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# Teixobactin: A Novel Antibiotic in 30 Years and the Key to Beat Resistance

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**Abstract**
*Teixobactin, is first new type of antibiotic in 30 years with properties that minimise development of bacterial resistance. It is discovered by scientist from Northeastern University and Novobiotic Pharmaceuticals by isolating it with the help of iChip technology. Unlike other antibiotics which act on protein targets and develop resistance, it acts on unique target in cell wall synthesis and so there is lack of resistance. It is active against MRSA, M. tb and many other superbugs. It is undergoing preclinical studies and clinical trials will take several years before the drug reaches the pharmacy shelves.*
**Key words:** *Teixobactin, iChip, Eleftheria terrae.*

## 1. INTRODUCTION

Teixobactin is the new type of antibiotic to be discovered first in nearly 30 years. The discovery carries more significance especially, where antibiotic resistance has garnered headlines in recent years.

Producing new antibiotics in the 21st century has been a daunting task, the reason being poor economic return on investment of antibiotics,[1] so pharmaceutical companies have instead turned their attention to the far more profitable ventures of drugs for chronic diseases, like diabetes or heart disease.

Yet as antibiotics have been overused by healthcare workers (often at the demand of patients), sold over-the-counter in many countries, and wasted by agricultural misuse (due to some farmers who are engaged in intensive farming methods gave antibiotics to their animals in order to boost the meat quantity), we have seen their efficacy diminish and thus antibiotic resistance accelerated.

Globally, deaths due to antibiotic resistance are estimated at 700,000/year. The studies estimate that300 million people are expected to die prematurely because of drug resistance over the next 35 years and the world's GDP will be 2 to 3.5% lower than it otherwise would be in 2050. This means that between now and 2050 the world can expect to lose between 60 and 100 trillion USD worth of economic output if antimicrobial drug resistance is not tackled. [2]

A ray of light was brought by team of scientists led by Kim Lewis from Northeastern University and Novobiotic Pharmaceuticalswho produced this new antibiotic, teixobactin, by a new species of soil-dwelling gram negative β-proteobacteria provisionally named Eleftheriaterrae, which belongs to a new genus related to Aquabacteria, by using iChip technology, with properties that minimize the development of bacterial resistance. Teixobactin is a cyclic depsipeptide containing an unusual amino acid enduracidine, methylphenylalanine, and four D-amino acids.[3]

## 2. MECHANISM OF ACTION AND RESISTANCE OF TEIXOBACTIN

It acts on unique targets in the cell wall synthesis pathway. It binds to a highly conserved non-peptide motiff of peptidoglycan precursor (lipid II) and teichoic acid precursor(lipid III), resulting in inhibition of cell wall synthesis and subsequent

lysis. It has shown to be potent in vitro against a wide range of gram positive bacteria (Table 1), including multidrug resistant organisms such as Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin intermediate S. aureus (VISA), Vancomycin- resistant enterococci(VRE), Clostridium difficile, Streptococcus pneumonia, Bacillus anthracis and Mycobacterium tuberculosis.[3]

Unlike other cell wall inhibitor antibiotics, it does not act on protein targets which may readily develop mutational resistance on continued exposure. In fact, the absence of resistant mutants of Staphylococcus aureus and M. tuberculosis after prolonged exposure of teixobactin in sub lethal concentrationfor as long as 27 days in the case of the formerhave generated immense interest on its development and introduction for clinical use.[3,4]

In vivo studies in the mouse corroborated the activity of teixobactin against methicillin resistant S. aureus and Streptococcus pneumonia, and even after multiple rigorous attempts, the authors could not select teixobactin resistant mutants of S. aureus or M. tuberculosis. [3]

**Table 1** | Activity of teixobactin against pathogenic microorganisms[3]

| Organism and genotype | Teixobactin MIC (μg/ml) |
|---|---|
| S. aureus (MSSA) | 0.25 |
| S. aureus + 10% serum | 0.25 |
| S. aureus (MRSA) | 0.25 |
| Enterococcus faecalis (VRE) | 0.5 |
| Enterococcus faecium (VRE) | 0.5 |
| Streptococcus pneumoniae (penicillin$^R$) | ≤0.03 |
| Streptococcus pyogenes | 0.06 |
| Streptococcus agalactiae | 0.12 |
| Viridans group streptococci | 0.12 |
| B. anthracis | ≤ 0.06 |
| Clostridium difficile | 0.005 |
| Propionibacterium acnes | 0.08 |
| M. tuberculosis H37Rv | 0.125 |
| Haemophilus influenza | 4 |
| Moraxella catarrhalis | 2 |
| Escherichia coli | 25 |
| Escherichia coli (asmB1) | 2.5 |
| Pseudomonas aeruginosa | >32 |
| Klebsiella pneumonia | >32 |

The MIC (Minimal inhibitory concentration) was determined by broth microdilution. MSSA, methicillin-sensitive S. aureus; VRE, vancomycin-resistant enterococci.

### 3. MULTICHANNEL DEVICE iChip

99% of bacteria cannot be grown in normal laboratory conditions, this greatly limits the number of these compounds that we can investigate. Ling et al. were able to isolate teixobactinby screening previously unculturable bacteria present in a sample of soil from "a grassy field in Maine[5], using the iChip (isolation chip).[6]iChip (Fig 1) uses an assembly of three (central, top and bottom) flat hydrophobic plastic polyoxymethylene plates containing multiple through holes and polycarbonate membranes to compose an array of miniature diffusion chambers and each chamber allows growth of only one microorganism. [6] The central plate is dipped in a dilution of an environmental sample, such as a soil suspension. This plate is clampedto membranes and top and bottom plastic platesto allow growth of producing microorganisms as well as diffusion of any antimicrobial compounds.The growth recovery by this method approaches 50%, as compared to 1% of cells from soil that will grow on a nutrient Petri dish.This novel method of screening will greatly facilitate the discovery of new antibiotics as it allows compounds to be isolated from environmental microorganisms that do not grow under normal laboratory conditions and the discovery of teixobactin could be considered as its first success. [3] "Novo Biotic has since assembled about 50,000 strains of uncultured bacteria and discovered 25 new antibiotics, of which teixobactin is the latest and most interesting," said Prof Lewis, who is the senior author of the paper published in the journal Nature.

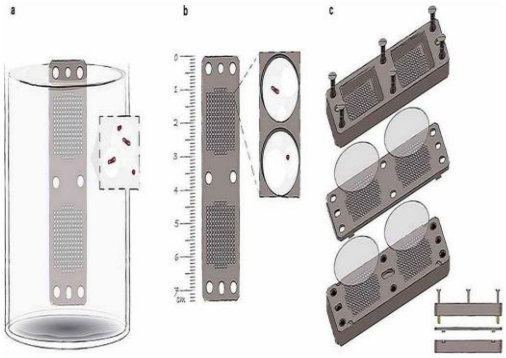

**Figure 1:** The iChip. a–c, The iChip (a) consists of a central plate (b) which houses growing microorganisms, semi-permeable membranes on each side of the plate, which separate the plate from the environment, and two supporting top and bottom plates. (c) The central plate and side plates have multiple matching through-holes. When the central plate is dipped into suspension of cells in molten agar, the through-holes capture small volumes of this suspension, which solidify in the form of small agar plugs. Alternatively, molten agar can be dispensed into the chambers. The membranes are attached and the iChip is then placed in soil from which the sample originated.

## 4. LIMITATIONS OF TEIXOBACTIN

However, there are certain limitations of teixobactin. There is an issue regarding spectrum of activity. It has shown potent activity only against gram positive bacteria. There is no activity against gram negative bacteria like pseudomonas or Kliebsiella because teixobactin is not effective against them as it is extracted from a type of gram negative bacterium (Eleftheriaterrae). The antibiotic cannot naturally be effective against gram-negative microorganisms; otherwise the bacterium would inhibit its own growth through extruding the antibiotic chemical. Ling et al. showed that teixobactin had no activity against E. coli, suggesting that E. coli is impermeable to teixobactin or it is effluxed (or both) and so it is unlikely to be effective against other Gram negative bacteria. [3]

Secondly, history has taught us that lack of resistance to teixobactin in vitro should be viewed with great caution. Similar claims were made about vancomycin, because it targeted an essential component of bacterial cell walls thought to be irreplaceable. However, after large- scale use of vancomycinbegan in 1980s, resistance emerged though it took 30 years. [3]So it is possible that such resistance genes are already present in nature or that mutational resistance will arise in vivo after prolonged use of teixobactin.[7]

Third, teixobactin is yet to be formulated so that the antibiotic remains active in vivo at clinically relevant sites of infection and is long way from human clinical trials to make sure that the drug is safe, well tolerated and efficacious in patients. Clinical trial will take several years, so even if the drug passes all the required tests, it still will not be available for five or six years.

Additionally, the research in mice was carried out using intravenous injection of the compound, and it seems likely that in humans, too, the antibiotic would have to be injected rather than taken as an oral tablet.[8]

## 5. CONCLUSION

Isolation of teixobactin from soil using iChip technology has not only led to development of new antibiotic but has also provided a new technology to explore useful molecules from microbial kingdom in soil. Human clinical trials of teixobactin are predicted to be few more years away. Even if teixobactin cannot be turned into a new drug, it has raised hopes of newer discoveries to tackle the problem of growing antibiotic resistance. As Ed Yong puts it, “Teixobactin is a fish; the iChip is the rod. Having the rod guarantees that we’ll get more fish – and we desperately need more.”

## REFERENCES

1. Boucher HW, Talbot GH, Benjamin DK Jr, et al. Progress- development of new drugs active against gram-negative bacilli; an update from the Infectious Diseases Society of America. Clin Infect Dis. 2013; 56: 1685-94.

2. O'Neill, J, chair. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance. 2014 Dec. [last assessed on 2016 Feb. 9]
3. Available from: http://www.jpiamr.eu/wp-content/uploads/2014/12/AMR-Review-Paper-Tackling-a-crisis-for-the-health-and-wealth-of-nations_1-2.pdf
4. Ling LL, Schneider T, Peoples AJ, Spoering AL, Conlon BP, et al. A new antibiotic kills pathogens without detectable resistance. Nature. 2015; 517 (7535): 455-59.
5. Wright G. Antibiotics: An irresistible newcomer. Nature 2015; 517 (7535): 442-44.
6. Denise, Grady (7 January 2015). "From a pile of dirt, hope for a powerful new antibiotic". The New York Times. 2015 Jan. 7. [last assessed on 2016 Feb. 9]
7. Available from:http://www.nytimes.com/2015/01/08/health/from-a-pile-of-dirt-hope-for-a-powerful-new-antibiotic.html
8. Nichols D, Cahoon N, Trakhtenberg EM, Pham L, Mehta A, Belanger A, Kanigan T, Lewis K, Epstein SS (2010). "Use of ichip for high-throughput in situ cultivation of "uncultivable" microbial species". Appl. Environ. Microbiol. 76 (8): 2445–50.
9. Teixobactin. 2015 Jan.[last assessed on 2016 Feb. 9] Available from: https://en.wikipedia.org/wiki/Teixobactin.
10. Lauren F Friedman, Reuters. Ingenious' Antibiotic Discovery 'Challenges Long-Held Scientific Beliefs.2015 Jan. [last assessed on 2016 Feb. 9]. Available from: http://www.businessinsider.in/Ingenious-Antibiotic-Discovery-Challenges-Long-Held-Scientific-Beliefs/articleshow/45802663.cms.