Future antibiotics scenarios: is the tide starting to turn?

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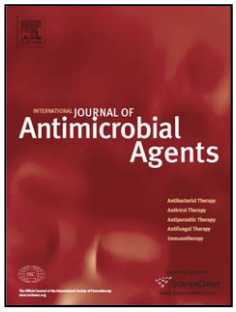

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Future antibiotics scenarios: is the tide starting to turn?

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Abstract

The fight against multidrug-resistant (MDR) pathogens continues. This article discusses the gap between the need for new antibiotics and lean research and development (R&D) pipelines. Many large pharmaceutical companies have terminated their antibacterial research programmes as they focus on potentially more lucrative therapeutic areas. At the same time, an increasingly dry funding situation hampers smaller start-up companies. Antibacterial innovation proceeds in waves. Following a wave of broad-spectrum antibiotics in the 1980s and 1990s, many companies focused on the development of small-spectrum antibiotics targeted at Gram-positive bacteria. In recent years, MDR Gram-negative bacteria have emerged and spread rapidly. The resulting intensified need for new therapeutic options against Gram-negative bacteria appears to promise financially rewarding return on investment for pharmaceutical companies within this small market niche. Thus, interest in antibiotics, particularly in drugs effective against MDR Gram-negative bacteria, is back. We appear to be at the start of a new wave of antibacterial drug R&D that will hopefully yield new therapeutic options in the future (10–15 years). Until then, the problem of MDR Gram-negative bacteria must continue to be addressed with a multifaceted set of solutions based on currently available tools.

1. Introduction

Over the last two decades the flow of new antibacterial drugs into the market has slowed, leaving a frequent gap between diagnosis of resistant pathogens and effective treatment options. Coupled with the rise of challenging infections, such as those caused by hospital- and community-acquired meticillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant (MDR) Gram-negative bacteria, this situation is of increasing concern to clinicians [1–4].

As has been observed in many fields, innovation in general proceeds in waves. This has been the historical case in the development of anti-infectives. The discovery of a new class of antimicrobials with novel mechanisms of action is usually followed by modified and improved molecules of the same class. For instance, in the 1970s to 1990s a wide variety of broad-spectrum antibiotics became available, such as cephalosporins, penicillin/β-lactamase inhibitor combinations, carbapenems and fluoroquinolones. Empirical usage and coverage of a broad range of pathogens became an integral part of the therapeutic management, with little applied concern regarding the development of resistance. The industry's focus on blockbuster drugs (peak annual single product global sales of at least $1 billion) generated economic drivers completely at odds with the medical and social goals of anti-infectives [5,6]. This business model, driven by hugely ambitious revenue and profit goals with expectations of short-term returns from the capital market, was not compatible with the short treatment of acute diseases. As many big companies focused on the search for products targeted at the far more lucrative chronic disease and life-style condition markets, they abandoned antibacterial research and development (R&D) in

the 1990s OR earlier. As a consequence, research sites were shut down, the accumulated knowledge dispersed and most R&D activities shifted to small companies.

With mostly broad-spectrum antibiotics available and in wide use, resistance problems developed. Indeed, numerous studies based on routine surveillance data indicate a strong relationship between use and resistance [7]. Still, many years passed before an ever-increasing mass of critical public health concerns regarding the rapid rise of MRSA forced open a market niche window leading to a wave of anti-Gram-positive R&D mainly in small companies. Antibiotics focused on Gram-positive bacteria, including MRSA, are proving to be commercially attractive and are encouraging investment in R&D, as has been shown with the commercial success of Pfizer's linezolid and later Cubist's daptomycin in the USA. This success has further influenced the positive perception of the commercial potential of narrow-spectrum antibiotics that target a small, but clinically critical and easily accessible, market segment.

Numerous economic, societal, political, bacterial, scientific and medical factors are driving the development of antibiotics; this review cannot cover in any depth all of the important relevant aspects. Instead, it will present an outlook for the next 5–7 years for new systemic antibiotics that may be available for the treatment of resistant pathogens. Additionally, based on talks with industry leaders and other stakeholder groups, as well as reviewing available published sources, I will draft a future scenario for the next 10–15 years. If it is on target, this scenario will give rise to

some hope but will also require a change in usage patterns of antibiotics to bridge the gap in availability of novel drugs.

2. Current Gram-positive pipelines

Table 1 presents drugs in clinical development with focus on Gram-positive bacteria, including MRSA. The table illustrates that, within just a few years, there will be many new options available to the clinician. Most of these new antibiotics build on well known antibiotic groups (Fig. 1). Considering the bleak economic situation in most countries, rising healthcare costs and indicated political changes in the USA, price and proven benefit will be key factors in deciding the uptake of new antibiotics.

A few companies pursue novel programmes with new targets that are now in early clinical development and focus mainly on Gram-positive bacteria. These drug development achievements will enrich our treatment options for infections caused by Gram-positive bacteria, especially MRSA, in the foreseeable future (Table 1). The wave of Gram-positive focus in R&D continues to flow but appears to have hit its peak.

2.1. Analogues of existing molecules

For many years companies have been focusing on improving existing antibiotic groups with the goal of addressing MRSA. Typically, antibiotics with a Gram-positive focus are developed first for complicated skin and soft-tissue infection (cSSTI), which is the most suitable entrance indication for a new product (Fig. 2). Primarily, β-

lactam and quinolone molecules were modified to include MRSA. Examples are the new cephalosporins, ceftobiprole and ceftaroline. Ceftobiprole has completed clinical development, won approval in Canada and Switzerland for cSSTI (including diabetic foot infections) and is awaiting a decision at the European Medicines Agency (EMEA). The US Food and Drug Administration (FDA) has asked for additional clinical-site audits before moving forward with the approval process. Ceftobiprole was first developed for cSSTI but will follow soon with hospital-acquired pneumonia (HAP) and severe community-acquired pneumonia (CAP) applications. However, non-inferiority to comparators in ventilator-acquired pneumonia (VAP) could not be established. Ceftaroline completed Phase 3 trials for cSSTI and is recruiting patients for a Phase 3 trial in patients with severe CAP. The carbapenem PZ-601 is currently being tested in Phase 2 for cSSTI. None of these modified β-lactams overcomes group resistance in Gram-negative bacteria but they are active against MRSA.

Four quinolones, including one non-fluorinated quinolone in Phase 2 or Phase 1 clinical development, have been optimised to include coverage of MRSA. They will be available in intravenous (i.v.) and oral forms and are targeted at cSSTI and/or CAP.

Three oxazolidinones in Phase 2 or Phase 1 may show some improvements over linezolid, such as lower minimum inhibitory concentrations (MICs), activity against linezolid-resistant strains, once-daily dosage and additional activity against *Haemophilus influenzae*.

Some years ago, glyco/lipopeptides arose as an active R&D field. Improvements have focused on bactericidal activity, long half-life and activity against vancomycin-resistant strains. Encouraged by the recent commercial success of daptomycin (primarily in the USA), three other glycopeptides were further developed and submitted for approval. So far, only one of the glycopeptides appears to have been successful. In the USA, telavancin (Theravance Inc.) received a favourable opinion from the FDA advisory committee despite some safety concerns that will be managed by risk evaluation and mitigation strategy (REMS). As usual, the first indication for telavancin was cSSTI. In Europe, the application has been withdrawn but may be resubmitted with results including Gram-positive HAP data. Pfizer's dalbavancin was withdrawn due to repeated rejections by the FDA. Oritavancin, the third antibiotic in this group, was also rejected by the FDA owing to inconclusive efficacy in MRSA patients in one Phase 3 clinical trial that was carried out some years ago by the out-licenser. Oritavancin's European application is still pending.

Another old group that has been revived and improved is the tetracycline group with the derivate amadacycline (PTK 0796) (Paretek Pharmaceuticals, Inc). It has completed Phase 2 and oral/i.v. forms are being developed for cSSTI and CAP.

2.2. Novel molecules, new targets

All the abovementioned antibacterial compounds build on well known groups (Fig. 1). Despite the scientific, technical and financial risks, a few compounds against novel targets are showing up in antibacterial pipelines. New advanced approaches include a chimeric monoclonal antibody against lipoteichoic acid that is being tested

as a staphylococcal prophylaxis in very low birth weight neonates. Another new approach is a *S. aureus* vaccine for patients scheduled for cardiothoracic surgery as well as other at-risk patients.

Fatty acid biosynthesis (Fab) inhibitors are another example of a novel class of antibiotics [8]. It would be premature to predict the clinical usefulness of the Fab inhibitors currently in early clinical development. Pleuromutilins (targeting the 23S rRNA of the 50S bacterial ribosome subunit) have been known for a long time and are available as topical antibiotics (retapamulin) [9]. Systemically available pleuromutilins are now coming on the scene (Nabriva Therapeutics).

3. Current Gram-negative pipelines

Over the last few years the increase in MDR Gram-negative isolates has become apparent and even outpaces MRSA in certain European countries and elsewhere [10]. Compared with Gram-positives, the pipelines for infections caused by MDR Gram-negative pathogens are remarkably lean (Table 2). This situation has been extensively discussed in the infectious disease community [11–16]. Here I provide information regarding drugs in pre-clinical and clinical testing that may be ca. 8–10 years (if pre-clinical) to ca. 5 years (Phase 2) away from availability for routine usage in the clinics.

3.1. Analogues of existing molecules

Most drugs in pre-clinical and clinical development are analogues of existing molecules and, as would be expected, their targets are not novel. Ceftazidime, a widely used off-patent cephalosporin, is combined with the new non-β-lactam β-lactamase inhibitor NXL 104 (Novexel), which increases the cephalosporin's activity against most β-lactamase-producing enterobacteria. Since the approval of piperacillin/tazobactam in 1993, this would be the first resumption of this established approach to protect a β-lactam antibiotic against resistance caused by β-lactamases.

CXA-101 (Calixa Therapeutics), a cephalosporin in pre-clinical development, is comparable with ceftazidime but is more stable to AmpC β-lactamases [17]. This new cephalosporin overcomes some resistance determinants but does not solve the problem of multiresistance in *Pseudomonas aeruginosa*. This is also the case for the combination of Forest's investigational cephalosporin ceftaroline in combination with the abovementioned β-lactamase inhibitor NXL 104. In addition to the improved activity of ceftaroline against staphylococci, this combination in pre-clinical development promises to be stable against most β-lactamases in Gram-negative bacteria [18]. In contrast to the abovementioned cephalosporins with a broad spectrum, the pre-clinical monobactam BAL 30072 (Basilea Pharmaceutica Ltd.) focuses on non-fermenters, particularly *Acinetobacter*. The underexplored group of monobactams is inherently stable against class B β-lactamases (metallo enzymes). BAL 30072 is also stable against AmpC enzymes but lacks stability against extended-spectrum β-lactamases) [19].

Another example of the improvement of an old group is the development of new aminoglycosides. Two programmes are in pre-clinical and clinical Phase 1 (ACHN-490) (Achaogen) development with the goal of overcoming aminoglycoside-specific resistance mechanisms.

In specific patient populations with localised infections, such as *Pseudomonas* infections in cystic fibrosis (CF) or ventilated patients in the Intensive Care Unit, a wide range of reformulations of old drugs for inhalation treatment have been pursued. The commercial success of inhaled tobramycin has accelerated efforts in this field [20]. Aztreonam, five new formulations of tobramycin, two formulations of amikacin, and one formulation each of ciprofloxacin, fosfomycin, levofloxacin and gentamicin are in clinical or pre-clinical development as adjunct therapy to systemic treatment. Only three compounds of novel classes (BL-2060, a peptidomimetic; CSA-13, a cationic steroid; and gallium nitrate) are in pre-clinical development for inhalation treatment. In the near future we may have a new arsenal of inhaled antibiotics available that may overcome resistance, at least temporarily, through high topical concentrations.

3.2. Novel molecules, new targets

Considering the widespread resistance problem and the propensity to intensify the effect of class-specific resistance mechanisms, most specialists would prefer a novel chemical class with no pre-existing potential cross-resistance [21]. Discovery activities that show the first encouraging results in this regard have been presented and have progressed to or completed pre-clinical studies. Typically only scanty

information is publicly disclosed for novel compounds in discovery or early research. Examples of such novel compounds are Cubist's lipopeptide, Novexel's non-β-lactam penicillin-binding protein inhibitor, and Achaogen's membrane biosynthesis inhibitor. Each of these has shown promising activity against enterobacteria and non-fermenters. Additionally, Polyphor's protein epitope mimetic, a medium sized, synthetic cyclic peptide-like molecule, specifically targets *P. aeruginosa* [22].

Similarly, a *Pseudomonas*-only approach is being pursued by two antibody companies with human monoclonal antibodies in Phase 2 clinical studies. KaloBios' PEGylated monoclonal antibody fragment targets the PcrV protein of the Type III secretion system of *P. aeruginosa* [23]. Kenta Biotech's human monoclonal antibody KBPA101 targets the O antigen in the bacterial surface and is specific for *Pseudomonas* serotype O11. Considering the narrow spectrum of some new compounds, diagnostic–therapeutic partnerships are particularly attractive in this field. For instance, Kenta Biotech has pioneered diagnostic therapeutic co-development by linking their monoclonal antibody against *P. aeruginosa* with a rapid diagnostic test for serotype O11. The field of antibacterial antibodies is expected to expand in the coming years fuelled by success in the viral and other fields.

Pseudomonas causes infections in highly defined patient populations such as CF and VAP. Considering the high impact on healthcare costs, an effective preventive approach would be highly desirable. Intercell is testing a recombinant subunit vaccine against *Pseudomonas* in a Phase 2 trial in VAP patients. If successful and expanded to other indications, prevention of infection would likely resolve many of the challenges of MDR *Pseudomonas* strains.

4. Future scenario for antibacterial research and development

Over recent years the resistance situation in Gram-negative infections has received substantial attention [10,24]. Reports regarding MDR *P. aeruginosa*, *Acinetobacter* spp. and enterobacteria such as *Klebsiella* spp. caused a revival in the use of very old and less characterised drugs such as colistin [25,26]. Owing to the intensified need for new therapeutic options against MDR Gram-negative bacteria, the variables of the economic assessment in pharmaceutical companies have changed. So after many years of broad-spectrum antibiotics for empirical usage, the tide appears to have turned to the Gram-negative field and to more targeted therapy. Although not yet apparent in the clinical pipelines shown in Table 2, there are early signs that we are now facing the rise of a new wave of renewed interest in the long-neglected Gram-negative R&D field. Based on personal communication with company representatives, news on recent research collaborations between big and small companies, as well as the founding of new start-up companies, the interest in antibiotics—and more precisely in anti-Gram-negative antibiotics—is back. Company officials are preparing for the era of the 'niche buster,' with drugs ranging from activity against MDR enterobacteria and non-fermenters, to one-pathogen-only (*Pseudomonas* antibodies), to the extreme approach of targeting only specific serotypes of *Pseudomonas*. As development of resistance against the hospital's workhorse cephalosporins, carbapenems and quinolones continue to develop and the therapeutic options become even more limited, we should expect to see more premium-priced, novel, small-spectrum antibiotics in the 2020s.

Whilst current medical practice makes empirical therapy a necessity [27,28], all signs and trends point towards targeted therapy options and more efficient usage of diagnostics [29–31]. Driven by financially challenged healthcare systems worldwide and enticed by successful examples of applied personalised medicine in the oncology field, the concurrent rise of reliable, easy to use, rapid molecular diagnostic capabilities promises to change treatment paradigms in everyday clinical practice. Molecular diagnostics are the cornerstones of the emerging fields of pharmacogenomics and personalised medicine and are becoming increasingly entwined with the development of pharmaceutical drugs [32]. Serving as a model, companion development of rapid diagnostics and small-spectrum antibiotics provides an incentive for companies to study more seriously ill patients in late clinical development [33]. Usage of rapid diagnostics promises more efficient and faster enrolment of patients and also has the potential to provide robust evidence for safety and effectiveness in the exact group of patients in whom the drugs can make the most difference in decreasing mortality [34]. The coming years are expected to bring further advances in diagnostic technology and applications [36]. In the clinical setting, the diagnosis of bacterial infections carries numerous challenges that may be partly addressed by reliable rapid detection of pathogens [36] and guide selection of new targeted small-spectrum antibiotics.

The pendulum is swinging back to R&D in the Gram-negative field. Another sign for this trend is the interest in treatment approaches outside the mainstream. Whilst not taken seriously a few years ago, the situation is now ripe for innovative treatments such as monoclonal and polyclonal antibodies, therapeutic vaccines, antivirulence drugs, phage formulations and antibacterial peptides. Many of these activities are in

an early phase of discovery and will not be available for testing in clinical trials for a few more years.

5. Conclusion

Markets create resistance and resistance creates markets [37]. The rise in MDR Gram-negative bacteria has become a worldwide threat and new classes of antimicrobials with novel mechanisms of action are urgently required. This increasing need has created a promising market opportunity for the pharmaceutical industry, with the prospect of a satisfying return of investment via targeted high prices deployed in small niche markets. My prediction based on monitoring activities in this field is that the next wave of antibacterial drug development has begun. Changed market conditions are opening up a new era of interest in the development of Gram-negative drugs. As these drugs have a narrow spectrum, they will be accompanied by a new generation of rapid and reliable companion diagnostics. However, owing to reduced resources and research infrastructure, as well as the typically protracted research and clinical development time, it will take many years to harvest the fruits of these efforts. The success of the next wave of antibiotics will require changes to the regulatory, clinical and reimbursement landscape and considerable challenges are ahead. Yet clear signs of renewed interest in the development of new antibiotics against the most problematic Gram-negative pathogens will take 10–15 years to be delivered into clinical practice. We must continue to address the challenge of multidrug resistance today in order to bridge the gap in antibacterial development.

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Fig. 1. Number of antibiotics in clinical development (Phases 1, 2 and 3 or filed new drug application (NDA)] according to antibacterial group.

Fig. 2. Number of antibiotics in clinical development (Phases 1, 2 and 3 or filed new drug application (NDA)] according to indications. cSSTI, complicated skin and soft-tissue infection; MRSA, meticillin-resistant *Staphylococcus aureus*; HAP, hospital-acquired pneumonia; Staph. Inf., staphylococcal infection; CAP, community-acquired pneumonia; cUTI, complicated urinary tract infection.

Table 1

Investigational drugs with focus on multidrug-resistant staphylococci in clinical development [a]

Development phase (Jan. 2009) [b]	Compound (Company)	Group	Major indication
FDA: NDA submitted, favourable recommendation from AIDAC, risk management strategy EMEA: MAA withdrawn, new MAA will be submitted including HAP/VAP data	Telavancin i.v. (Theravance/Astellas)	Glycopeptide	cSSTI, Gram-positive HAP/VAP (bacteraemia: Phase 2)
FDA: rejected by AIDAC EMEA: MAA submitted	Oritavancin i.v. (Lilly/InterMune/Targanta/The Medicines Company)	Glycopeptide	cSSTI
All marketing applications withdrawn	Dalbavancin i.v. (Pfizer)	Lipoglycopeptide	cSSTI (bacteraemia: Phase 2)
FDA: not approvable in its current form EMEA: MAA submitted	Iclaprim i.v./oral (Arpida)	Dihydrofolate reductase inhibitor	cSSTI

FDA: submitted, delay (additional clinical-site audits necessary) EMEA: submitted, positive opinion from CHMP Approved in Canada, Switzerland	Ceftobiprole i.v. (Basilea/Johnson & Johnson)	Cephalosporin	cSSTI (including diabetic foot infections) (HAP, severe CAP: Phase 3 completed)
Phase 3	Ceftaroline i.v. (Forest)	Cephalosporin	cSSTI (Phase 3 completed), CAP (Phase 3)
Phase 2b/3	Pagibaximab i.v. (Biosynexus)	Chimeric monoclonal antibody against lipoteichoic acid	Staphylococcal prophylaxis in very birth low weight neonates
Phase 2 completed	Amadacycline i.v./oral (Baer/Paratek/Merck)	Tetracycline derivate	cSSSI (i.v.–oral), diabetic foot infection, CAP
Phase 2 completed	Delafloxacin = RX-3341 i.v. (oral) (Wakunaga/Abbott/Rib-X)	Quinolone	cSSTI, CAP (oral: Phase 2)
Phase 2 completed	V710 (Intercell/Merck)	*Staphylococcus aureus* vaccine	Single dose for patients scheduled for cardiothoracic surgery, kidney disease patients

Phase 2, oral; Phase 1, i.v.	Nemonoxacin oral/i.v. (Procter & Gamble/TaiGen Biotechnology)	Non-fluorinated quinolone	CAP, diabetic foot infections (oral, Phase 2), HAP (i.v.)
Phase 2 (further development deferred)	TD-1792 i.v. (Theravance)	Vancomycin + cephalosporin	cSSTI, bacteraemia
Phase 2 (oral)	Radezolid = Rx-1741 oral/i.v. (Rib-X)	Oxazolidinone	Mild-to-moderate CAP, uSSTI (oral)
Phase 2	PZ-601 i.v. (Dainippon Sumitomo/Protez/Novartis)	Carbapenem	cSSSI (CAP, cIAI, cUTI)
Phase 2	NXL 103 = linopristin/flopristin, oral (Novexel)	Streptogramin	CAP
Phase 2 (oral)	Torezolid (TR-701), i.v./oral (Dong-A /Trius)	Oxazolidinone	cSSSI, HAP
Phase 2 (India); nadifloxacin is approved and widely used as topical agent (acne)	WCK-771 i.v. (oral prodrug WCK-2349, Phase 1) (Wockhardt)	Quinolone (active isomer of nadifloxacin)	Gram-positive infections
Phase 2	Zabofloxacin i.v./oral = (DW-224a) (Dong Wha/Pacific Beach BioSciences)	Quinolone	Community-acquired respiratory infections
Phase 1 completed	CEM-101 oral (Cempra)	Macrolide	CAP

Phase 1 completed (oral)	BC-3205 oral/i.v. (Nabriva)	Pleuromutilin	cSSSI, CAP
Phase 1	RWJ-416457 (Johnson & Johnson)	Oxazolidinone	Gram-positive infections
Phase 1	PMX-30063 i.v. (PolyMedix)	Small molecule mimetic of host defence proteins	Staphylococcal infections
Phase 1	AFN-1252 i.v./oral (Affinium)	FabI inhibitor	Staphylococcal infections
Phase 1 (development status unclear)	Platensimycin (Merck)	FabF inhibitor	Staphylococcal infections

FDA, US Food and Drug Administration; EMEA, European Medicines Agency; NDA, new drug application (FDA); MAA, marketing authorisation application (EMEA); AIDAC, Anti-Infective Drugs Advisory Committee (FDA); CHMP, Committee for Medicinal Products for Human Use (EMEA); i.v. intravenous; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; CAP, community-acquired pneumonia; cSSTI, complicated skin and soft-tissue infection; cSSSI, complicated skin and skin-structure infection; uSSTI, uncomplicated skin and soft-tissue infection; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection.

[a] Information based on the proprietary database of the Center for Anti-Infective Agents (CEFAIA).

[b] Pre-clinical, in vitro and in vivo testing to determine toxicity and pharmacokinetics; Phase 1, testing in healthy volunteers to determine pharmacokinetics and safety; Phase 2, testing in a small number of patients to determine safety and efficacy; Phase 3, testing in a large number of patients to determine efficacy and safety.

Table 2

Investigational intravenous drugs with focus on multidrug-resistant Gram-negative bacteria, including *Pseudomonas*, in pre-clinical and clinical development [a]

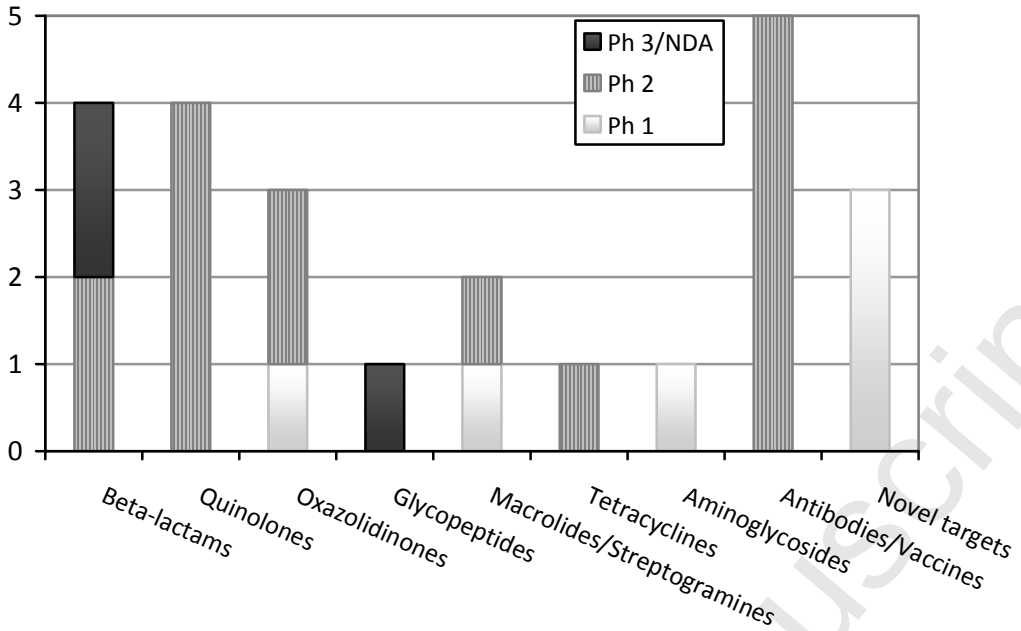
Development phase (Jan. 2009) [b]	Compound (Company)	Group	Notes
Phase 2	Ceftazidime + NXL 104 (Novexel)	Cephalosporin + new β-lactamase inhibitor	Stable against class A (ESBL) and class C β-lactamases; cUTI
Phase 2	IC43 (Chiron/Pelias/Intercell)	Vaccine	Recombinant subunit vaccine consisting of two outer membrane proteins of *Pseudomonas aeruginosa*; VAP
Phase 2	KBPA101 (Kenta Biotech)	Human monoclonal antibody	Targets *P. aeruginosa* serotype O11 Co-development of a multivalent diagnostic test for rapid serotyping
Phase 1/2	KB001 (KaloBios)	PEGylated monoclonal antibody fragment	Antivirulence antibody targets PcrV protein of the Type III secretion system of *P. aeruginosa*; CF and VAP
Phase 1	ACHN-490 (Achaogen)	Aminoglycoside	Active against aminoglycoside-resistant Gram-negative pathogens, MRSA

Pre-clinical completed	CB-182804 (Cubist)	Lipopeptide	*Escherichia coli*, *Acinetobacter*, *P. aeruginosa* and *Klebsiella*
Pre-clinical completed	Ceftaroline + NXL 104 (Forest/Novexel)	Cephalosporin + new β-lactamase inhibitor	Stable against class A (ESBL) and class C β-lactamases; enterobacteria, *P. aeruginosa*, MRSA
Pre-clinical completed	Polyphor	Protein epitope mimetics (novel class)	*P. aeruginosa*-specific
Pre-clinical	FR 264205 = CXA-101 (Astellas/Calixa)	Cephalosporin	Comparable with ceftazidime, more stable against class C β-lactamases
Pre-clinical	BAL 30072 (Basilea)	Monobactam	Stable against class C and class B enzymes (metallo-β-lactamases); *Acinetobacter*, *P. aeruginosa*, enterobacteria
Pre-clinical	NXL105 (Novexel)	PBP inhibitor (novel class)	Gram-negative bacteria
Pre-clinical	Aminoglycoside (SelectX)	Aminoglycoside	More stable against aminoglycoside-modifying enzymes
Pre-clinical planned	Achaogen	Membrane biosynthesis inhibitors (novel class)	Enterobacteria, *P. aeruginosa*

ESBL, extended-spectrum β-lactamase; cUTI, complicated urinary tract infection; VAP, ventilator-associated pneumonia; CF, cystic fibrosis; MRSA, meticillin-resistant *Staphylococcus aureus*; PBP, penicillin-binding protein.

[a] Information based on the proprietary database of the Center for Anti-Infective Agents (CEFAIA).

[b] pre-clinical, in vitro and in vivo testing to determine toxicity and pharmacokinetics; Phase 1, testing in healthy volunteers to determine pharmacokinetics and safety; Phase 2, testing in a small number of patients to determine safety and efficacy; Phase 3, testing in a large number of patients to determine efficacy and safety.



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