Trakia Journal of Sciences, Vol. 18, Suppl. 1, pp 118-121, 2020

Available online at:
http://www.uni-sz.bg

ISSN 1313-3551 (online) **doi:10.15547/tjs.2020.s.01.021**

CORBOMYCIN: A NEW ANTIBIOTIC WITH A UNIQUE APPROACH TO KILLING PATHOGENS

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ABSTRACT

Introduction: Humanity has benefited from the presence of antibiotics to treat bacterial infections for decades. However, due to the overuse of antibiotics bacteria develop resistance against these drugs, leading to the emergence of untreatable superbugs. Antibiotic resistance is one of the biggest threats to global health. It is rising to dangerously high levels with hundreds of thousands of deaths reported worldwide every year. Dealing with the ongoing antibiotic crisis requires the discovery of compounds with novel mechanisms of action that are capable to treat drug-resistant infections. A newly found antibiotic from a glycopeptides family with "a unique approach" to attacking and killing bacteria was announced in 2020. The purpose of our work is to provide information about Corbomycin. Materials and methods: a review of scientific literature and studies that provide information on Corbomycin. Conclusion: In recent years, researchers have been increasingly searching for new approaches to treat life-threatening bacterial infections. Corbomycin – an antibiotic that kills bacteria by blocking the function of their cell wall is a promising clinical candidate in the fight against antimicrobial resistance.

Key words: Corbomycin, glycopeptides, antibiotic resistance, superbugs.

INTRODUCTION

The introduction of antibiotics, in the early 1940s revolutionised the treatment of infectious diseases on a global scale. No longer was a bacterial infection a death sentence, and no longer the average life expectancy only 47 years old (1). Its impact soared through the scientific, medical and pharmaceutical fields, bringing with it hope for all humanity. Once celebrated a life saver however, antibiotics today are alarming researches all over the world. Since 2014, the World Health Organisation (2) has been warning of a 'post-antibiotic era' in which common infections could once again kill. Antibiotic resistance (AR) is one of the biggest threats to global health (3) causing 25000 deaths annually in the European Union alone (4). Every 15 minutes, an individual in the United States dies due to AR (5) and there are over 160 new AR infections every single day in England (6). The time for discovering new antibiotics has never been more crucial. Recently, in February of this year, Culp and her colleagues (7) discovered a new antibiotic called Corbomycin; named after 'Nid de Corbeau' or Crow's Nest Pass in Canada, where the soil bacterium was collected. A pubmed search currently yields only 2 research papers regarding the new molecule (7, 8). Below outlines the different methods in which the novel drug was found i.e. a phylogeny-guided approach, its unique mechanism of action and its efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA).

PHYLOGENY- GUIDED APPROACH

Culp et al. (7) sourced the genome of the bacteria in the *Actinomycetes* family, revealing an untapped reservoir of 71 biosynthetic gene clusters (BGCs). Antibiotic BGCs encode not only the biosynthetic apparatus, but also the resistance genes to protect from self-intoxication. The latter of which act as a genomic label as they provide pertinent clues about how the antibiotic will work. Therefore,

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the researchers hypothesised that BGCs lacking any known resistance genes are likely to encode natural products with novel mechanisms of action; which they later proved correct by constructing a phylogenetic tree **(Figure 1).** The tree enabled them to map the presence of every shared gene within the BGCs and to find common resistance determinants such as vanHAX and vanY; both of which accumulated within a single clad **(Figure 2).** More importantly, they found 2 other clads that lacked any known resistant determinant, one of which is Corbomycin.

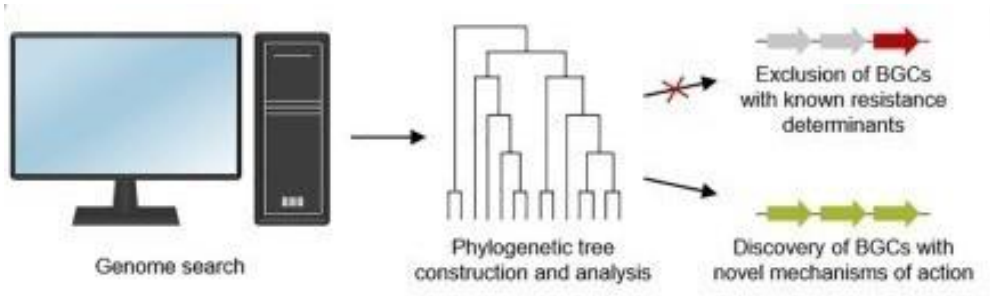

Figure 1. Schematic of the phylogeny-guided approach to drug discovery (8)

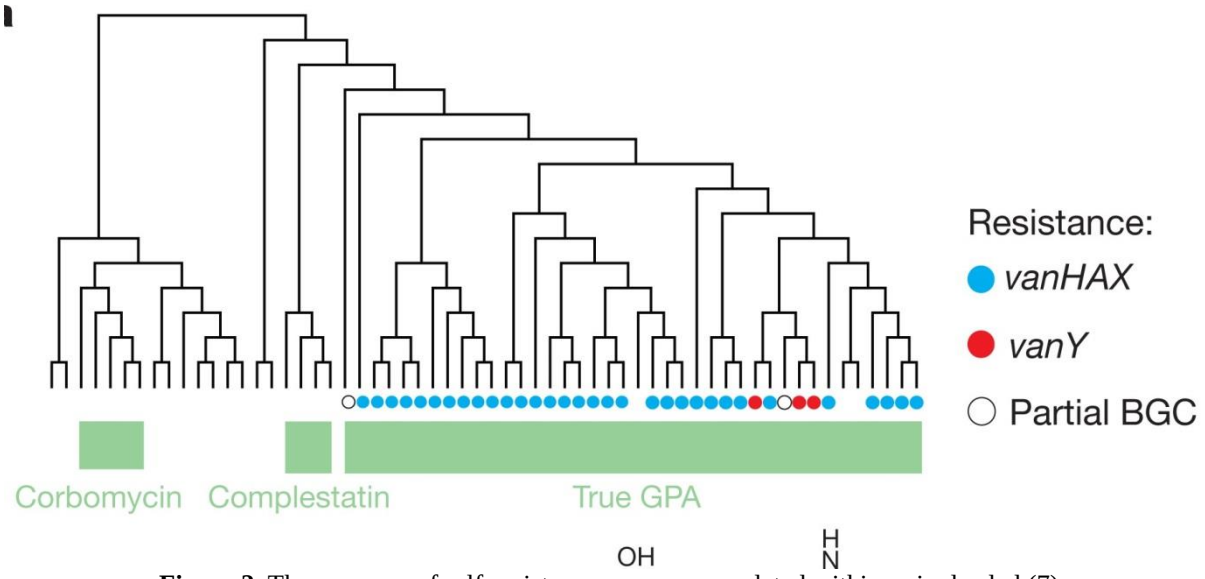

Figure 2. The presence of self-resistance genes accumulated within a single clad (7)

UNIQUE MECHANISM OF ACTION

Although Corbomycin belongs to the same family of antibiotics as Vancomycin and Teicoplanin, i.e. the glycopeptide group, it utilizes a different mechanism of action- a novel approach which has not been witnessed before. Corbomycin inhibits the cell wall from being broken down by binding directly to different sites on the peptidoglycan (PGN), subsequently blocking autolysin activity. Autolysins are required to cleave the pre-existing PGN, allowing new PGN subunits to be incorporated during synthesis, ultimately aiding in the bacterial division. **Figure 3** highlights the effects of hindering these bacteriolytic enzymes which leads to: an irregular septa formation, thickening of the cell wall and distortion of the cytoplasm; eventually leading to its characterised twistedphenotype **(Figure 4).** Although autolysins have been known for many years, the study of them has been hampered by their great number and functional redundancy (9). It is an exciting contrast to its well-known cousin Vancomycin, which relies on binding to a specific (D-ala-D-ala) end of the peptide, inhibiting cell wall synthesis. Resistant strains however show an alteration of their PGN terminus (D-ala-D-lac). An adjustment, that appears simple but only surfaced in 2002 (10), 44 years after it was introduced clinically. Corbomycin nonetheless, blocks a broad range of structurally unrelated autolysins by binding to the same substrate i.e. PGN, suggesting that if resistant mechanisms occur, they may take a much longer time to do so, as it will require sophistically orchestrated effort from the bacterium itself.

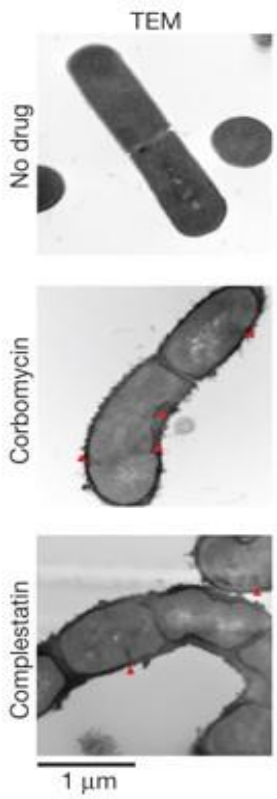

Figure 3. TEM images of sites of irregular septa formation, thickened cell wall and distortion of the cytoplasm (marked with red triangles) (7)

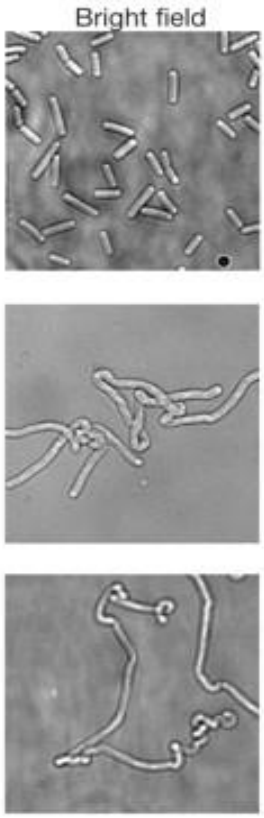

Figure 4. Bright field microscopy comparing normal bacteria (above) to Corbomycin (below). Note twisted phenotype (7)

EFFICACY AGAINST MRSA

Culp et al. (7) demonstrate that Corbomycin significantly reduces the bacterial load of MRSA by around 100-fold at 33 h post-infection **(Figure 5).** It is worth noting however, that the results where yielded from 6 neutropenic mice, after establishing an MRSA superficial skin infection. The researchers stipulate that their choice of using a skin model is due to the poor water solubility of Corbomycin. Indeed, its' many phenolic groups **(Figure 6)** poses difficulties surrounding its practical implementations regarding the treatment of life threatening, systemic infections. The research paper does provide sound evidence that topical Corbomycin shows a similar efficacy to fusidic acid (P values 0.0157 and 0.0003 respectively). However, one simply cannot generalise the results from 6 mice to the wider population. These findings should nonetheless, provoke an urge within the research community to commence a similar study using more specimens with a strong aim of stretching beyond the pre-clinical phase.

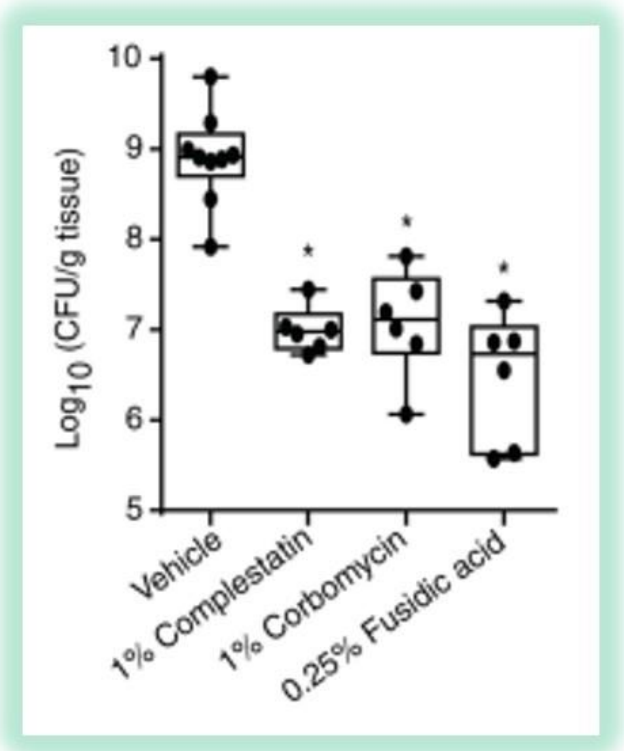

Figure 5. The cfu per gram of tissue (7)

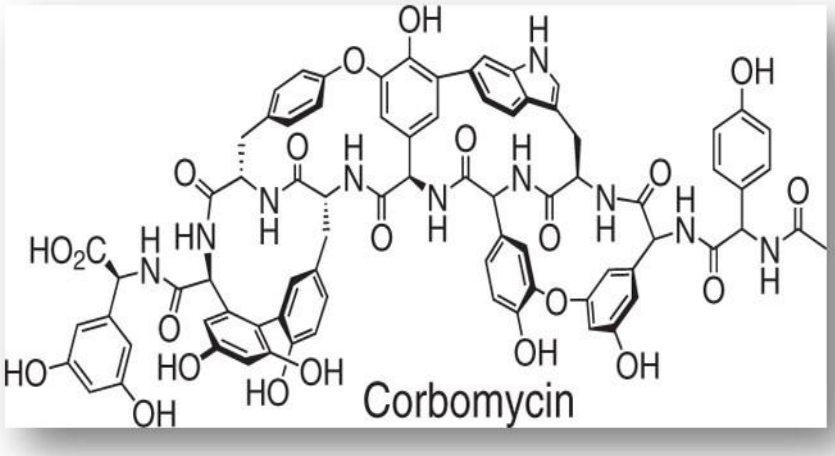

Figure 6. Corbomycin structure (7)

CONCLUSION

Albeit further trials are warranted to confidently generalise Corbomycin' efficacy against topical MRSA infections in a human population; the paper still demonstrates that it may not be an impossibility. Corbomycin represents the first instance of PGN remodelling inhibition. The involvement of blocking many autolysins, by binding to different sites on the PGN, raises the suggestion that AR may take longer to develop than that of Vancomycin. Most worthy of note however, is the exciting approach that leads to the new molecules' discovery-mapping of the phylogenetic tree. This methodology unleashes a massive potential for the finding of new drugs from different antibiotic classes. Each bringing with it the opportunity to benefit from novel mechanisms of action, and the hope to buy more time in the fight against antibiotic resistance.

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