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MRSA Infections: From Classical Treatment to Suicide Drugs

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Abstract: Infections caused by the methicillin-resistant *Staphylococcus aureus* (MRSA) are today a major burden in nosocomial disease control. The global trend shows an alarming increase of MRSA infections as well as multi-drug resistance (MDR). The problem is exacerbated by the fact that infections with community-associated (CA) MRSA strains showing increased virulence and fitness add to infections with multi-drug resistant hospital-associated (HA) MRSA. The toxicity of pathogens and limited effectiveness of available treatment have led to high mortality rates and vast expenses caused by prolonged hospitalization and usage of additional antibiotics. Recently approved drugs still have classical targets and upcoming resistance can be expected. In a new approach by targeting co-factor syntheses of bacteria, the drug target and the affected pathways are uncoupled. This novel strategy is based on the thought of a classical pro-drug which has to be metabolized before becoming toxic for the bacterium as a dysfunctional co-factor, named suicide drug. Ideally these metabolizing pathways are solely present in the bacterium and absent in the human host, such as vitamin biosyntheses. This mini-review discusses current ways of MRSA infection treatment using new approaches including suicide drugs targeting co-factor biosyntheses.

Keywords: B vitamins, co-factor starvation, drug discovery, MRSA, multi drug resistance, pro-drug, suicide drug.

INTRODUCTION

S. aureus is a commensal gram-positive bacterium that colonizes mostly the nasal mucosa of 20 % of the healthy population permanently and up to 60 % transiently [1, 2]. This colonization is a risk factor and a correlation was indicated between colonizing strains and subsequent infections originating from this reservoir [3-5] in consideration of predisposition factors like surgery, catheters or wounds [4, 6, 7]. It has been estimated that up to 25 % of asymptomatic colonized individuals develop an infection with *S. aureus* [8]. Community-associated MRSA (CA-MRSA) strains emerged recently and differ significantly in terms of virulence, fitness and resistance patterns from hospital-associated MRSA (HA-MRSA) strains [9]. It has been reported that HA-MRSA strains acquired resistance to most antibiotics [10, 11], but showed reduced virulence in contrast to CA-MRSA strains [12]. CA-MRSA strains evolved in convergent evolution and caused epidemiologically unassociated outbreaks throughout the world [9, 11]. Skin and soft tissue infections (SSTI) account for approximately 90 % of clinical symptoms caused by CA-MRSA [9], but the infamous pandemic clone USA300 has been implicated also for fatal outcomes [13-15]. Previously, life threatening conditions like endocarditis, pneumonia and sepsis were only associated with immunocompromised individuals in the hospital environment [16].

Phenol-soluble modulin (PSM) peptides, a group of secreted staphylococcal peptides were identified in CA-MRSA to recruit, activate and lyse human neutrophils and thus countering the main human cellular defense [17]. Also the enhanced expression level of other toxins like alpha-toxin and Panton-Valentine leukocidin (PVL) have been discussed in terms of the altered virulence in CA-MRSA strains [18]. *in vitro* results exhibit a lower fitness burden linked to the methicillin-resistance mediating staphylococcal cassette chromosome *mec* (SCC*mec*) IV [19-21], which is characteristic for all CA-MRSA strains [9]. In summary, the occurrence of CA-MRSA infections in addition to infections with multi-drug resistant HA-MRSA strains increases the burden of *S. aureus* disease control.

The presence of multi-drug resistant strains is the consequence of antibiotic misuse for decades by treatment of non-bacterial infections with antibiotics or inadequate compliance with the regulations for drug ingestion and the exceeding ability of the pathogen to become progressively more resistant [22]. After launch of penicillin in the 1940s, *S. aureus* rapidly evolved specific resistance mechanisms [23] (*i.e.* beta-lactamases [24]), prompting the development of novel compounds (*i.e.* oxacillin) to be used for treatment of these penicillin resistant strains [25]. However, only few years after introduction of oxacillin into general therapy guide lines, methicillin-resistant strains were recognized being oxacillin-resistant through expression of a new variant

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of the penicillin binding protein 2 (PBP2) [26]. For years vancomycin was the drug of choice for treating these infections caused by MRSA. Intriguingly, first reports now recognized the appearance of MRSA strains exhibiting a reduced susceptibility even against vancomycin [27].

Although the epidemiology is subject to temporal alteration, the occurrence of methicillin-resistant *S. aureus* isolates in Europe is clearly an alarming factor. In twelve of 28 countries participating in the surveillance program, resistance exceeds 20% [22]. In Hungary, Spain and France levels of over 20 % remain stable within the last years. The UK and Ireland were able to decrease levels by 50%, by implementation of national surveillance systems [28, 29], consequential changes in antibiotic prescription and improvement of hygiene in the hospitals [30, 31]. However, the actual level is still high. The highest number of positive isolates were identified (>50 %) in Rumania and Portugal. Even in Scandinavia and the Netherlands, revealing a lower occurrence of MRSA positive isolates, the frequency of resistant strains is increasing [32, 33] (Fig. **1**). Within 29 European countries 25,000 patients die each year due to MRSA infections [22]. Therefore the development of drugs with efficient antimicrobial activity represents the highest priority for the WHO in Europe [22].

In comparison to the situation in Europe, in other parts of the world like USA, Taiwan, Hong-Kong, Singapore, Japan, much of South America, as well as in the Middle East the rate of MRSA occurrence is even exceeded [33-36].

The global prevalence of colonized individuals has transferred the problem from predominantly industrial countries also to tropical and developing countries. Therefore, it has been recently considered as a novel neglected disease in Africa [37].

Furthermore, the conjunction with the opportunistic pathogen *S. epidermidis* plays a critical role in staphylococcal infections. *S. epidermidis* is the most frequently found bacterium among coagulase negative staphylococci [38]. It is able to produce biofilms, a complex extracellular matrix, which protects it and other pathogens like *S. aureus* from host-defense mechanisms or antibiotics [39, 40]. These biofilms facilitate to bypass the epithelial barrier during infection or at catheter entry-sites [41]. Bacteria living in biofilms show a reduced activity of distinct cell processes, which makes it difficult for antibiotics to interfere with the cell division, DNA replication and protein biosynthesis and to efficiently inhibit these bacterial targets [42].

Bioinformatics tools, combining active site parameters to analyze the druggability of proteins revealed that proteins involved in vitamin biosyntheses are scored within the highest category as druggable [43]. The respective pathways are absent in humans and therefore reduced side effects can be expected.

So far, in terms of serving as a drug target, co-factors have been examined sparsely and hence could be the basis for the development of an entire new drug discovery strategy. This strategy starts with a component that infiltrates the co-factor pathway, appearing like a substrate and is metabolized - taking up the idea of a pro-drug which is an inactive compound and must be converted into a biologically active substance by metabolic processes. As already outlined before, ideally these pro-drug metabolizing enzymes or pathways, particularly vitamin biosyntheses, are solely present in the pathogen which prevents the formation of the active drug in the human host organism. In contrast to classical pro-drugs, the linear relationship between drug and target is changed, due to the co-factor's remarkable influence on different enzymes of the bacterial life cycle and thereby various pathways are lockable with just one compound. As a consequence, the effect of a compound targeting co-factor biosyntheses (*e.g.* vitamin biosyntheses) is amplified and accelerated, as the resulting dysfunctional co-factor cannot be used in a large number of co-factor dependent reactions. These drugs (termed suicide drugs), which are converted/metabolized into dysfunctional co-factors, uncouple the drug application and target location by poisoning co-factor dependent enzymes. Consequently, the selective pressure will be transferred and is not anymore focused on the application/infiltration location.

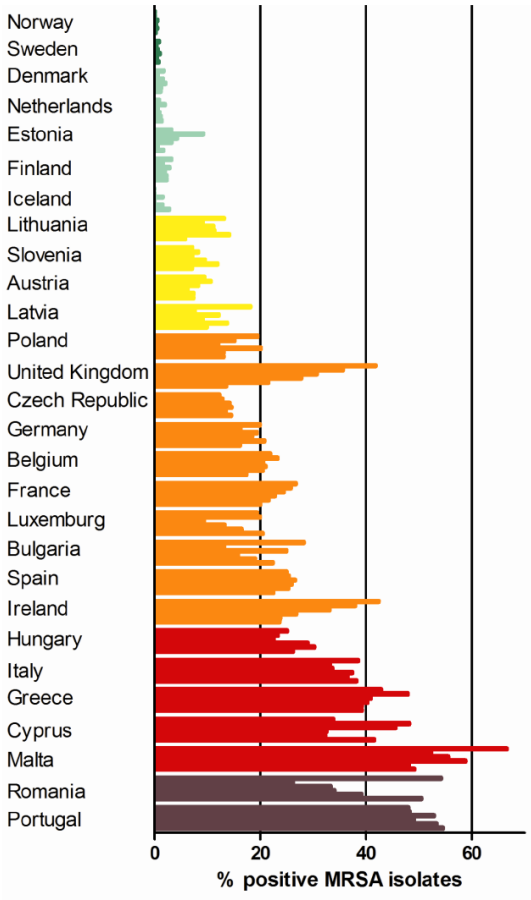


Fig. (1). Overview of MRSA positive isolates in Europe from 2006-2011 [32] sorted by numbers of positive isolates from 2011. Colors were chosen on the basis of positive isolates from 2011: green: < 1 %, light green 1 to 5 %, yellow: 5 to 10 %, orange 10 to 25 %, red: 25 to 50 %, purple > 50 %.

In *S. aureus* the thiamin (vitamin B1), riboflavin (vitamin B2) pantothenate (vitamin B5), folate (vitamin B9), pyridoxal/pyridoxine (vitamin B6) and vitamin K biosyntheses are present and can be of utmost importance in the introduced suicide drug approach.

SELECTION OF CURRENTLY AVAILABLE TREATMENTS AND DRUGS IN LATE CLINICAL DEVELOPMENT TO TARGET *S. AUREUS* INFECTIONS

Although new drugs have been approved, their targets remain invariable compared to existing antibiotics. The classical targets like cell wall synthesis and protein biosynthesis are still in focus of the drug development process.

Despite the existence of some new antibiotics (daptomycin, linezolid and tigecycline (Table **1**) adding to the classical antibiotics (trimethoprim/ sulfamethoxazole, clindamycin (Table **1**) the glycopeptide antibiotic vancomycin (Table **1**) remains the first-line drug for MRSA treatment although it has several major limitations that may contribute to the development of further persistence of MRSA [44].

Glycopeptide antibiotics inhibit crosslinking of the bacterial cell wall by interference with a terminal L-aa-D-alanyl-D-alanine group as a part of murein [45]. Thus, important components like N-acetylglucosamin and N-acetylmuramic acid cannot be integrated into the cell wall. Albeit rarely found, first vancomycin resistant isolates were identified [46] and also tigecycline resistance has been detected [47].

The semi-synthetic glycopeptide dalbavancin carries additional sugars and a C-terminal dimethyl-aminopropyl group (Table **1**). These modifications enhance activity also against vancomycin resistant staphylococci and VRE [48-51]. It has been approved in the US by the Food and Drug Administration (FDA) in 2007, but Pfizer withdrew the global market application for additional phase-III trials in 2008 [52]. Also the glycopeptide oritavancin (Table **1**) carries additional side chains which can on the one hand interfere with the bacterial cell wall synthesis and on the other hand disrupt cell membrane potential. This would make oritavancin an additional drug to treat vancomycin resistant bacteria [53]. In 2008, global market application was withdrawn by the FDA to conduct additional clinical studies [52], which are expected to be completed in 2013 [54].

Telavancin shares this twofold mode of action as seen for oritavancin [55]. It is approved by the FDA since 2009 [56] and also approved by the European Medicine Agency (EMA) since 2011 [57] (Table **1**).

The lipophilic glycopeptide daptomycin disrupts cell membrane potential and is used to treat bacteremia, endocarditis [58] and complicated tissue infection [59], but not pneumonia [60] (Table **1**).

Ceftaroline belongs to the antibiotic class of cephalosporins, a class of β-lactam antibiotics. It shows increased stability against β-lactamases compared to first generation cephalosporins [61] (Table **1**). It is FDA approved for complicated skin and skin structure infections and community acquired pneumonia [62] and was recently approved by the EMA [63].

Linezolid is an oxazolidinone compound and interacts with the 50S ribosomal subunit, but it has notable side effects like bone marrow suppression, lactic acidosis, peripheral and optic neuropathy and serotonin syndrome [64] (Table **1**). These results limit the applicability for MRSA bacteremia [65].

Retapamulin, a pleuromutilin, is used to treat bacterial skin infections such as impetigo and interacts with the 50S ribosomal subunit by a different mechanism than quinolones and β-lactams as it exhibits antimicrobial activity against clinical isolates carrying resistance determinants to these classes of protein synthesis inhibitors [66] (Table **1**).

Clindamycin from the group of lincosamides acts bacteriostatic by inhibiting the protein biosynthesis via interference with the 23S rRNA portion of the 50S ribosomal subunit.

Trimethoprim/ sulfamethoxazole, clindamycin (Table **1**) and the tetracyclines are presently used to treat CA-MRSA skin and soft tissue infection [67], whereas vancomycin showed better results regarding the duration of bacteremia, sterilisation of wound culture and reduction of fever [68]. Trimethoprim/ sulfamethoxazole inhibit the folate biosynthesis which results in purine starvation, but it may be less effective in the presence of pus from which *S. aureus* is able to salvage thymidine [69]. Recently it was shown, that an upcoming resistance for combinatorial therapy with cotrimoxazole is occurring [47]. Iclaprim is a dihydrofolate reductase inhibitor and one of the potential new antibacterial agents forwarded to further clinical development.

Rifampicin is an effective drug, but it has notable side-effects like teratogenicity [70, 71]. Therefore, the application is limited to combinatorial therapy (Table **1**). However, an inhibition of Panton-Valentin leukocidin (PVL) production has been demonstrated [72].

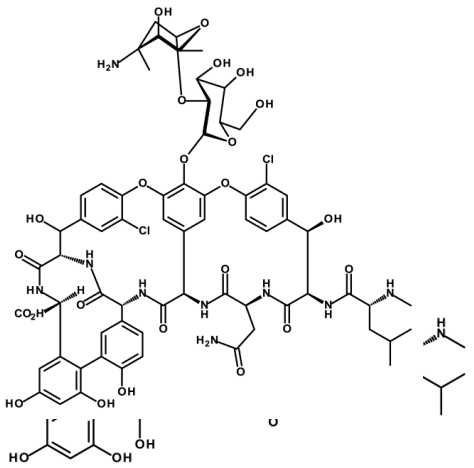
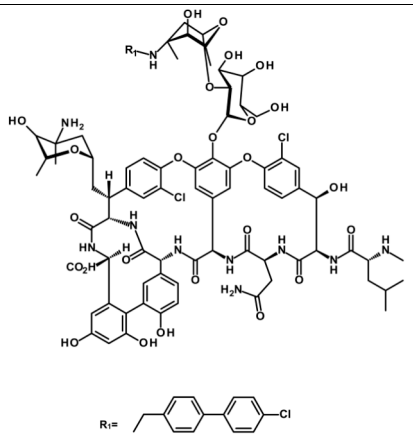
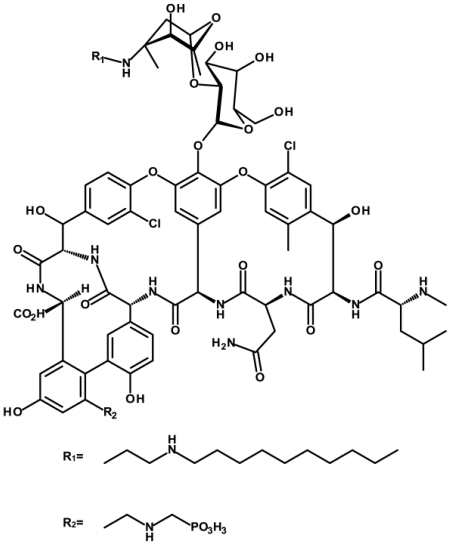
To prevent antibiotic resistance, the treatment with narrow-spectrum antibiotics is desirable, but not always feasible. In the case of sepsis, the evidence of MRSA can be determined in blood culture tests. In case of internal infections like pneumonia or endocarditis, data from retrograde colonization test could help to identify the pathogen [73]. However, the proof of pathogen is time-consuming and under life-threatening conditions physicians have to rely on antibiotics with additional anti-gram negative activity. Antibiotics should be selected based on local epidemiology, but if the pathogen is unknown, a broad-spectrum approach has to be applied [74]..

NOVEL TRIALS FOR ANTIBIOTIC DEVELOPMENT: PRO-DRUGS AND CO-FACTOR BIOSYNTHESES IN THE FOCUS OF ANTIMICROBIAL RESEARCH

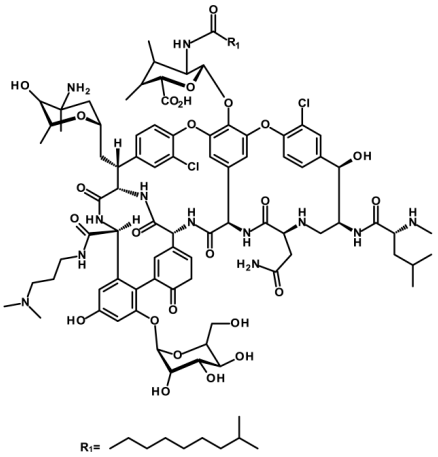
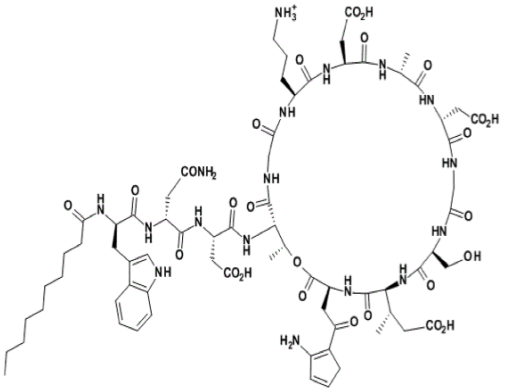
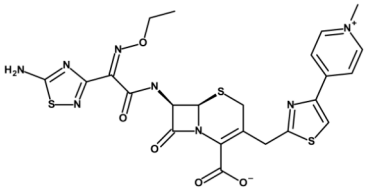
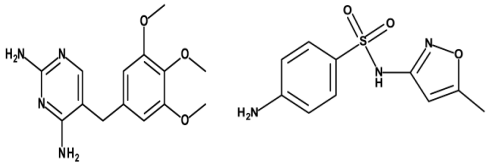
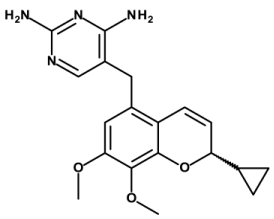
As summarized before, the efficient treatment of MRSA infections is limited and recently approved drugs mainly inhibit classical targets. New approaches have been applied to discover new antibiotics, but despite emerging resistance there was a 75 % reduction of approved antibiotic drugs by the FDA from 1983 to 2007 [75] due to diminishing focus of the pharmaceutical industry on antibiotic research [76, 77] as antibiotics have a poor return on investment.

Classically, a pro-drug is defined as a biologically active compound which is chemically modified and has to react in the organism to liberate the prototype compound (drug latentiation). So far, two general strategies have been proposed: (i) in the first strategy the pharmacokinetic properties of a given compound are changed by linking the active

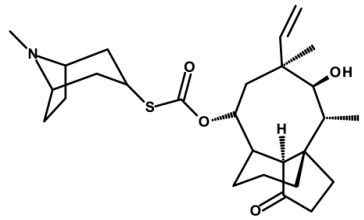
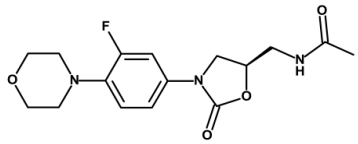
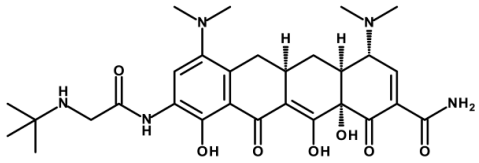
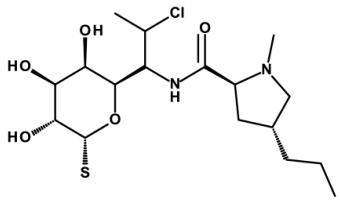
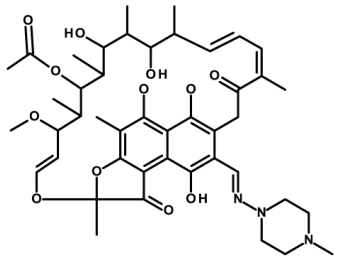
Table 1. Selected Antibiotics to Treat MRSA Infections Being Approved or in Late Clinical Development. MIC_{90}: Minimum Inhibitory Concentration Required to Inhibit the Growth of 90% of Organisms Referred to *Staphylococcus Aureus* if not Specified.

Drug	Class	Target	Dose/ Dosage Form/ Half-Life	MIC_{90} [µg/ml]	Chemical Structure
Vancomycin	Glycopeptide	Bacterial cell wall biosynthesis	2 g/d in four single doses/ intravenous/ 6 h [99]	1-2 [100, 101]	
Oritavancin	Glycopeptide	Bacterial cell wall biosynthesis	200 mg/d/ intravenous/ 144 h [102, 103]	0.12 [104]	
Telavancin	Lipoglycopeptide	Bacterial cell wall biosynthesis	10 mg/kg/d/ intravenous/ 7-9 h [102]	0.5 (CA-MRSA) [105]	

(Table 1) contd….

Drug	Class	Target	Dose/ Dosage Form/ Half-Life	MIC_{90} [µg/ml]	Chemical Structure
Dalbavancin	Lipoglycopeptide	Bacterial cell wall biosynthesis	1 g first day, 500mg eighth day, afterwards 7,5 mg/kg/ parenteral/ 7 d [58]	0.06 [106]	
Daptomycin	Lipopeptide	Bacterial cell wall biosynthesis	4 mg/kg/ intravenous/ 7-10 h [99]	1 [107]	
Ceftaroline	Cephalosporins	Bacterial cell wall biosynthesis	600 mg/12 h/ intravenous/ 2,6 h [102]	1 (MRSA), 0.25–0.5 (MSSA) [108]	
Trimethoprim/ Sulfamethoxazole	Dihydrofolate reductase inhibitors	Bacterial folate biosynthesis.	T: 320 mg/d, S: 800 mg/kg in 2 single doses/ oral/ 11 h [99]	2000 (Cotrimoxazole) [109]	**Trimethoprim** **Sulfamethoxazole** 
Iclaprim	Dihydrofolate reductase inhibitors	Bacterial folate biosynthesis.	0,8 mg/kg/12 h/ intravenous/ 2,5 h [102]	0.06 (MRSA) [110]	

(Table 1) contd….

Drug	Class	Target	Dose/ Dosage Form/ Half-Life	MIC_{90} [µg/ml]	Chemical Structure
Retapamulin	Pleuromutilin	Bacterial protein biosynthesis (50S ribosomal subunit)	1% ointment twice daily [99]	0.12 [111]	
Linezolid	Oxazolidinone	Bacterial protein biosynthesis (50S ribosomal subunit)	600mg/d in 2 single doses/ oral/ 5-7 h [99]	1-4 (oxacilin suceptible strains) [112]	
Tigecycline	Glycylcycline	Bacterial protein biosynthesis (30S (16S rRNA) ribosomal subunit)	Loading dose 100 mg, afterwards 50 mg/d/ parenteral/ 42 h [99]	0.5 [113]	
Clindamycin	Lincosamide	Bacterial protein biosynthesis (50S (23S rRNA) ribosomal subunit)	8-40 mg/kg/d in 3-4 single doses/ oral/ 3 h [99]	0.12 [114]	
Rifampicin	Rifamycin	Bacterial DNA-dependent RNA synthesis	600 mg/d/ oral/ 3-5 h [99]	0.03 (coagulase-negative staphylococci) [115]	

compound to a carrier molecule. This carrier molecule could enhance the membrane crossing via a lipophilic group (in most cases addition of an ester) or the stability or the distribution via this derivatization [78]. (ii) In the second strategy, the bioactive compound is chemically modified and needs to be metabolized (like e.g. hydrolyzed, carboxylized or esterified) to become fully functional. This can result in a better bioavailability, specificity or prolonged lifetime.

To prevent resistance in protozoan parasites and mycobacteria, the use of pro-drugs has been considered recently, but these pro-drugs have been poorly investigated so far [79]. In this approach a pro-drug like nitazoxanide, can directly inhibit a protein function after activation. It has been approved by the FDA as a pro-drug for protozoan infections [79] and does not show any resistant mutants in mycobacterial infections [80]. Also a class of pro-drugs to treat multi-drug-resistant tuberculosis (MDR-TB) activated by a Baeyer Villiger (BV) monooxygenase was optimized by a second drug that abolishes BV repressor function [79].

Filamentous phages have been exploited to treat bacterial infections, but so far antibody-based targeting has been used only for cancer cells and was not applicable to bacterial cells due to the lack of bacterial internalization process. Therefore, filamentous phages were only used to deliver drugs to bacterial cell by binding to pathogen specific antigens. Yacoby and colleagues reported an improved phage with solubility enhancing linkers to overcome hydrophobicity of bacteriostatic drug chloramphenicol via the aminoglycoside neomycin. The potency was improved by a factor of approx. 20,000 compared to the free drug, but the system analyzed does not reflect *in vivo* studies [81]. However, phage resistant variants were observed when applied as monophage

therapy [82] and might limit the application of phage therapy as shown for *Klebsiella pneumoniae* [83]. All studies to discover non-drug therapies like vaccines or antibodies failed [75].

Complete genome sequencing for many pathogens allows to date the identification of new enzymes and pathways that are absent in humans and thus are most desirable targets for antimicrobial drug-discovery [84]. Besides unique pathways, also transport systems can be identified, which allows an analysis of nutrient biosynthesis and uptake to distort the pathogen's metabolism [85].

Via genetic footprinting putative targets have been identified for broad-spectrum antibiotic use. These genes encode for pathways that are conserved in various bacteria, but not in the human host or are structurally unrelated to the human counterpart and encode for soluble proteins. In various pathogens including *S. aureus,* the biosynthesis of the adenylate cofactor NAD, coenzyme A (CoA) and flavin adenine dinucleotive (FAD) have been extensively studied. With respect to NAD biosynthesis only *Helicobacter pylori* is expected to have useful targets in this pathway, as it lacks the niacin salvage. In contrast, *S. aureus* is able to scavenge this cofactor, such as cobalamin (vitamin B12), what relativize the NAD and cobalamin biosyntheses as useful drug-targets [86].

The pantothenate kinase (PK), the first enzyme of the pantothenate pathway, is structurally different compared to eukaryotic PKs and therefore a good target for antibiotic treatment in a broad-spectrum approach [86].

In the case of the vitamin B1 *de novo* synthesis in *S. aureus*, four main thiamin pyrophosphate dependent enzymes, which have a high impact on energy and amino acid balances of the pathogen, are targeted: transketolase, involved in pentose phosphate pathway, branched chained amino acid dehydrogenase (involved in amino acid metabolism), pyruvate dehydrogenase, connecting the glycolysis with the citric acid cycle and oxoglutarate dehydrogenase, which is part of the latter cycle. Recently, the thiamin biosynthesis pathway has been characterized in *S. aureus* [87] and for the first time it has been suggested on a structural basis as drug target [88, 89].

Lysostaphin is a bacteriocin with lytic activity against staphylococci [90]. It was shown that lysostaphin is able to eradicate susceptible *S. aureus* and *S. epidermidis* biofilms [91]. In a rabbit model it could show effectiveness against keratitis [92], but it is not in clinical use.

Chhabra and colleagues presented the structure of 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase (*Sa*HP PK) from the folate biosynthesis pathway in *S. aureus* and performed an *in silico* screen which identified a compound with an inhibitory profile in the low micro molar range [93].

The B6 vitamers have moved into focus of antiprotozoal drugs. The malaria parasite *Plasmodium falciparum* is able to synthesize pyridoxal 5-phosphate (PLP) in their erythrocytic state or salvage it from its host. Pro-drugs applied to the parasite *in vitro* are trapped within the parasite and mimic PLP which can subsequently poison PLP dependent enzymes. A new compound could inhibit plasmodial growth with an IC_{50} at a low micro molar level [94].

The vitamin K biosynthesis which is also conserved in bacteria but not in humans has been considered as a drug target for *Mycobacterium tuberculosis*. Inhibitors interfering with this pathway show promising reduction of mycobacterial growth [95].

Most vitamin or co-factor precursor biosyntheses for anti-staphylococcal drug discovery have not yet been exploited. As many of these pathways are controlled by riboswitch elements [96] an aptamer based approach could also be suggested, which fits the strategy of targeting a pathway to interfere with a completely different pathway.

ENHANCEMENT OF THE CLASSICAL PRO-DRUG APPROACH: FUTURE PERSPECTIVE WITH SUICIDE DRUGS

In terms of drug discovery, a major goal is to identify differences between bacteria and the respective host organism which is exploited for the proliferation of the pathogen. Therefore, ideal drug targets are significantly different or even absent in the human host when compared to the pathogenic bacteria. For example the bacterial cell wall- and protein-synthesis or DNA replication are still targets of choice.

As time is going by, the applied methodologies have changed due to upcoming drug resistance and limitation of natural medication therapies. Structure based approaches were developed to identify potential drug targets and subsequently the deriving potential inhibitors were screened [93]. The combination to analyze the structure of target enzymes and bioinformatics, such as *in silico* screening tools led to the identification of novel compounds [97] that might be exploitable for both, drug- and pro-drug-discovery. Pro-drug approaches improving half-life, bioavailability or distribution of a given compound are now in use for almost 50 years [98]. In certain cases, the pro-drug is converted from an *in vitro* active compound to a clinical applicable medication by altering the chemical formulation or optimization of the ADME profile (absorption, distribution, metabolism, and excretion) respectively.

All compounds to address MRSA infections, which are in clinical trials or already commercially available, are sharing one mode of action: they act as partial, full or inverse agonist or antagonist in an orthosteric way or allosteric as partial or full agonists on only one defined target. Consequently, these targets are in the focus of a high selective pressure.

As mentioned before, the idea of drugs targeting co-factor metabolisms in bacteria is promising. Due to the short reproduction time and the capability of horizontal gene transfer, bacteria like *S. aureus* are highly adaptable to any kind of environmental changes which will consequently lead to the occurrence of drug resistance especially if only one target (enzymatic step) will be in focus. In order to circumvent this problem, an option would be to target a variety of different enzymes and /or metabolic pathways during a single drug application. By following this strategy, the use of suicide drugs is highly favored, because these special compounds are intended to mimic the natural substrate. Consequently, this special pro-drug will be metabolized by the pathogenic enzymes and thereby channeled into the respective product pool. Applying this methodology on vitamin B biosynthetic

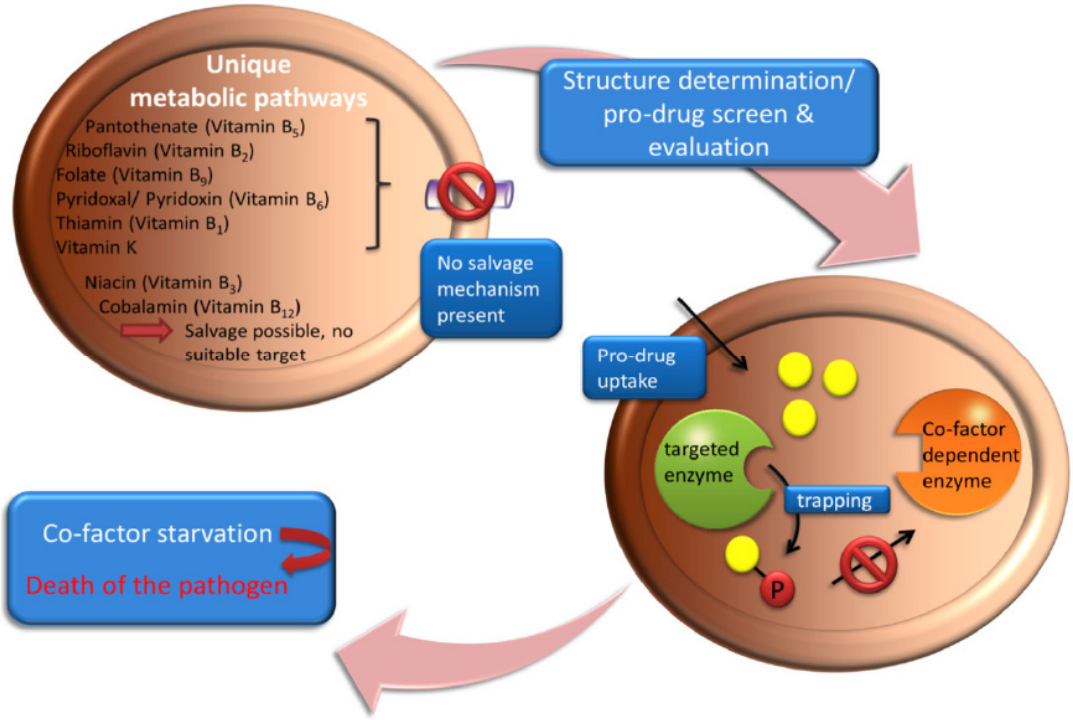


Fig. (2). A novel approach to target MRSA infections identifies metabolic pathways unique to the bacterium, considering that there is no salvage mechanism present for these nutrients. In a further step, enzymes involved in the co-factor biosynthesis are investigated on structural level. After a pro-drug screen and biochemical evaluation these pro-drugs are metabolized by the bacterium and yield a co-factor which is non-functional for the bacterium. Via co-factor starvation the pathogen dies and resistance is prevented as none of these pathways is blocked.

pathways, the product pool will harbor besides the endogenous co-factor also the non-functional suicide co-factor which will subsequently poison vitamin B-dependent enzymes and result in bacteria's death. However, in this context, the potential co-factor uptake has to be taken into consideration (Fig. **2**).

This strategy should be considered more widely in future drug discovery procedures. So far, targeting the co-factor biosyntheses has been used for a number of different pathogens, but the use of suicide drugs is only rarely taken into account to present. Recent development in anti-staphylococcal drug discovery towards a thiamin precursor-analogue to block thiamin dependent enzymes, raises hope to escape from the vicious circle of resistance and to reduce the burden of nosocomial, especially MRSA, infections.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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