also need to be carried out to ensure that there are no adverse reactions or drug-drug interactions following administration of teixobactin. [NovoBiotic Pharmaceuticals](http://en.wikipedia.org/wiki/NovoBiotic_Pharmaceuticals) owns the novel chemical entities produced by the iChip and it has been stated that the hope is that teixobactin will be ready for a clinical trial in 2017. Whether it will be fully developed as a new drug remains to be seen, not least because it is questionable whether more drugs against Gram-positive bacteria are required. However, as teixobactin is active against *M. tuberculosis*, it could offer the opportunity for a new treatment for patients with tuberculosis. Teixobactin may also fulfil the requirements for approval by the FDA under the qualified infectious disease product (QIDP) framework as envisaged in the USA Generating Antibiotic Incentives Now (GAIN) Act so it could be licensed quickly. Even if teixobactin itself cannot be turned into a new drug, it is probably the first of a series of new antibiotics in its class.

**Transparency Declaration**

The authors declare no conflict of interest.

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