Journal **Concepts in Structural Biology & Bioinformatics** (JSBB)

ANTIBIOTICS RESISTANCE ARTICLES

Concept article: Review

Antibiotic Resistance: A Global Public Health Crisis and Current Strategies for Combatting It

BENABBOU Taha Ahmed[1], BENREGUIEG Mokhtar[1], BELLIL Yahia[1,2], CHAHROUR Wassila[1,2]

1. Laboratory of Biotoxicology, Pharmacognosy and biological valorisation of plants Compus Ain El Hadjar, Faculty of Sciences, Department of Biology, University of Saida Dr Tahar Moulay, 20100 Saida, Algeria.
2. Laboratory of Applied Microbiology, Department of Biology, Faculty of Nature Science and Life, University of Oran 1 Ahmed BENBELLA, B.P. 16, Es-Sénia,31100 Oran, Algeria.

Correspondence:
E. mail : t.a.benabbou@gmail.com , taha.benabbou@univ-saida.dz

Abstract

Antimicrobial resistance is a significant global public health problem. Antibiotic-resistant bacteria have emerged as a result of inappropriate and excessive use of antibiotics, rendering treatment ineffective and increasing morbidity and mortality rates. The effectiveness of currently available antibiotics has already been compromised due to the emergence of multi-resistant bacteria. Steps have been taken globally to prevent and combat antibiotic resistance by promoting best practices in infection control, encouraging the judicious use of antibiotics, developing new antibacterial drugs, and raising public awareness. Current approaches to combating antibiotic resistance are reviewed in this article, including methods for improving antibiotics, halting the spread of antibiotic resistance, and investigating unconventional therapies such as antimicrobial peptides, riboregulators, nanoparticles, and phage therapy. Current problems and future prospects in the fight against antibiotic resistance are also discussed.

Key words: Antibiotic-resistant, antimicrobial peptides, ATP synthase inhibitors, Riboregulators, Nanoparticles, Phage therapy, CRISPR-Cas

Introduction

Antibiotic resistance is a growing public health issue on a global scale. Antibiotics were discovered more than 80 years ago and have saved millions of lives by treating bacterial illnesses (Martens & Demain, 2017). However, their inappropriate and excessive use has resulted in the development of bacteria resistant to antibiotics, rendering treatments ineffective and raising the rates of morbidity and mortality (Wang et al., 2021).

Antibiotic resistance can result from a variety of factors, including inappropriate or excessive antibiotic use, the spread of antibiotic-resistant bacteria from one person to another, a lack of infection prevention and hygiene measures, and the widespread use of antibiotics in farm animals (Bungau et al., 2021). However, due to multi-resistant bacteria, currently available antibiotics are already at their limit. According to OMS estimates, if superbugs continue to spread over the world, there will be 10 million infection-related deaths annually by the year 2050, with a cost to the global economy of more than $100 billion (Engström, 2021).

International action has been taken to create measures to avoid and combat antibiotic resistance as a result of this public health issue. Governments, health organizations, and health professionals are collaborating to promote good infection control procedures, advocate the prudent use of antibiotics, develop new antibacterial medications, and increase public awareness of the significance of antibiotic resistance (Engström, 2021).

We shall examine current tactics to tackle antibiotic resistance in this essay. We'll talk about several strategies for preventing antibiotic resistance as well as continuing initiatives to create new medications and enhance antibiotic prescribing procedures. Finally, we'll look at the ongoing issues and potential future developments in the fight against antibiotic resistance.

Current strategies to combat antibiotic resistance

Since the discovery of the first case of antibiotic resistance in the 1940s, pharmaceutical companies have continued to develop solutions and strategies, including pharmacological ones, to limit its occurrence. The main current strategies to fight antibiotic resistance can be summarized in several points (Fig. 1).

1. Strategies for improving antibiotics: optimizing existing structures and creating new molecules

Two crucial strategies in the battle against antibiotic resistance are altering the structure of existing antibiotics and developing novel ones.

The first strategy entails enhancing the chemical composition of outdated antibiotics. An antibiotic's structure can be changed by scientists to improve the antibiotic's capacity to kill resistant bacteria or to more effectively reach its bacterial target. Additionally, structural alterations can lessen the antibiotic's toxicity for the patient.

Penicillin was changed to produce β-lactam antibiotics as an illustration of how outdated antibiotics might be strengthened structurally. Although β-lactams are frequently used as antibiotics to treat bacterial infections, resistance to them is on the rise. Scientists have created third-generation cephalosporins, which are more potent and efficient against resistant bacteria, as new β-lactam antibiotics to address this issue.

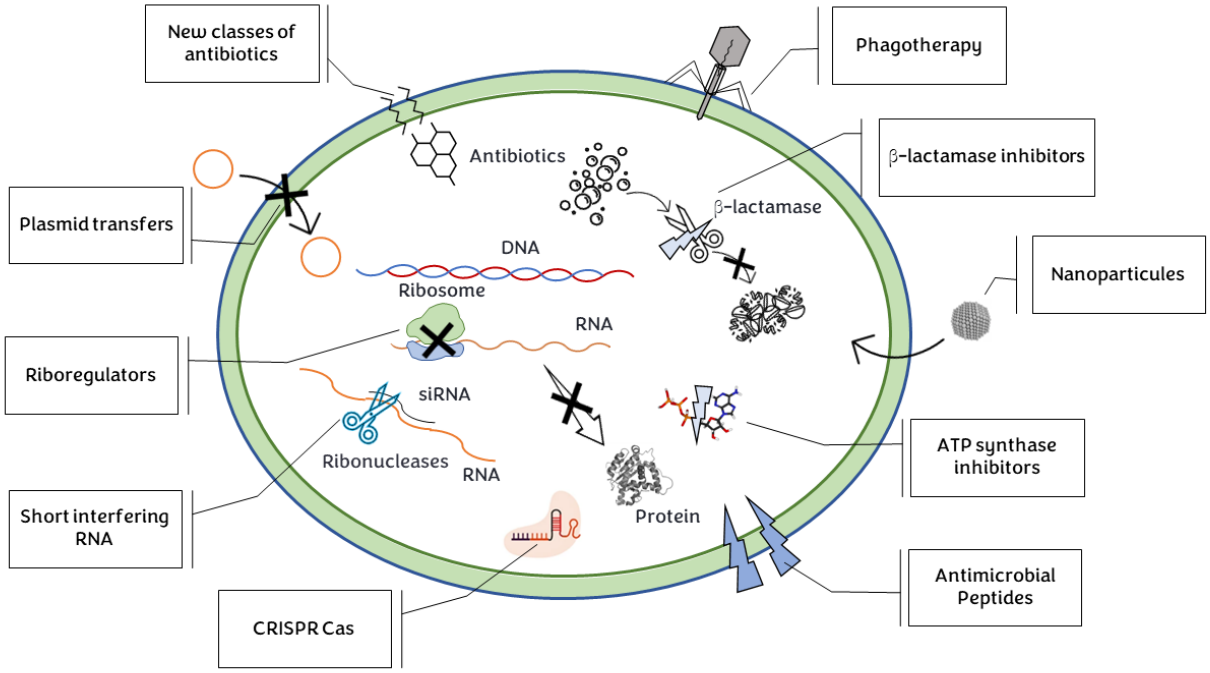

Fig. 1: Strategies and bacterial targets used to combat antibiotic resistance

In clinical investigations including more than 2,500 patients with skin and soft tissue infections as well as community-acquired bacterial pneumonia (File et al., 2011), ceftaroline, a chemical from the same family as beta-lactams that was created in 2008, was proven to be beneficial. An important step forward in the fight against antibiotic resistance is represented by this chemical (Zhanel et al., 2009).

In a similar vein, plazomicin is a brand-new chemical from the aminoglycosides class that was created to reduce antibiotic resistance (Becker & Cooper, 2013; Bush, 2012). Contrarily, eravacyline, a member of the new tetracycline generation, was created for the same goal as plazomicin, namely, to restrict bacterial resistance, notably against particular active efflux and ribosome protection (Grossman et al., 2015).

The use of β-lactamase inhibitors such as clavulanic acid (Matsuura et al., 1980), sulbactam (Bush, 2012), tazobactam (Kuti et al., 2015), avibactam (Olsen, 2015; Soroka et al., 2016), and relbactam can reinforce the structural improvement of older antibiotics (Lucasti et al., 2016; Olsen, 2015). These inhibitors allow for the neutralization of the enzymes that some bacteria produce in order to resist antibiotics. In addition, the use of selenium (sodium bismuth citrate) in conjunction with metronidazole and tetracycline can effectively combat *Helicobacter pylori*, the bacterium that causes gastrointestinal infections (Bouyssou, 2014). These tactics are crucial ways to increase the effectiveness of currently used antibiotics and make them more bacterial resistance-resistant.

2. The antimicrobial peptides (AMPs)

The discovery of the enzyme lysozyme in 1922 by Alexander Fleming was a major breakthrough in our understanding of how the immune system fights bacterial diseases. Lysozyme was the first example of an antimicrobial agent that was found to be naturally occurring in the body (Alexander Fleming, 1922). However, it took several decades for researchers to identify other antimicrobial peptides (AMPs), which are tiny molecules produced by the body in response to bacterial or fungal infections. The first AMPs were discovered in Drosophila in the 1990s, and this discovery paved the way for further research into the development of antimicrobial medications and a better understanding of how AMPs can prevent infections (Unckless et al., 2016).

AMPs are an important tool in the fight against a wide range of pathogens, including pathogenic bacteria and fungi. One of the most intriguing aspects of AMPs is their ability to combat antibiotic resistance, as they only result in limited bacterial resistance compared to conventional antibiotics. Most AMPs work by breaking down the bacterial cell membrane, causing permeabilization and cell lysis, which has a bactericidal effect (Fig. 2). Some AMPs can also penetrate the bacterial membrane and target anionic molecules, such as enzymes or nucleic acids, which disrupt the bacterial cell's biological functions. This dual mechanism of action makes AMPs a promising avenue for future research and drug development (Mahlapuu et al., 2016; Spohn et al., 2019).

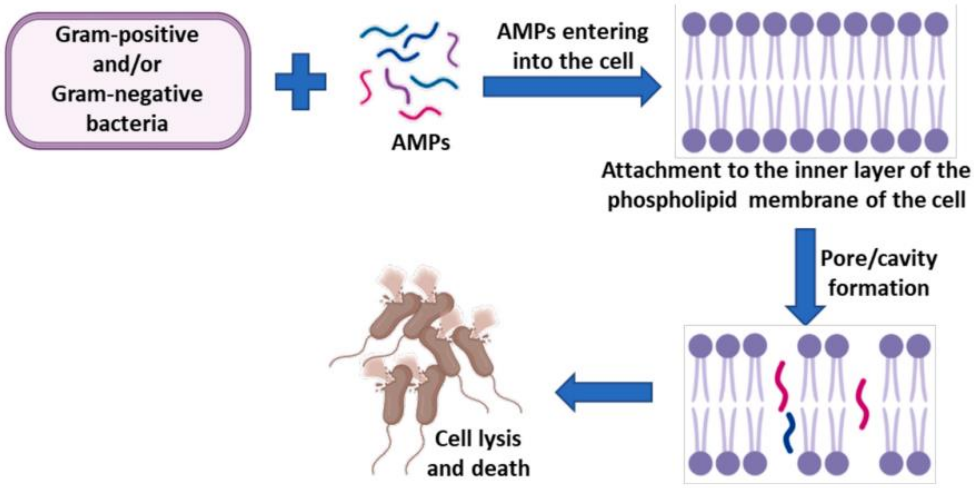

Fig. 2: Mechanism of action of antimicrobial peptides (Fatima et al., 2021)

3. Riboregulators

Riboregulators are RNA molecules that interact with target mRNAs to regulate the expression of certain genes. They can either stop protein synthesis by binding to the mRNA and blocking its translation or start it by allowing the mRNA to be translated. In 2007, researchers proposed the idea of using ribregulators as potential targets to interfere with the production of critical proteins in bacteria, using them as an alternative to the conventional strategy of targeting bacterial proteins (Ogawa & Maeda, 2007).

Complex mechanisms that trigger gene expression in response to antibiotic exposure frequently control antibiotic resistance genes. Recent research reveals that the expression of several resistance genes is significantly regulated by cis-active non-coding RNAs known as riboregulators. These RNAs, known as riboregulators, are found in the 5'UTR region of regulated genes and detect the presence of antibiotics by directing translating ribosomes to short, non-coding upstream reading frames (uORFs), which are embedded in the RNA. Antibiotics that limit translation cause the ribosomes to stop on the uORF, changing the structure of the regulator RNA and causing the expression of the resistance gene to become active (Fig. 3). The ability of these regulators to identify particular antibiotic classes depending on the size and make-up of the relevant uORF determines how specific they are (Dar & Sorek, 2017).

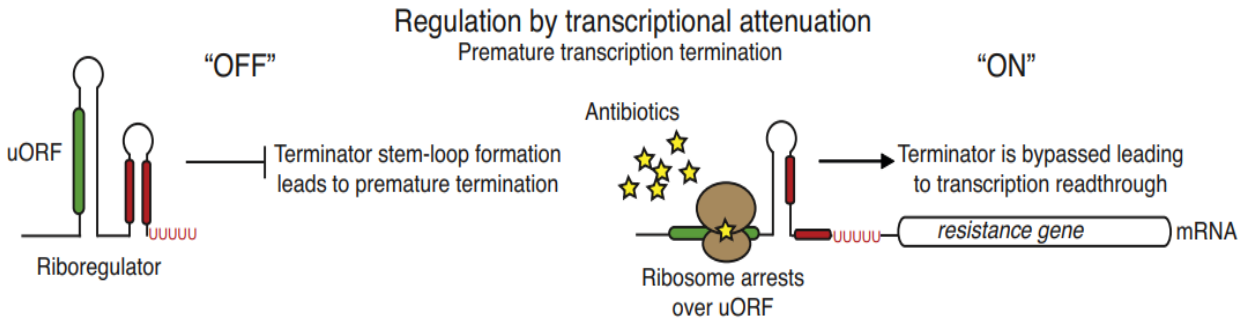

Fig. 3: By managing the creation of a premature transcription terminator, which is a stem-loop structure followed immediately by a poly uridine tract, transcriptional attenuation controls expression. Antibiotics are not present, so transcription starts but ends early. The resistance gene's transcription is aided by ribosome pausing over the uORF, which prevents the development of terminator stem loops (Dar & Sorek, 2017).

Studies have shown that specific binding of a chemical, PC1, to a guanine ribo regulator in *S. aureus* inhibits bacterial growth in vitro and in vivo in mice by binding to the regulatory region of the target RNA. These results suggest that rioregulators may be a promising target for the development of new antibiotics by interfering with the production of critical proteins in bacteria (Mulhbacher et al., 2010).

4. Prevention of horizontal genetic material transfer between bacteria

One of the main factors contributing to the spread of antibacterial resistance is the exchange of genetic material between bacterial communities. In fact, bacteria are capable of exchanging resistance genes with one another, allowing them to develop a resistance to new antibiotics. This strategy relies on the use of conjugation inhibitors since inhibiting proteins that participate in conjugation (such as relaxase, pili, and others) prevents the transfer of plasmides to different hosts, promoting the eradication of plasmides from bacterial populations (Fig. 4) (Cabezón et al., 2017; Dimitriu et al., 2014; Getino & de la Cruz, 2018). Several strategies, including the use of ionophores, chlortetracycline, bacitracin, and combinations of ionophores/antimicrobials, have been investigated to restrict the horizontal transfer of antibiotic resistance. According to studies, these techniques are particularly good at preventing the horizontal spread of antibiotic resistance in *E. coli*. Various natural substances, including flavonoids, plant extracts, and antimicrobial peptides, have been proven in other investigations

to be able to prevent horizontal gene transfer. Similar to this, artificial compounds have been created that precisely target the bacterial conjugation-related proteins.

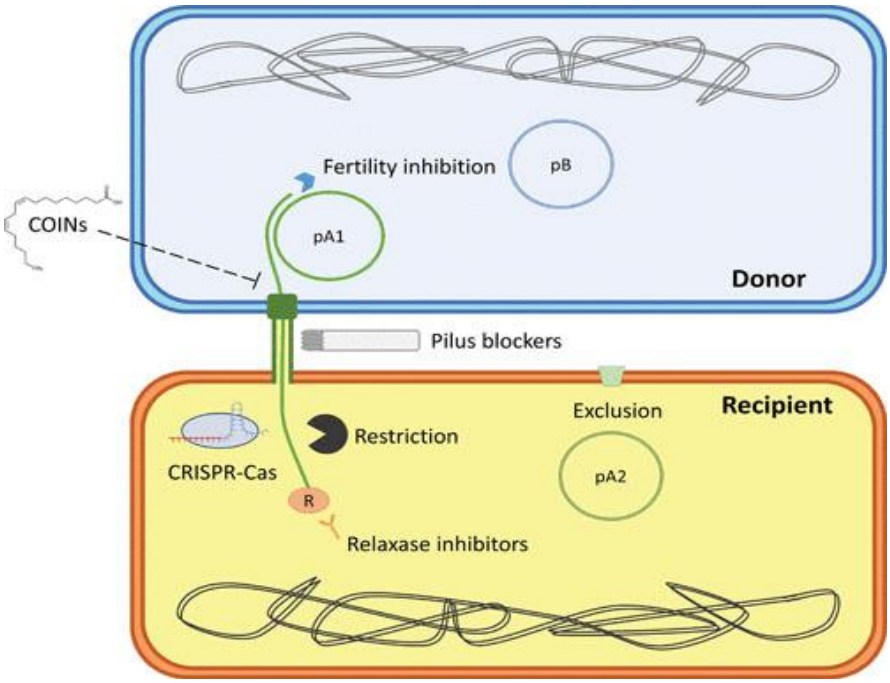

Fig. 4: Natural and Artificial Mechanisms Controlling Conjugative Plasmid Transmission: RM and CRISPR-Cas Systems, Exclusion Systems, and Fertility Inhibition Systems as Natural Mechanisms, and Relaxase, Pilus, and ATPase Interference as Artificial Mechanisms (Getino & de la Cruz, 2018)

5. ATP synthase inhibitors

A new class of antibiotics, known as ATP synthase inhibitors, includes the antitubercular drug Bedaquiline. It works by preventing the synthesis of ATP, a vital energy molecule for bacterial growth and survival, especially for *Mycobacterium tuberculosis*, the causative agent of tuberculosis. Bedaquiline limits bacterial growth by obstructing its energy metabolism by selectively blocking ATP synthase. This approach works well against *Mycobacterium tuberculosis* strains that are resistant to widely used drugs (Hards et al., 2015).

The efficacy of Bedaquiline in the treatment of tuberculosis has been supported by numerous studies, notably in patients with multidrug-resistant forms of the disease. To increase its potency and reduce the possibility of resistance forming, Bedaquiline is frequently used in conjunction with other antibiotics. Additionally, research continues to explore other ATP

synthase inhibitors and understand their mode of action to improve the treatment of tuberculosis and other bacterial infections (Hards et al., 2015; Maitre et al., 2017).

The mechanism of action of bedaquiline, the first drug to target mycobacterial ATP synthase, is illustrated in Fig. 5 ATP synthase is a crucial enzymatic complex for the production of ATP, necessary for cellular survival in both prokaryotes and eukaryotes. The complex consists of a transmembrane domain (F0) and a cytoplasmic domain (F1), and protonation through the F0 domain leads to a rotation of the c and γ subunits of the F1 domain, resulting in ATP synthesis. Bedaquiline binds to the binding site between the a and c subunits of the F0 domain and inhibits ATP production by blocking proton flow and subsequent conformational changes, resulting in cell death in both replicating and non-replicating mycobacteria. Despite the high similarity in protein sequence with the human homologue, bedaquiline is selective towards mycobacterial ATP synthase (Goulooze et al., 2015; Guglielmetti & Robert, 2015; Singh et al., 2017)

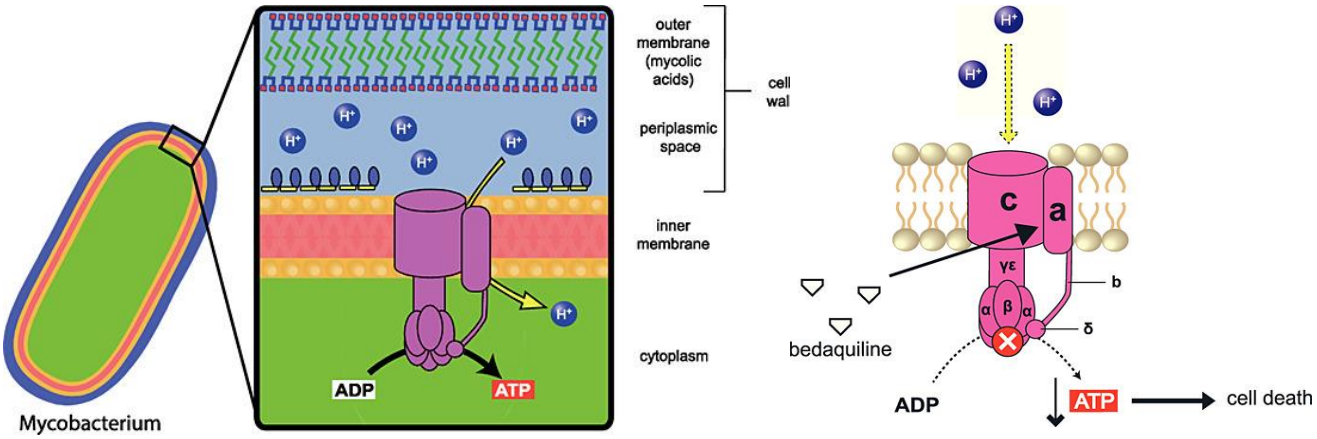

Fig. 5: Mechanism of action of bedaquiline (Goulooze et al., 2015)

6. Nanoparticles

The use of nanotechnology in medicine is a cutting-edge strategy that attempts to enhance the treatment of many serious diseases. Using nanovectors, which are incredibly small particles (on the scale of nanometers) capable of transporting active ingredients to their pharmacological target in the body, medications are administered using this technology (Haleem et al., 2023). In comparison to traditional medication administration techniques,

nanovectors have improved bioavailability and more controlled release of active components. They can also target diseased cells or damaged tissues directly, minimizing adverse effects and collateral harm to healthy organs (Damodharan, 2021).

The antibacterial activity of nanoparticles has been explained by a number of different mechanisms of action. The electrostatic interaction between positively charged nanoparticles and the negatively charged bacterial cell membrane, which can result in cell membrane breakdown, the release of poisonous metal ions, and the eradication of bacteria, is one of the most researched mechanisms (Staroń & Długosz, 2021). Nanoparticles can also interfere with biological functions like respiration, protein synthesis, and DNA replication in order to impair bacterial metabolic processes. Free radicals, unstable molecules with unpaired electron atoms that can harm bacterial membranes and proteins, can also be produced by nanoparticles (Sánchez-López et al., 2020). Additionally, bacterial biofilms, which are bacterial colonies enmeshed in a protective extracellular matrix, can interact with nanoparticles. Chronic infections are frequently linked to biofilms, which are notorious for their resistance to conventional medicines. By disrupting the extracellular matrix and penetrating biofilms, nanoparticles can make bacteria more susceptible to antibiotic therapy (Gudkov et al., 2021; Sánchez-López et al., 2020).

Recent studies have also emphasized the antibacterial characteristics of specific nanoparticle components such iron, zinc, copper, and silver oxide. Particularly against Gram-positive bacteria like *S. aureus* and *Bacillus subtilis* as well as Gram-negative bacteria like *P. aeruginosa* and *E. coli*, these capabilities have been noted (Franci et al., 2015; Marslin et al., 2015; Yu et al., 2020).

7. Short interfering RNA

Utilizing short interfering RNA (siRNA) is a potential strategy to combat antibiotic resistance (Edson & Kwon, 2014). This method targets specific DNA or RNA regions on a bacteria that are crucial for the development of proteins implicated in antibiotic resistance. Genes that make the β-lactamases, which degrade drugs from the β-lactam family, are potential targets (Edson & Kwon, 2014).

RNA segments of roughly 20 base pairs are produced when these places are found. The capacity of these RNA segments to accurately attach to specific sites results in the formation of a double-stranded RNA pair that can be recognized by ribonucleases. The double-stranded

RNA is subsequently destroyed, inhibiting the production of resistance-related proteins (Yanagihara et al., 2006).

8. Phage therapy

An old technique for treating bacterial illnesses called phage treatment uses viruses called phages to kill dangerous bacteria. Phages are viruses that target and particularly infect bacteria, lysing them or causing them to rupture. Even before the development of antibiotics, this approach was contemplated, but it was later abandoned due to its unfavorable immunological consequences. Phage treatment, however, has recently attracted renewed interest due to the growth in antibiotic resistance. Because they are unique to their bacterial target and don't disturb the gut flora, phages have the advantage of lowering the possibility of phage resistance (Brives & Pourraz, 2020).

Phage variety and the requirement to select the appropriate phage for each bacterial illness are two problems that must be overcome for phage therapy to be effective. A new phage must be chosen for every new resistant bacterial strain since bacteria can evolve phage resistance very quickly (Pires et al., 2020; Torres-Barceló, 2018).

Utilizing phage-derived peptides, which are protein fragments produced from phages that are capable of cytolyzing or rupturing bacterial cell membranes, is an additional strategy. These peptides can be created in a lab and have the benefit of being more stable than whole phages. They can also be changed to more effectively and steadily target particular bacterial strains or to make them more stable (Lin et al., 2017).

9. CRISPR-Cas

It may be possible to use the revolutionary method of genome editing known as CRISPR-Cas to combat antibiotic resistance. Researchers can target and cut specific DNA areas in bacteria using the CRISPR-Cas system. If the genes in bacteria that make them resistant to antibiotics were targeted and rendered dormant, drugs might become effective once more (Uribe et al., 2021).

The CRISPR-Cas system has shown promise in the fight against antibiotic resistance in a number of studies. The CRISPR-Cas system can directly kill bacteria since it can target genes on chromosomes and plasmids (Fig. 6) (Citorik et al., 2014; Vercoe et al., 2013). For instance, CRISPR-Cas was used in one study (Gomaa et al., 2014) to target and deactivate an antibiotic

resistance gene in *E. coli* bacteria, restoring the effectiveness of antibiotics against these pathogens. The CRISPR-Cas system can be used to target antibiotic resistance genes in dangerous bacteria like *S. aureus* and *S. pneumoniae*, as has been shown in prior studies (Bikard et al., 2012, 2014).

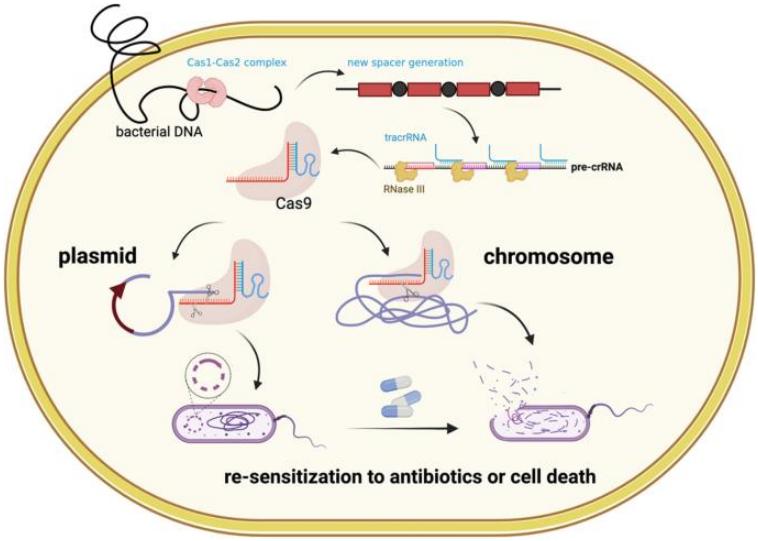

Fig. 6: Utilizing CRISPR-Cas systems as antibiotics. Together with the guide RNA that will instruct it to cut a target sequence, the Cas9 RNA-guided nuclease is expressed. The target may be carried on a plasmid or chromosome, which could result in cell death from chromosome disintegration or antibiotic resistance (Wu et al., 2021).

Conclusion

Antibiotic resistance is a major public health problem as bacteria have acquired resistance to all classes of antibiotics currently in use. This can pose significant therapeutic challenges for some infections, such as Staphylococci, Enterococci, and Acinetobacter. The responsibility for the discriminant use of antibiotics is often debated, but it is now accepted that it is essential to use these drugs prudently to prolong their effectiveness.

As is mentioned in this article, new strategies are currently being developed to combat antibiotic resistance. In vitro and in vivo studies have shown that these strategies could be promising for the future of antibiotic therapy, as well as for the development of new classes of antibiotics. However, it is important to note that antibiotic resistance is a complex and multifactorial problem that requires concerted action by the medical community, policymakers, and the general public.

In order to combat antibiotic resistance, it is deemed essential that research and development of new classes of antibiotics continue to be invested in. Furthermore, effective strategies must be implemented to promote the prudent and responsible use of antibiotics, in order to preserve their long-term effectiveness. If these efforts are combined with increased public awareness of the seriousness of antibiotic resistance, a future where antibiotics remain an effective weapon against bacterial infections can be hoped for.

References

Alexander Fleming. (1922). On a remarkable bacteriolytic element found in tissues and secretions. *Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character*, *93*(653), 306–317. https://doi.org/10.1098/rspb.1922.0023

Becker, B., & Cooper, M. A. (2013). Aminoglycoside Antibiotics in the 21st Century. *ACS Chemical Biology*, *8*(1), 105–115. https://doi.org/10.1021/cb3005116

Bikard, D., Euler, C. W., Jiang, W., Nussenzweig, P. M., Goldberg, G. W., Duportet, X., Fischetti, V. A., & Marraffini, L. A. (2014). Exploiting CRISPR-Cas nucleases to produce sequence-specific antimicrobials. *Nature Biotechnology*, *32*(11), 1146–1150. https://doi.org/10.1038/nbt.3043

Bikard, D., Hatoum-Aslan, A., Mucida, D., & Marraffini, L. A. (2012). CRISPR Interference Can Prevent Natural Transformation and Virulence Acquisition during In Vivo Bacterial Infection. *Cell Host & Microbe*, *12*(2), 177–186. https://doi.org/10.1016/j.chom.2012.06.003

Bouyssou, C. (2014). Une nouvelle approche thérapeutique pour l'éradication de Helicobacter pylori. *Actualités Pharmaceutiques*, *53*(536), 31–35. https://doi.org/10.1016/j.actpha.2014.02.026

Brives, C., & Pourraz, J. (2020). Phage therapy as a potential solution in the fight against AMR: obstacles and possible futures. *Palgrave Communications*, *6*(1), 100. https://doi.org/10.1057/s41599-020-0478-4

Bungau, S., Tit, D. M., Behl, T., Aleya, L., & Zaha, D. C. (2021). Aspects of excessive antibiotic consumption and environmental influences correlated with the occurrence of resistance to antimicrobial agents. *Current Opinion in Environmental Science and Health*, *19*. https://doi.org/10.1016/j.coesh.2020.10.012

Bush, K. (2012). Improving known classes of antibiotics: an optimistic approach for the future.

Current Opinion in Pharmacology, *12*(5), 527–534. https://doi.org/10.1016/j.coph.2012.06.003

Cabezón, E., de la Cruz, F., & Arechaga, I. (2017). Conjugation Inhibitors and Their Potential Use to Prevent Dissemination of Antibiotic Resistance Genes in Bacteria. *Frontiers in Microbiology*, *8*. https://doi.org/10.3389/fmicb.2017.02329

Citorik, R. J., Mimee, M., & Lu, T. K. (2014). Sequence-specific antimicrobials using efficiently delivered RNA-guided nucleases. *Nature Biotechnology*, *32*(11), 1141–1145. https://doi.org/10.1038/nbt.3011

Damodharan, J. (2021). Nanomaterials in medicine – An overview. *Materials Today: Proceedings*, *37*, 383–385. https://doi.org/10.1016/j.matpr.2020.05.380

Dar, D., & Sorek, R. (2017). Regulation of antibiotic-resistance by non-coding RNAs in bacteria. *Current Opinion in Microbiology*, *36*, 111–117. https://doi.org/10.1016/j.mib.2017.02.005

Dimitriu, T., Lotton, C., Bénard-Capelle, J., Misevic, D., Brown, S. P., Lindner, A. B., & Taddei, F. (2014). Genetic information transfer promotes cooperation in bacteria. *Proceedings of the National Academy of Sciences*, *111*(30), 11103–11108. https://doi.org/10.1073/pnas.1406840111

Edson, J. A., & Kwon, Y. J. (2014). RNAi for silencing drug resistance in microbes toward development of nanoantibiotics. *Journal of Controlled Release*, *189*, 150–157. https://doi.org/10.1016/j.jconrel.2014.06.054

Engström, A. (2021). Antimicrobial Resistance as a Creeping Crisis. In *Understanding the Creeping Crisis* (pp. 19–36). Springer International Publishing. https://doi.org/10.1007/978-3-030-70692-0_2

Fatima, H., Goel, N., Sinha, R., & Khare, S. K. (2021). Recent strategies for inhibiting multidrug-resistant and β-lactamase producing bacteria: A review. *Colloids and Surfaces B: Biointerfaces*, *205*, 111901. https://doi.org/10.1016/j.colsurfb.2021.111901

File, T. M., Low, D. E., Eckburg, P. B., Talbot, G. H., Friedland, H. D., Lee, J., Llorens, L., Critchley, I. A., Thye, D. A., Pullman, J., Giordano, P., Welker, J., Manos, P., Mehra, P., File, T., De Santo, J., Venkateswaralu, B., Gerald Schrock, C., Tillis, W., … Plutinsky, J. (2011). FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *Journal of*

Antimicrobial Chemotherapy, *66*(Supplement 3), iii19–iii32. https://doi.org/10.1093/jac/dkr096

Franci, G., Falanga, A., Galdiero, S., Palomba, L., Rai, M., Morelli, G., & Galdiero, M. (2015). Silver Nanoparticles as Potential Antibacterial Agents. *Molecules*, *20*(5), 8856–8874. https://doi.org/10.3390/molecules20058856

Getino, M., & de la Cruz, F. (2018). Natural and Artificial Strategies To Control the Conjugative Transmission of Plasmids. *Microbiology Spectrum*, *6*(1). https://doi.org/10.1128/microbiolspec.MTBP-0015-2016

Gomaa, A. A., Klumpe, H. E., Luo, M. L., Selle, K., Barrangou, R., & Beisel, C. L. (2014). Programmable Removal of Bacterial Strains by Use of Genome-Targeting CRISPR-Cas Systems. *MBio*, *5*(1). https://doi.org/10.1128/mBio.00928-13

Goulooze, S. C., Cohen, A. F., & Rissmann, R. (2015). Bedaquiline. *British Journal of Clinical Pharmacology*, *80*(2), 182–184. https://doi.org/10.1111/bcp.12613

Grossman, T. H., Murphy, T. M., Slee, A. M., Lofland, D., & Sutcliffe, J. A. (2015). Eravacycline (TP-434) Is Efficacious in Animal Models of Infection. *Antimicrobial Agents and Chemotherapy*, *59*(5), 2567–2571. https://doi.org/10.1128/AAC.04354-14

Gudkov, S. V., Burmistrov, D. E., Serov, D. A., Rebezov, M. B., Semenova, A. A., & Lisitsyn, A. B. (2021). A Mini Review of Antibacterial Properties of ZnO Nanoparticles. *Frontiers in Physics*, *9*. https://doi.org/10.3389/fphy.2021.641481

Guglielmetti, L., & Robert, J. (2015). Bédaquiline : de l'in vitro aux essais cliniques d'un nouvel antituberculeux. *Journal Des Anti-Infectieux*, *17*(2), 60–66. https://doi.org/10.1016/j.antinf.2014.12.003

Haleem, A., Javaid, M., Singh, R. P., Rab, S., & Suman, R. (2023). Applications of nanotechnology in medical field: a brief review. *Global Health Journal*. https://doi.org/10.1016/j.glohj.2023.02.008

Hards, K., Robson, J. R., Berney, M., Shaw, L., Bald, D., Koul, A., Andries, K., & Cook, G. M. (2015). Bactericidal mode of action of bedaquiline. *Journal of Antimicrobial Chemotherapy*, *70*(7), 2028–2037. https://doi.org/10.1093/jac/dkv054

Kuti, J. L., Pettit, R. S., Neu, N., Cies, J. J., Lapin, C., Muhlebach, M. S., Novak, K. J., Nguyen, S. T.,

Saiman, L., & Nicolau, D. P. (2015). Microbiological activity of ceftolozane/tazobactam, ceftazidime, meropenem, and piperacillin/tazobactam against Pseudomonas aeruginosa isolated from children with cystic fibrosis. *Diagnostic Microbiology and Infectious Disease*, *83*(1), 53–55. https://doi.org/10.1016/j.diagmicrobio.2015.04.012

Lin, D. M., Koskella, B., & Lin, H. C. (2017). Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. *World Journal of Gastrointestinal Pharmacology and Therapeutics*, *8*(3), 162. https://doi.org/10.4292/wjgpt.v8.i3.162

Lucasti, C., Vasile, L., Sandesc, D., Venskutonis, D., McLeroth, P., Lala, M., Rizk, M. L., Brown, M. L., Losada, M. C., Pedley, A., Kartsonis, N. A., & Paschke, A. (2016). Phase 2, Dose-Ranging Study of Relebactam with Imipenem-Cilastatin in Subjects with Complicated Intra-abdominal Infection. *Antimicrobial Agents and Chemotherapy*, *60*(10), 6234–6243. https://doi.org/10.1128/AAC.00633-16

Mahlapuu, M., Håkansson, J., Ringstad, L., & Björn, C. (2016). Antimicrobial Peptides: An Emerging Category of Therapeutic Agents. *Frontiers in Cellular and Infection Microbiology*, *6*. https://doi.org/10.3389/fcimb.2016.00194

Maitre, T., Aubry, A., Jarlier, V., Robert, J., Veziris, N., Bernard, C., Sougakoff, W., Brossier, F., Cambau, E., Mougari, F., & Raskine, L. (2017). Multidrug and extensively drug-resistant tuberculosis. *Médecine et Maladies Infectieuses*, *47*(1), 3–10. https://doi.org/10.1016/j.medmal.2016.07.006

Marslin, G., Revina, A. M., Khandelwal, V. K. M., Balakumar, K., Sheeba, C. J., & Franklin, G. (2015). PEGylated ofloxacin nanoparticles render strong antibacterial activity against many clinically important human pathogens. *Colloids and Surfaces B: Biointerfaces*, *132*, 62–70. https://doi.org/10.1016/j.colsurfb.2015.04.050

Martens, E., & Demain, A. L. (2017). The antibiotic resistance crisis, with a focus on the United States. *The Journal of Antibiotics*, *70*(5), 520–526. https://doi.org/10.1038/ja.2017.30

Matsuura, M., Nakazawa, H., Hashimoto, T., & Mitsuhashi, S. (1980). Combined antibacterial activity of amoxicillin with clavulanic acid against ampicillin-resistant strains. *Antimicrobial Agents and Chemotherapy*, *17*(6), 908–911. https://doi.org/10.1128/AAC.17.6.908

Mulhbacher, J., Brouillette, E., Allard, M., Fortier, L.-C., Malouin, F., & Lafontaine, D. A. (2010). Novel Riboswitch Ligand Analogs as Selective Inhibitors of Guanine-Related Metabolic

Pathways. *PLoS Pathogens*, *6*(4), e1000865. https://doi.org/10.1371/journal.ppat.1000865

Ogawa, A., & Maeda, M. (2007). Development of a New-type Riboswitch Using an Aptazyme and an anti-RBS Sequence. *Nucleic Acids Symposium Series*, *51*(1), 389–390. https://doi.org/10.1093/nass/nrm195

Olsen, I. (2015). New promising β-lactamase inhibitors for clinical use. *European Journal of Clinical Microbiology & Infectious Diseases*, *34*(7), 1303–1308. https://doi.org/10.1007/s10096-015-2375-0

Pires, D. P., Costa, A. R., Pinto, G., Meneses, L., & Azeredo, J. (2020). Current challenges and future opportunities of phage therapy. *FEMS Microbiology Reviews*, *44*(6), 684–700. https://doi.org/10.1093/femsre/fuaa017

Sánchez-López, E., Gomes, D., Esteruelas, G., Bonilla, L., Lopez-Machado, A. L., Galindo, R., Cano, A., Espina, M., Ettcheto, M., Camins, A., Silva, A. M., Durazzo, A., Santini, A., Garcia, M. L., & Souto, E. B. (2020). Metal-Based Nanoparticles as Antimicrobial Agents: An Overview. *Nanomaterials*, *10*(2), 292. https://doi.org/10.3390/nano10020292

Singh, P., Kumari, R., & Lal, R. (2017). Bedaquiline: Fallible Hope Against Drug Resistant Tuberculosis. *Indian Journal of Microbiology*, *57*(4), 371–377. https://doi.org/10.1007/s12088-017-0674-0

Soroka, D., Ourghanlian, C., Compain, F., Fichini, M., Dubée, V., Mainardi, J.-L., Hugonnet, J.-E., & Arthur, M. (2016). Inhibition of β-lactamases of mycobacteria by avibactam and clavulanate. *Journal of Antimicrobial Chemotherapy*, dkw546. https://doi.org/10.1093/jac/dkw546

Spohn, R., Daruka, L., Lázár, V., Martins, A., Vidovics, F., Grézal, G., Méhi, O., Kintses, B., Számel, M., Jangir, P. K., Csörgő, B., Györkei, Á., Bódi, Z., Faragó, A., Bodai, L., Földesi, I., Kata, D., Maróti, G., Pap, B., … Pál, C. (2019). Integrated evolutionary analysis reveals antimicrobial peptides with limited resistance. *Nature Communications*, *10*(1), 4538. https://doi.org/10.1038/s41467-019-12364-6

Staroń, A., & Długosz, O. (2021). Antimicrobial properties of nanoparticles in the context of advantages and potential risks of their use. *Journal of Environmental Science and Health, Part A*, *56*(6), 680–693. https://doi.org/10.1080/10934529.2021.1917936

Torres-Barceló, C. (2018). Phage Therapy Faces Evolutionary Challenges. *Viruses*, *10*(6), 323.

https://doi.org/10.3390/v10060323

Unckless, R. L., Howick, V. M., & Lazzaro, B. P. (2016). Convergent Balancing Selection on an Antimicrobial Peptide in Drosophila. *Current Biology*, *26*(2), 257–262. https://doi.org/10.1016/j.cub.2015.11.063

Uribe, R. V., Rathmer, C., Jahn, L. J., Ellabaan, M. M. H., Li, S. S., & Sommer, M. O. A. (2021). Bacterial resistance to CRISPR-Cas antimicrobials. *Scientific Reports*, *11*(1), 17267. https://doi.org/10.1038/s41598-021-96735-4

Vercoe, R. B., Chang, J. T., Dy, R. L., Taylor, C., Gristwood, T., Clulow, J. S., Richter, C., Przybilski, R., Pitman, A. R., & Fineran, P. C. (2013). Cytotoxic Chromosomal Targeting by CRISPR/Cas Systems Can Reshape Bacterial Genomes and Expel or Remodel Pathogenicity Islands. *PLoS Genetics*, *9*(4), e1003454. https://doi.org/10.1371/journal.pgen.1003454

Wang, J.-Q., Yang, Y., Cai, C.-Y., Teng, Q.-X., Cui, Q., Lin, J., Assaraf, Y. G., & Chen, Z.-S. (2021). Multidrug resistance proteins (MRPs): Structure, function and the overcoming of cancer multidrug resistance. *Drug Resistance Updates*, *54*, 100743. https://doi.org/10.1016/j.drup.2021.100743

Wu, Y., Battalapalli, D., Hakeem, M. J., Selamneni, V., Zhang, P., Draz, M. S., & Ruan, Z. (2021). Engineered CRISPR-Cas systems for the detection and control of antibiotic-resistant infections. *Journal of Nanobiotechnology*, *19*(1), 401. https://doi.org/10.1186/s12951-021-01132-8

Yanagihara, K., Tashiro, M., Fukuda, Y., Ohno, H., Higashiyama, Y., Miyazaki, Y., Hirakata, Y., Tomono, K., Mizuta, Y., Tsukamoto, K., & Kohno, S. (2006). Effects of short interfering RNA against methicillin-resistant Staphylococcus aureus coagulase in vitro and in vivo. *Journal of Antimicrobial Chemotherapy*, *57*(1), 122–126. https://doi.org/10.1093/jac/dki416

Yu, B., Wang, Z., Almutairi, L., Huang, S., & Kim, M.-H. (2020). Harnessing iron-oxide nanoparticles towards the improved bactericidal activity of macrophage against Staphylococcus aureus. *Nanomedicine: Nanotechnology, Biology and Medicine*, *24*, 102158. https://doi.org/10.1016/j.nano.2020.102158

Zhanel, G. G., Sniezek, G., Schweizer, F., Zelenitsky, S., Lagacé-Wiens, P. R. S., Rubinstein, E., Gin, A. S., Hoban, D. J., & Karlowsky, J. A. (2009). Ceftaroline. *Drugs*, *69*(7), 809–831. https://doi.org/10.2165/00003495-200969070-00003