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Review Article

RECENT PROMISING ADVANCES IN DEVELOPMENT OF ANTIMICROBIAL AGENTS: A REVIEW

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ABSTRACT

Antimicrobial resistance is a serious global threat. There is a global menace of antibiotic resistant “super bug”, though the extent and the severity of the problem varies. Resistance hampers therapeutic options and drives clinicians to use newer and more expensive drugs. In serious cases, multi-resistance provides no treatment options. To overcome resistance, a continuous supply of new antibiotics offers an obvious way; but the pipeline of agents in development by the Pharmaceutical industry is very limited. There is an ever-evolving need to develop and evaluate newer alternative strategies for countering a worsening clinical situation to overcome resistance and reduce the morbidity and mortality associated with infections caused by antibiotic-resistant bacteria. The widespread distribution of Antimicrobial resistance has not been paralleled by the development of newer antimicrobials. This happens due to the process of drug discovery and clinical trials of new antimicrobials taking longer time and only a few new agents been approved for use. In modern era, where obstacles like chemo-resistance and mutations torment medicine, scientists across the world are looking to adapt lateral approaches in encountering diseases.

Keywords: antimicrobial resistance, super bug, antibiotics

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INTRODUCTION

Antimicrobial resistance is a serious global threat. There is a global menace of antibiotic resistant “super bug”, though the extent and the severity of the problem varies^{1, 2}. Resistance hampers therapeutic options and drives clinicians to use newer and more expensive drugs. In serious cases, multi-resistance provides no treatment options. To overcome resistance, a continuous supply of new antibiotics offers an obvious way; but the pipeline of agents in development by the Pharmaceutical industry is very limited. There is an ever-evolving need to develop and evaluate newer alternative strategies for countering a worsening clinical situation to overcome resistance and reduce the morbidity and mortality associated with infections caused by antibiotic-resistant bacteria^{3, 4}. The widespread distribution of Antimicrobial resistance has not been matched up to by the

development of newer antimicrobials. This occurs because the process of drug discovery and clinical trials of newer antimicrobials taking longer time and only a few new agents been approved for use⁵.

In this review paper, we will briefly focus on novel antimicrobial strategies tackling antimicrobial resistance.

DEVELOPMENT OF NEW ANTIMICROBIALS

Majority of antimicrobial obtained from different natural sources tend to cause inhibition of various cellular processes viz. DNA replication, cell wall biosynthesis, and protein synthesis. However with the increase of AMR, the investigation of alternative essential cellular processes has been screened, as the drug targets for the next progeny of antimicrobials⁶. For instance, bedaquiline is a drug targeting the FOF1 ATP synthase⁷.

Irrespective of architectural conservation of the bc1 complex in many species, Q203- an optimized imidazopyridine amide selectively inhibits the respiratory cytochrome bc1 complex in mycobacteria similar to bedaquiline⁸. Another promising strategy for antimicrobial activity can be caused by attacking the central cell wall division mediator FtsZ, which leads to the inhibition of Bacterial cell division. This antimicrobial attack can occur either by interfering with the normal dynamics and activity of FtsZ during the cell cycle. It can also lead to the activation of a protease bacterial enzyme to cause destruction of FtsZ, therefore inflicting microbe death during a self-destructive manner⁹.

Another attractive newer site of drug action- an asymmetric outer cell membrane in Gram-negative bacteria has been observed. This outer membrane is a permeability barrier and tends to save the cell from the various external stresses and forces like the presence of antimicrobials. By interacting with the selected β -barrel outer membrane proteins including BamA and LptD, a novel macrocyclic peptide, JB-95, shows selective disruption of the outer cell membrane of the Gram negative bacteria^{10, 11, 12}. Likewise, a target for removal of Pathogens is by targeting the bacterial protein secretion pathway. Employing the Sec-pathway for antimicrobial activity is based on two principles; SecA, the energy driven motor protein causing the movement of pre-proteins across the membrane and Type I signal peptidase enzyme, that leads to removal of signal peptide to cause release of mature proteins from the cytoplasmic membrane¹³. Another strategy to overcome resistance is by employing them in combination with the standard antimicrobial drugs. AMR occurs by: inactivation of drug, reduced permeability of the drug, change in drug target and increase in the efflux of the drug. In response to physiological signals, efflux pumps serve important physiological functions¹⁴⁻¹⁷. Many recent researches have tried to revert the resistance phenotype of efflux pump activation¹⁸. Adding efflux pump inhibitors partially improved the potency and efficacy of the drug in anti-Mycobacterium drug therapy¹⁹. Designing and structuring of compounds with β -lactam is a promising approach to the development of metallo- β -lactamase inhibitors such as penicillin derivatives, carbapenem derivatives, cephalosporin derivatives, etc²⁰.

DEVELOPMENT OF iCHIP DEVICE

Procedure to cultivate microorganisms under lab conditions remained the same for so many years and a large population of these microorganisms failed to grow. This is called the Great plate Anomaly which is the observation that most of the microbes seen in the microscope cannot currently be grown under laboratory conditions, some may actually be nonviable, and others are viable but non culturable²¹. The researchers couldn't study the chemicals that were released by these microbes which showed antimicrobial activity and which could serve as a potential for the synthesis of antibiotics. However, many years later, a device was made which could grow many samples together. This new device was known as iChip. Researchers had to dip this chip in the

bacterial stock, added with agar, which locked the sample inside the secure diffusion membrane, placed in a large stock sample from the original environment. Every cell then acts as a small diffusion chamber. Thousands of new bacteria have now been cultured by iChip and development of newer antibiotics for e.g. Teixobactin²²⁻²⁶.

PEPTIDOMIMETIC ANTIMICROBIALS

Antimicrobials that occur naturally or can be synthesized as antimicrobial peptides (AMPs) could form a basis for the development of newer functional classes of antimicrobials^{27, 28}. Antimicrobial peptides, being selective agents, show their activity on the prokaryotic membrane. These cause membrane modifications which leads to total membrane disintegration^{29, 30, 31}. However, the clinical utilization of AMPs has been limited. The AMPs show high susceptibility to proteolytic enzymes, may cause toxicity due to larger quantities of drug needed for therapy and above all cost manufacturing³². Also other characteristics that may restrict use of AMPs include higher protein binding and high clearance causing a decreased half life. To overcome these limitations, generation of proteolytically resistant moieties of natural peptides by complete or partial substitution of L-moieties with synthetic or non natural D- or B- moieties is been studied. McGrath et al. synthesized a newer peptide called as (KLAKLAK)₂ which showed decreased toxicity to the mammalian cells^{33,34}.

FimH-INHIBITORS

Uropathogenic E. coli (UPEC), the organism responsible for causing more than 85% of all Urinary tract infections have progressively become more resistant to antibiotics. AMR is not just restricted to community agents but broad spectrum antimicrobials like Beta-lactams and fluoroquinolones, thereby causing a therapeutic problem^{35, 36}. UPEC invades the urinary tract by using type 1 pili tipped with the FimH adhesin to attach to mannose receptors present on the luminal surface of the human bladder epithelial cells. Thereby causing the process of colonization and invasion of bacteria in the bladder. As a part of innate defense mechanism, bladder cells can expel UPEC from the epithelial cells, but a single bacterial cell can replicate to 104-105 which can then combine in a type 1 pilus-dependent manner to form an intracellular bacterial community (IBC) within the epithelial cell. After IBC mature, bacteria detach from the IBC and spread to other neighbouring cells to form several further IBCs. FimH is necessary for invasion, IBC formation and the capability of bacteria to invade and colonise the bladder. Therefore, agents that target the FimH are been developed. In every strain of E.Coli, the mannose-binding pocket of FimH is composed of amino acid residues. Changes in these residues which are same in all strains disrupt mannose binding and attenuate virulence³⁷. Basically FimH inhibitors were derived from mannosides that consist of D-mannose units. FimH inhibitors show excellent cellular potency and low molecular weight. Cusumano et al.³⁸ generated a series of 6 candidates with an aim to

generate orally available agents which can be a therapeutic option to treat and prevent chronic UTI^{39,40}.

QUORUM SENSING APPROACHES

Management of *P. aeruginosa* infections involves complex fluid and ventilator management, definitive surgical debridement and advanced technologies. In addition, various antimicrobial agents are also employed against antibiotic resistant strains of *P. aeruginosa* such as colistin. Studies in *P. aeruginosa* pathogenesis has revealed a complex regulatory communication system, called as quorum sensing (QS), which is responsible for controlling about 10% of *P. aeruginosa* genes⁴¹. Quorum sensing (QS), is a cell-density-dependent process, which is based on the release of low-molecular weight moieties that co-ordinate gene expression in a given cell population⁴². *P. aeruginosa* releases moieties, in response to high population density, which act as specific chemical signals. These chemical signals control the synthesis of virulence factors that manifest acute infection. The QS regulator termed as multiple virulence factor regulator (MvfR) helps in controlling the expression of majority acute virulence of *P. aeruginosa*'s factors that manifest acute infection in addition to several various excreted anthranilic acid derivatives, majority of which constitute the 4-hydroxy-2-alkylquinolines (HAQs) family. These HAQs, in combination with MvfR, serve in the positive regulation of the transcription of two operons which encode biosynthesis of the virulence molecules. Que et al.⁴³ showed the presence of HAQs in necrotic burn tissue, fat, pus and liquefied fat and drainage liquid. They proposed that by targeting QS using anti-QS inhibitors may reduce infections caused by MDR bacteria. Hence QS could be a promising drug target for new antimicrobials because it controls pathogenesis of disease and is evolutionarily conserved among pathogenic bacteria⁴⁴.

NEWER TARGETS FOR THE NEXT GENERATION ANTIMICROBIALS FOR COMBATING DRUG RESISTANCE

In today's world various good potent antimicrobials are used. However with the development of antimicrobial resistance, these have been rendered almost less effective. Mostly they act as bacteriostatic and work either by inhibition of protein or cell-wall synthesis. This situation stresses on the need for creation and designing of newer antimicrobial agents with exploring newer targets.

Targeting bacterial proteins

Antimicrobials can act on newer bacterial proteins for e.g. by inhibiting the enzyme β -ketoacyl-acyl-carrier-protein synthase I/II which is required for fatty-acid biosynthesis in bacteria. One such agent, Platensimycin is in pre-clinical trials which targets enzymes involved in the fatty acid biosynthesis⁴⁵.

Targeting the virulence factors

Toxin function could be a potential target for virulence inhibitors. For instance catalytic activity of *B. anthracis* lethal factor; toxin delivery by blocking various bacterial

systems such as type II or type III secretion; virulence gene expression regulated by virulence gene and bacterial attachment to host cells⁴⁶.

Modulating the host response pathways

Antimicrobial peptides that activate the adaptive immune response to combat infections are produced by toll-like receptor activators and modulators. These may potentially have an antimicrobial role⁴⁷.

Therapeutic use of bacteriophages

Genes can be delivered via delivery bacteriophage that can bind and inactivate bacterial DNA for e.g. small, acid-soluble protein (SASPs) genes could be delivered to *S. aureus* by a *S. aureus*-specific delivery bacteriophage; this results in the release of SASPs which then bind to and cause inactivation of bacterial DNA⁴⁸.

Antibiotics with bioenhancers

Bioenhancer tend to increase the systemic availability and potency of a drug with which it is administered with. The bioenhancer doesn't possess any pharmacological activity of its own at the therapeutic dose used⁴⁹. It is employed to increase the potency and efficacy of the commonly used antibiotics. For e.g. Tetracycline with non-antibiotic Loperamide, increases the activity of tetracycline by enhancing its permeability⁵⁰.

Novel strategies for antibacterial drug discovery

Majority of the current traditional approaches for antibacterial drug discovery have become saturated. This has paved way for the development and exploration of newer strategies in antibacterial drug discovery.

Antimicrobial peptides

AMPs work by interfering with metabolism, acting on cytoplasmic components and causing disruption of cell membranes. These work as immunomodulators, increase the immunity and therefore serve as newer potential therapeutic target. Examples are dermaseptin (from frog skin), defensin and crustin (from crustacean family) etc. omiganan and pexiganan are the drugs under clinical trials in this class⁵¹.

Engineering a prodrug

Employing a prodrug form of a drug, which gets transformed into a highly potent drug within the micro-organism, is another strategy. This can help to bypass the common resistance mechanisms and thereby serves as a promising avenue for new drug development.

Engineering hybrid antibacterial drugs

Combination of two drugs can serve as potential to overcome antibiotic resistance. For e.g. Mutilin-quinolone hybrid AM-3005 (Type II topoisomerase inhibitor + a protein synthesis inhibitor) can cover two targets simultaneously⁵².

Alternative form of drug delivery methods

Unorthodox forms of drug delivery methods can be employed such as treatment of chronic *P. aeruginosa* lung infections in cystic fibrosis patients by using inhaled amikacin available as nanoscale liposomal

formulation. Advantages of this are biofilm penetration and sustained release from liposomes and hence serve as alternative form of drug delivery method⁵³.

Herbal derivatives as lead molecules

Plant drugs and their derivatives can work as lead molecules and play a vital role in new drug discovery and development. A recent study of Nautiyala *et al.*

observed that 1 hr treatment with medicinal smoke, lead to 94% reduction of bacterial counts⁵⁴.

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