**Defeating Antibiotic Resistance**

Author: Bailey Brown
Major: Microbiology/ Cell and Molecular Biology
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

**Key Words:**

Antibiotic resistance, Teixobactin, treatment, infection

**The misuse of antibiotics has led to one of the largest health care crises that we face today. Scientist such as Losee L. Ling, Tonja Scneider, and colleagues are working to find a solution to this scare. In order to find a solution, knowledge on why antibiotics are becoming resistant is crucial. Scientists have conducted experiments that study the mechanisms of action of the antibiotics and how bacteria become resistant to them. A recent breakthrough of the synthetic antibiotic, known as Teixobactin, has shown great success and is unlikely to experience resistance. Teixobactin inhibits cell wall synthesis by targeting lipid II and lipid III in Gram-positive bacteria but has also shown success in targeting an unknown area in Gram-negative bacteria.**

**Introduction**

Antibiotic resistance is growing faster than the creation of new antibiotics. For as long as antibiotic resistance exists, there will be a demand for new antibiotics. In the United States, it is reported that over 2 million people are infected with an antibiotic resistant bacteria, leading to 23,000 deaths reported.2 The mechanisms for how antibiotic resistance occurs are still being described, but some of the common forms, other than intrinsic resistance, are from gene mutations and horizontal gene transfers.2 Intrinsic resistance is due to the absence of a specific target that an antibiotic is meant for in a specific species. Some common antibiotics that are known to have intrinsic resistance are being researched to look at the specific genes that are responsible for this.2 The four common mechanisms that antibiotics work are inhibition of cell wall synthesis, protein synthesis, DNA synthesis, and antimetabolite.

**Past Research**

To better understand how bacteria become resistant, Timothy J. Opperman and Son T. Nguyen researched the resistance in Gram-negative bacteria in 2015. They claim that antibiotic resistance in Gram-negative bacteria is caused by the overexpression of Resistance-Nodulation-Division-type efflux pumps (RND).3 The RND pump is responsible for pumping antibiotics and biocides to the outside of the cell, therefore they hypothesize the following: “Because of the broad-substrate specificity, overexpression of the RND efflux pumps results in decreased susceptibility to diverse array of antibacterial agents and biocides.”3 To conquer this, they believe they can utilize efflux pump inhibitors to counteract the overexpression of Resistance-Nodulation-Division-type efflux pumps. This would increase the potency of the existing antibiotics and lower antibiotic resistance.3

In 2014, Losee L. Ling was also apart of another research team before the Teixobactin project, working with Ekaterina Gavrish, Clarissa S. Sit, and others where they grew uncultured organisms by the use of the iChip that will be discussed later, which led to the discovery of Lassomycin. Lassomycin was found to kill drug-resistant forms of *M. tuberculosis*.4 They show that “Lassomycin binds to a highly acidic region of the ClpC1 ATPase complex and markedly stimulates its ATPase activity without stimulating ClpP1P2-catalyzed protein breakdown, which is essential for viability of mycobacteria.”4 With this breakthrough, it is now apparent how important it is to explore uncultured bacteria, which leads to the Teixobactin project.

**Recent Progress**

Although the importance of growing uncultured bacteria is known, approximately 99% of all species are actually unable to be grown in laboratories outside of their natural environment. But, while antibiotic resistance is on the rise, there is hope for the creation of new antibiotics from uncultured bacteria, such as Lassomycin, with the help of the iChip.1 The iChip is used to create another new antibiotic, known as Teixobactin, by artificially growing it from uncultured bacteria. Because many species are unable to be grown outside their natural environment, the iChip keeps bacteria in their environmental conditions by mimicry, also know as “in situ”, or by using specific growth factors.1 The iChip isolated colonies and were then antimicrobial screened on plates overlaid with *S. aureus*. After testing the effectiveness of Teixobactin on numerous species, it was found extremely effective on Gram-positive bacteria, and was even treating bacteria that were antibiotic resistant and/or difficult to treat. Naming a few that were successful were *M. tuberculosis,* *Clostridium difficile*, which infects over 200,000 people a year, *Bacillus anthracis*, and *S. aureus*. Although Teixobactin is extremely effective in Gram-positive bacteria, success in Gram-negative bacteria was not as frequent.1

Because Teixobactin is not effective on all bacterial infections, it was examined in order to determine what was successful and what specific cell components Teixobactin targeted.1 Teixobactin was found to inhibit the synthesis of peptidoglycan, but had little to no effect on label incorporation into DNA, RNA, and protein. This does not necessarily mean it is a bad thing. Because it does not target a protein, it actually makes this a long lasting antibiotic breakthrough because it won’t develop resistance.1

With this anti-resistant antibiotic breakthrough, Teixobactin was found to exhibit similar qualities as the antibiotic vancomycin.1 To test whether it was more effective than vancomycin, vancomycin resistant bacteria were incubated with the Teixobactin and the results were shocking. As anticipated, the Teixobactin was an effective form of treatment, so to speak, and growth was susceptible.1 Therefore, Teixobactin was able to bind the previously modified forms of lipid II that were making vancomycin ineffective.1

Further research indicated Teixobactin inhibits cell wall synthesis by binding to lipid II and lipid III.1 Because lipid II is a precursor of peptidoglycan, which is found only in Gram-positive bacteria, this is why Teixobactin is such an effective antibiotic.1 Lipid III is a precursor of teichoic acid, which is also only found in Gram-positive cell walls. Therefor targeting lipid III is another reason for its effectiveness.

With the success in the lab after testing the inhibition of Teixobactin on lipid II and lipid III, mice were then tested on to explore the idea of using it as a therapeutic.1 They were injected with a serum of Teixobactin and the results were great because the “compound retained its potency in the presence of serum, was stable, and had good microsomal stability and low toxicity”.1 They were also infected with *S. pneumoniae* and after being treated with Teixobactin and the colonies were reduced the lungs.1

**Discussion**

The newly discovered uncultured bacteria that were discussed in this paper are possibly the start to the end of antibiotic resistance. Defeating antibiotic resistance is extremely important and the iChip can be the solution for growing the 99% of bacteria that has not been able to be grown for all these years. Because the iChip has been used to grow two difficult bacteria and were later discovered to be efficient antibiotics, further cultivation of bacteria should proceed. To further research Teixobactin after it has been tested on mice, Teixobactin still needs more testing before being administered to humans in order to test possible side effects and ensure safety. Although the new antibiotic was found to target specific areas in bacteria that inhibit growth, it does not explain why it is effective in Gram-negative bacteria.1 Gram-negative cell walls consist of a very thin peptidoglycan layer but do not consist of teichoic acid. Because it is not clearly understood how Gram-negative cells are inhibited, they need to have more testing done.

**References**

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