

## Supporting Information

### Prospects for Antibacterial Discovery & Development

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#### **Supplementary Tables S2**

|                                    |    |
|------------------------------------|----|
| Table S1. Antibiotic Targets ..... | S2 |
| Table S2. Antibiotic Leads .....   | S9 |

**Table S1.** Antibiotic Targets.

A representative list of known antibiotic targets was analyzed during the preparation of this perspective. To determine if a target has a close human homolog, the human gene sequence was compared with the target gene sequence from *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. Sequences were aligned and compared using BLAST. If the human gene had greater than 40% identity to the bacterial genes, the target was identified as having a close human homolog. Additionally, a target could be marked as having a close human homolog if there were reports of the similarities between bacterial and human versions of the target. All representative inhibitors listed are molecules with known *in vitro* activity against at least one bacterium. Inhibitors listed in bold have received approval for clinical use from the United States Food and Drug Administration. The PMID reference to a suggested article is included for more information about the target of interest.

| Name   | Representative Pathogens  | Close Human Homolog? | Representative Inhibitors                                      | Subcellular Localization | PMID Reference |
|--|---|----------------------|--|--------------------------|----------------|
| Penicillin-binding proteins                            | <i>A. baumannii</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>N. gonorrhoeae</i>                             | N                    | <b>Penicillins, cephalosporins, carbapenems, monobactams</b>   | Transmembrane            | 18266856       |
| Lipid II   | <i>C. difficile</i> , <i>S. pneumoniae</i> , <i>S. aureus</i> , <i>Enterococcus spp.</i>                          | N                    | <b>Vancomycin</b> , ramoplanins, lantibiotics, mannopeptimycin | Cell wall                | 30725496       |
| Transglycosylases                                      | <i>S. pneumoniae</i> , <i>Enterococcus spp.</i> , <i>S. aureus</i>  | N                    | Moenomycins  | Inner membrane/periplasm | 20730219       |
| Undecaprenyl-pyrophosphate (lipid precursor transport) | <i>S. aureus</i>  | N                    | <b>Bacitracin</b> , amphomycin                                 | Inner membrane           | 12121761       |
| MurA (PEP transferase)                                 | <i>M. tuberculosis</i> , <i>P. aeruginosa</i> , <i>A. baumannii</i> , <i>S. aureus</i> , <i>Enterococcus spp.</i> | N                    | <b>Fosfomycin</b>  | Cytoplasm                | 28062557       |
| Membrane depolarization/damage                         | <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Salmonella spp.</i> , <i>M. tuberculosis</i>                         | Y                    | <b>Daptomycin, polymyxins</b> , teixobactin, XF-73             | Membrane                 | 26514603       |
| MraY   | <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>M. tuberculosis</i>  | N                    | Muraymycin, liposidomycin, capuramycin                         | Inner membrane           | 29600753       |
| Signal peptidase I (LepB)                              | <i>P. aeruginosa</i> , <i>M. tuberculosis</i> , <i>S. aureus</i>  | N                    | Arylomycins, actinocarbasins, G0775                            | Transmembrane/periplasm  | 22082289       |
| Signal peptidase II                                    | <i>S. aureus</i> , <i>Salmonella spp.</i>   | N                    | Globomycin, myxovirescin                                       | Transmembrane/periplasm  | 31214988       |
| SecA   | <i>S. aureus</i>  | N                    | CJ-21058, Rose Bengal, erythrosin B                            | Inner membrane           | 26062397       |
| MscL   | <i>C. difficile</i>   | N                    | Ramizol  | Transmembrane            | 17350877       |
| BamA   | <i>P. aeruginosa</i> , <i>Salmonella spp.</i>   | N                    | Darobactin, MRL-494  | Outer membrane           | 30788339       |
| LptD   | <i>P. aeruginosa</i>  | N                    | Murepavadin, protegrin I, POL7001                              | Outer membrane           | 23534363       |
| LpxC   | <i>P. aeruginosa</i>  | N                    | CHIR-090, LPC-009  | Cytoplasm                | 27235477       |
| LoICDE   | <i>E. coli</i>  | N                    | G0507  | Transmembrane            | 29339384       |
| Name   | Representative Pathogens  | Close Human Homolog? | Representative Inhibitors                                      | Subcellular Localization | PMID Reference |

|  |   |                             |   |                                 |                       |
|--|---|-----------------------------|---|---------------------------------|-----------------------|
| Undecaprenyl pyrophosphate synthase            | <i>S. aureus</i> , <i>E. faecalis</i>   | N                           | Viridicatumtoxin B, spirohexaline, 4-oxo-2-thioxo-1,3-thiazolidines   | Cytosoplasm                     | 26718796              |
| MurG   | <i>S. aureus</i>  | N                           | Murgocil  | Inner membrane                  | 27571111              |
| Glutamine synthetase                           | <i>Salmonella spp.</i>  | N                           | Phosphinothricin, tabtoxinine beta-lactam   | Cytoplasm                       | 18279655              |
| Outer membrane permeabilization (as adjuvants) | <i>P. aeruginosa</i> , <i>A. baumannii</i>  | N                           | Pentamidine, various cationic peptides (ex. Magainin II)  | Outer Membrane                  | 9033483               |
| MreB   | <i>P. aeruginosa</i>  | N                           | Sceptrin, CBR-4830, A22   | Inner membrane/cytoplasm        | 31998684              |
| GyrA   | <i>A. baumannii</i> , <i>P. aeruginosa</i> , <i>M. tuberculosis</i> , <i>S. aureus</i>      | N                           | <b>Fluoroquinolones</b>   | Cytoplasm                       | 31301408              |
| GyrB   | <i>A. baumannii</i> , <i>P. aeruginosa</i> , <i>M. tuberculosis</i> , <i>S. aureus</i>      | N                           | <b>Novobiocin</b> , zoliflodacin, cyclothialidine   | Cytoplasm                       | 31301408              |
| Other topoisomerases                           | <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Enterococcus spp.</i> , <i>S. pneumoniae</i>   | N                           | Kibdelomycin, gepotidacin   | Cytoplasm                       | 33142421              |
| Direct DNA damage                              | <i>M. tuberculosis</i> , <i>E. faecalis</i>   | Y                           | <b>Metronidazole</b> , actinomycin, mitomycin C, MGB-BP-3   | Cytoplasm                       | 29077920              |
| DnaN/sliding clamp                             | <i>M. tuberculosis</i>  | N                           | Griselimycin  | Cytoplasm                       | 26045430              |
| DNA Ligase (LigA)                              | <i>E. coli</i> , <i>S. aureus</i>   | Y                           | (2S,3R,4R,5S)-2-((S)-7-amino-5-(cyclopentyloxy)-3H-indol-3-yl)-4-azido-5-(fluoromethyl)tetrahydrofuran-3-ol | Cytoplasm                       | 27784238              |
| FtsZ (cell division, not DNA directly)         | <i>P. aeruginosa</i> , <i>A. baumannii</i> , <i>S. aureus</i> , <i>S. pneumoniae</i>        | N                           | Zantrin Z3, TXA709, PC58538, SRI-3072   | Cytoplasm/Inner membrane        | 32692252              |
| DNA polymerase III                             | <i>C. difficile</i> , <i>S. aureus</i> , <i>E. faecalis</i>                                 | N                           | Ibezapolstat  | Cytoplasm                       | 31221610              |
| Thymidylate kinase                             | <i>Enterococcus spp.</i> , <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>M. tuberculosis</i> | N                           | TK-666  | Cytoplasm                       | 23394555              |
| <b>Name</b>                                    | <b>Representative Pathogens</b>   | <b>Close Human Homolog?</b> | <b>Representative Inhibitors</b>  | <b>Subcellular Localization</b> | <b>PMID Reference</b> |

|                                    |   |                             |  |                                 |                       |
|------------------------------------|---|-----------------------------|--|---------------------------------|-----------------------|
| DNA-directed RNA polymerase        | <i>M. tuberculosis</i> , <i>P. aeruginosa</i> , <i>A. baumannii</i> , <i>S. aureus</i>      | N                           | <b>Rifampicin, rifabutin</b> , sorangicin A, myxopyronins  | Cytoplasm                       | 30647141              |
| DNA Minor Groove                   | <i>C. difficile</i>   | N                           | Distamycin, MGB-BP-3                                       | Cytoplasm                       | 14754456              |
| Dihydropteroate synthase           | <i>A. baumannii</i> , <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>Salmonella spp.</i>      | N                           | <b>Sulfadiazine, dapsone</b>                               | Cytoplasm                       | 22383850              |
| Dihydrofolate reductase            | <i>A. baumannii</i> , <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>Enterococcus spp.</i>    | N                           | <b>Trimethoprim</b>  | Cytoplasm                       | 32298876              |
| 4-amino-4-deoxychorismate synthase | <i>M. tuberculosis</i> , <i>S. aureus</i> , <i>E. faecalis</i>                              | N                           | Abyssomicin  | Cytoplasm                       | 34073764              |
| FOLD                               | <i>S. pneumoniae</i>  | Y                           | Carolacton   | Cytoplasm                       | 29142318              |
| Translation initiation (23S rRNA)  | <i>M. tuberculosis</i> , <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>Enterococcus spp.</i> | N                           | <b>Linezolid</b> , contezolid                              | Cytoplasm                       | 9835522               |
| 50S ribosome                       | <i>S. pneumoniae</i> , <i>N. gonorrhoeae</i> , <i>P. aeruginosa</i>                         | N                           | <b>Erythromycin, chloramphenicol, Synercid, lefamulin</b>  | Cytoplasm                       | 28664582              |
| 30S ribosome                       | <i>M. tuberculosis</i> , <i>P. aeruginosa</i> , <i>A. baumannii</i> , <i>S. aureus</i>      | Y                           | <b>Amikacin, tetracycline, clindamycin</b> , odilorhabdins | Cytoplasm                       | 21957007              |
| 70S ribosome (both 30S and 50S)    | <i>S. pneumoniae</i> , <i>M. tuberculosis</i> , <i>P. aeruginosa</i> , <i>S. aureus</i>     | Y                           | <b>Viomycin</b> , thermorubin, bactobolin, thiostrepton    | Cytoplasm                       | 26755601              |
| EF-G                               | <i>S. aureus</i> , <i>C. difficile</i> , <i>Streptococcus spp.</i>                          | Y                           | Fusidic acid, argyris B                                    | Cytoplasm                       | 27325008              |
| EF-Tü                              | <i>C. difficile</i> , <i>A. baumannii</i> , <i>S. aureus</i> , <i>E. faecalis</i>           | Y                           | Kirromycin, enacyloxin IIa, pulvomycin, GE2270A            | Cytoplasm                       | 16876786              |
| Peptide deformylase                | <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>S. aureus</i> , <i>M. tuberculosis</i>     | N                           | LBM415, GSK1322322, hydroxamates                           | Cytoplasm                       | 16904375              |
| Methionine aminopeptidase          | <i>M. tuberculosis</i>  | Y                           | Bengamides, clioquinol                                     | Cytoplasm                       | 22118830              |
| Ile-tRNA synthetase                | <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>H. influenzae</i>                              | N                           | <b>Mupirocin</b> , CB432, PLD-118                          | Cytoplasm                       | 8431015               |
| <b>Name</b>                        | <b>Representative Pathogens</b>   | <b>Close Human Homolog?</b> | <b>Representative Inhibitors</b>                           | <b>Subcellular Localization</b> | <b>PMID Reference</b> |
| Ser-tRNA synthetase                | <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>N. gonorrhoeae</i>                             | N                           | SB-217452, albomycins                                      | Cytoplasm                       | 30181560              |

|   |   |                             |   |                                 |                       |
|---|---|-----------------------------|---|---------------------------------|-----------------------|
| Thr-tRNA synthetase   | <i>S. aureus</i>  | Y                           | Borrelidin, oblafluorin                         | Cytoplasm                       | 25824639              |
| Trp-tRNA synthetase   | <i>H. pylori, S. aureus</i>                                       | N                           | Indolmycin, chuangxinmicin                      | Cytoplasm                       | 19546369              |
| Phe-tRNA synthetase   | <i>H. influenzae, S. pneumoniae, S. aureus</i>                    | N                           | Ochratoxin A, phenyl-thiazolylurea-sulfonamides | Cytoplasm                       | 14742205              |
| Leu-tRNA synthetase   | <i>A. baumannii, S. pneumoniae, S. aureus</i>                     | N                           | GSK2251052, granaticin A, DS86760016            | Cytoplasm                       | 29437618              |
| Met-tRNA synthetase   | <i>S. aureus, S. pneumoniae, E. faecium, C. difficile</i>         | N                           | CRS3123, REP8839                                | Cytoplasm                       | 16189106              |
| N-acetylornithine transaminase (arginine synthesis)           | <i>E. amylovora</i> (non human-pathogenic)                        | N                           | Pantocin B                                      | Cytoplasm                       | 11592872              |
| L-histidinol phosphate aminotransferase (histidine synthesis) | <i>E. amylovora</i> (non human-pathogenic)                        | N                           | Pantocin A                                      | Cytoplasm                       | 12833353              |
| FabI  | <i>S. aureus, M. tuberculosis</i>                                 | N                           | PT-166, AFN-1252, <b>isoniazid</b>              | Cytoplasm                       | 24739388              |
| FabB/F  | <i>S. aureus, Enterococcus spp., S. pneumoniae, H. influenzae</i> | N                           | Platensimycins, cerulenin, thiolactomycin       | Cytoplasm                       | 11050088              |
| FabH  | <i>S. aureus, E. faecalis, H. influenzae</i>                      | N                           | Platencin, aminothiazoles                       | Cytoplasm                       | 27626097              |
| ACCCase (AccD)  | <i>S. aureus, E. faecalis, H. influenzae</i>                      | N                           | Andrimid, pyridopyrimidine, pyrrolocin C        | Cytoplasm                       | 18768797              |
| ATP synthase (c subunit - AtpE)                               | <i>M. tuberculosis, S. aureus</i>                                 | N                           | <b>Bedaquiline</b> , oligomycin, Tomatidine     | Transmembrane                   | 33299175              |
| Pyruvate ferredoxin oxidoreductase                            | <i>C. difficile, H. pylori, C. jejuni</i>                         | N                           | <b>Nitazoxanide</b> , amoxicile                 | Cytoplasm                       | 28874750              |
| Quorum sensing (LasR)   | <i>P. aeruginosa</i>  | N                           | PD12, V-06-018                                  | Cytoplasm                       | 16966394              |
| Histidine Kinase/two component response (YycG/YycF)           | <i>S. pneumoniae, S. aureus, E. faecium</i>                       | N                           | Aranorosinol B, walkmycin                       | Transmembrane                   | 25436989              |
| NADH: ubiquinone oxidoreductase complex                       | <i>S. aureus, P. aeruginosa, V. cholerae</i>                      | N                           | Diphenyliodonium, HQNO, korormicin              | Transmembrane                   | 30135204              |
| <b>Name</b>   | <b>Representative Pathogens</b>                                   | <b>Close Human Homolog?</b> | <b>Representative Inhibitors</b>                | <b>Subcellular Localization</b> | <b>PMID Reference</b> |
| ClpXP chambered proteases (ClpP)                              | <i>M. tuberculosis, S. aureus, S. pneumoniae</i>                  | N                           | ADEPs, cyclomarin A, lassomycin                 | Cytoplasm                       | 27899793              |
| Thioredoxin reductase   | <i>S. aureus, E. faecalis, C. difficile</i>                       | N                           | Auranofin, ebselen                              | Cytoplasm                       | 33936021              |

|   |  |                             |  |                                 |                       |
|---|--|-----------------------------|--|---------------------------------|-----------------------|
| Biofilm formation                           | <i>P. aeruginosa</i> , <i>S. aureus</i> (as adjuvant)  | N                           | SPI009, HT-61, halogenated phenazines                            | Various                         | 28515440              |
| DXP Reductoisomerase (MEP pathway) (DXR)    | <i>P. aeruginosa</i> , <i>E. coli</i> , <i>P. falciparum</i>                                       | N                           | Fosmidomycin   | Intracellular                   | 16321944              |
| Succinate Dehydrogenase                     | <i>P. aeruginosa</i>   | N                           | Promysalin   | Transmembrane                   | 29300464              |
| Iron Chelator                               | <i>A. baumannii</i> , <i>E. coli</i>   | ---                         | DHBA, VK28   | Extracellular                   | 22850524              |
| Glyoxylate Shunt Pathway (Isocitrate lyase) | <i>S. aureus</i> , <i>Legionella spp.</i> , <i>A. baumannii</i>                                    | N                           | Itaconate, 3-nitropropionate                                     | Cytoplasm                       | 24354272              |
| Beta-lactamase                              | <i>Enterobacteriaceae spp.</i> , <i>Acinetobacter spp.</i> , <i>Pseudomonas spp.</i> (as adjuvant) | N                           | <b>Clavulanic acid, Avibactam, aspergillomarasmine A</b>         | Periplasm                       | 30959050              |
| Aminoglycoside-modifying enzymes            | <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>E. faecium</i> (as adjuvant)                          | N                           | Aranorosin, biverlactones  | Cytoplasm                       | 23110460              |
| Efflux pumps                                | <i>P. aeruginosa</i> , <i>S. enterica</i> , <i>Shigella f.</i> (as adjuvant)                       | N                           | Phenylalanine-arginine beta-naphthylamide, D13-9001, MBX-2319    | Membrane                        | 25114133              |
| Mcr-1 (colistin resistance protein)         | <i>E. coli</i> , <i>A. baumannii</i> , <i>K. pneumoniae</i> (as adjuvant)                          | N                           | Pterostilbene, osthole, genistein                                | Inner membrane                  | 30851289              |
| Type III Secretion (virulence)              | <i>P. aeruginosa</i> , <i>Salmonella spp.</i>  | N                           | phenoxyacetamides, salicylidene acylhydrazides, hydroxyquinolone | Membrane                        | 9618447               |
| Alanine racemase (alr)                      | <i>P. aeruginosa</i> , <i>H. influenzae</i> , <i>S. aureus</i>                                     | N                           | <b>D-cycloserine</b> , phosphonopeptides                         | Cytoplasm                       | 26024289              |
| DlaT (dihydrolipoamide acyltransferase)     | <i>M. tuberculosis</i>   | N                           | Rhodanines   | Cytoplasm                       | 18329613              |
| NadE  | <i>M. tuberculosis</i>   | N                           | Urea-sulfonamides  | Cytoplasm                       | 28827112              |
| Menaquinone biosynthesis (MenG)             | <i>M. tuberculosis</i>   | N                           | SQ109, DG70  | Intracellular membrane domain   | 24568559              |
| Autolysins (Blockage) (CwIO)                | <i>N. gonorrhoeae</i> , <i>S. aureus</i> , <i>E. faecium</i>                                       | N                           | Corbomycin, complestatin   | Secreted/Cell Wall              | 32051588              |
| <b>Name</b>                                 | <b>Representative Pathogens</b>  | <b>Close Human Homolog?</b> | <b>Representative Inhibitors</b>                                 | <b>Subcellular Localization</b> | <b>PMID Reference</b> |
| Cystathionine gamma lyase (CSE)             | <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>E. coli</i>   | Y                           | NL1  | Cytoplasm                       | 34112687              |

**Table S2.** Antibiotic Leads.

A representative list of known antibiotic leads was analyzed during the preparation of this perspective. Leads represent a molecule class; in some cases, a specific example of the class is listed in brackets. Leads were identified as being primarily produced synthetically or isolated as a natural product. In cases where a natural product is most often obtained through synthetic methods, it is marked as “Synthetic” even if it was originally isolated as a natural product. “Representative pathogens” indicates species where the lead has demonstrated *in vitro* or *in vivo* activity with a MIC < 10 µg/mL. “*In vivo* Activity” indicates whether the molecule has known antibacterial activity in at least one animal model. The PMID reference for a suggested article is provided for more information about the lead.



| Name                    | Target   | Source          | Representative Pathogens   | In vivo Activity? | PMID Reference |
|-------------------------|--|-----------------|--|-------------------|----------------|
| Penicillins             | Penicillin-binding proteins                            | Natural Product | <i>S. aureus</i> , <i>H. influenzae</i> , <i>N. gonorrhoeae</i> , <i>S. pneumoniae</i>   | Y                 | 17142469       |
| Cephalosporins          | Penicillin-binding proteins                            | Natural Product | <i>S. aureus</i> , <i>K. pneumoniae</i> , <i>H. influenzae</i> , <i>S. pneumoniae</i>    | Y                 | 18676578       |
| Cefoperazone            | Penicillin-binding proteins                            | Synthetic       | <i>S. pneumoniae</i> , <i>S. aureus</i> , <i>H. influenzae</i>                           | Y                 | 6221381        |
| Carbapenems [Ertapenem] | Penicillin-binding proteins                            | Natural Product | <i>S. pneumoniae</i> , <i>Salmonella spp.</i> , <i>H. influenzae</i> , <i>S. aureus</i>  | Y                 | 28324783       |
| Lactivicin              | Penicillin-binding proteins                            | Synthetic       | <i>S. pyogenes</i> , <i>P. aeruginosa</i>  | N                 | 17676039       |
| Monobactams [Aztreonam] | Penicillin-binding proteins                            | Synthetic       | <i>K. pneumoniae</i> , <i>H. influenzae</i> , <i>P. aeruginosa</i> , <i>A. baumannii</i> | Y                 | 1943248        |
| D-cycloserine           | Alanine Racemase                                       | Synthetic       | <i>M. tuberculosis</i>   | Y                 | 30496460       |
| Alaphosphin             | Alanine Racemase                                       | Synthetic       | <i>E. coli</i> , <i>H. influenzae</i> , <i>K. pneumoniae</i>                             | Y                 | 525987         |
| Complestatin            | Autolysins   | Natural Product | <i>S. aureus</i> , <i>N. gonorrhoeae</i>   | Y                 | 32051588       |
| Corbomycin              | Autolysins   | Natural Product | <i>S. aureus</i> , <i>N. gonorrhoeae</i> , <i>E. faecalis</i>                            | Y                 | 32051588       |
| Vancomycin              | Lipid II   | Natural Product | <i>S. aureus</i> , <i>C. difficile</i>   | Y                 | 25753888       |
| Ramoplanins             | Lipid II   | Natural Product | <i>S. aureus</i>   | Y                 | 15784805       |
| Mersacidin              | Lipid II   | Natural Product | <i>S. aureus</i> , <i>B. subtilis</i>  | Y                 | 7793878        |
| Mannopectimycin         | Lipid II   | Natural Product | <i>S. pneumoniae</i> , <i>S. aureus</i>  | Y                 | 12499170       |
| Lantibiotics [nisin]    | Lipid II   | Natural Product | <i>S. aureus</i>   | Y                 | 26678028       |
| Moenomycins             | Transglycosylases                                      | Natural Product | <i>S. aureus</i> , <i>P. aeruginosa</i>  | Y                 | 20730219       |
| Bacitracin              | Undecaprenyl-pyrophosphate (lipid precursor transport) | Natural Product | <i>Staphylococcus spp.</i> , <i>Streptococcus spp.</i> , <i>N. gonorrhoeae</i>           | Y                 | 12121761       |
| Amphomycin              | Undecaprenyl phosphate                                 | Natural Product | <i>S. aureus</i> , <i>E. faecalis</i>  | N                 | 21464247       |
| Fosfomycin              | MurA (PEP transferase)                                 | Synthetic       | <i>M. tuberculosis</i> , <i>P. aeruginosa</i> , <i>A. baumannii</i>                      | Y                 | 28062557       |

| Name           | Target                         | Source          | Representative Pathogens                                   | In vivo Activity? | PMID Reference |
|----------------|--------------------------------|-----------------|--|-------------------|----------------|
| Daptomycin     | Membrane depolarization/damage | Natural Product | <i>S. aureus</i>   | Y                 | 29059358       |
| Boromycin      | Membrane depolarization/damage | Natural Product | <i>M. tuberculosis, S. aureus, E. faecalis</i>             | N                 | 4247775        |
| Polymyxin B/E  | Membrane depolarization/damage | Natural Product | <i>P. aeruginosa, A. baumannii</i>                         | Y                 | 17914915       |
| Lysocin E      | Membrane depolarization/damage | Natural Product | <i>S. aureus</i>   | Y                 | 26911796       |
| Teixobactin    | Membrane depolarization/damage | Synthetic       | <i>S. aureus</i>   | Y                 | 28991382       |
| Gramicidin     | Membrane depolarization/damage | Natural Product | <i>S. aureus, E. faecalis, A. baumannii, P. aeruginosa</i> | Y                 | 26886453       |
| FcPNA          | Membrane depolarization/damage | Synthetic       | <i>S. aureus</i>   | N                 | 23578171       |
| Irresistin-16  | Membrane depolarization/damage | Synthetic       | <i>S. aureus, E. faecalis, A. baumannii, S. pneumoniae</i> | Y                 | 32497502       |
| Lugdunin       | Membrane depolarization/damage | Natural Product | <i>S. aureus</i>   | Y                 | 33779184       |
| Octapeptin C4  | Membrane depolarization/damage | Synthetic       | <i>P. aeruginosa, A. baumannii, K. pneumoniae</i>          | Y                 | 29396290       |
| Bacaucin-1     | Membrane depolarization/damage | Synthetic       | <i>S. aureus</i>   | Y                 | 28106348       |
| Balsacone C    | Membrane depolarization/damage | Natural Product | <i>S. aureus</i>   | N                 | 31681206       |
| XF-73          | Membrane depolarization/damage | Synthetic       | <i>E. faecalis, S. aureus, S. pneumoniae, C. difficile</i> | Y                 | 20346634       |
| Reutericyclin  | Membrane depolarization/damage | Natural Product | <i>E. faecalis, S. aureus</i>                              | N                 | 11010877       |
| Muraminomicins | MraY                           | Natural Product | <i>S. aureus, S. pneumoniae</i>                            | Y                 | 31413314       |
| Tunicamycin    | MraY                           | Natural Product | <i>B. cereus</i>   | N                 | 30850266       |
| Mureidomycin   | MraY                           | Natural Product | <i>P. aeruginosa</i>                                       | Y                 | 31266949       |
| Liposidomycin  | MraY                           | Natural Product | <i>M. tuberculosis</i>                                     | N                 | 31582803       |

| Name  | Target                    | Source          | Representative Pathogens  | In vivo Activity? | PMID Reference |
|---|---------------------------|-----------------|---|-------------------|----------------|
| Capuramycin                                   | MraY                      | Natural Product | <i>M. tuberculosis</i>  | Y                 | 25269459       |
| Muraymycin                                    | MraY                      | Natural Product | <i>S. aureus</i>  | Y                 | 27340469       |
| Pacidamycins                                  | MraY                      | Natural Product | <i>P. aeruginosa</i>  | N                 | 20514371       |
| Arylomycins                                   | Signal peptidase I (LepB) | Natural Product | <i>S. aureus, P. aeruginosa</i>                                   | N                 | 21095572       |
| Actinocarbasins                               | Signal peptidase I (LepB) | Natural Product | <i>S. aureus</i>  | Y                 | 22710113       |
| G0775   | Signal peptidase I (LepB) | Synthetic       | <i>K. pneumoniae, A. baumannii, P. aeruginosa, S. aureus</i>      | Y                 | 30209367       |
| Globomycin                                    | Signal peptidase II       | Natural Product | <i>K. pneumoniae, S. typhimurium</i>                              | N                 | 26912896       |
| Myxovirescin                                  | Signal peptidase II       | Natural Product | <i>K. pneumoniae, S. typhimurium</i>                              | N                 | 22232277       |
| CJ-21058                                      | SecA                      | Natural Product | <i>S. aureus, E. faecalis</i>                                     | N                 | 11918061       |
| Rose Bengal                                   | SecA                      | Synthetic       | <i>S. aureus</i>  | N                 | 26432604       |
| Erythrosin B                                  | SecA                      | Synthetic       | <i>B. subtilis</i>  | Y                 | 22354575       |
| Ramizol                                       | MscL                      | Synthetic       | <i>C. difficile, S. aureus, S. pneumoniae</i>                     | Y                 | 25649856       |
| Darobactin                                    | BamA                      | Natural Product | <i>P. aeruginosa, K. pneumoniae, S. typhimurium, A. baumannii</i> | Y                 | 31747680       |
| MRL-494                                       | BamA                      | Synthetic       | <i>S. aureus</i>  | N                 | 31591200       |
| Murgocil                                      | MurG                      | Synthetic       | <i>S. aureus</i>  | N                 | 23957438       |
| Murepavadin [POL7080]                         | LptD                      | Synthetic       | <i>P. aeruginosa</i>  | Y                 | 20167788       |
| Protegrin I                                   | LptD                      | Synthetic       | <i>A. baumannii, N. gonorrhoeae</i>                               | Y                 | 9257752        |
| POL7001                                       | LptD                      | Synthetic       | <i>P. aeruginosa</i>  | Y                 | 27297477       |
| CHIR-090                                      | LpxC                      | Synthetic       | <i>P. aeruginosa</i>  | Y                 | 16342948       |
| LPC-009                                       | LpxC                      | Synthetic       | <i>P. aeruginosa, E. coli</i>                                     | N                 | 22414079       |
| Isoindolin-1-ones                             | LpxC                      | Synthetic       | <i>P. aeruginosa, K. pneumoniae, S. aureus</i>                    | N                 | 31804826       |
| 1,2-dihydro-3H-pyrrolo[1,2-c]imidazole-3-ones | LpxC                      | Synthetic       | <i>P. aeruginosa, K. pneumoniae</i>                               | N                 | 31804826       |

| Name  | Target                              | Source          | Representative Pathogens  | In vivo Activity? | PMID Reference |
|---|-------------------------------------|-----------------|---|-------------------|----------------|
| 4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-ones   | LpxC                                | Synthetic       | <i>P. aeruginosa</i> , <i>K. pneumoniae</i>   | Y                 | 31804826       |
| G0507                                       | LoiCDE                              | Synthetic       | <i>E. coli</i>  | N                 | 29339384       |
| Viridicatumtoxin B                          | Undecaprenyl pyrophosphate synthase | Natural Product | <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>E. faecalis</i>                                      | N                 | 32437130       |
| Spirohexaline                               | Undecaprenyl pyrophosphate synthase | Natural Product | <i>S. aureus</i>  | N                 | 23168407       |
| 4-oxo-2-thioxo-1,3-thiazolidines            | Undecaprenyl pyrophosphate synthase | Synthetic       | <i>S. aureus</i> , <i>Enterococcus spp.</i> , <i>L. monocytogenes</i>                             | N                 | 24827744       |
| Pentamidine                                 | Outer membrane permeabilization     | Synthetic       | <i>P. aeruginosa</i> , <i>A. baumannii</i> , <i>K. pneumoniae</i> (as adjuvant)                   | Y                 | 28263303       |
| Cationic peptides [Magainin II]             | Outer membrane permeabilization     | Natural Product | <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>E. faecalis</i> , <i>K. pneumoniae</i> (as adjuvant) | Y                 | 9033483        |
| Loperamide                                  | Outer membrane permeabilization     | Synthetic       | <i>Shigella spp.</i> , <i>P. aeruginosa</i> (as adjuvant)   | Y                 | 21516114       |
| Tyrocidine                                  | Pore Former                         | Synthetic       | <i>E. faecalis</i> , <i>S. aureus</i> , <i>S. epidermidis</i>                                     | N                 | 17728134       |
| Sceptrin                                    | MreB                                | Synthetic       | <i>S. aureus</i> , <i>P. aeruginosa</i>   | N                 | 18479102       |
| CBR-4830                                    | MreB                                | Synthetic       | <i>P. aeruginosa</i>  | N                 | 17644596       |
| A22   | MreB                                | Synthetic       | <i>S. typhimurium</i> , <i>P. aeruginosa</i>  | N                 | 15564663       |
| Quinolones/fluoroquinolones [Ciprofloxacin] | DNA gyrase                          | Synthetic       | <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>M. tuberculosis</i> , <i>S. pneumoniae</i>           | Y                 | 29407984       |
| Aminocoumarins [Novobiocin]                 | DNA gyrase                          | Natural Product | <i>S. aureus</i> , <i>K. pneumoniae</i> , <i>S. pneumoniae</i>                                    | Y                 | 24079980       |
| Spiropyrimidinetriones [Zoliflodacin]       | DNA gyrase                          | Synthetic       | <i>N. gonorrhoeae</i> , <i>S. aureus</i> , <i>E. faecalis</i> , <i>S. pneumoniae</i>              | Y                 | 32329999       |
| Cyclotialidine                              | DNA gyrase                          | Natural Product | <i>S. aureus</i> , <i>E. faecalis</i>   | Y                 | 8022866        |

|  |   |                 |   |                          |                       |
|--|---|-----------------|---|--------------------------|-----------------------|
| Metronidazole  | Direct DNA damage                                   | Synthetic       | <i>C. difficile</i> , <i>M. tuberculosis</i>  | Y                        | 29077920              |
| Nitrofurantoin   | Direct DNA damage                                   | Synthetic       | <i>K. pneumoniae</i>  | Y                        | 26066581              |
| Actinomycin  | Direct DNA damage                                   | Natural Product | <i>S. aureus</i> , <i>S. flexneri</i> , <i>K. pneumoniae</i> , <i>S. typhi</i>        | N                        | 15995596              |
| <b>Name</b>  | <b>Target</b>                                       | <b>Source</b>   | <b>Representative Pathogens</b>   | <b>In vivo Activity?</b> | <b>PMID Reference</b> |
| Dynemicin A  | Direct DNA damage                                   | Natural Product | <i>S. aureus</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>                        | N                        | 8427581               |
| Mitomycin C  | Direct DNA damage                                   | Natural Product | <i>S. aureus</i> , <i>P. aeruginosa</i>   | Y                        | 34228538              |
| MGB-BP-3   | Direct DNA damage                                   | Synthetic       | <i>S. aureus</i> , <i>C. difficile</i>  | Y                        | 33116952              |
| Bleomycin  | Direct DNA damage                                   | Natural Product | <i>S. aureus</i> , <i>K. pneumoniae</i>   | N                        | 31508840              |
| Griselimycin   | DnaN/sliding clamp                                  | Natural Product | <i>M. tuberculosis</i>  | Y                        | 26045430              |
| (2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i> )-2-(( <i>S</i> )-7-amino-5-(cyclopentyloxy)-3 <i>H</i> -indol-3-yl)-4-azido-5-(fluoromethyl)tetrahydr ofuran-3-ol | DNA Ligase (LigA)                                   | Synthetic       | <i>S. pneumoniae</i> , <i>S. aureus</i>   | N                        | 21719282              |
| SRI-3072   | FtsZ (cell division, not DNA directly)              | Synthetic       | <i>M. tuberculosis</i>  | N                        | 12096015              |
| Viriditoxin  | FtsZ (cell division, not DNA directly)              | Natural Product | <i>S. aureus</i> , <i>E. faecalis</i> , <i>S. pneumoniae</i>                          | N                        | 12952956              |
| PC58538  | FtsZ (cell division, not DNA directly)              | Synthetic       | <i>S. pneumoniae</i>  | N                        | 16174771              |
| Zantrin Z3   | FtsZ (cell division, not DNA directly)              | Synthetic       | <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>S. pneumoniae</i>                        | N                        | 15289600              |
| TXA709   | FtsZ (cell division, not DNA directly)              | Synthetic       | <i>S. aureus</i>  | Y                        | 26033735              |
| PC190723   | FtsZ (cell division, not DNA directly)              | Synthetic       | <i>S. aureus</i>  | Y                        | 20212044              |
| Ibezapolstat   | DNA polymerase III                                  | Synthetic       | <i>C. difficile</i>   | Y                        | 32285102              |
| TK-666   | Thymidylate kinase                                  | Synthetic       | <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>E. faecalis</i>                          | Y                        | 22908966              |
| Diazaquinomycin  | Thymidylate Synthase (but some conflicting reports) | Natural Product | <i>M. tuberculosis</i> , <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>E. faecalis</i> | N                        | 26594660              |

|                             |                             |                 |  |                          |                       |
|-----------------------------|-----------------------------|-----------------|--|--------------------------|-----------------------|
| Amycolamicin                | Topoisomerases (Type IV)    | Natural Product | <i>S. aureus, P. aeruginosa, E. faecalis, S. dysenteriae</i>   | N                        | 23129443              |
| Gepotidacin                 | Topoisomerases (Type II)    | Synthetic       | <i>S. aureus, S. pneumoniae, H. influenzae, N. gonorrhoeae</i> | Y                        | 30757898              |
| <b>Name</b>                 | <b>Target</b>               | <b>Source</b>   | <b>Representative Pathogens</b>                                | <b>In vivo Activity?</b> | <b>PMID Reference</b> |
| Kibdelomycin                | Topoisomerases (Type II)    | Natural Product | <i>S. aureus, S. pneumoniae, E. faecalis, H. influenzae</i>    | Y                        | 25845866              |
| Rifabutin                   | DNA-directed RNA polymerase | Synthetic       | <i>M. tuberculosis, S. aureus, P. aeruginosa</i>               | Y                        | 8785253               |
| Rifampicin                  | DNA-directed RNA polymerase | Synthetic       | <i>S. aureus, E. faecalis, H. influenzae, N. gonorrhoeae</i>   | Y                        | 6635433               |
| Sorangicin A                | DNA-directed RNA polymerase | Natural Product | <i>S. aureus, P. aeruginosa, M. tuberculosis</i>               | N                        | 33199626              |
| Fidaxomicin                 | DNA-directed RNA polymerase | Natural Product | <i>C. difficile, E. faecalis, S. aureus, N. gonorrhoeae</i>    | Y                        | 22752863              |
| Myxopyronin                 | DNA-directed RNA polymerase | Natural Product | <i>S. aureus</i>   | N                        | 15482944              |
| Streptolydigin              | DNA-directed RNA polymerase | Natural Product | <i>S. aureus</i>   | N                        | 24342645              |
| Corallopyronin              | DNA-directed RNA polymerase | Natural Product | <i>S. aureus, Wolbachia spp.</i>                               | Y                        | 24079981              |
| Ripostatin                  | DNA-directed RNA polymerase | Natural Product | <i>S. aureus, E. faecium, C. difficile</i>                     | N                        | 25112727              |
| Salinamide                  | DNA-directed RNA polymerase | Natural Product | <i>H. influenzae</i>   | N                        | 24843001              |
| GE23077                     | DNA-directed RNA polymerase | Natural Product | <i>S. pyogenes</i>   | N                        | 24755292              |
| Pseudouridimycin            | DNA-directed RNA polymerase | Natural Product | <i>S. pneumoniae, S. pyogenes, S. aureus</i>                   | Y                        | 28622509              |
| MGB-BP-3                    | DNA Minor Groove            | Synthetic       | <i>C. difficile, S. aureus</i>                                 | Y                        | 33116952              |
| Sulfonamides [Sulfadiazine] | Dihydropteroate synthase    | Synthetic       | <i>S. aureus, P. aeruginosa</i>                                | Y                        | 9844622               |
| Dapsone                     | Dihydropteroate synthase    | Synthetic       | <i>S. aureus</i>   | Y                        | 12165212              |
| Trimethoprim                | Dihydrofolate reductase     | Synthetic       | <i>S. aureus, E. faecalis, S. typhimurium</i>                  | Y                        | 9844622               |
| Irresistin-16               | Dihydrofolate reductase     | Synthetic       | <i>S. aureus, E. faecalis, A. baumannii, S. pneumoniae</i>     | Y                        | 32497502              |
| Iclaprim                    | Dihydrofolate reductase     | Synthetic       | <i>S. aureus, S. pneumoniae, H. influenzae</i>                 | Y                        | 19211577              |

|                                |                                    |                 |  |                          |                       |
|--------------------------------|------------------------------------|-----------------|--|--------------------------|-----------------------|
| Abyssomicins                   | 4-amino-4-deoxychorismate synthase | Natural Product | <i>S. aureus, E. faecalis, M. tuberculosis</i>                 | N                        | 34073764              |
| Carolacton                     | FoID                               | Natural Product | <i>S. pneumoniae</i>   | N                        | 29142318              |
| <b>Name</b>                    | <b>Target</b>                      | <b>Source</b>   | <b>Representative Pathogens</b>                                | <b>In vivo Activity?</b> | <b>PMID Reference</b> |
| Oxazolidinones [linezolid]     | Translation initiation (23S rRNA)  | Synthetic       | <i>S. aureus, S. pneumoniae, E. faecalis</i>                   | Y                        | 9835522               |
| Cadazolid                      | Translation initiation (23S rRNA)  | Synthetic       | <i>C. difficile</i>  | Y                        | 28286992              |
| MRX-I [contezolid]             | Translation initiation (23S rRNA)  | Synthetic       | <i>S. aureus, E. faecalis, S. pneumoniae</i>                   | Y                        | 24694071              |
| Macrolides [erythromycin]      | 50S ribosome                       | Natural Product | <i>S. aureus, S. pneumoniae, N. gonorrhoeae, H. influenzae</i> | Y                        | 30054232              |
| Chloramphenicol                | 50S ribosome                       | Synthetic       | <i>S. aureus, H. influenzae, S. pneumoniae, K. pneumoniae</i>  | Y                        | 8688636               |
| Streptogramins [Synercid]      | 50S ribosome                       | Synthetic       | <i>S. pneumoniae, S. aureus, E. faecium</i>                    | Y                        | 9511057               |
| Pleuromutilins [Lefamulin]     | 50S ribosome                       | Synthetic       | <i>S. aureus, S. pneumoniae, E. faecium, H. influenzae</i>     | Y                        | 30019769              |
| Thiazomycin                    | 50S ribosome                       | Natural Product | <i>S. aureus, E. faecalis, S. pneumoniae</i>                   | Y                        | 28096545              |
| Aminoglycosides [streptomycin] | 30S ribosome                       | Natural Product | <i>S. aureus, M. tuberculosis, P. aeruginosa</i>               | Y                        | 23110460              |
| Tetracyclines                  | 30S ribosome                       | Natural Product | <i>S. aureus, E. faecalis, S. pneumoniae, H. influenzae</i>    | Y                        | 26989065              |
| Lincosamides [clindamycin]     | 30S ribosome                       | Synthetic       | <i>S. aureus, S. pneumoniae</i>                                | Y                        | 30137858              |
| Odilorhabdins [NOSO-95179]     | 30S ribosome                       | Natural Product | <i>K. pneumoniae</i>   | Y                        | 29625040              |
| Edeine                         | 30S subunit                        | Synthetic       | <i>B. subtilis, C. albicans</i>                                | N                        | 11296217              |
| Thermorubin                    | 70S ribosome (both 30S and 50S)    | Natural Product | <i>S. aureus, S. pneumoniae</i>                                | Y                        | 22240456              |
| Viomycin                       | 70S ribosome (both 30S and 50S)    | Natural Product | <i>M. tuberculosis, K. pneumoniae, S. typhosa</i>              | Y                        | 26755601              |
| Bactobolin A                   | 70S ribosome (both 30S and 50S)    | Natural Product | <i>S. aureus, K. pneumoniae</i>                                | N                        | 25562208              |
| Thiostrepton                   | 70S ribosome (both 30S and 50S)    | Natural Product | <i>S. aureus, M. tuberculosis</i>                              | Y                        | 31835481              |

|                                   |                           |                 |  |                          |                       |
|-----------------------------------|---------------------------|-----------------|--|--------------------------|-----------------------|
| Fusidic acid                      | EF-G                      | Natural Product | <i>S. aureus</i>   | Y                        | 6988070               |
| Argyirin B                        | EF-G                      | Natural Product | <i>P. aeruginosa</i>   | N                        | 22970117              |
| <b>Name</b>                       | <b>Target</b>             | <b>Source</b>   | <b>Representative Pathogens</b>                                | <b>In vivo Activity?</b> | <b>PMID Reference</b> |
| Kirromycin/efrotomycin            | EF-Tü                     | Natural Product | <i>E. faecium, N. gonorrhoeae, H. influenzae</i>               | Y                        | 3904612               |
| LFF571                            | EF-Tü                     | Synthetic       | <i>E. faecalis, S. aureus, C. difficile</i>                    | Y                        | 22315981              |
| Pulvomycin                        | EF-Tü                     | Natural Product | <i>S. aureus, E. faecalis, A. baumannii, P. aeruginosa</i>     | N                        | 16734421              |
| Enacyloxin IIa                    | EF-Tü                     | Natural Product | <i>N. gonorrhoeae</i>  | N                        | 16257965              |
| Factumycin                        | EF-Tü                     | Natural Product | <i>A. baumannii</i>  | N                        | 7166535               |
| GE2270 A                          | EF-Tü                     | Natural Product | <i>S. aureus, S. pneumoniae, E. faecalis, C. difficile</i>     | Y                        | 16734421              |
| GSK1322322                        | Peptide deformylase       | Synthetic       | <i>S. pneumoniae, H. influenzae, S. aureus</i>                 | Y                        | 23478958              |
| Hydroxamates [BB-3497]            | Peptide deformylase       | Synthetic       | <i>S. aureus, E. faecalis, H. influenzae, S. pneumoniae</i>    | Y                        | 11158755              |
| Bengamide B                       | Methionine aminopeptidase | Synthetic       | <i>M. tuberculosis</i>   | Y                        | 31591407              |
| Mupirocin                         | Ile-tRNA synthetase       | Natural Product | <i>S. aureus, S. pneumoniae, H. influenzae, N. gonorrhoeae</i> | Y                        | 30551435              |
| CB432                             | Ile-tRNA synthetase       | Synthetic       | <i>S. aureus</i>   | Y                        | 9837850               |
| Albomycins                        | Ser-tRNA synthetase       | Natural Product | <i>S. aureus, S. pneumoniae, N. gonorrhoeae</i>                | Y                        | 17459767              |
| Borrelidin                        | Thr-tRNA synthetase       | Natural Product | <i>M. luteus, E. coli</i>                                      | N                        | 25824639              |
| Obafluorin                        | Thr-tRNA synthetase       | Natural Product | <i>S. aureus, P. aeruginosa</i>                                | N                        | 31675206              |
| Indolmycin                        | Trp-tRNA synthetase       | Natural Product | <i>S. aureus, M. tuberculosis</i>                              | Y                        | 15243028              |
| Chuangxinmycin                    | Trp-tRNA synthetase       | Natural Product | <i>S. aureus</i>   | N                        | 12372526              |
| Ochratoxin A                      | Phe-tRNA synthetase       | Natural Product | <i>S. aureus, E. faecalis</i>                                  | N                        | 27092524              |
| Phenyl-thiazolylurea-sulfonamides | Phe-tRNA synthetase       | Synthetic       | <i>S. aureus, S. pneumoniae, H. influenzae</i>                 | Y                        | 14742205              |



|                                     |   |                 |   |                          |                       |
|-------------------------------------|---|-----------------|---|--------------------------|-----------------------|
| GSK2251052                          | Leu-tRNA synthetase   | Synthetic       | <i>P. aeruginosa, H. influenzae, A. baumannii</i>     | Y                        | 29437618              |
| Granaticin B                        | Leu-tRNA synthetase   | Natural Product | <i>S. aureus, S. epidermidis</i>                      | N                        | 3372358               |
| <b>Name</b>                         | <b>Target</b>   | <b>Source</b>   | <b>Representative Pathogens</b>                       | <b>In vivo Activity?</b> | <b>PMID Reference</b> |
| Diaryldiamine [CRS3123/REP3123]     | Met-tRNA synthetase   | Synthetic       | <i>C. difficile, MRSA, S. pneumoniae, E. faecalis</i> | Y                        | 33857480              |
| REP8839                             | Met-tRNA synthetase   | Synthetic       | <i>S. aureus, S. pneumoniae, E. faecalis</i>          | N                        | 19015366              |
| Tabtoxinine beta-lactam             | Glutamine synthetase  | Natural Product | <i>E. coli</i>  | N                        | 29039929              |
| Pantocin B                          | N-acetylornithine transaminase (arginine synthesis)           | Natural Product | <i>E. amylovora</i> (non-human pathogenic)            | N                        | 11592872              |
| Pantocin A                          | L-histidinol phosphate aminotransferase (histidine synthesis) | Natural Product | <i>E. amylovora</i> (non-human pathogenic)            | N                        | 12833353              |
| Triclosan                           | FabI  | Synthetic       | <i>S. aureus, S. pneumoniae, E. coli</i>              | Y                        | 10201369              |
| Isoniazid                           | FabI  | Synthetic       | <i>M. tuberculosis</i>                                | Y                        | 17074073              |
| Ethionamide                         | FabI  | Synthetic       | <i>M. tuberculosis</i>                                | Y                        | 11823459              |
| PT166                               | FabI  | Synthetic       | <i>S. aureus</i>                                      | Y                        | 24739388              |
| AFN-1252                            | FabI  | Synthetic       | <i>S. aureus, S. epidermidis</i>                      | Y                        | 25644789              |
| CG-549                              | FabI  | Synthetic       | <i>S. aureus</i>                                      | Y                        | 17606482              |
| Benzofuran naphthyridine [Afabicin] | FabI  | Synthetic       | <i>S. aureus</i>                                      | Y                        | 32747361              |
| Platensimycin                       | FabF/B  | Natural Product | <i>S. aureus, E. faecalis, S. pneumoniae</i>          | Y                        | 16710421              |
| Cerulenin                           | FabF/B  | Natural Product | <i>M. tuberculosis, M. smegmatis,</i>                 | N                        | 11050088              |
| Thiolactomycin                      | FabH and FabF/B   | Natural Product | <i>E. coli</i>  | N                        | 11050088              |
| Phomallenic acid C                  | FabH and FabF/B   | Synthetic       | <i>S. aureus, H. influenzae</i>                       | N                        | 16436705              |
| Platensin                           | FabH and FabF/B   | Natural Product | <i>S. aureus</i>                                      | Y                        | 17456595              |
| Fasamycins                          | FabF  | Natural Product | <i>S. aureus, E. faecalis</i>                         | N                        | 22224500              |
| GSK3011724A                         | KasA (beta-ketoacyl synthase)                                 | Synthetic       | <i>M. tuberculosis</i>                                | Y                        | 27581223              |

|                           |   |                 |   |                                 |                       |
|---------------------------|---|-----------------|---|---------------------------------|-----------------------|
| Andrimid                  | ACCase                                  | Natural Product | <i>S. aureus, E. coli, K. pneumoniae</i>        | N                               | 18768797              |
| <b>Name</b>               | <b>Target</b>                           | <b>Source</b>   | <b>Representative Pathogens</b>                 | <b><i>In vivo</i> Activity?</b> | <b>PMID Reference</b> |
| Pyridopyrimidine          | ACCase                                  | Synthetic       | <i>H. influenzae, E. coli</i>                   | Y                               | 19164768              |
| Pyrollocin C              | ACCase                                  | Natural Product | <i>S. aureus, E. faecalis</i>                   | N                               | 32470050              |
| Bedaquiline               | ATP synthase                            | Synthetic       | <i>M. tuberculosis</i>                          | Y                               | 33299175              |
| Oligomycin                | ATP synthase                            | Natural Product | <i>C. albicans, S. aureus</i>                   | N                               | 22869738              |
| Tomatidine                | ATP synthase                            | Natural Product | <i>S. aureus</i>                                | N                               | 29610201              |
| Venturicidin A            | ATP synthase                            | Natural Product | <i>S. aureus</i> (as adjuvant)                  | N                               | 32424122              |
| Nitazoxanide              | Pyruvate: ferredoxin oxidoreductase     | Synthetic       | <i>C. difficile, H. pylori</i>                  | Y                               | 22585229              |
| Amoxicile                 | Pyruvate: ferredoxin oxidoreductase     | Synthetic       | <i>C. difficile, P. gingivalis, H. pylori</i>   | Y                               | 27090174              |
| PD12                      | Quorum sensing                          | Synthetic       | <i>P. aeruginosa</i>                            | N                               | 16966394              |
| V-06-018                  | Quorum sensing                          | Synthetic       | <i>P. aeruginosa</i>                            | N                               | 16966394              |
| Aranorosinol B            | Histidine Kinase/two component response | Natural Product | <i>B. subtilis</i>                              | N                               | 15015732              |
| Walkmycin                 | Histidine Kinase/two component response | Natural Product | <i>S. aureus, B. subtilis</i>                   | N                               | 20057515              |
| ADEPs (Acyl depsipeptide) | ClpXP Proteases                         | Natural Product | <i>S. aureus, S. pneumoniae, E. faecalis</i>    | Y                               | 24422534              |
| Bortezomib                | ClpXP Proteases                         | Synthetic       | <i>M. smegmatis</i>                             | N                               | 31517045              |
| Lassomycin                | ClpXP Proteases                         | Natural Product | <i>M. tuberculosis</i>                          | N                               | 24684906              |
| Cyclomarin A              | ClpXP Proteases                         | Natural Product | <i>M. tuberculosis</i>                          | N                               | 24022489              |
| Armeniaspirols            | ClpXP Proteases                         | Natural Product | <i>S. aureus, E. faecium</i>                    | N                               | 34293284              |
| HQNO                      | NADH: ubiquinone oxidoreductase complex | Synthetic       | <i>S. aureus</i> (as adjuvant)                  | N                               | 31363032              |
| Diphenyleneiodonium       | NADH: ubiquinone oxidoreductase complex | Synthetic       | <i>M. tuberculosis, S. aureus, A. baumannii</i> | Y                               | 28912539              |

|                        |   |                 |  |                          |                       |
|------------------------|---|-----------------|--|--------------------------|-----------------------|
| VK28                   | Iron Chelator   | Synthetic       | <i>E. coli</i> , <i>A. baumannii</i>   | N                        | 22850524              |
| <b>Name</b>            | <b>Target</b>   | <b>Source</b>   | <b>Representative Pathogens</b>  | <b>In vivo Activity?</b> | <b>PMID Reference</b> |
| Auranofin              | Selenium sequestration                                    | Synthetic       | <i>S. aureus</i> , <i>E. faecalis</i>  | N                        | 30252208              |
| Polyphenols [EGCG]     | Biofilm formation   | Natural Product | <i>E. faecalis</i> , <i>P. gingivalis</i> , <i>S. pneumoniae</i> (as adjuvant)       | Y                        | 31261858              |
| Usnic acid             | Biofilm formation   | Synthetic       | <i>S. aureus</i> , <i>E. faecalis</i> (as adjuvant)                                  | N                        | 15504865              |
| Halogenated Phenazines | Biofilm formation   | Synthetic       | <i>S. aureus</i> , <i>E. faecium</i> (as adjuvant)                                   | N                        | 30811834              |
| HT-61                  | Biofilm formation   | Synthetic       | <i>S. aureus</i> (as adjuvant)   | Y                        | 28156093              |
| SPI009                 | Biofilm formation   | Synthetic       | <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> (as adjuvant)         | N                        | 29312259              |
| Fosmidomycin           | DXP Reductoisomerase (MEP pathway)                        | Synthetic       | <i>P. aeruginosa</i> , <i>E. coli</i> , <i>P. falciparum</i>                         | Y                        | 16321944              |
| Rhodanines             | DlaT (dihydrolipoamide acyltransferase)                   | Synthetic       | <i>M. tuberculosis</i>   | N                        | 18329613              |
| Ethambutol             | Arabinosyl Transferase                                    | Synthetic       | <i>M. tuberculosis</i>   | Y                        | 8876238               |
| Pyrazinamide           | PanD  | Synthetic       | <i>M. tuberculosis</i>   | Y                        | 32245967              |
| Urea Sulfonamides      | NadE  | Synthetic       | <i>M. tuberculosis</i>   | N                        | 28827112              |
| SQ109                  | Menaquinone Biosynthesis                                  | Synthetic       | <i>M. tuberculosis</i>   | Y                        | 16172107              |
| DG70                   | Menaquinone Biosynthesis                                  | Synthetic       | <i>M. tuberculosis</i> , <i>M. bovis</i>   | N                        | 28196957              |
| Ridinilazole           | Cell Growth (Precise Mechanism Still Under Investigation) | Synthetic       | <i>C. difficile</i>  | Y                        | 30837785              |
| Promysalin             | Succinate Dehydrogenase                                   | Natural Product | <i>P. aeruginosa</i>   | N                        | 27096543              |
| Itaconate              | Glyoxylate Shunt Pathway - Isocitrate Lyase               | Natural Product | <i>M. tuberculosis</i> , <i>E. coli</i> , <i>K. pneumoniae</i>                       | N                        | 34020726              |
| Phenyl-diketo acid     | Glyoxylate Shunt Pathway - Malate Synthase                | Synthetic       | <i>M. tuberculosis</i>   | Y                        | 23261599              |
| Nigericin              | Proton Antiport Mechanism                                 | Natural Product | <i>S. aureus</i> , <i>S. pyogenes</i>  | N                        | 809402                |
| Vaborbactam            | Beta-lactamase  | Synthetic       | <i>Enterobacteriaceae spp.</i> , <i>K. pneumoniae</i> , <i>E. coli</i> (as adjuvant) | Y                        | 29038260              |
| Tazobactam             | Beta-lactamase  | Synthetic       | <i>S. aureus</i> , <i>E. coli</i> , <i>K. pneumoniae</i> (as adjuvant)               | Y                        | 8388201               |

| Name                                      | Target                              | Source          | Representative Pathogens   | In vivo Activity? | PMID Reference |
|---|-------------------------------------|-----------------|--|-------------------|----------------|
| Sulbactam                                 | Beta-lactamase                      | Synthetic       | <i>A. baumannii</i> (as adjuvant)  | Y                 | 25561334       |
| Aspergillomarasmine A                     | Beta-lactamase                      | Natural Product | <i>K. pneumoniae</i> , <i>E. coli</i> (as adjuvant)                            | Y                 | 24965651       |
| VNRX-5133 [taniborbactam]                 | Beta-lactamase                      | Synthetic       | <i>P. aeruginosa</i> , <i>K. pneumoniae</i> (as adjuvant)                      | Y                 | 31765155       |
| Clavulanic acid                           | Beta-lactamase                      | Natural Product | <i>S. aureus</i> , <i>N. gonorrhoeae</i> , <i>S. pneumoniae</i> (as adjuvant)  | Y                 | 12775671       |
| Diazabicyclooctane (DBOs)                 | Beta-lactamase                      | Synthetic       | <i>P. aeruginosa</i> , <i>E. coli</i> , <i>K. pneumoniae</i> (as adjuvant)     | Y                 | 21840248       |
| Quercetin                                 | Aminoglycoside-modifying enzymes    | Synthetic       | <i>P. aeruginosa</i> (as adjuvant)   | N                 | 33156838       |
| Aranorosin                                | Aminoglycoside-modifying enzymes    | Natural Product | <i>S. aureus</i> (as adjuvant)   | N                 | 22760297       |
| Phenylalanine-arginine beta-naphthylamide | Efflux Pumps                        | Synthetic       | <i>P. aeruginosa</i> (as adjuvant)   | N                 | 23544160       |
| SLUPP-225                                 | Efflux Pumps                        | Synthetic       | <i>E. coli</i> (as adjuvant)   | N                 | 28650638       |
| MBX2319                                   | Efflux Pumps                        | Synthetic       | <i>S. enterica</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> (as adjuvant) | N                 | 26976576       |
| Verapamil                                 | Efflux Pumps                        | Synthetic       | <i>M. tuberculosis</i> (as adjuvant)   | Y                 | 29463541       |
| D13-9001                                  | Efflux Pumps                        | Synthetic       | <i>P. aeruginosa</i> (potentially as adjuvant)                                 | N                 | 30420483       |
| Pterostilbene                             | Mcr-1 (colistin resistance protein) | Natural Product | <i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. aureus</i> (as adjuvant)         | Y                 | 28304328       |
| Phenoxyacetamides [MBX 1641]              | Type III Secretion (virulence)      | Synthetic       | <i>P. aeruginosa</i> (virulence)   | N                 | 20176902       |
| Salicylidene acylhydrazides               | Type III Secretion (virulence)      | Synthetic       | <i>P. aeruginosa</i> (virulence)   | N                 | 28396545       |