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Viewpoint

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Investigational Agents for the Treatment of Gram-Negative Bacterial Infections: A Reality Check

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ABSTRACT: Antibiotic-resistant Gram-negative bacteria are, arguably, the most difficult organisms to treat, with a limited number of new antibiotics in the development pipeline. Currently 24 new agents in phase 1, phase 2, or phase 3 clinical development were identified for the potential treatment of infections caused by Gram-negative bacteria. Of these agents, most are improved iterations of known antibiotic classes, including new aminoglycosides, β-lactams, β-lactamase inhibitors, quinolones, and tetracyclines with greater potency or a broader spectrum of activity. However, novel structures also appear, with host defense peptide mimetics, boronic acid, and bridged diazabicyclooctane β-lactamase inhibitors and unique bacterial topoisomerase inhibitors. Most of the new agents have received a Qualified Infectious Disease Product (QIDP) designation that may help to accelerate FDA drug approvals. Because resistance will inevitably arise to any antibacterial agent, it will be necessary to continue to identify additional new agents in the future.

Alarms have been set off by organizations such as the Infectious Disease Society of America,[1] the British Society of Antimicrobial Chemotherapy,[2] and the European Union (EU)[3] deploring the lack of new antibacterial agents, particularly drugs to treat infections caused by multidrug-resistant (MDR) Gram-negative bacteria.[3,4] This has been attributed, in part, to the departure of large pharmaceutical companies from the business of antibiotic drug discovery. Pathogens such as MDR *Pseudomonas aeruginosa* or *Acinetobacter baumannii* and carbapenemase-producing *Klebsiella pneumoniae* have been singled out by the Centers for Disease Control (CDC) as serious, and urgent, antibiotic resistance threats, respectively,[5] with few, if any, new agents to treat infections caused by these bacteria.

Over the past few years, major changes in drug development approaches have taken place as a result of multiple lobbying and public campaigns. The EU has formed the Innovative Medicines Initiative (IMI)[6] that promotes public−private partnerships to aid in the development of new pharmaceutical agents. As a result, the IMI initiated the New Drugs for Bad Bugs (ND4BB) project to develop agents to treat diseases caused by antibiotic-resistant bacteria.[3] In 2012, the U.S. government passed the GAIN (Generate Antibiotic Incentives Now) act to provide incentives to pharmaceutical companies to develop new antibiotics. Under the GAIN act, new agents that may be used to treat antibiotic-resistant infections are eligible to receive the QIDP (Qualified Infectious Disease Product) designation that allows for expedited review by the U.S. Food and Drug Administration (FDA) and an additional five years of marketing exclusivity.[3] In addition, U.S. government funding from the Broad Spectrum Antimicrobial Program of the Biomedical Advanced Research and Development Authority (BARDA) has been used to support early development activities of smaller biotechnology organizations.[6] A recent estimate attributes over U.S. $1 billion in contributions to support antibiotic drug development from these governmental efforts, representing 20% of the global support for such activities.[6]

As a result of these efforts, antibiotic development has been stimulated to yield a relatively robust pipeline that includes agents active against many MDR pathogens.[7] A contributing factor to the increased enthusiasm for antibiotic research, particularly in smaller companies, has been the willingness of the FDA to work with sponsors to meet regulatory expectations for the development of drugs to treat antibiotic-resistant infections. New guidance documents have been issued that provide more flexibility in the approval process for new agents that may satisfy unmet medical needs.[4] Impressively, five new antibiotics with QIDP designations were approved by the FDA between May 2014 and February 2015: dalbavancin, oritavancin, tedizolid, ceftolozane-tazobactam, and ceftazidime-avibactam. Unfortunately, only the two cephalosporin-β-lactamase inhibitor (BLI) combinations are able to treat infections resulting from MDR Gram-negative bacteria: ceftolozane-tazobactam with its notable antibacterial activity against *P. aeruginosa* and ceftazidime-avibactam with activity against carbapenem-producing Enterobacteriaceae (CRE).[7]

In an unusual move, ceftazidime-avibactam was approved for use on the basis of a combination of animal model data and phase 2 clinical trials because of the perceived medical need for an agent to treat CRE.[8] The BLI avibactam is a reversible, covalent, bridged diazabicyclooctane (DBO) non-β-lactam, β-lactamase inhibitor with a novel mechanism of inhibition, in contrast to the "classical" BLIs, clavulanic acid and tazobactam, which act as suicide inhibitors to inactivate a set of class A β-lactamases. The breadth of the inhibitory spectrum of avibactam against class A, C, and D β-lactamases inspired other investigators to return to the BLI arena to examine the possibility of identifying other novel inhibitors that could alleviate carbapenemase-mediated resistance in CRE. At the current time, at least six other BLI

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Table 1. Investigational Agents That Have Entered Human Clinical Trials with the Potential To Treat Infections Caused by Antibiotic-Resistant Gram-Negative Bacteria

antibiotic class	agent[a]	company	phase of clinical development	novelty	antibacterial spectrum[b]
aminoglycoside	plazomicin	Achaogen	3	evades most aminoglycoside-modifying enzymes	Ac, CRE, GN, MRSA
monoclonal antibody	MEDI3902	MedImmune	1	antipseudomonal antibody	PA
β-lactam	BAL30072	Basilea	1	siderophore-containing monosulfactam	Ac, PA, some GN
	S-649266	Shionogi	2	siderophore-containing cephalosporin	some CRE and GN, PA
β-lactamase inhibitor combinations	RG6080[c]	Roche (partnered with Meiji/Fedora)	1	DBO[d] with unusually potent antibacterial activity alone	CRE, GN, PA
	cefepime-AAI101	Allecra	1	the only inhibitor combination with cefepime	GN, some PA
	aztreonam-avibactam	Actavis/AstraZeneca	2	DBO with monobactam stable to hydrolysis by zinc-containing carbapenemases	CRE, GN, some PA
	ceftaroline-avibactam	Actavis	2	DBO with anti-MRSA cephalosporin	CRE, some GN, MRSA
	imipenem-relebactam	Merck	3	DBO with a carbapenem	Most CRE, GN, PA
	meropenem-RPX7009	The Medicines Company	3	boronic acid inhibitor with a carbapenem	CRE, GN, PA
peptide mimetics	RG7929	Roche/Polyphor	2	inhibits LptD, a novel target	PA
	brilacidin	Cellceutix	2	modeled after host defense peptides	GN, MRSA
pleuromutilins	lefamulin	Nabriva	2	first pleuromutilin to be dosed systemically	GN (respiratory bacteria), MRSA
quinolones	finafloxacin	MerLion	2	notable activity against *Helicobacter pylori*	GN
	lascufloxacin	Kyorin	1	all have similar bacterial spectra focusing on Gram-positive activity and respiratory pathogens, with modest Gram-negative activity.	GN, MRSA
	avarofloxacin	Furiex	2		
	nadifloxacin	Wockhardt	2		
	delafloxacin	Melinta	3		
	nemonoxacin	TaiGen	3		
	zabofloxacin	Pacific Beach Biosciences	3		
tetracyclines	eravacycline	Tetraphase	3	evades most tetracycline resistance mechanisms	AC, CRE, GN
	omadacycline	Paratek	3	evades most tetracycline resistance mechanisms	AC, CRE, GN
topoisomerase inhibitors	ETX0914	Entasis	2	novel spiropyrimidinetrione	*Neisseria gonorrheae*
	GSK2140944	GlaxoSmithKline	2	novel aminopiperidine	MRSA, *Neisseria gonorrheae*

[a]Structures for these agents may be found in ref 7. [b]Ac, *Acinetobacter* spp.; CRE, carbapenem-resistant *Enterobacteriaceae*; GN, Gram-negative enteric bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*. [c]Undefined β-lactam partner. [d]DBO, bridged diazabicyclooctane.

combinations have completed phase 1 clinical trials and appear to be moving into full clinical development. Among these are two additional avibactam combinations, one with ceftaroline, an anti-MRSA cephalosporin, and one with aztreonam, a monobactam that is not hydrolyzed by metallo-β-lactamases; the latter BLI combination is being developed through the ND4BB initiative in Europe. In addition, the BLIs relebactam and RG6080, DBO non-β-lactam inhibitors like avibactam, have inhibitory activity similar to that of the avibactam combinations and are being developed as BLI combinations with a β-lactam partner. RPX7009 is a novel boronic acid inhibitor of many class A and class C carbapenemases and is being developed with meropenem for the treatment of CRE.

Beyond the BLIs, other investigational drugs that have at least some activity against MDR Gram-negative bacteria include many molecules from known antibiotic classes, as shown in the Table1. All of the agents in the compilation have entered human clinical trials, with almost 80% of them in therapeutic (phase 2 or phase 3) studies. Of the 24 agents in Table1, 29% belong to the quinolone ($n = 7$) class and 33% include a β-lactam antibiotic ($n = 8$) as part of their dosing regimen.[9] Most of the quinolones target the same sets of Gram-positive organisms, generally MDR streptococci and methicillin-resistant *Staphylococcus aureus* (MRSA). They have limited activity against most resistant enteric bacteria and *P. aeruginosa*, but have reasonable activity against atypical bacteria and the respiratory pathogens *Haemophilus influenzae* and *Moraxella catarrhalis*. Overall, the

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BLI combinations have more diversity in their antibacterial spectrum and greater potency against MDR enteric bacteria and, often, *P. aeruginosa* than most of the new quinolones. Almost all of the new BLIs inhibit class A carbapenemases (e.g., KPC enzymes in many CRE), in addition to the β-lactamases currently inhibited by clavulanic acid or tazobactam. However, the new BLI combinations that include a cephalosporin or carbapenem as the accompanying β-lactam exhibit only minor differences in targeted organisms. Siderophore-containing β-lactams with enhanced entry into Gram-negative bacteria are represented by the cephalosporin S-649266 and the monosulfactam BAL30072, which may possibly be combined with meropenem to provide coverage against ESBL-producing enteric bacteria. Other familiar antibiotic classes such as the tetracyclines, represented by eravacycline and omadacycline, and the aminoglycoside class with plazomicin as its representative are among the new drugs in late-stage clinical development, each of which circumvents at least some of the class-specific resistance mechanisms.[7]

A few novel agents from structural classes not previously exploited are in clinical development to treat Gram-negative infections. The host defense peptide mimetic brilacidin has antimicrobial activity against enteric bacteria as well as MRSA. Other novel agents include the unique bacterial topoisomerase inhibitors ETX0914 and GSK2140944 being developed to target drug-resistant *Neisseria gonorrhea*, another pathogen listed as an urgent threat by the CDC,[5] and the peptidomimetic RG7929, which targets the protein LptD that functions in assembly of the *P. aeruginosa* outer membrane. In addition, the monoclonal antibody MEDI3902 is being developed for the treatment of nosocomial *Pseudomonas* pneumonia. It is noteworthy that most of these agents are being developed for species-specific indications rather than as broad-spectrum agents. Single-pathogen drugs were once considered to be a niche area for antibiotic development. However, now that rapid bedside diagnostic testing is approaching reality, *Pseudomonas*-specific or gonorrhea-specific agents are considered to be commercially viable products.

On the basis of the pipeline as depicted in Table 1, it is clear that novelty is provided primarily by clever medicinal chemists and molecular modelers who use well-defined scaffolds to improve the potency or spectrum of activity of known antibiotic classes. A few more novel structures are recognized in a compilation of antibiotics with Gram-positive activity, but the majority of new agents derive from familiar structures or utilize known bacterial targets. Although the boronic acid and diazabicyclooctane non-β-lactam BLIs represent novel chemical entities, their targets are β-lactamases that can easily mutate to become less susceptible to the selecting agent. The new tetracyclines, aminoglycoside and topoisomerase inhibitors, also interact with targets that are capable of mutation or modification. Despite the fact that common resistance mechanisms may arise for a drug class, specific mechanisms may not affect all members of the class. New members of a class may be optimized on the basis of avoidance of known resistance mechanisms. A classic example was the design of the anti-MRSA cephalosporins to bind tightly to PBP2a in MRSA, the primary resistance mechanism for all (other) β-lactam antibiotics.[7] Similarly, plazomicin, the new aminoglycoside, circumvents all but one of the aminoglycoside-modifying enzymes. An expansion of the spectrum of activity or increased potency in target affinities may also be observed in next-generation drugs, as shown by the improved activity of molecules such as eravacycline, plazomicin, or BAL30072 against *Acinetobacter* spp. Thus, new agents in the same class should not necessarily be considered to be replicates of previous drugs in the class.

Other advantages of multiple drugs in the same class have emerged during the history of antibiotic development. Improvements in adverse event profiles have been demonstrated in the past as new cephalosporins and quinolones were introduced. More expedient dosing regimens such as once-a-day administration of ceftriaxone or levofloxacin resulted in well-accepted drugs based partly on convenience. The availability of both oral and parenteral formulations is important for treatment of community-acquired infections or for patients who may be able to be released from the hospital before an infection has completely cleared. As bacteria continue to evolve and new MDR pathogens emerge, it will continue to be prudent to consider modifications to known antibiotics that have satisfactory safety profiles and well-understood pharmacological properties. Thus, although there are new agents in the pipeline for the treatment of Gram-negative bacteria, there is still the inescapable realization that new scaffolds for new agents will continue to be necessary.[10] Regardless of the source of the new agent, it is inevitable that resistance will be selected to each new drug, and new molecules will be needed to counteract this threat.

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Notes

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