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Research Article

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The Ongoing Effort to Thwart Antimicrobial Resistance

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Abstract

Eighty years ago Nobelist Alexander Fleming predicted the development of antimicrobial resistance. In recent years, research has demonstrated new bacterial resistance actions suggesting our attempts to thwart antimicrobial resistance may never be fully realized. Recently identified resistance mechanisms are reviewed with important implications for human health. Importantly, several new and invigorated approaches and concepts to thwart antimicrobial resistance are explored and are reviewed, including a role for Artificial Intelligence and CRISPR-Cas9. The combined effort and thrust of innovative research will continue to make progress to impede antimicrobial resistance.

Keywords: Antimicrobial resistance; Mechanism of bacterial resistance; Development of new antimicrobials; Artificial Intelligence

Introduction

Presentations shared two decades ago along with recent reports on innovative uses of Artificial Intelligence (AI) and new scientific microbiologic findings prompted this commentary. The presentations were from Nobel Laureates in 1945 and 1965. The first lecture was from Alexander Fleming in 1945 when he delivered his Nobel prize acceptance speech for the discovery of penicillin [1]. In that talk, he predicted that with overuse of penicillin, bacteria, specifically Staphylococcus, would soon become resistant to the inhibitory capacity of penicillin. In the second presentation by Francois Jacob in 1965, one of the three Nobelists who won the prize that year for their studies on the lac operon model in *E. coli* and diauxic growth of bacteria, Jacob stated that "it is the dream of every bacterium to become two" [2]. With that simple statement he summarized the inherent driving force of bacteria to multiply and overcome inhibitory compounds and was an early prediction of the issue of antimicrobial resistance. In the following, recent discoveries of new resistance mechanisms and innovative methods such as AI and CRISPR used to thwart resistance are reviewed.

New Antimicrobial Resistance Mechanisms

In the more than sixty years since Jacob's presentation, the concerns about antimicrobial resistance continue to plague science. Recent articles suggest that our attempts to thwart antimicrobial resistance may never be fully realized. The communication from Li et al [3] proposes that the inhibitory activity, specifically, the bactericidal action of selected antibiotics are associated with increases in ATP consumption, cellular respiration, and the formation of reactive oxygen species. These bacterial self-protective activities, which Li and colleagues refer to as "bioenergetic stress" reinforce the development of antibiotic resistance. The concept that the antimicrobial activity of antibiotics enhances bacterial self-protective mechanisms and contribute to resistance has never before been posited. Additionally, Li et al note that the effects of bioenergetic stress contributes to antibiotic persistence, the impact of antibiotics on dormant bacteria that can lead to resistance.

Further, new mechanisms of resistance continue to be revealed. Another recently identified concern is the threat of bacteria acquiring antimicrobial resistance via the acquisition of mobile integrons [4]. Mobile integrons represent genetic elements that promote rapid bacterial adaptation. Mobilized by transposons, these elements are capable of supporting countless anti-phage and an-

timicrobial resistance cassettes, ARCs. Initially discovered in the 1950s, these ARCs, common to several Gram-negative species have been known to enter the hospital environment and contribute to intrahospital antimicrobial resistance. The potential application of phage therapy, which has been considered and trialed to combat resistance, may also be threatened by ARC effects [5]. The outcome of each of these advances to prevent bacterial infections have resulted in resistance in experimental and clinical settings [5].

In other research, Adedeji-Olulana et al [6] uncovered that MRSA (methicillin-resistant *Staphylococcus aureus*) adopts an alternate mode of cell division that requires modified peptidoglycans of the cell wall to escape methicillin activity. This mechnism is another newly identified resistance technique emplyed by bacteria.

New Approaches to Combat Resistance

Given the newly identified resistance mechanisms, novel approaches are needed to address and prevent their impact. Several new and invigorated approaches and concepts to thwart antimicroial resistance are summarized in (Table1).

Innovations	Reference
Phage Therapy	5
Development of New Antimicrobials with Unique MOAs	7
Enhancing Clinicians' Knowledge and Approaches using AI to Develop Novel and Targeted Treatment of Infections.	8, 9
mRNA Vaccines Targeted vs. ESKAPE Microorganisms	10
Application of CRISPR-Cas9 to Delete Resistance Genes	11

Table 1: Summary of Novel Concepts to Thwart Antimicrobial Resistance.

Key Abbreviations

AI: Artificial intelligence, CRISPR-Cas9: Clustered Regularly Interspaced Short Palindromic Repeats- CRISPR-associated protein 9, ESKAPE: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp,* MOA: Mechanism of Action.

Some may propose that the approach to addressing ongoing antimicrobial resistance and the associated morbidity and mortality is to develop new antibiotics with unique modes of action. Wu et al [7] designed and synthesized a distinctive bridged macrocyclic antibiotic antibiotic compound, cresomycin. However, antimicrobial resistance persisted. Uncovering other unique antimicrobial pathways could be developed using large language learning and AI techniques [8]. In addition, use of assisted computerized AI tools, as described by Amsterdam [8] and Harandi [9], are becoming more commonplace in efforts to combat resistance. Harandi, et al [9] provides an expansive review that addresses how AI and machine learning (ML) can control and/or limit antimicrobial resistance in different global settings of high-income countries and low and middle income countries. The authors summarize the proposed application of various algorithms for selection of empiric antibiotics or prediction of antibiotic resistance such as antibiotic change intervention via antibiotic stewardship, dose adjustment and/or dose adequacy Multiple algorithms were used which included logistic regression, XG boost, and light GBM among others. In Amsterdam [8] the application of AI coupled with ML and antibiotic stewardship in the local hospital setting i.e. within a medical center and/or community, is explored. AI tools can help clinicians and clinical microbiological laboratories must remain on the "cutting edge" and knowledgeable about the advances of technical initiatives and breakthroughs noted above. They must be able to rapidly apply innovations for patient assessment and care. Using such systems would allow medical practioners in different clinical settings in high-income or low and middle income countries to administer the "right antimicrobial agent at the "right" time and duration, to the "right" patient, the key tenets of antimicrobial stewardship [10], needed to limit overuse of antimicrobial agents thus thwarting resistance.

Another novel way to curb bacterial infections and limit the associated morbidity and mortality, could be the development of vaccines akin to mRNA viral vaccines. Bergstrom et al [11] have proposed this approach. However, it would be onerous to conceive of the synthesis and manufacture of mRNA vaccines for all known bacterial pathogens. But, clearly, limiting the number to the most egregious species would seem prudent and advisable. The target for the selected development of bacterial mRNA vaccines would be the ESKAPE group of microorganisms namely: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp*.

An alternative approach to limiting antimicrobial infections' development of resistance and the associated complications could be the utilization of the cellular surgical tool, CRISPR-Cas9. Zohra et al [12] have commented on this innovation. This would require identification of the specific bacterial gene(s) responsible for the identified resistance and upon "CRISPR-Cas9 surgical correction' enable the antibiotic-susceptible bacteria to "take over" the bacterial population; this approach is the challenge.

Conclusion

Although the search for effective antimicrobial agents is ongoing and has recently been invigorated by AI, the likelihood of eliminating antimicrobial resistance remains a challenge. Scientists

have realized that when an effective new antimicrobial agent is discovered, its ongoing use in that directed bacterial population wanes due to previously unrecognized resistance mechanisms. The combined effort and thrust of innovative research will impede antimicrobial resistance. Continued education, awareness, and antimicrobial stewardship will enable scientists to thwart the scourge of increasing antimicrobial resistance and the associated morbidity and mortality facing humankind.

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