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Research Article

RECENT ADVANCES IN ANTIBACTERIAL DRUG DEVELOPMENT

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ABSTRACT

Rapid rise in antibiotics resistance among bacteria becomes a serious health problem. To solve it, a multitude of efforts has been undertaken in recent years. In the short review, we describe major strategies employed in the last 2 years and how they impact the future drug development.

INTRODUCTION

In recent years, there has been a rapid rise in antibiotics resistance worldwide. While the problem has gained attention in the press, the situation may not be as critical portrayed.

The steady rise in resistance over last 20 years has led to selection of 2 classes of antibiotics: β-lactamase and DNA gyrase/topoisomerase inhibitors. While the former is effective against non-metal dependent β-lactamases and relatively safe, the latter is connected to many serious side effects and not as safe as the former. Recent appearance of metal-dependent β-lactamases has provided a health problem for hospitals and pharmaceutical companies. Therefore, there have been attempts to find novel treatments which would overcome the resistance. In the current short review, the focus will be on the recent 2 years of research.

Established drugs, novel delivery

Reactive oxygen species generators. Song *et al.* (Song, 2016) used conjugates of TiO_2as a photocatalyst to ssDNA aptamers, selected specifically for binding to *E. coli*, in measuring pathogen's sensitivity towards UV radiation. The conjugates were able to reduce bacterial load by 2 orders of magnitude within 30 min.

Cell wall synthesis

Ampicillin. Aptamers targeting bacterial flagella were selected for *Salmonella choleraesuis* and conjugated to ampicillin (Lijuan, 2017). The combination was able to penetrate biofilms and at 10μM aptamer concentration prevented biofilm formation.

Vancomycin. Formation of polymers with a controlled release of drug was shown for pegylated oleic acid conjugates of vancomycin (Omolo, 2017). The conjugates formed micelles which were effective against *S. aureus* and multidrug resistant *S. aureus* (MRSA) for up to 3 days while non-conjugated vancomycin kept its activity for up to 24 hr.

In Lipid-dendrimer hybrid nanoparticles (LDHN) (Sonawane, 2016). Prepared LDHNs of vancomycin had a very uniform size with 55 nm diameter. The formulation was slightly worse than bare vancomycin in killing bare *S. aureus* and MRSA but had a 4-day stability period after preparation.

Bacitracin. Bacitracin was encapsulated in a polymer by Hong *et al*. (Hong, 2017). The encapsulation rendered bacitracin bactericidal against *E. coli*, *P. aeruginosa* and *S. typhimurium* and was only slightly worse than standard polymyxin B treatment of its normal Gram-positive targets: *S. aureus*, *S. pneumonia* and *T. pyogenes*.

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Antibiotics sensitizers. The approach was demonstrated for *Burkholderia sp*. A biodegradable polymer composed of N-acetyl-glucosamine (PAAG) was used (Narayanaswamy, 2017) as a potential antibiotic delivery vehicle by Narayanaswamy *et al*. in a combination of 3 primary antibiotics. The formulation showed a significant synergy in the presence of polymer.

Old targets, novel drugs

DNA gyrase/topoisomerase IV. A novel bifunctional inhibitor of DNA gyrase and topoisomerase IV linked to a oxabicyclooctane was tested by Tan *et al*. (Tan, 2017). The combination was able to clear *S. aureus* infection in mice model of infection by *i.v.* or *p.o.* routes with the former route more efficient than the latter.

A novel inhibitor of DNA gyrase/topoisomerase IV was testedagainst *N. gonorrhoeae* (Farrell, 2017). The novel antibiotic could clear bacterial growth of 2 *N. gonorrhoeae* isolates within 24 h at 5-10 times MIC_{50} concentrations.

Random screening. A series of aminopyrimidinyl benzimidazole derivatives (Liu, 2018) was made and used for phenotypic screening. It identified a lead compound with MIC_{50} below 10 μg/mL. The compound had MIC_{50} below 10 μg/mL against *P. aeruginosa*, *S. aureus* and MRSA. Potential target, DNA gyrase, was suggested by *in silico* methods.

Cvijetic *et al*. (Cvijetic, 2017) used ciprofloxacin as a related scaffold for aryl diketo acids derivatives. Testing identified 1 compound with reasonable values against *S. aureus* and *E. faecalis* but not *B. subtilis*. Virtual docking of compounds to known bacterial targets suggested that best compound was the most promiscuous.

Metabolic pathways

Methionine aminopeptidase. John *et al*. (John, 2016) used an HTS phenotypic screen to find small molecule inhibitors against *M. tuberculosis* enzymes, MtMetAP1a and MtMetAP1c. The best compound had IC_{50} values about 5 μM against bacterial enzymes while at least 30 times higher values against human orthologues HsMtAP1 and HsMtAP2. The MIC_{50} values against replicating and non-replicating *M. tuberculosis* were determined at 5-10 μg/mL and around 2 μg/mL, respectively.

Histidine kinases. Velikova *et al*. (Velikova, 2017) incorporated previously identified (Velikova, 2016) small molecule inhibitors into poly-L-Lysine-caped nanoparticles. The formulation increased the potency of inhibitors up to 90 times compared to bare compounds against *E. coli* and *S. marcescens* with the best compounds having MIC_{50} around 6 μg/mL. The formulation also easily penetrated zebrafish embryos and did not interfere with the LPS response of raw macrophages.

Efflux pumps

AcrB efflux pumps. Aron and Opperman (Aron and Opperman, 2016) optimized pyranopyrimidine compounds to obtain a novel compound with very good pharmacokinetic properties. The efficacy of the compound in blocking drug resistance was reported by Sjuts *et al*. (Sjuts, 2016) and shown that the best compound had biological activity at 0.1 μM concentration when tested for potentiation of time killing by ciproflaxacin in *E. coli*.

Wang *et al*. (Wang, 2017) optimized 2-naphtamide derivatives for inhibition of AcrB pump in *E. coli*. The best compound showed significant biological activity at concentrations around 500 μg/ml, could not penetrate the outer bacterial membrane and did not disturb inner membrane potential in bacteria.

NorA efflux pumps. Coelho *et al*. (Coelho, 2016) showed that some terpenoids could potentiate sensitivity to norfloxacinin a NorA-expressing strain of *S. aureus*. The best compounds could halve drug resistance at 128 μg/mL concentration.

Capsular saccharides

Lipopolysaccharide. Nielsen *et al*. (Nielsen, 2017) immunized mice with sub-lethal concentration of hypervirulent *A. baumannii* and isolated a monoclonal antibody against capsular saccharides. The antibody could enhance phagocytosis of opsonized human macrophages for the hypo- and hypervirulent strains of *A. baumannii*. In a *i.v.* infection mice model of sepsis, the protection of animals from pathogen by antibody decreased with the increased time of post-infection antibody application. However, almost complete protection required addition of bactericide colistin during treatment. Analogous experiments for aerosol delivery route showed that the delay of treatment of up to 4 h post-infection did not have effect on animal survival rates. Bacterial burden in lungs was reduced only by 2 orders by antibody treatment while the burden in blood - by at least 4 orders by the same treatment.

Biofilm

Biofilm production repression. A random screen of compounds was used to identify compounds for gene expression repression using *P. aeruginosapelB* gene as the readout by van Tilburg Bernardes *et al*. (van Tilburg Bernardes, 2017). The compounds showed approximately 50% reduction of biofilm formation at 20 μM concentration and an increase in survival rates of nematodes in *C. elegans* model of infection. The compounds also showed increase of *P. aeruginosa* PAO1 strain to antibiotics sensitivity, the largest for ciprofloxacin and gentamycin and less pronounced for colistin and polymyxin B. Sensitivity towards tobramycin was only marginally improved.
Biofilm dispersal. Dong *et al*. (Dong, 2016) used nanoparticles for biofilm removal by coupling encapsulated system generating NO under near infrared radiation (NIR) with synthetic quaternary ammonium salts. In the designed system, application of NIR caused generation of NO generation which removed biofilm and the exposed bacteria were then killed by quaternary ammonium salts. The system could remove up to 80% of biofilm in an *in vitro* experiment after optimization and could reduce bacterial loads on catheters by 8 orders of magnitude in a mouse model of biofilm formation.

Cell division

Straniero *et al*. (Straniero, 2017) selected an essential cell division protein FtsZ as their target to design novel drugs. Scaffold was selected based on known inhibitors of mammalian β-tubulin and derivatives were made synthetically. The strategy was to stabilize polymeric state of FtsZ which would prevent it from reusing during cell division and to preserve its GTPase activity. Selected compounds were shown to induce

polymerization of FtsZ at 20 μg/mL concentration and to enhance its GTPase activity. The best compounds showed Minimal Inhibitory Concentration at 50% inhibition (MIC_{50}) and Minimal Bactericidal Concentration at 50% inhibition (MBC_{50}) values below 10 μg/mL, with best compound having MIC and MBC values of 0.625 μg/mL against both *S. aureus* strains.

Cell wall synthesis

Mohammad *et al*. (Mohammad, 2016) used phenylthiazole-substituted aminoguanidines known to block cell wall synthesis by interfering with utilization of UDP-N-acetylmuramylpentapetide. A total of 3 compounds were tested against vancomycin-resistant *E. faecium* and *E. faecalis*, of which 2 showed acceptable toxicity towards *C. elegans*. The best compound had MIC_{50} values 0.5-64 μg/ml towards ESKAPE pathogens (*A. baumannii*, *E. coli* O157:H7, *E. cloacae*, *K. pneumoniae*, *P. aeruginosa*, *E. faecium*). The action was potentiated by inclusion of colistin in the treatment. The best compound could remove resistance or potentiate sensitivity of vancomycin-resistant *E. faecium* and *E. faecalis*.

Novel targets

Glutamate racemase. The enzyme is essential for peptidoglycan synthesis by interconverting L-glutamate to D-glutamate used in bacterial cell synthesis. The *B. cenocepacia* recombinant enzyme was expressed in *E. coli* and its activity analyzed in the presence of small molecule inhibitors by Israyilova *et al*. (Israyilova, 2016). The best one had IC_{50} above 512 μg/mL.

Phosphoribosyl-AMP cyclohydrolase. The enzyme was identified *in silico* as a drug target for *Brucella melitensis* by Gupta *et al*. (Gupta, 2018). Analysis of metabolic networks identified histidine biosynthesis pathway as a target and one of its enzymes, HisI, as a specific target. Computational search identified top scoring compounds which were selected and tested *in silico* for binding stability.

Iron-sulfur cluster. *S. aureus* is a facultative anaerobic pathogen. Mike *et al*. (Mike, 2013) identified small molecule compound with a highly different effect on pathogen: it was mildly toxic (IC_{50}≈160 μM) under aerobic conditions while very toxic (IC_{50}≈5 μM) during growth under anaerobic conditions. Analysis of the mechanism of toxicity identified Suf Fe-S cluster as the compound's target (Choby, 2017). It was suggested that blocking assembly of Suf Fe-S cluster during anaerobic growth led to blockage of virulence factors production by the pathogen.

Peptides

Peptidomimetics. Kuppusamy *et al*. (Kuppusamy, 2018) selected short, positively charged peptidomimetics based on biphenyl backbone as novel compounds against pathogenic bacteria. In biological tests of microbial killing of Gram-positive *S. aureus*, the best peptide 25g had MIC_{50}=15.6 μM. Tests of other peptides against *P.aeruginosa* showed that the best compounds had MIC_{50} values above 125 μg/mL. In a biological system, disruption of cytoplasmic membranes of *S. aureus* was observed at concentrations above 30 μM. Biofilm disruption was tested against *S. aureus* and *E. coli* at 250 μM.

Micrococcin. Degiacomi *et al*. (Degiacomi, 2016) used microcin P1 for antibacterial therapy against *M. tuberculosis*. The MIC_{50} value against pathogen was found to be in the sub-micromolar range using RAW 264.7 macrophage-like cell line infection model. The compound's target was identified as *rplK* gene and the mechanism was confirmed as inhibition of protein synthesis in mycobacteria.

Antimicrobial coatings

Floroian *et al*. (Floroian, 2016) employed laser to print metamaterials containing doxycycline on stainless steel. The metamaterial was composed of bioglass and poly-methyl methacrylate mixed with antibiotic doxycycline. The coating was stable for at least 80 days in a simulated body fluid and biofilm formation was negligible. Most of the doxycycline leaked out from the coating after 2 days which suggests that the effect of biofilm formation prevention was not due to the bactericidal effects of antibiotic. A closer examination of liquid-solid interface suggested that after 7 days there was a measurable absorption on the surfaces. Exposure of coated surfaces to *E. coli* and *S. aureus* for up to 24 h did not result in biofilm formation.

Unknown mechanism

AbdelKhalek *et al*. (AbdelKhalek, 2016) made derivatives of rhodanine and tested them pathogens. The compounds showed MIC_{50} below 10 μg/mL against every *E. faecalis*strain tested, including the vancomycin-resistant ones. The methicillin-resistant *S. aureus* (MRSA) strains were universally sensitive to the rhodanine compounds. Similar situation was observed for vancomycin-resistant *S. aureus* (VRSA), *B. anthracis* and *B. cereus, M. smegatis*, a substitute for *M. tuberculosis*, and *C. difficile*. However, none of the compounds was effective against Gram-negative pathogens: *P. aeruginosa*, *Acinetobacter spp*., *K. pneumoniae*, *S. typhimurium* and *E. coli*. The *C. albicans* strains were universally insensitive to all rhodanine compounds. Unfortunately, the antimicrobial activity disappeared when tested in the presence of 4% human serum albumin (HSA) in TSB medium.

CONCLUSIONS

Review of recent approaches to combat drug resistant bacteria suggested that the majority of approaches were based on 2 basic strategies: a) use of old drugs in different formulations or b) use of old targets and potentially novel drugs. While the former does not deal with drug resistance directly, the latter addresses the key problem of finding new drugs against ever drug-resistant pathogens. A small part of studies tried to identify novel targets for pathogens which may lead to completely new treatments for bacteria. Among them were attempts to use *in silico* system analysis to identify potential targets and the old fashioned phenotypic screening of potential antibacterial hits. The use of *in silico* tools is becoming more widespread as the availability of DNA sequences allows for reconstruction of metabolic pathways and the biology of pathogens to a large degree. In the future, designing novel drugs, antibiotics or indirect-acting compounds and strategies, by employing system biology tools, may become a solution of choice for many groups. The strategy is relatively cheap, fast and would level the playing field for groups independently of their financial resources. In other words, the time of new drug

designs in academia or small-to-medium companies is becoming a reality.

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