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## Repurposing non-antimicrobial drugs and clinical molecules to treat bacterial infections

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### Abstract

There is a pressing need to develop novel antimicrobials to circumvent the scourge of antimicrobial resistance. The objective of this study is to identify non-antibiotic drugs with potent antimicrobial activity, within an applicable clinical range. A library, containing 727 FDA approved drugs and small molecules, was screened against ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*). Drugs that showed antimicrobial activity in an applicable clinical range were further tested *in vitro* and *in vivo* in an infected mouse model. The initial screening identified 24 non-antibiotic drugs and clinical molecules active against Gram-positive pathogens including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) isolates. Two non-antibiotic drugs showed activity against Gram-negative pathogens. Among the active non-antibiotic drugs, only ebselen (EB) and 5-fluoro-2'-deoxyuridine (FdUrd), showed bactericidal activity, in an applicable clinical range, against multi-drug-resistant *Staphylococcus* isolates including MRSA, vancomycin-resistant *S. aureus* (VRSA), and vancomycin-intermediate *S. aureus* (VISA). The minimum inhibitory concentration at which 90% of clinical isolates of *S. aureus* were inhibited (MIC<sub>90</sub>) was found to be 0.25 and 0.0039 mg/L for EB and FdUrd, respectively. Treatment with EB orally significantly increased mice survival in a lethal model of septicemic MRSA-infection by (60%) compared to that of control. FdUrd oral and intraperitoneal treatment significantly enhanced mouse survival by 60% and 100%, respectively. These data encourage screening and repurposing of non-antibiotic drugs and clinical molecules to treat multidrug-resistant bacterial infections.

### Keywords

repurposing; antibiotics; MRSA; antimicrobial; repositioning

## 1. Introduction

Bacterial infections have become a serious threat to the global public health due to the dearth of effective antimicrobials. Moreover, the development of new antibiotics is becoming increasingly difficult and is unable to keep pace with the rapid emergence of

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resistant pathogens. Hence, novel drugs and new approaches are urgently needed. Both *de novo* drug discovery and drug repurposing have been used in the search for effective antibiotics. Unlike the lengthy and costly process of *de novo* drug discovery, drug repurposing can reduce the time, cost and risk associated with drug innovation [1]. Drug repurposing has already resulted in successes in a number of disease areas, including infectious diseases [2]. Though antibiotics have been repurposed for other clinical indications, to date, not a single non-antibiotic drug has been repurposed and approved for use as an antibacterial. Given the crucial problem posed by multidrug resistant pathogens, especially ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp), additional effort needs to be focused on using drug repurposing to uncover new treatment options.

Several non-antibiotic drugs have been found to exhibit bactericidal activity; however, they possess high minimum inhibitory concentration (MIC) values that cannot be achieved clinically. In an intensive search for antimicrobial activity in an applicable clinical range among non-antimicrobial drugs, we identified two drugs, ebselen (EB) and 5-fluoro-2'-deoxyuridine (FdUrd), with potent antibacterial activities against Gram-positive pathogens, including highly multidrug-resistant clinical isolates of *S. aureus*. These two drugs showed antibacterial activity against clinical isolates of methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), and vancomycin-intermediate *S. aureus* (VISA) with MIC values in submicromolar concentrations. Additionally, both drugs significantly increased mice survival in a lethal model of septicemic MRSA-infection.

## 2. Materials and methods

### 2.1. Bacterial strains

ESKAPE pathogens vancomycin resistant *E. faecium* ATCC 700221 (VRE), MRSA USA300, carbapenemase (KPC)-producing *bla*<sub>KPC+</sub> *K. pneumoniae* ATCC BAA-1705, multi-drug-resistant *A. baumannii* ATCC BAA-1605, *P. aeruginosa* ATCC 15442, and *E. cloacae* ATCC BAA-1143 were used for the initial screening. Clinical isolates of methicillin-sensitive *S. aureus* (MSSA), MRSA, VRSA, VISA, and *S. epidermidis* are described in Table 1.

### 2.2. Compounds and library

The NIH Clinical Collections 1 and 2 (<http://www.nihclinicalcollection.com>) containing 727 FDA approved drugs and small molecules previously used in human clinical trials with known safety profiles [3] were screened against ESKAPE pathogens. The library was initially screened at a single concentration of 16  $\mu$ M to identify “hit” non-antibacterial drugs. Once the antimicrobial activity of the drugs was confirmed, we determined their MICs and minimum bactericidal concentrations (MBCs) according to the Clinical and Laboratory Standards Institute (CLSI) [4]. We selected drugs that showed potent antimicrobial activity in an applicable clinical range for further screening and testing *in vitro* and *in vivo* in an infected mouse model.

### 2.3. Animals

Animal procedures were approved by the Purdue University Animal Care and Use Committee (PACUC) (protocol no. 1311000988). Eight-week-old female BALB/c mice (Harlan Laboratories, Indianapolis, IN) were used for this study. Mice were rendered neutropenic by treatment with cyclophosphamide intraperitoneally (IP) 150 and 100 mg/kg at four days and one day before infection, respectively. Neutropenic mice were inoculated IP with  $8 \times 10^8$  MRSA USA200. At one hour after infection, the mice were divided into five groups (n = 10 per group), and two groups were treated orally with either EB 30 mg/kg or FdUrd 25 mg/kg. Two groups were treated IP with either EB 30 mg/kg or FdUrd 25 mg/kg. One group was used as a control with no treatment. Treatment was continued once daily for two more days (animals received three doses total). Mortality was monitored four times daily for six days, and the cumulative percent survival was determined. The data were subjected to statistical analysis using Kaplan-Meier survival curves. A log rank test was performed for 95% confidence intervals by GraphPad Prism 6.0 (GraphPad Software, La Jolla, CA).

## 3. Results

### 3.1. In vitro antimicrobial activity

Our initial screening identified 24 non-antibiotic drugs and clinical molecules active against Gram-positive pathogens MRSA and VRE (Table 2). Among the active non-antimicrobial drugs against MRSA identified in the NIH Clinical Collections, EB and FdUrd showed potent bactericidal activity in a nano-molar (clinically achievable) range. Both drugs demonstrated potent bactericidal activity against clinical multi-drug-resistant *Staphylococcus* isolates. The MIC at which 90% of *S. aureus* isolates were inhibited (MIC<sub>90</sub>) was found to be 0.25 and 0.0039 mg/L for EB and FdUrd, respectively (Table 1). Only two non-antibiotic drugs showed activity against Gram-negative pathogens (Table 2).

### 3.2. Protection of mice against MRSA infection

EB oral treatment, but not IP, significantly increased mice survival (60%) compared to that of control (Figure 1A). FdUrd oral and IP treatment significantly enhanced mouse survival by 60% and 100%, respectively, compared to that of control (Figure 1B).

## 4. Discussion

It is well established that currently approved antimicrobials are losing the battle in the fight against multidrug-resistant pathogens. Without a doubt, novel antimicrobials and novel approaches to develop them are urgently needed; however, new antimicrobials are becoming increasingly difficult to develop. Repurposing FDA-approved drugs, with well-characterized toxicology and pharmacology, to find new applications outside the scope of the original medical indication is a novel way to reduce both the time and cost associated with antimicrobial innovation.

Whole-cell screening assays of non-antibiotic drugs and clinical safe molecules in the NIH Clinical Collections against ESKAPE pathogens revealed several non-antibiotic drugs with antimicrobial activity (Table 2). Although some of these drugs were known to have

antibacterial activity, many were unexpected because their clinical indications are unrelated to treatment of microbial infections.

Among the active non-antimicrobial drugs against MRSA, EB and FdUrd showed potent bactericidal activity in a nano-molar (clinically achievable) range. Both drugs demonstrated potent bactericidal activity against clinical multi-drug-resistant *Staphylococcus* isolates, including linezolid-resistant *S. aureus*, VRSA, VISA, and MRSA. Additionally, the activities of EB and FdUrd exceeded those determined for vancomycin and linezolid. Furthermore, they exhibited strong antimicrobial activity against other important Gram-positive pathogens, including VRE and methicillin-resistant *S. epidermidis*.

EB, an organoselenium compound, is considered clinically safe but without proven use [3]. It has been widely studied for its anti-inflammatory, anti-atherosclerotic, and antioxidative properties [5]. Independent of its anti-inflammatory effect, EB also has been shown to exhibit antimicrobial activity *in vitro* [6–8]. It inhibits the thioredoxin reductase enzyme in *Escherichia coli*, and it inhibits the antigen 85 (Ag85) complex in *Mycobacterium tuberculosis* [7, 8]. However, clinical applications and the underlying mechanism of action for its antibacterial activity against *S. aureus* still remain unclear. Treatment with EB orally, but not IP, significantly increased mice survival (60%) in a lethal model of septicemic MRSA-infection compared to that of control (Figure 1A). EB is rapidly absorbed from the gastrointestinal tract, and it maintains a plasma concentration of 2.91 mg/L with 30mg/kg dose (according to increase in selenium concentration in the blood of  $0.84 \pm 0.1 \text{ mg/L}^{-1}$ ) [9], several-fold higher than MIC<sub>90</sub>. Higher doses or multiple doses might be required to achieve 100% protection. Furthermore, the recognized anti-inflammatory response [5] of EB, combined with the potent antimicrobial activity, make it an excellent candidate for topical treatment of MRSA skin infections.

FdUrd is an anticancer drug used to treat colorectal cancers [10]. FdUrd inhibits thymidylate synthase (a key enzyme in DNA synthesis) and acts as a nucleoside analog that impairs the metabolism and structure of nucleic acids [10]. The antimicrobial activity of nucleoside analog against *S. aureus* has been demonstrated *in vitro* [11]. FdUrd oral and IP treatment significantly enhanced mouse survival in a lethal model of septicemic MRSA-infection by 60% and 100%, respectively, compared to that of control (Figure 1B). The bioavailability of oral FdUrd is unpredictable, which probably contributed to a lower protection rate compared to an IP route [12]. While FdUrd shows preclinical promise as a medication for the treatment of MRSA infections, the therapeutic dose can be reduced significantly to avoid drug-associated toxicity. The achieved plasma concentration of the drug after receiving a therapeutic dose is estimated to be more than a thousand-folds higher than the required MIC<sub>90</sub> against MRSA [13–15].

Although the direct antimicrobial activity of several non-antimicrobial drugs is well documented, to date, no FDA-approved drug has been repurposed to treat bacterial infections. The non-antibiotic drugs that showed antimicrobial activity serve as untapped reservoir for new antibiotic leads that could lead to identification of new targets which will guide the future development of improved antimicrobial agents. The library we screened represents only 7% of the total drugs known to clinical medicine [1]. Finding two hits in a

clinical range illustrates the potential to identify more drugs with potent antimicrobial activity and encourage the screening of all clinical compounds to complement current antibiotics. The fact that auranofin, a FDA-approved gold compound used for treating rheumatoid arthritis, recently has been granted orphan-drug status from the FDA for treatment of human amebiasis, further validates antimicrobial repurposing approach.[2]

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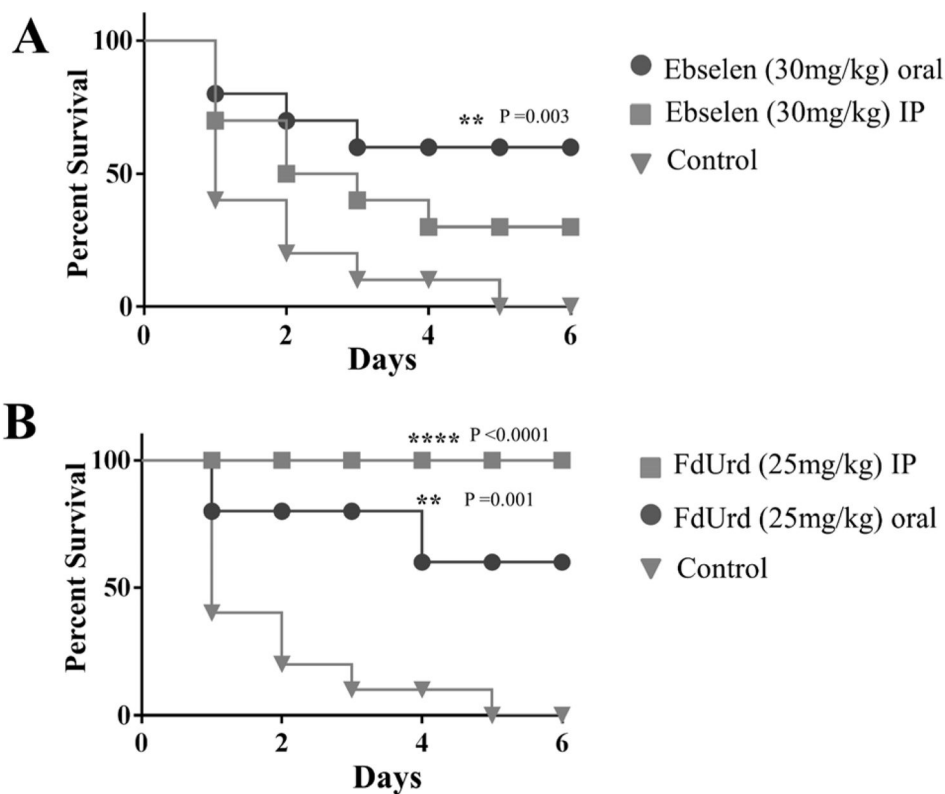
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**Figure 1.** Efficacy of treatment of MRSa septicemic infection with ebselen (A) and FdUrd (B). Mice received one treatment daily for three days. Mice were monitored for six days and the cumulative percent survival was determined. The data were subjected to statistical analysis using Kaplan-Meier survival curves. A log rank test was performed for 95% confidence intervals by GraphPad Prism 6.0.

Table 1

The MIC and MBC of Ebselen and FdUrd against Gram-positive Pathogens

Strains type	Strain ID	Isolation		Phenotypic properties	MIC/MBC (mg/L)	
		Origin	year		Ebselen	FdUrd
Vancomycin-resistant <i>S. aureus</i> (VRSA)	VRSA1	United States	2002	Resistant to erythromycin and spectinomycin as well as being multiresistant to other commonly used therapeutic agents	0.25/0.25	0.0078/0.0078
	VRSA2	United States	2002	Resistant to erythromycin and spectinomycin as well as being multiresistant to other commonly used therapeutic agents	0.25/0.25	0.0039/0.0156
	VRSA3a	United States	2004	Resistance to tetracycline, macrolides, lincosamides and aminoglycoside	0.25/0.25	0.000975/0.000975
	VRSA3b	United States	-	-	0.25/1	0.00049/0.00049
	VRSA4	United States	2005	Resistant to erythromycin and spectinomycin	0.125/0.125	0.00195/0.0039
	VRSA5	United States	2005	Resistant to erythromycin and spectinomycin	0.25/0.25	0.00195/0.00195
	VRSA6	United States	-	Resistant to vancomycin	0.25/0.5	0.00049/0.00195
	VRSA7	United States	2006	Resistant to $\beta$ -lactams, erythromycin and spectinomycin	0.5/0.5	0.00195/0.0039
	VRSA8	United States	2007	Resistant to erythromycin and spectinomycin	0.125/0.125	0.00049/0.000975
	VRSA9	United States	2007	Resistant to erythromycin and spectinomycin	0.25/0.5	0.000975/0.00195
	VRSA10	United States (Michigan)	2009	Resistant to ciprofloxacin, clindamycin, erythromycin, gentamicin, and vancomycin	0.25/0.25	0.000975/0.000975
	VRSA11a	United States	2010	Resistant to erythromycin and spectinomycin	0.125/0.25	0.000975/0.0156
	VRSA11b	United States	2010	Resistant to erythromycin and spectinomycin	0.25/0.25	0.000975/0.0039
VRSA12	United States	-	Resistant to vancomycin	0.25/0.5	0.00195/0.0039	
VRSA13	United States	-	Resistant to vancomycin	0.25/0.25	0.00195/0.0156	
Methicillin resistant <i>S. aureus</i> (MRSA)	NRS382	United States (Ohio)	-	Resistant to ciprofloxacin, clindamycin, erythromycin, and methicillin	0.125/0.125	0.000975/0.0078
	NRS383	United States (NorthCarolina)	-	Resistant to ciprofloxacin, clindamycin, erythromycin, gentamicin, and methicillin	0.125/0.125	0.0078/0.0078
	NRS 384	United States (Mississippi)	-	Resistant to erythromycin, methicillin, and tetracycline	0.125/0.125	0.00195/0.00195
	NRS 385	United States (Connecticut)	-	Resistant to ciprofloxacin, clindamycin, erythromycin, gentamicin, methicillin, tetracycline, and trimethoprim	0.5/1	0.0315/0.0315
	NRS 386	United States (Louisiana)	-	Resistant to erythromycin and methicillin	0.125/1	0.00195/0.0078



Strains type	Strain ID	Isolation		Phenotypic properties	MIC/MBC (mg/L)	
		Origin	year		Ebselen	FdUrd
Methicillin sensitive <i>S. aureus</i> (MSSA)	NRS 387	United States (Washington)	-	Resistant to methicillin	0.125/0.25	0.0039/0.0156
	NRS 483	United States (Vermont)	-	Resistant to erythromycin and methicillin	0.125/0.5	0.00195/0.0078
	NRS 484	United States (Alaska)	-	Resistant to methicillin	0.25/0.25	0.000975/0.0039
	NRS70	Japan	1982	Resistant to clindamycin, erythromycin and spectinomycin	0.25/0.25	0.0039/0.00315
	NRS71	United Kingdom	-	Resistant to tetracycline and methicillin	0.25/0.25	0.00195/0.00195
	NRS100	United Kingdom	-	Resistant to tetracycline	0.25/0.5	0.000975/0.000975
	NRS108	France	-	Resistant to gentamicin	0.25/0.25	0.0078/0.0156
	NRS119	United States (Massachusetts)	2001	Resistant to linezolid	0.125/0.25	0.0039/0.0156
	NRS123	United States	1998	Resistant to methicillin; susceptible to nonbeta-lactam antibiotics	0.25/0.5	0.000975/0.0039
	NRS194	United States (North Dakota)	1999	Resistant to methicillin	0.25/1	0.0039/0.0625
	NRS72	United Kingdom	-	Resistant to penicillin	0.25/0.5	0.000975/0.00195
	NRS77	United Kingdom	1960	Used for typing phase 47 and is considered to be the original strain for most <i>S. aureus</i> genetic research.	0.25/1	0.00049/0.00049
Vancomycin intermediate <i>S. aureus</i> (VISA)	NRS846	-	-	-	0.125/>64	0.0039/0.0039
	NRS860	-	-	-	0.25/0.25	0.00195/0.00195
	NRS 1	Japan	1996	Resistant to aminoglycosides and tetracycline (minocycline) Glycopeptide-intermediate <i>S. aureus</i>	0.125/0.125	0.00195/0.00195
	NRS19	United States (Illinois)	1999	Glycopeptide-intermediate <i>S. aureus</i>	0.25/0.025	0.00049/0.00195
	NRS37	France	1995	Glycopeptide-intermediate <i>S. aureus</i>	0.125/0.125	0.00195/0.0078
	NRS 101	United States	-	Prototype biofilm producer, Resistant to methicillin and gentamicin	0.5/0.5	0.0078/0.0078
<i>Enterococcus</i> species	<i>E. faecalis</i> ATCC 51229 (VRE)	Peritoneal fluid, St. Louis, MO	-	Low-level vancomycin-resistant, VanB Resistant to Vancomycin. Sensitive to Teichoplanin.	0.5/0.5	0.125/0.125
	<i>E. faecium</i> ATCC 700221 (VRE)	Human feces, Connecticut	-	Resistant to Vancomycin and Teicoplanin	0.5/1	0.0625/0.125

**Table 2**  
MIC and MBC of non-antibacterial drugs against Gram-positive and negative pathogens

N	NCC structure	Name	Description	MIC/MBC $\mu$ M	
				MRSA	VRE
1	CPD000466308	Epirubicin	Antineoplastic	16/64	8
2	CPD000469213	Toremifene	Antineoplastic	16/16	16
3	CPD000058267	Isoproterenol	Bronchodilator	16/64	>16
4	CPD001491671	Tamoxifen	Antineoplastic	16/16	>16
5	CPD001317855	Clomid	Treat infertility in women	16/32	16
6	CPD001906781	Daunorubicin	Antineoplastic	16/16	8
7	CPD000469293	Oxiconazole	Antifungal	2/32	>16
8	CPD000466357	Triclabendazole	Anthelmintic	8/32	>16
9	CPD000466363	Carmofur	Antineoplastic	2/4	>16
10	CPD000466355	Idarubicin	Antineoplastic	4/4	4
11	CPD000466278	MK-886	Leukotriene antagonist	8/16	8
12	CPD000058970	Bifonazole	Antifungal	8/>64	>16
13	CPD000058306	Clotrimazole	Antifungal	4/64	>16
14	CPD000466300	5-Nonyloxytryptamine	Serotonin receptor agonist	4/8	8
15	CPD000058445	Ebselen	Mimic glutathione peroxidase	<0.5/0.5	0.5/1
16	CPD001370749	Econazole	Antifungal	4/32	>16
17	CPD000058733	Miconazole	Antifungal	4/8	>16
18	CPD000038082	5-Fluorouracil	Antineoplastic	4/16	>16
19	CPD001496941	FdUrd	Antineoplastic	<0.5/0.5	<0.5/0.5
20	CPD000059106	Florafur	Antineoplastic	>16	16
21	CPD000469217	Raltitrexed	Antineoplastic	>16	2
22	CPD000469227	Dactinomycin	Antineoplastic	>16	0.5
23	CPD000058394	Acetazolamide	Antiglaucoma	>16	1
24	CPD000058202	Furosemide	Diuretic	>16	4

N	Drug	MIC/MBC $\mu$ M			
		<i>K. pneumoniae</i>	<i>A. baumannii</i>	<i>E. cloacae</i>	<i>P. aeruginosa</i>
1	5-Nonyloxytryptamine	>16	16	16	>16
2	FdUrd	8	>16	>16	>16

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