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Discovery and development of new antibacterial drugs: learning from experience?

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Synopsis (241 words)

Antibiotic (antibacterial) resistance is a serious global problem and the need for new treatments is urgent. The current antibiotic discovery model is not developing new agents at a rate that is sufficient to combat present levels of antibiotic resistance. This has led to fears of the arrival of a 'post antibiotic era'. Scientific difficulties, an unfavourable regulatory climate, multiple company mergers and the low financial returns associated with antibiotic drug development led to the withdrawal of many pharmaceutical companies from the field. The regulatory climate has now begun to improve, but major scientific hurdles still impede the discovery and development of novel antibacterial agents. To facilitate discovery activities there must be increased understanding of the scientific problems experienced by pharmaceutical companies. This must be coupled with addressing the current antibiotic resistance crisis so that compounds and ultimately drugs are delivered to treat the most urgent clinical challenges. By understanding the causes of the failures and successes of the pharmaceutical industry's research history, duplication of discovery programmes will be reduced so increasing the productivity of the antibiotic drug discovery pipeline by academia and small companies. The most important scientific issues to address are getting molecules into the Gram-negative bacterial cell and avoiding their efflux. Hence screening programmes should focus their efforts on whole bacterial cells rather than cell-free systems. Despite falling out of favour with pharmaceutical companies, natural product research still holds promise for providing new molecules as a basis for discovery.

Introduction

Antibiotic resistance is a serious global problem and the need for new treatments is urgent. Antibacterial drugs have revolutionised our ability to control bacterial disease, and their clinical availability has led to dramatic decreases in morbidity and mortality.[1] As such, these therapeutics underpin modern medicine. Despite the integral role of antibiotics in the maintenance of our modern lifestyle, they are undervalued in both cost and significance by society. Over the past century, their use has provided a strong selective pressure on micro-organisms, leading to preferential survival and spread of those harbouring antibiotic resistance mechanisms. Multi-drug resistance (MDR) is now commonplace amongst bacterial pathogens and antibiotic resistance now affects all antibiotic classes.[2] This is particularly worrisome in the case of Gram-negative bacteria, (e.g. *Pseudomonas aeruginos*a and *Acinetobacter baumannii*) for which treatment options are already limited.[3] The "broken" economics of antibacterial research and development (R&D) is often quoted as the main reason for a lack of new therapies but the truth is it is hard to discover new antibacterial drugs, and the science is not sufficiently advanced to enable efficient and effective antibacterial drug discovery. This has led to fears of a 'post antibiotic era'. It has been proposed that between 5 and 20 novel antibacterial drugs need to enter the clinical development pipeline in order to effectively contend with the current resistance problem. However, given the attrition rate within the existing drug discovery model, a minimum of 200 discovery programmes would optimistically be needed in order to achieve this outcome. Hence, new approaches to antibiotic discovery are needed.

The antibiotic pipeline is not what it once was.[4] Pharmaceutical companies that were once the main provider of novel antibiotic molecules withdrew from the late 1990s to the present day because of their lack of success and low financial returns in delivering new antibacterial drugs to the market.[5] The environment of discovering and developing new antibiotics was different during the so called 'golden era' of drug discovery. Antibiotics worked remarkably well because resistance was low and physicians had access to a variety of efficacious antibiotics. The objectives of antibiotic R&D programmes tended to be around improved

pharmacology to achieve less frequent dosing e.g. once a day, rather than innovative new antibiotics. Natural product screening strategies tended to result in rediscovery of rather than new compounds. There was also no need to take on the speculative improvement of natural products with undesirable properties, such as toxicity. Today, only a few large companies, including GlaxoSmithKline, Novartis, Merck and Roche actively research and develop antibiotics, with many of the historically major antibiotic providers (Bristol-Myers Squibb, Bayer and Eli Lilly), having left the area.

Industry has discovered few new antibiotics, and increasingly this activity is performed by academia and the private sector in the form of small companies (small medium enterprises; SMEs) (Table 1).[6,7] Furthermore, programmes that have advanced to late stage clinical evaluation or have had marketing approval have emerged from projects that had originated in large companies and subsequently licensed to SMEs (e.g. ceftazidine-avibactam). Successful strategies include semi-synthetic natural products such as dalbavancin, novel natural product based chemistry e.g. omadacycline, eravacycline, and plazomycin, novel lactamase inhibitor chemistry, e.g. vaborbactam and fast-following approaches e.g. tedizolid and cadazolid. What is clear is that innovative chemistry is a key contributor to success.

During the last two decades, antibacterial R&D has suffered from changing clinical and investor priorities as the focus moved from MRSA to *C. difficile* and most recently to Gram-negative bacteria. The changing regulatory advice also created uncertainty and additional financial risks. The recent regulatory focus for antibiotics and a collective will to create innovative regulatory pathways for antibacterial drugs should create an environment that will stimulate discovery, research and development. The community now needs to address other barriers to success.

SMEs and academia will continue to lead future antibiotic drug discovery efforts[6] but they can only advance new therapies so far. The clinical development capabilities of pharmaceutical companies and their supply chain are essential components in delivering new therapies and patient benefits. The future delivery of new therapies will require effective partnerships between all stakeholders. By learning from its past failures and successes,

pharmaceutical companies should work with academia, charities and SMEs to provide a more effective antibiotic discovery model.

It has become clear that antibacterial innovation is needed now and in the long-term. Discovering new antibiotics that are immune to resistance development is unlikely. Training and infrastructure must be put in place to create the capabilities and capacities required to deliver new antibacterial therapies regularly over decades and centuries. This generation may be the last to benefit from cheap antibiotics. This is a critical time and stakeholders' actions now will be judged by historians. We should endeavour to create a solid foundation for future generations to continually respond and innovate as they face their antimicrobial resistance (AMR) challenges.

Which antibacterials are needed?

As antibacterial discovery shifts towards an academia/SME-driven discovery activity there is a risk that research funding (called 'push') rather than the clinical need (called 'pull') will define the active programmes. Research-led programmes without consideration of clinical use, manufacturing, regulatory practices, feasibility of clinical study designs and reimbursement, are inefficient and probably futile activities. Recently, the WHO published a list of bacteria for which new antibiotics are urgently needed.[8] The next step is to provide internationally agreed target product profiles (TPPs) that will define what the properties of suitable antibacterial therapies are. Pharmaceutical companies have detailed descriptions of what they consider ideal and acceptable characteristics for new antibacterials. These include indication, patient identification, potency, efficacy, pharmacology, toxicology, safety and dosage etc. These TPPs could be used by other researchers to ensure that their research is aligned with the most urgent medical needs. TPPs could also be used by funders and investors to select projects most likely to have clinical impact. If this is not done, there will continue to be research on new antibiotics and their development that does not address the most urgent needs.

Targets for monotherapy

The emergence and spread of antibiotic resistant bacteria is responsible for the dwindling number of effective antibacterials. If the success of a new drug is to be ensured, the potential to develop resistance and the consequences of resistance must be determined. Basic studies are needed to estimate the potential for developing resistance such as determining the MIC, resistance frequencies, concentrations for preventing mutation selection and exploring the consequences of resistance mechanisms. These should be researched in the early stages of drug discovery.[9] In the past, many had hoped that lack of the emergence of resistance in animal models of infection might indicate that resistance may not be an issue in the clinic, but this does not always prove to be the case (e.g. GSK2251052/AN3365).[10]

Target validation plays a central role in the development of a successful therapeutic. The traditional view of antibacterial target validation was that an essential protein or process is a good target. Target essentiality is now viewed as the beginning of the validation process, as opposed to the end. To develop novel drugs, there needs to be a focused effort to understand the biology of the target and impact of target inhibition. This will provide insights into how resistance could occur or how essentiality could be bypassed when that target is inhibited. For instance, before screening candidate inhibitors against a potential target, genetic studies to assess the mutability of a drug-binding pocket should be undertaken. Such studies would reveal how likely mutations that alter the drug target and confer resistance will occur. Studies should also be carried out to determine whether changes to the drug target affect the fitness of the bacterium and its ability to cause infection.

Considerable advances have been made over the last decade in identifying gene products that are important or essential to bacterial physiology and pathogenic attributes. As a result, there have been numerous suggestions in the literature that such factors could comprise novel targets for new antibiotics. However, there is a considerable gap between identifying an essential or important bacterial factor, and inhibitors that are able to form the basis for developing a new drug. This is because a drug discovery programme needs to identify

inhibitors that are amenable to medicinal chemistry which can provide the basis of a new drug.

Academia can contribute towards the basic understanding of bacterial cellular processes, pathogen biology and pathways that may influence resistance development. A better understanding in this area could help to avoid some of the problems encountered in the past regarding target validation and resistance. It is probable that both small compounds and natural products that provide a good basis for antibacterial drug monotherapies have been identified. Any new targets will require extensive validation before being developed further. Good monotherapies comprise a single compound that targets multiple essential protein activities and for which multiple mutations to the gene encoding the target, or the evolution of target modifying enzymes, antibiotic degrading enzymes, efflux pumps, or all of these are needed to develop clinically relevant resistance. Inhibiting the products of single genes, whether they are essential or conditionally essential e.g. virulence or pathogenicity factors, is unlikely to lead to effective treatment by a drug containing only one small compound or natural product.

Screening: Overcoming the Gram-negative permeability barrier

The discovery of novel, broad and narrow spectrum inhibitors of Gram-negative bacteria has proven difficult. The last broad-spectrum class of antibacterial agents to enter the clinic was the quinolones, discovered in the 1960s.[11] This is due to their intrinsic resistance to many different drugs. This is largely attributed to the architecture of the Gram-negative cell envelope and multi-drug efflux pumps. The outer membrane and the efflux machinery work together to reduce the intracellular concentration of many different types of antibiotic so that the bacterium resists the action of a range of structurally diverse, antibacterial compounds.[12] The differences in antibiotic activity between Gram-positive and Gram-negative bacteria is rarely (e.g. daptomycin)[13] due to target differences between the two groups of organisms, but instead is a result of the additional permeability and efflux barrier which Gram-negative bacteria possess.[9,14]

There remains a fundamental lack of understanding regarding the physiology and permeability properties of the Gram-negative cell envelope. Academia play a pivotal role increasing knowledge in this area, driving new basic research on how to avoid efflux and ensure the entry of drugs to the bacterial cytoplasm. The generation of 'rules of entry', regarding the chemical properties that are required of compounds to accumulate within the cytoplasm of Gram-negative bacteria and reach their respective intracellular targets will greatly aid the development of novel broad-spectrum antibiotics. The recent findings of Richter et al[15], will help generate these rules. There has been some progress improving activity of the oxazolidinone class of drugs against *Escherichia coli* and identifying the structural properties required to penetrate cells.[16] Furthermore, a complete understanding of the orientation and binding of lipopolysaccharide molecules (LPS) on the outer monolayer of the Gram-negative outer membrane could facilitate the development of cationic molecules to disrupt it. To successfully develop a new antibiotic to treat infections by Gram-negative bacteria, the ability of the drug and whether it is susceptible to efflux mechanisms must be tracked throughout the drug optimisation process. This can be achieved by including whole-cell screening assays comparing activities in wild type and in efflux mutants. However, care over the choice of efflux mutants is essential; point mutations inactivating the transporter process whilst maintaining the presence of the protein should be used rather than deletion mutants.[17] Recent clinical isolates should be included during optimization programmes to ensure compounds are effective against those bacteria giving current clinical problems.

The importance of overcoming the barriers to antibiotic entry in Gram-negative pathogens has also been highlighted in the, 'Scientific Roadmap for Antibiotic Discovery', from the Pew Charitable Trust.[18] The primary objectives outlined for antibiotic drug development include overcoming the permeability barrier of particularly impermeable, Gram-negative bacteria and subsequently tailoring chemical matter for this discovery process.

Sources of antibacterial compounds

Natural products dominate the existing antibacterial compendium, with around 75% of available antibiotics being of natural origin.[19] The importance of the natural world as a source of antibacterial drugs is also evident from the history of the antibiotic pipeline, which has continued to be re-stocked with semi-synthetic derivatives of established, natural product classes. However, despite previous successes, the labour intensive, low-throughput nature of natural product drug discovery and diminishing returns eventually caused the pharmaceutical industry to stop active research in this area. During the late 1990s, the focus of attention shifted to synthetic compound libraries, which were utilised in high-throughput screens to search for novel, target specific inhibitors *in vitro*.[9] This method of drug discovery did not prove fruitful as it did not discover novel antibacterial compounds amenable to drug discovery.[5] The failures of the genomic era to deliver novel drug targets and scaffolds, coupled with the threat of a 'post-antibiotic era' have prompted a revival of natural product drug discovery in both academia and the biotechnology sector. As pharmaceutical companies are less active in this area, they cannot offer a sustainable contribution to natural product discovery on their own. It is likely that many readily accessible sources of potent, broad-spectrum antibacterial compounds have already been exhausted by past discovery efforts by pharmaceutical companies. Therefore, natural product sources should be investigated as a source for potential, untapped leads, especially when combined with novel assays.

Slow-growing, uncultivable environmental organisms may represent a large potential untapped resource of novel antibiotics, and recent innovations could allow natural product discovery to be carried out in a sustainable manner. For instance, the development of the *in situ* culture device, the iChip, has allowed the high throughput cultivation of environmental microorganisms.[20] The merit of this device can be seen from the discovery of teixobactin, a compound of a novel antibiotic class which possesses activity against Gram-positive bacteria but hits a well characterized target – the bacterial cell wall biosynthesis machinery.[21] Alternatively, cryptic biosynthetic pathways could be activated (which lead to the production of novel secondary metabolites with antibiotic activity).[22] Metagenomics (analysis of

genomes from DNA from microorganisms in environmental samples) could be used to investigate the secondary metabolite diversity of non-cultivatable environmental organisms. Lastly, a key process in natural product drug discovery is the inclusion of de-replication techniques such as high-resolution LC-MS/MS, which ensures the elimination of previously characterised compounds from further study.

It is possible that all the antibacterial molecules amenable to drug discovery have been identified and that the search for novelty may not pay off. In this case, substantial investment into innovative chemistry on and around the known molecules would be prudent to determine the advances that can be made. This less speculative, directed chemistry is surprisingly difficult to fund and yet is a successful strategy to overcome resistance and or side effects.

It may be that all the good targets for single drug therapy have been identified. Therefore, to find alternative chemical classes to inhibit these targets investment in innovative chemistry is required.

Efficacy

Animal models of bacterial infection can be highly predictive of efficacy in clinical use. Marketed antibiotics perform well in these models and researchers have come to expect high levels of bacterial kill by candidate drugs. However, some compounds with modest potency in *in vivo* studies may have been overlooked or de-prioritized in optimization programmes. The community does not know what level of animal model efficacy is the minimum necessary to deliver clinical benefit for a monotherapy. Until recently a three-log reduction in bacterial burden was considered the necessary level of efficacy to continue research and development in a pharmaceutical company. Many now consider a two-log reduction adequate and indicative of potential clinical utility.[23] Is a one-log reduction or just bacteriostasis sufficient? Research on this area is urgently required.

Resistance

The community urgently requires evidence-based guidelines from regulators on what levels of *in vitro* evolution to give drug resistance are acceptable for antibiotics in development. Current target product profiles for monotherapy products vary by orders of magnitude from $<10^{-8}$ to $<10^{-12}$. The metric may depend on the consequences of resistance, what increase in MIC of a drug resistant mutant provides, and whether the mutant is attenuated in infection models. Understanding all aspects of resistance and transmission of drug-resistant bacteria is essential if new drugs are to have longevity.[24]

A key metric of an antibiotic in considering it as a new monotherapy is the mutant prevention concentration (MPC). This is the drug concentration at which no mutants survive. When a culture of drug-susceptible susceptible bacteria is exposed to a new antibacterial compound, pre-existing rare point mutations that confer resistance to the compound may be selected.[25] The activity of the compound against these insusceptible mutants is likely to be less than for wildtype bacteria and a multiple of the MIC of the compound may be required to kill or inhibit a mutant's growth. To suppress resistance development in clinical use, bacteria must be exposed to a concentration of the antibiotic which kills both the susceptible and first step mutants of the species. Typically, bacteria require two or more mutations to become insusceptible at the MPC and this happens rarely *in vitro*, but is not uncommon once a drug has been licensed. One example of this is with the fluoroquinolone drugs (note, mutations have been found in the same and different genes).[26]

If the MIC of a strain with a first-step mutation does not greatly increase, only a modest increase in drug concentration is required to achieve the MPC. If there is a big increase in the MIC of the first step mutation a much higher dose is required to achieve the MPC. To stop resistance developing in clinical use, bacteria at the site of infection must be exposed to free-drug concentrations above the MPC for a significant period of the dosing interval (e.g. 8 hours). In practice, this means that antibacterials have to be potent and well tolerated to achieve these exposures. Too few antibacterial drug R&D programmes demonstrate understanding of the pharmacology of managing resistance and fail to build this into their

programmes. When thoroughly analysed, many of the novel target – new compound programmes fail to adequately address resistance because sufficient exposure to doses above the MPC cannot be achieved.

Combinations

As monotherapies have proven so challenging to discover and develop, much focus has turned towards antibacterial combinations and it here that academia has much to offer. This approach is much like those adopted for the treatment of HIV or tuberculosis, where different drugs with different modes of action are used as part of a combination treatment. When used, current combinations of antibiotics, such as those used to treat patients with sepsis, focus is on covering Gram-positive and Gram-negative bacteria as well as ensuring adequate drug concentration at the probable site of infection.[27]

There is much literature on *ad hoc* combinations of antibiotics and their effects on laboratory strains and clinical isolates; this has led to suggestions of novel combinations that could be used to treat Gram-negative bacterial infections. However, definitive large-scale studies have been lacking. This area would be enabled by widespread open access to well characterized drug-resistant and multi-drug resistant isolates. Double, triple and quadruple combinations that are able to inhibit challenging strains may be feasible and might be unpredictable. As resources are the only barrier, exhausting combination opportunities now from drugs already available for human use should be investigated. Unfortunately, such studies are rare; the focus on resolving the crisis of AMR has focused on establishing economic incentives to stimulate pharmaceutical companies to stay (or return) to this field. Furthermore, companies have no incentive to support studies on combinations of old drugs and has been generally unsupportive of this approach.

There are examples in the literature of antibiotics and non-antibacterial marketed drugs that could be used to potentiate the activity of an antibiotic against insusceptible or drug-resistant bacteria sometimes called ‘resistance breakers’.[28] The marketed drug may alter permeability through the bacterial cell membrane, interfere with efflux or act via alternative mechanisms.

While the titles of some publications look appealing it is unclear whether any clinically useful new combinations have emerged. Not only does the activity of combinations of drugs for multi-drug resistant clinical isolates need to be established, but the primary pharmacology of the drug to be combined with an antibiotic may not be amenable to clinical use in a co-delivered combination. For example, the dose may be much higher than approved dose. Alternatively, the toxicity and safety at higher doses, plus the requirement for matched or manageable pharmacology of the combination must be considered.

Instead of using marketed drugs, some are developing bespoke non-antibiotic and antibiotic combinations that disrupt the bacterial cell membrane and increase antibiotic access (e.g. Spero Therapeutics). Industry, SMEs and academics working on novel targets and chemistries have created programmes that have failed as monotherapies; these may provide options for the creation of novel combination products. While the development may be challenging and risky, partnering the right projects could create useful new therapies. LpxC is an essential enzyme required for LPS biosynthesis in Gram-negative bacteria.[29] As inhibition of LpxC tends to increase susceptibility to other antibacterials, combination of LpxC-inhibitors with antibiotics may be a fruitful line of discovery.

Anti-virulence compounds

During the genomic-led antibacterial discovery period the community thought it was limited by the number of targets for antibiotics. As a result, inhibition of conditionally essential single-gene virulence targets was proposed as a way to increase the number of targets available. While there are claims that inhibition of virulence targets will circumvent resistance development, drugs targeting virulence will be subject to evolutionary pressures and it is probable that resistance will develop, particularly where small compounds are used. Anti-virulence monoclonal antibodies, may be less susceptible to the evolution of resistance. This is because of the much larger surface area through which they interact.

Funding

Despite spending considerable resources over the last two decades, the pharmaceutical industry has largely failed to discover or deliver new antibacterial drugs. Future discovery programmes will have to work smarter, use effective collaboration and be adequately resourced for a sustained period to have any chance of delivering new antibacterials. Such collaborations have started to emerge such as the Community for Open Antimicrobial Drug Discovery,[30] where they have a screening facility and will take compounds and screen them. What is lacking is a seamless flow from academic discovery to SME and large pharmaceutical companies so that the requisite early discovery hit to lead optimization research can be carried out. Historically, the area of antibiotic drug discovery was considered the domain of large pharmaceutical companies and consequently, the existing funding structure for academia and SME remains inadequate for the task. This is despite the advent of CARB-X,[31] The Global Antibiotic Research and Development Partnership (GARDP),[32] and initiatives by numerous national funding agencies. Addressing AMR requires a sustained and concerted effort with all stakeholders working together to make the case for unprecedented levels of funding and delivering new processes to use that funding effectively.

How do we prioritize?

The last two decades have shown that chasing novelty in terms of targets or compound scaffolds has been inefficient and that time establishing firm foundations of science upon which to build future activities is required. We recommend that (1) investment is needed to provide innovative chemistry on and around known clinically effective drug scaffolds; (2) alternative ways to inhibit the function of clinically validated targets; (3) understand resistance mechanisms and how they can be inhibited; (4) understand the utility of animal models and the risks around reducing drug-efficacy hurdles; and (5) establish the levels of *in vitro* resistance development that are unacceptable.

Currently, too many academic and SME programmes are research-push driven without appreciation of the manufacturing, regulatory and clinical hurdles their approaches present.

A substantial and sustained programme of investment in training of the next generation of AMR researchers to equip them to understand how to create feasible projects is required. To our knowledge there are at least three new doctoral training programmes designed to fill this gap.[33-35] More are needed across the world.

Society must not assume short term solutions can be found and there is no point in prioritizing programmes that are unlikely to be feasible in the next 10 to 30 years. Investment must be prioritized on the feasible projects and where possible additional funding used for more speculative programmes.

Conclusions and future perspectives

There is still much to discover in regards to bacterial physiology that would benefit the field of antibiotic R & D and so academia has an essential role to play. Academic research groups can assist by undertaking a systems biology approach to the understanding of potential targets, and increasing our understanding of the permeability barrier and multi-drug efflux in Gram-negative bacteria. A new paradigm for preclinical research has been proposed.[36] It should be helpful to those engaged in early drug discovery. However, early discovery research should be in partnership with SMEs and large companies and not in isolation in academia. Otherwise, there is the danger of spending considerable time and funding on research that will never deliver a new drug.

The natural world remains the largest source of novel chemical drug scaffolds and natural product drug discovery remains a viable option in the search for new antibiotic compounds. Advances in bacterial culture techniques, molecular biology and metagenomics will continue to improve the ease and cost effectiveness of natural product drug discovery, which have been a major limiting factor in the past. Screening procedures must include whole-bacterial cell assays, addressing the issue of bacterial permeability and efflux early in the discovery process.[37] Additionally, the generation of training schemes by and with pharmaceutical companies, in relation to all aspects of the pipeline and including natural product drug discovery, are essential and will ensure that expertise is passed to future researchers.

Investment should also be made into the study of previously characterized lead compounds that did not reach the clinic, so called ‘old leads’. The reasons that led these compounds to be dropped from further development vary, ranging from financial issues, dosing problems, to trial design and toxicity issues. It may be that there is now sufficiently improved technology and expertise to develop these as efficacious, safe antibacterials, and the study of ‘old leads’ could provide an additional source of novel antimicrobials. A freely accessible database of antibiotics that were not developed has been recently launched, Antibiotic DB;[38] prevent replication of discovery efforts. Another database comprising ‘old natural product leads’ would also help the community. However, care must be taken to review all previous research on the compound(s) of interest to ensure that the failures of the past are not repeated.

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Table. Source of discoveries, clinical developer and recently approved antibiotics (in alphabetical order and by development phase)

Antibiotic	Discovered by	Developed by and transfer between companies over time	Status
Approved since 2015			
Ceftazidime+avibactam (Avycaz)	Sanofi	Novexel; AstraZeneca-Forest/Actavis	Approved in USA and EU
Ceftobiprole (Zevtera)	Roche	Basilea	Not approved in USA. Approved in13 EU countries plus several others
Ceftolozane+tazobactam (Zerbaxa)	Astellas	Calixa, Cubist=Merck	Approved in USA and EU
Dalbavancin (Xydalba)	**Lepetit Research Center/Vicuron**	Pfizer, Durata, Actavis	Approved in USA and EU
Oritavancin (Orbactive)	Eli Lilly	Intermune, Targanta, The Medicine Company	Approved in USA and EU
Solithromycin, (Cemprex)	**Optimer**	Cempra	Approved in USA and EU

Tedizolid (Sivextro)	**Dong-A**	Trius, Bayer/Cubist=Merck	Approved in USA and EU
New Drug Application (NDA) submitted			
Carbavance (vaborbactam+meropenem)	**Rempex**	**Rempex**, The Medicines Company	Phase 3
Delafloxacin	Wakunaga	Abbott, Wakunaga, Rib-X (Melinta Therapeutics)	Phase 3
In development			
BC-(Lefamulin) 3781	Sandoz/Novartis	Nabriva, Forest/Actavis, Nabriva	Phase 3
Cadazolid	Actelelion	Actelion Pharmaceuticals	Phase 3
Iclaprim	Hoffman LaRoche, Arpida	MotifBio PLC	Phase 3
Imipenem/cilastatin + Relebactam (MK- 7655)	Merck & Co Inc	Merck & Co Inc	Phase 3
Omadacycline	**Paratek**	**Paratek**/Bayer, Paratek/Merck, Paratek Novartis, **Paratek**	Phase 3

Plazomicin	**Isis**	Achaogen	Phase 3
S-649266	Shionogi	Shionogi Inc	Phase 3
Solithera (Solithromycin)	Cempra Inc,		
Taksta (fusidic acid)	Leo Pharmaceuticals	Cempra	Phase 3
Eravacycline TP- 434	**Harvard University**	Tetraphase	Phase 3
Zabofloxacin	Dong Wha	Dong Wha Pharmaceuticals Co Ltd	Phase 3
Aztreonam + avibactam		Actavis, Allergon PLC, Astra-Zeneca, Pfizer	Phase 2
CG400549	Crystal Genomics Inc	Crystal Genomics Inc	Phase 2
Afabicin (Debio 1450)	Debiopharm International SA		
ETX0914	Astra-Zeneca	Entasis Therapeutics Inc	Phase 2
Finafloxacin	Centre for Natural Product Research Singapore-Institute of	Merlion Pharmaceuticals Pte Lted	Phase 2

	Molecular and Cell Biology		
Gepotidacin (GSK2140944)	GSK	GSK	Phase 2
MRX-1	MicuRx Pharmaceuticals Inc		Phase 2
Nemonoxacin	**TaiGen**	Procter & Gamble, Warner Chilcott,TaiGen	Phase 2
Brilacidin PMX-30063	**University of Pennsylvania**	Polymedix, Cellceutix Corporation	Phase 2
POL7080	**University of Zurich**	**Polyphor**, Roche, **Polyphor**	Phase 2
Ramoplanin	Merrell Dow Research Institute	**Nanoterapeutics Inc**	Phase 2
Ridinilazole (SMT19969)	**Summit Therapeutics Inc**		Phase 2
WCK 4873	**Wockhardt Ltd**		Phase 2

CRS3123	Crestone Inc.	Phase 1
ETX2514SUL	Entasis Therapeutics Inc.	Phase 1
GSK*3342830	GlaxoSmithKline PLC (Shionogi licensee)	Phase 1
KBP-7072	KBP BioSciences Pharmaceutical Technical Co. Ltd.	Phase 1
LCB0 1-0371	LegoChem Biosciences Inc	Phase 1
MGB-BP-3	MGB Biopharma Ltd	Phase 1
OP0595 (RG6080)	Meiji Seika Pharma Co. Ltd./Fedora Pharmaceuticals Inc (Roche licensee)	Phase 1

SPR741	**Spero Therapeutics**		
TD-1607	**Theravance Biopharma Inc.**		Phase 1
TP-271	**Tetraphase Pharmaceutials Inc.**		Phase 1
TP-6076	Tetraphase Pharmaceuticals Inc.		Phase 1
WK 771	Wockhardt Ltd		Phase 1
WK 2349	Wockhardt Ltd		Phase 1
Zidebactam + cefepime (WCK 5222)	Wockhardt Ltd		Phase 1

Drugs no longer under development

AFN-1252/Debio 1450	**University of Toronto**	Affinium, Debiopharm SA

Radezolid (RX-1741)	**Yale University**	Rib-X (Melinta Therapeutics)
Ceftaroline + avibactam		Actavis Allergon PLC, Astra-Zeneca, Pfizer
BAL30072	**Basilea Pharmaceutica Ltd**	
JNJ-(Avarofloxacin) Q2	**J&J (Janssen Pharm.)**	Furiex, Forest/Actavis

Bold font indicated those agents discovered by academia and SMEs.

Adapted from from references.[7,39,40]