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Discovery and development of new antibacterial agents targeting Gram-negative bacteria in the era of pandrug resistance: is the future promising?

Malcolm GP Page[1] and Karen Bush[2]

Multidrug-resistant Gram-negative bacteria continue to pose a threat, with many infections caused by these pathogens being virtually untreatable. A number of new antibacterial agents are in late stage clinical development to treat these infections. Drugs in known classes such as new quinolones, aminoglycosides, tetracyclines, and β-lactams have been designed to evade many of the known resistance mechanisms, whereas newer drug classes include novel β-lactamase inhibitors in combination with new or approved β-lactams, and a peptidomimetic that have entered full clinical development. The establishment of public–private partnerships and an increase in pharmaceutical interest in antibacterial R&D are encouraging signs for the future.

Addresses
[1] Basilea Pharmaceutica International Ltd, Basel, Switzerland
[2] Indiana University, Simon Hall, 212 S. Hawthorne Drive, Bloomington, IN, USA

Corresponding author: Bush, Karen (karbush@indiana.edu)

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Introduction

Infections caused by multidrug-resistant (MDR) Gram-negative bacteria are among some of the most severe challenges in today's hospital setting [1]. Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs) appeared globally in the 1990s and have become virtually untreatable except by carbapenems, as the organisms accumulated multiple resistance determinants. Within a decade of the original outbreaks of ESBLs, medical centers began to encounter MDR enteric bacteria unresponsive to carbapenems, now known as carbapenem-resistant Enterobacteriaceae (CRE) [2]. These CRE are associated with high morbidity, and mortality as high as 56% among children and seriously ill patients [3–5]. In 2013 the Centers for Disease Control (CDC) issued a report on antibiotic resistance threats in the United States and listed CRE in the 'urgent' category, with ESBL-producing Gram-negative bacteria in the 'serious' group of resistant pathogens [6••]. Non-fermentative bacteria are also creating problems of their own, with *Pseudomonas aeruginosa* and *Acinetobacter baumannii* being the most worrisome: both are noted in the CDC list as 'serious' threats [6••]. Co-colonization of patients with CRE and *P. aeruginosa* or *A. baumannii* results in even increased mortality [7].

New agents to treat infections caused by these pathogens appeared to have disappeared in the early 2000s when the emphasis in pharmaceutical companies was on developing antibacterial drugs that targeted Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) rather than MDR Gram-negative bacteria [8]. The Infectious Disease Society of America (IDSA) has been a driver in calling attention to the lack of drug development to address the Gram-negative problems [9]. In 2013, they still considered the drug pipeline to be 'unacceptably lean' regarding the late stage development of agents to treat infections caused by the MDR Gram-negative organisms [10]. However, several recent publications have provided some optimism in the Gram-negative arena [11,12,13••], as they listed a number of potential agents in Phase 2 and Phase 3 clinical development for the purpose of addressing MDR Gram-negative pathogens. The more enthusiastic perspective will be further explored in this review.

Overview of investigational drugs in development

Several new quinolones with enhanced activity against fluoroquinolone-resistant Gram-positive bacteria, including MRSA, are in clinical development: the fluoroquinolones avarofloxacin, delafloxacin, and finafloxacin and the desfluoroquinolone nemonoxacin (Table 1). Avarofloxacin and nemonoxacin have antibacterial activity against enteric bacteria, similar to moxifloxacin [14,15]. Delafloxacin (Phase 3 clinical development) and finafloxacin (Phase 2 development) have enhanced activity in acidic environments, including intracellular infections, giving some improvement in activity also against Gram-negative bacteria [16,17]. DS-8587 is a fluoroquinolone with improved activity against both Gram-negative and Gram-positive bacteria. The compound is especially effective against *A. baumannii* [18] and is currently in Phase 1 clinical trials (URL: http://www.daiichisankyo.com/rd/pipeline/pdf/Pipeline_EN.pdf). GC-072 is an oxoquinolizine that has strong activity against fluoroquinolone-resistant

Table 1

Characteristics of investigational agents with activity against Gram-negative pathogens

Antibacterial agent	Antibiotic class	Sponsoring company	QIDP[a]	Development stage[b]	Targeted pathogens
Plazomicin	Aminoglycoside	Achaogen	Y	Phase 2 (complete)	MRSA MDR/CRE-*Enterobacteriaceae* *Acinetobacter* spp.
AIC499	β-Lactam	AICuris (IMI)[c]	N	Preclinical	MDR-Gram-negative bacteria *P. aeruginosa*
S200 and S201	β-Lactam (cephalosporin)	Sopharmia	N	Preclinical	MDR-Gram-negative bacteria Includes some MBL-producers
CB-618	β-Lactamase inhibitor	Cubist	N	Phase 1	MDR-Gram-negative bacteria
FPI-1465	β-Lactamase inhibitor	Fedora	N	IND enabling studies	MDR-Gram-negative bacteria *P. aeruginosa* Includes some MBL-producers
S-649266	β-Lactam (cephalosporin)	Shionogi	N	Phase 1	MDR-Gram-negative bacteria Little information
BAL30072	β-Lactam (monosulfactam)	Basilea Pharmaceutica	N	Phase 1	Many MDR-Gram-negative bacteria, includes MBL-producers *P. aeruginosa* *Acinetobacter* spp.
Aztreonam–avibactam	β-Lactamase inhibitor combination	AstraZeneca (IMI)[c]	N	Phase 1 (complete)	MDR-Gram-negative bacteria *P. aeruginosa* Includes some MBL-producers
Meropenem-RPX7009	β-Lactamase inhibitor combination	The Medicines Company	Y	Phase 3 (complete)	MDR-Gram-negative bacteria *P. aeruginosa*
Ceftaroline–avibactam	β-Lactamase inhibitor combination	Forest Laboratories/ AstraZeneca	N	Phase 2	MRSA MDR-Enterobacteriaceae
Imipenem-MK-7655	β-Lactamase inhibitor combination	Merck	N	Phase 2	MDR-Gram-negative bacteria, incl. *P. aeruginosa*
Ceftazidime–avibactam	β-Lactamase inhibitor combination	Forest Laboratories/ AstraZeneca	Y	Phase 3	MDR-Gram-negative bacteria, incl. *P. aeruginosa*
Ceftolozane–tazobactam	β-Lactamase inhibitor combination	Cubist	Y	NDA	Some MDR-Gram-negative bacteria *P. aeruginosa*
DS-8587	Fluoroquinolone	Daiichi-Sankyo	N	Phase 1	MRSA Atypical respiratory pathogens Enteric bacteria, *Acinetobacter* spp.
Finafloxacin	Fluoroquinolone	MerLion	Y	Phase 2	MRSA *H. pylori* *Acinetobacter* spp.
Avarofloxacin	Fluoroquinolone	Furiex	Y	Phase 2 (complete)	MRSA Atypical respiratory pathogens Enteric bacteria[d]
Delafloxacin	Fluoroquinolone	Melinta	Y	Phase 3	MRSA Enteric bacteria *N. gonorrheae*
Nemonoxacin	Desfluoroquinolone	TaiGen	Y	Phase 3	MRSA Atypical respiratory pathogens Enteric bacteria[d]
GC-072	Oxoquinolizine	Evolva	N	Preclinical	MRSA Enterobacteriaceae *Acinetobacter* spp.
ACHN-975	LPS biosynthesis inhibitor	Achaogen	N	Phase 1 (complete)	Enterobacteriaceae *P. aeruginosa*
POL7080	Peptidomimetic	Roche	N	Phase 1 (complete)	*P. aeruginosa*
Eravacycline	Tetracycline	Tetraphase	Y	Phase 2 (complete)	MRSA Many MDR enteric bacteria *Acinetobacter* spp.
Omadacycline	Tetracycline	Paratek	Y	Phase 2 (complete)	MRSA Many MDR enteric bacteria

[a] QIDP, qualified infectious disease product designation granted by FDA.
[b] Development status was verified either through www.clinicaltrials.gov or through the company website.
[c] Codevelopment through IMI ND4BB initiative.
[d] Potency and spectrum similar to moxifloxacin.