ACIN
ASOCIACIÓN COLOMBIANA DE INFECTOLOGÍA

infectio

REVISIÓN

New antibiotics against bacterial resistance

Lorena Liseth Cárdenas[1], Maritza Angarita Merchán[1], Diana Paola López[1,*]

Abstract

The evolution of bacterial resistance is generating a serious public health problem due to the indiscriminate use of antibiotics, the application of non-optimal doses, the irregularity in the taking of medicines sent by the health professional, factors that have affected the increase in the rate of antimicrobial resistance; It is important to generate strategies that contribute to diminishing it, including the rational use of antibiotics and the constant research of new therapeutic alternatives such as teixobactin, which is a product of the Gram negative bacterium called *Eleftheria terrae,* related to the genus *Aquabacterium*, is a microorganism that presents extremophile conditions, for which, a multichannel system of semipermeable membranes called Ichip was developed for its isolation. Eravacycline is a new fully synthetic bacteriostatic antibiotic of the tetracycline family, is a potent inhibitor based on the mechanism of the bacterial ribosome and exerts potent activity against a broad spectrum of susceptible and multiresistant bacteria.

Keywords: teixobactin, eravacycline, tetracycline, bacterial resistance, lipid II, *Eleftheria Terrae*, Ichip.

Nuevos antibióticos contra la resistencia bacteriana

Resumen

La evolución de la resistencia bacteriana ha generado un serio problema de salud pública debido al uso indiscriminado antibioticos, la aplicación de dosis no óptimas, la irregularidad en la toma de medicinas prescritas por el profesional de la salud han llevado a un aumento en la tasa de resistencia antimicrobiana; por ello es importante generar estrategias que contribuyan a disminuirla incluyendo el uso racional de anitibioticos y la búsqueda constante de nuevos antibioticos. La teixobactina es un producto de bacterias gram negativas llamadas *Eleftheria terrae*, relacionadas con el género *Aquabacterium*, el cual es un microorganismo que presenta condiciones extremofilas. Para el aislamiento de este nuevo compuesto se utilizó un sistema multicanal de membranas semipepermeables llamadas Ichip. Eravaciclina es un nuevo antibiotico síntetico bacteriostatico de la familia de las tetraciclinas y es un potente inhibidor de la maquinaria ribosomal bacteriana, con una potente actividad contra un amplio espectro de bacterias multirresistentes.

Keywords: teixobactina, eravacyclina, tetracyclina, resistencia bacteriana, lipid II, *Eleftheria Terrae*, Ichip.

Introduction

Currently, pharmaceutical industries are lacking therapeutic alternatives against pathogenic bacteria, due to multiresistance mechanisms developed by these ones against the different commercialized antibiotics[1]. In the last decade, several key organizations, as the Infectious Diseases Society of America (IDSA), Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the World Economic Forum (WEF), have made of the antibiotic resistance the focal point of the reports, by conferences to accelerate the restriction and control activity faced with antimicrobials[2]. Bacterial resistance evolution is generating a serious problem in public health[3], as a result of the indiscriminate use of antibiotics, the application of non-optimal doses, the irregularity in medication taking referred by the professional in health, these are factors that have influenced in the antimicrobial resistance rate rising[4]; being relevant to generate strategies that contribute to decrease it, including the rational use of antibiotics[5]. That is why it has been necessary constant researches and the perseverant development of new therapeutic alternatives[6]. Approximately five years ago, professor Kim Lewis from Northeastern University in Boston, directs the research that discovered a new natural antibiotic extracted from the ground called teixobactin; this research has been developed together with NovoBiotic Pharmaceuticals, which headquarters are located in Cambridge, Massachusetts and are the owners of the patent[7]. The objective of this review is to describe new antibiotics generated as therapeutic alternatives faced with the bacterial resistance emergence, their obtaining methods and actions mechanisms.

1 Grupo de Investigación de Bacteriología y Laboratorio Clínico (GRIBAC). Facultad Ciencias de la Salud
* Autor para correspondencia.
Correo electrónico: dplopez@uniboyaca.edu.co

Recibido: 26/11/2018; Aceptado: 10/02/2019

Cómo citar este artículo: L.L. Cárdenas, *et al*. New antibiotics against bacterial resistance. Infectio 2019; 23(4): 382-387
http://dx.doi.org/10.22354/in.v23i4.807

Materials and methods

It was made a bibliographic search on data bases as Science Direct, Redalyc, Google Scholar, NCBI, Pubmed, Pro-quest, Dialnet, Lilacs and Toxnet; they were used the next key words teixobactin, eravacycline, tetracycline, bacterial resistance, lipid II, *Eleftheria Terrae*, Ichip validated in MeSH. It was established for the search of thirteen combinations, finding a total of 70 articles. They were selected original and revision articles published from 2012 to 2018 available in Spanish, English and Portuguese.

Results

Teixobactin

Teixobactin is a depsipeptide that consists of eleven residues of amino acids (aa), including seven L-aa residues and four D-aa ones, among them it is found an inusual L-*allo*-enduracididine (L-*allo*-End), which is part of the C-terminal tetrapeptide lactone substructure formed by an ester bond between D-Thr8 and L-Ile11. (Figure 1)[8]. This is a product of a Gram negative bacterium called *Eleftheria terrae,* which belongs to the proteobacteria group (betaproteobacteria), related to *Aquabacterium* gender[9], from this bacterium, it has been isolated a compound called teixobactin with a molecular weight of 1.242 Daltons, which biosynthetic route is made up of two genes *txo1* y *txo2*[10]; the technique used to discovered it, entails a higher impact that i sable to originate a new encouraging era in the discovery of new natural antibiotics[11], because of the description of its action mechanism in the organism which possibly avoids the creation and expression of any kind of bacterial resistance[12].

Technology for microorganisms obtaining: IChip Method

The microorganisms are cultivated in a laboratory where it is analyzed its pathogenicity, its capacity of producing antibiotics and its evolution, through the control of growth conditions, taking into account those necessary for an optimal development and proliferation[13], however; approximately 99% of the bacteria is not able to be cultivated in the laboratory due to extract growth demands[14].

Eleftheria terrae is a microorganism that presents extremophile conditions, faced with this, it was developed a semipermeable plastic membrane system called IChip (isolation chip) (Figure 2), which creates an analogous natural environment of bacteria and fungi[15], allowing the growth in its "natural environment" by simulating their environment in the laboratory. IChip is able to cultivate organisms from soil, sea water, saliva, marshes, and sewage water bioreactors[16].

This multichannel device with 192 compartments is used for an initial microorganisms isolation followed by stimulating the proliferation of bacteria which present a difficult growth in the laboratory[17]; from a soil sample collected in the state of Maine (U.S.A.) it was found an ecosystem composed by all kind of microorganisms (bacteria, fungi, protozoans), this consists on a central dish (a), which is home to growing microorganisms in their semipermeable membranes in each side of the dish which are separated from the environment and two lateral support panels (b) the central dish and the lateral panels possesses multiple holes (c), when the dish is immersed in cells suspension in molten agar, the holes capture small volumes which get solidified forming small agar plugs, then the membranes join together and the I chip is placed on the soil where the strain came from[18].

By means of this technique, they were isolated about 10.000 bacterial strains from the soil, for this, they were prepared agar extracts and nutrients in order to identify which presented antibiotic activity, discovering in this way, a gram negative bacterium called *Eleftheria terrae,* which produced a substance that

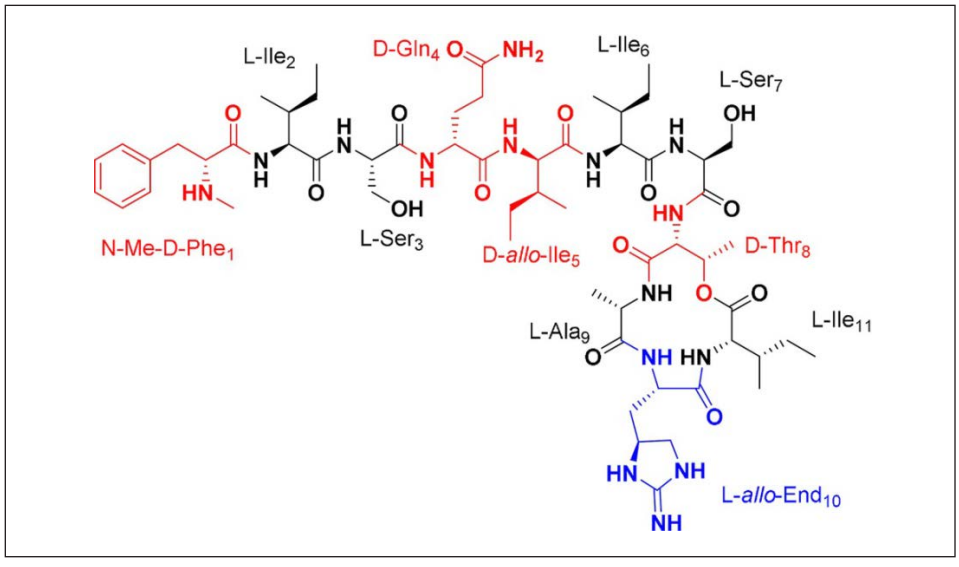

Figure 1. Teixobactin Chemical Structure.
Source: Guo C, Mandalapu D, Ji X, Gao J, Zhang Q. Chemistry and Biology of Teixobactin. Chem - A Eur J. 2018; 24 (21):5406–22.

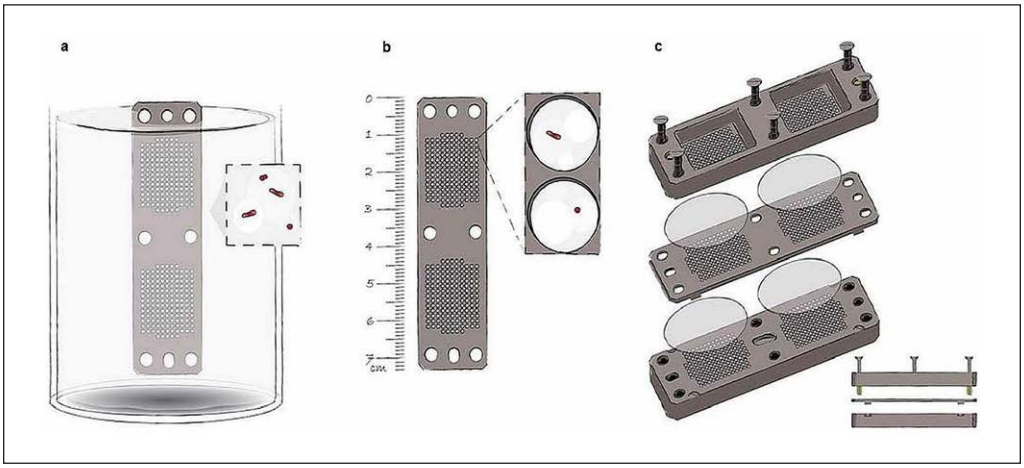

Figure 2. I chip
Source: Losee L. Ling, Tanja Schneider. Kim Lewis. A new antibiotic kills pathogens without detectable resistance. Nature. 2015

inhibited *Staphylococcus aureus* growth[19]; after several tests, they observed that this technique also worked successfully for *Mycobacterium tuberculosis* and *Clostridium difficile*[20].

Teixobactin action mechanism

Teixobactin exerts its bactericide effects joining to two bacterial polymers precursors from the cell wall: lipid II (peptidoglycan) and lipid III (teichoic acid)[21]. (Figure 3)

Peptidoglycan is essential to conform the bacterial cell wall structure, teichoic acid has net negative charge, affixing cations that bring rigidity to the cell wall structure[22]; this attraction to those lipids explains the efficacy of the compound faced with Gram positive bacteria[23]. Teixobactin Works differently to other antibiotics when attacking not only lipids, but also cell walls[24], lysing them quickly, stopping in this way the development of resistance mechanisms to this compound[25]; literature mentions that when inoculating mice with teixobactin, which were infected with *Staphylococcus aureus* or *Streptococcus pneumoniae,* their infection gets reduced without any toxicity[26].

Teixobactin is ineffective against Gram negative bacteria, since the cell wall composition in its external membrane contains phospholipids and polysaccharides that block the Access of lipid II[27], besides these bacteria lack techoic acids, main components in order to make the antibiotic exerts its bactericide action[28].

Lewis determined the activity of teixobactin by means of methicilin resistant *Staphylococcus aureus* (MRSA)[29], deducting that it had an excellent bactericide activity faced with this microorganism, which is superior to vancomycin in the destruction of populations in exponential phase and kept the bactericide activity against intermediate resistance, as it is shown in the figure 4.

Eravacycline

Eravacycline is a new bacteriostatic antibiotic entirely synthetic belonging to tetracycline family[30], the compound has exposed a powerful activity against a wide spectrum of sensitive and multiresistant bacteria[31], in its activity spectrum they

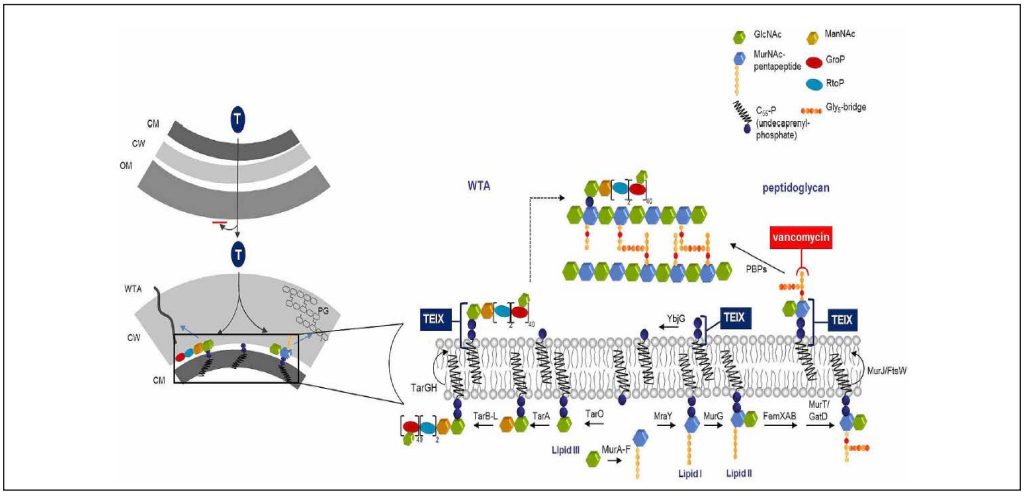

Figura 3. Teixobactin action mechanism model
Fuente: Losee L. Ling, Tanja Schneider. Kim Lewis. A new antibiotic kills pathogens without detectable resistance. Nature. 2015

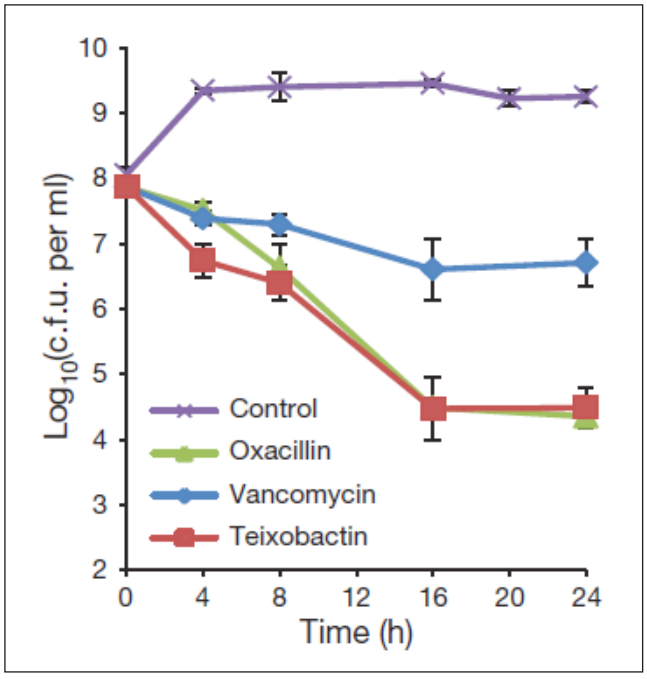

Figure 4. Destruction of pathogenes depending on the time for teixobactin
Source: Losee L. Ling, Tanja Schneider. Kim Lewis. A new antibiotic kills pathogens without detectable resistance. Nature. 2015; 517. 456

are found Gram positive bacteria as *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus anginosus*; and Gram negative bacteria as *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae* and anaerobic bacteria *Clostridium perfringens*, *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Parabacteroides distasonis*[32].

Technology for the obtention of Eravacycline

As other members of tetracycline family, it has been demonstrated that eravacycline is a powerful inhibitor based on the bacterial ribosome mechanism[33]; it has modifications in the positions C-7 (fluoride) and C-9 2- (pyrrolidine-1-yl) ethanamide in the tetracycline nucleus which were possible by the use of an entirely synthetic route[34]. (Figure 5)

Two additional experiments were made to the third generation tetracycline molecule, with C9 substitutions in ring D and as a result it is obtained the eravacycline molecule, it was shown a wide spectrum activity against sensitive bacterial strains resistant to tetracycline[36]; the studies with radiolabelled tetracycline indicate that Eravacycline has a merger ten times higher for the ribosome tan for tetracycline, and inhibits *in vitro* translation to concentrations four times lower than tetracycline[37].

Eravacycline action mechanism

As other tetracyclines, they inhibit the elongation phase of the proteins synthesis joining together to the 30S ribosomal subunit of bacteria specifically 16S rRNA and blocking the merger of aminoacil ARNt to the acceptor site[38], it means, mRNA joins together with the bacterial 30S ribosomal subunit[39]. P-site (peptidyl) of the RNA 50S subunit contains the rising polypeptide chain; in normal conditions, eaminoacil tARN is charged with the next aminoacid (aa) which is added, moves to A-site (acceptor), with complementary bases pairing between the ARNt anticodon sequence and the mRNA codon[40], eravacycline joins together with 30S subunit, blocking the merger of ARNt with the A-site, therefore it inhibits proteins synthesis[41]; this is a bacteriostatic antibiotic, since the interaction between tetracyclines and ribosomes is reversible[42]. (Figure 6)

Tetracyclines generally enter to bacterial Gram negative cells through the porins of the external membrane by means of passive spreading or active transportation, this last one requires TFA and magnesium for the active uptake[43], however, it maintains the activity when there is the presence of common resistance specific tetracycline mechanisms acquired, it means, four known mechanisms to confer specific resistance to tetracycline as flow pumps, ribosomal protection proteins (RPP), drugs deterioration, and rRNA mutations; of this mechanisms, the efflux pumps and the RPP are the most common[44]; some Gram negative bacteria species demonstrate an inherent resistance to tetracycline due to specific lipopolysaccaride components in their external membranes. Specific tetracycline efflux bombs can be found in the cell membranes of Gram positive and Gram negative bacteria[45].

This synthetic process is constantly improving and discovering new tetracyclines with enhanced antimicrobial profiles related to previous generations[46]; Nowadays several candidates are in different phases of development using Eravacycline as main compound, a wide spectrum antibiotic for serious diseases[47].

Currently they are being proposed some antibiotics finding platforms in order to be studied, which follow directly the old practices and can be improved by means of the application of modern tools of validation[48], it will be needed the development of new data tools based on biology, which is totally feasible taking into account what is currently known[49]. The establishment of rules implied in the penetration of molecules in the bacterial wrap will allow that high technology platforms be applied effectively[50].

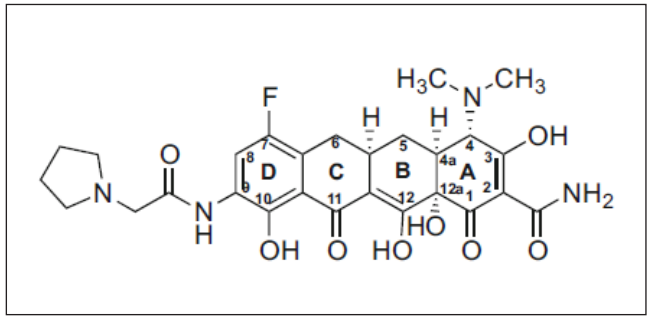

Figura 5. Eravacycline chemical structure
Source: Magnus Ronn*, Zhijian Zhu, Philip C. Process R&D of Eravacycline: The First Fully Synthetic Fluorocycline in Clinical Development. Organic Process Research & Development 2013 17[5], 838-845[35]

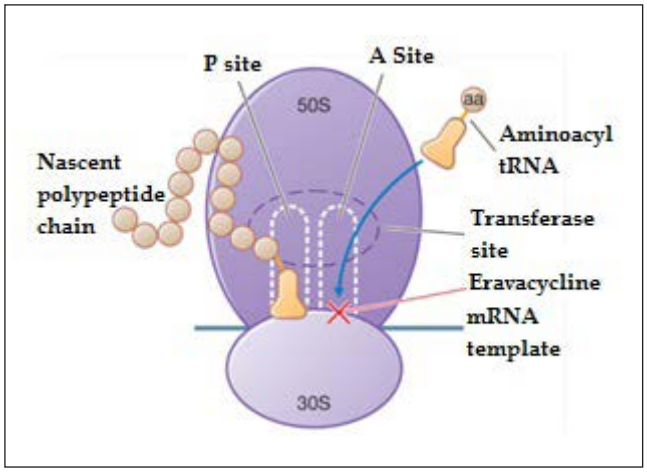

Figure 6. Eravacycline action mechanism model
Source: Inhibidores de la síntesis de proteína y antibacterianos diversos, Hilal-Dandan R, Brunton LL. Goodman & Gilman. Manual de farmacología y terapéutica, 2e; 2015.

Conclusions

Thanks to the researches that have been made looking for an effective therapy against bacteria, Scientist have had to look for new alternatives for amplifying the therapeutic arsenal and obtaining new molecules that replace the ones that do not work anymore.

The search of new treatments against pathogenic bacteria proposes new strategies, as the development of methods to cultivate and stimulate the growth of this organisms by means of *in situ* culture, using specific growth factors in chambers that allow the spreading by using electronic chips and the isolation of the chemical compounds with an antibiotic reach, taking into account that currently this new technique is a source not so explored.

Researchers are making modifications to the action mechanisms, to their chemical and molecular compounds, of the antibiotics previously used, transforming them in synthetic molecules for therapeutic use.

The synthesis of new antibiotics has been tested by the FDA (Food and Drug Administration), a fact that has favored to decrease the adverse effects. There are currently new antimicrobials as omadacycline for bacterial pneumonia and acute skin diseases, arikayce indicated for the treatment of pulmonary diseases caused by *Mycobacterium avium* complex, plazomicin with activity against Gram negative pathogens, including enterobacteria resistant to carbapenems and and tedizolid which indication is the treatment of complicated sin infections and its soft structures.

Funding

This research was supported by Universidad de Boyacá, Tunja, Colombia.

Conflict of interests

The authors declare there is not any conflict of interests.

References

1. Lam YC, Crawford JM. Discovering antibiotics from the global microbiome. Nat Microbiol [Internet]. 2018;3(4):392–3. Available from: http://dx.doi.org/10.1038/s41564-018-0135-5
2. Cars O. Securing access to effective antibiotics for current and future generations. Whose responsibility? Ups J Med Sci. 2014;119(2):209–14. Availablefrom: http://www.tandfonline.com/doi/full/10.3109/03009734.2014.912700
3. Strategia V, Anexa S-, Rom SG, Proiect R, Eir P, Dezvolt M, et al. Resistencia bacteriana: un problema de salud pública mundial de difícil solución. 2016;14(1):45–6.
4. Nathan C, Cars O. Antibiotic Resistance — Problems, Progress, and Prospects. N Engl J Med [Internet]. 2014;371(1):1761–3. Available from: http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:New+engla+nd+journal#0
5. Rocha C, Reynolds N, Simons MP. Resistencia emergente a los antibióticos: una amenaza global y un problema crítico en el cuidado de la salud. Rev Peru Med Exp Salud Publica [Internet]. 2015;32(1):139–45. Available from: /scielo.php?script=sci_arttext&pid=&lang=pt
6. Cruz Cruz M. Antibióticos vs . resistencia bacteriana Antibiotics vs . bacterial resistance. Rev Electrónica Dr Zoilo E Mar Vidaurreta. 2015;40.
7. Gautman N. Científicos descubren un nuevo y potente antibiótico. Wall Str J Am [Internet]. 2015;1–2. Available from: https://search.proquest.com/docview/1643185345?accountid=43592%0A(c)
8. Giltrap AM, Dowman LJ, Nagalingam G, Ochoa JL, Linington RG, Britton WJ, et al. Total Synthesis of Teixobactin. Org Lett [Internet]. 2016;18(11):2788–91. Available from: http://dx.doi.org/10.1038/ncomms12394
9. Piddock LJV. Teixobactin, the first of a new class of antibiotics discovered by ichip technology? J Antimicrob Chemother. 2015;70(10):2679–80.
10. Guo C, Mandalapu D, Ji X, Gao J, Zhang Q. Chemistry and Biology of Teixobactin. Chem - A Eur J. 2018;24(21):5406–22.
11. Buckland D. New antibiotic candidates that offer potential. 2017;(January).
12. Arias CA, Murray BE. A New Antibiotic and the Evolution of Resistance. N Engl J Med [Internet]. 2015;372(12):1168–70. Available from: http://www.nejm.org/doi/10.1056/NEJMcibr1500292
13. López J. TEIXOBACTINA : UNA NUEVA FAMILIA DE ANTIBIÓTICOS. Northeast Univ. 2015;1:1–6.
14. Von Nussbaum F, Süssmuth RD. Multiple attack on bacteria by the new antibiotic teixobactin. Angew Chemie - Int Ed. 2015;54(23):6684–6.
15. Sherpa RT, Reese CJ, Aliabadi HM. Application of iChip to grow "uncultivable" microorganisms and its impact on antibiotic discovery. J Pharm Pharm Sci. 2015;18(3):303–15.
16. Kali A. Teixobactin: A novel antibiotic in treatment of gram positive bacterial infections. J Clin Diagnostic Res. 2015;9(3).
17. Abdel Monaim SAH, Jad YE, Ramchuran EJ, El-Faham A, Govender T, Kruger HG, et al. Lysine Scanning of Arg $_{10}$ –Teixobactin: Deciphering the Role of Hydrophobic and Hydrophilic Residues. ACS Omega [Internet]. 2016;1(6):1262–5. Available from: http://pubs.acs.org/doi/abs/10.1021/acsomega.6b00354
18. Viñuales JM. La teixobactina y el iChip : nuevas armas contra la resistencia antibiótica. MoleQla Rev Ciencias la Univ Pablo Olavide. 2016;23:1–3.
19. Monaim SAHA, Noki S, Ramchuran EJ, El-Faham A, Albericio F, Torre BG d. la. Investigation of the N-Terminus Amino Function of Arg10-Teixobactin. Molecules. 2017;22(10):1–9.
20. Kirby T. New antibiotic development hailed as game changing. Lancet Infect Dis [Internet]. 2015;15(3):271–2. Available from: http://dx.doi.org/10.1016/S1473-3099(15)70072-1
21. Parmar A, Iyer A, Prior SH, Lloyd DG, Leng Goh ET, Vincent CS, et al. Teixobactin analogues reveal enduracididine to be non-essential for highly potent antibacterial activity and lipid II binding. Chem Sci. 2017;8(12):8183–92.
22. Singh OJ, Debashree N, Raleng I. Teixobactin: an Antibiotic With Undetectable Resistance. J Evol Res Med Pharmacol [Internet]. 2015;1(1):21–2. Available from: http://jermp.com/data_pdf/3_debashree-Bha _Manju Duplicate.pdf
23. Reddy S, Dhara S, Gunjal V, Handore K. COMMUNICATION A Solution-Phase Synthesis of Macrocyclic Core of Teixobactin. European J Org Chem [Internet]. 2016;10:1–7. Available from: http://dx.doi.org/10.1002/ejoc.201600778
24. Abdel Monaim SAH, Ramchuran EJ, El-Faham A, Albericio F, De La Torre

BG. Converting Teixobactin into a Cationic Antimicrobial Peptide (AMP). J Med Chem. 2017;60(17):7476–82.
25. Ling LL, Schneider T, Peoples AJ, Spoering AL, Engels I, Conlon BP, et al. A new antibiotic kills pathogens without detectable resistance. Nature. 2015;517(7535):455–9.
26. Yang H, Chen KH, Nowick JS. Elucidation of the Teixobactin Pharmacophore. ACS Chem Biol. 2016;11(7):1823–6.
27. Lungu CN, Diudea M V. Binding Site and Potency Prediction of Teixobactin and other Lipid II Ligands by Statistical Base Scoring of Conformational Space Maps. Curr Comput Aided Drug Des [Internet]. 2018;14(1):29–34. Available from: http://www.eurekaselect.com/155894/article
28. Liu Y, Liu Y, Chan-Park MB, Mu Y. Binding Modes of Teixobactin to Lipid II: Molecular Dynamics Study. Sci Rep [Internet]. 2017;7(1):1–12. Available from: http://dx.doi.org/10.1038/s41598-017-17606-5
29. Lewis PO, Heil EL, Covert KL, Cluck DB. Treatment strategies for persistent methicillin-resistant Staphylococcus aureus bacteraemia. J Clin Pharm Ther. 2018;43(5):614–25.
30. Grossman TH, Starosta AL, Fyfe C, O'Brien W, Rothstein DM, Mikolajka A, et al. Target- and resistance-based mechanistic studies with TP-434, a novel fluorocycline antibiotic. Antimicrob Agents Chemother. 2012;56(5):2559–64.
31. Xiao XY, Hunt DK, Zhou J, Clark RB, Dunwoody N, Fyfe C, et al. Fluorocyclines. 1. 7-fluoro-9-pyrrolidinoacetamido-6-demethyl-6-deoxytetracycline: A potent, broad spectrum antibacterial agent. J Med Chem. 2012;55(2):597–605.
32. Solomkin J, Evans D, Slepavicius A, Lee P, Marsh A, Tsai L, et al. Assessing the efficacy and safety of Eravacycline vs Ertapenem in complicated intra-abdominal infections in the Investigating Gram-Negative Infections Treated with Eravacycline (IGNITE 1) trial a randomized clinical trial. JAMA Surg. 2017;152(3):224–32.
33. Clark RB, Hunt DK, He M, Achorn C, Chen CL, Deng Y, et al. Fluorocyclines. 2. Optimization of the C-9 side-chain for antibacterial activity and oral efficacy. J Med Chem. 2012;55(2):606–22.
34. Zhang Y, Lin X, Bush K. In vitro susceptibility of β-lactamase-producing carbapenem-resistant Enterobacteriaceae (CRE) to eravacycline. J Antibiot (Tokyo) [Internet]. 2016;69(8):600–4. Available from: http://dx.doi.org/10.1038/ja.2016.73
35. Ronn M, Zhu Z, Hogan PC, Zhang WY, Niu J, Katz CE, et al. Process R&D of eravacycline: The first fully synthetic fluorocycline in clinical development. Org Process Res Dev. 2013;17(5):838–45.
36. Nguyen F, Starosta AL, Arenz S, Sohmen D, Dönhöfer A, Wilson DN. Tetracycline antibiotics and resistance mechanisms. Biol Chem. 2014;395(5):559–75.
37. Thabit AK, Monogue ML, Nicolau DP. Eravacycline pharmacokinetics and challenges in defining humanized exposure in vivo. Antimicrob Agents Chemother. 2016;60(8):5072–5.
38. Snydman DR, McDermott LA, Jacobus N V., Kerstein K, Grossman TH, Sutcliffe JA. Evaluation of the in vitro activity of eravacycline against a broad spectrum of recent clinical anaerobic isolates. Antimicrob Agents Chemother. 2018;62(5):617–36.
39. Jenner L, Starosta AL, Terry DS, Mikolajka A, Filonava L, Yusupov M, et al. Structural basis for potent inhibitory activity of the antibiotic tigecycline during protein synthesis. Proc Natl Acad Sci [Internet]. 2013;110(10):3812–6. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.1216691110
40. Li W, Atkinson GC, Thakor NS, Allas U, Lu CC, Yan Chan K, et al. Mechanism of tetracycline resistance by ribosomal protection protein Tet(O). Nat Commun. 2013;4.
41. Wilson DN. Ribosome-targeting antibiotics and mechanisms of bacterial resistance. Nat Rev Microbiol [Internet]. 2014;12(1):35–48. Available from: http://dx.doi.org/10.1038/nrmicro3155
42. Solomkin JS, Ramesh MK, Cesnauskas G, Novikovs N, Stefanova P, Sutcliffe JA, et al. Phase 2, randomized, double-blind study of the efficacy and safety of two dose regimens of eravacycline versus ertapenem for adult community-acquired complicated intra-abdominal infections. Antimicrob Agents Chemother. 2014;58(4):1847–54.
43. Monogue ML, Thabit AK, Hamada Y, Nicolau DP. Antibacterial efficacy of eravacycline In Vivo against gram-positive and gram-negative organisms. Antimicrob Agents Chemother. 2016;60(8):5001–5.
44. Thabit AK, Monogue ML, Newman J V., Nicolau DP. Assessment of in vivo efficacy of eravacycline against Enterobacteriaceae exhibiting various resistance mechanisms: a dose-ranging study and pharmacokinetic/pharmacodynamic analysis. Int J Antimicrob Agents [Internet]. 2018;51(5):727–32. Available from: https://doi.org/10.1016/j.ijantimicag.2018.01.001
45. Goldstein EJC, Citron DM, Tyrrell KL. In vitro activity of eravacycline and comparator antimicrobials against 143 recent strains of Bacteroides and Parabacteroides species. Anaerobe [Internet]. 2018;52:122–4. Available from: https://doi.org/10.1016/j.anaerobe.2018.06.016
46. Zhou J, Tran BT, Tam VH. The complexity of minocycline serum protein binding. J Antimicrob Chemother. 2017;72(6):1632–4.
47. Avery LM, Nicolau DP. Investigational drugs for the treatment of infections caused by multidrug-resistant Gram-negative bacteria [Internet]. Vol. 27, Expert Opinion on Investigational Drugs. Taylor & Francis; 2018. 325-338 p. Available from: https://doi.org/10.1080/13543784.2018.1460354
48. Lewis K. Platforms for antibiotic discovery. Nat Rev Drug Discov [Internet]. 2013;12(5):371–87. Available from: http://dx.doi.org/10.1038/nrd3975
49. Braff D, Shis D, Collins JJ. Synthetic biology platform technologies for antimicrobial applications. Adv Drug Deliv Rev [Internet]. 2016;105:35–43. Available from: http://dx.doi.org/10.1016/j.addr.2016.04.006
50. Slomovic S, Pardee K, Collins JJ. Synthetic biology devices for in vitro and in vivo diagnostics. Proc Natl Acad Sci [Internet]. 2015;112(47):14429–35. Available from: http://www.pnas.org/lookup/doi/10.1073/pnas.1508521112