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Endless Resistance. Endless Antibiotics?

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Abstract

The practice of medicine was profoundly transformed by the introduction of the antibiotics (compounds isolated from Nature) and the antibacterials (compounds prepared by synthesis) for the control of bacterial infection. As a result of the extraordinary success of these compounds over decades of time, a timeless biological activity for these compounds has been presumed. This presumption is no longer. The inexorable acquisition of resistance mechanisms by bacteria is retransforming medical practice. Credible answers to this dilemma are far better recognized than they are being implemented. In this perspective we examine (and in key respects, reiterate) the chemical and biological strategies being used to address the challenge of bacterial resistance.

Introduction

Franklin's choice of the inevitability of "death and taxes" was surely not meant as an exclusive list. The modern observer of the diminishing efficacy of the chemotherapeutic armamentarium against bacterial infection would not hesitate to add "resistance" to his list. Bacterial resistance was, is, and forever shall be.^{1–4} It is found in the hospital, in the microbiome;⁵ in the animal manure of farms;^{6,7} in the soil;^{8–12} in remote caves;¹³ in the permafrost;^{14,15} in a centuries-old mummy;¹⁶ and in the remote reaches of the oceans.¹⁷ Moreover, given the impossibility of removing antibiotics from the environment—that is, removal of the evolutionary pressure—the evolution of the resistome cannot be reversed.¹⁸ We are compelled to live with the evolutionary legacy of antibiotics, both as ultimate pollutants in the environment and as persistent genes throughout the microbiome,¹⁹ even as we confront the consequences of this legacy. The question is less what we are to do, but how this confrontation must be done. The multi-factorial answers to this question are well known, and have been expressed in a chorus of different voices.^{20–38} Some of the answers to the question of what to do—such as limiting antibiotics in food sources; improving scientific,³⁹ environmental,⁴⁰ and clinical stewardship;^{41–46} and revising clinical trial design and creating post-registration financial incentives to reward the commercial investment in antibacterial discovery and development)^{47,48}—transcend science. The importance and the inseparability of each of these aspects are well recognized. Nonetheless, the slow translation of many of these aspects into the societal and political spheres raises the question whether the full value of the chemical arsenal against bacterial infection—the (isolated from Nature) antibiotics, the semi-synthetic antibiotics, and the synthetic antibacterials—can be preserved. Until this translation occurs, how can society, and how can science, sustain the future of all—both old and new—antibacterial entities? The immediate task for society is the

impeccable husbandry of the antibacterials that we already possess, as cogently argued by The Center for Disease Dynamics, Economics, and Policy.⁴⁹ Nonetheless, their world-wide assessment shows that we remain well short of this standard. The task for science is to contribute to the technologies that will contribute to this stewardship, while simultaneously preparing for the possibility that stewardship will not be enough. The antibacterial future will include the pragmatic resurrection (or repurposing) of existing structures,^{20,50} identifying advantageous structural permutations of these same structures, and the discovery of new antibacterial strategies and structures. The chemistry, biochemistry, microbiology, and medical aspects of resistance are inseparable. In this brief perspective we exemplify, using for the most part recent discoveries, how scientists are confronting resistance in order to secure an antibiotic future as endless as that of resistance. These discoveries are discussed first from a chemical, and then a biological, perspective.

Endless antibiotics: a chemical perspective

The most fundamental chemical perspective is the antibacterial as a composition of matter. The simplest proposal to address the diminishing ability of existing antibacterials is the discovery of better ones. If only this discovery was the simple matter of wishing! The daunting challenge of the discovery of new chemical matter that is efficacious, as a result of the compromise of one of the limited number of validated bacterial targets, is the theme of two separate lamentations from two separate industrial discovery teams.^{51,52} Is antibacterial discovery so exceptionally challenging? The chemical structures useful against bacterial infection are sourced from two realms. The first realm is the synthetic: structures that are unprecedented, or are only partly preceded, in Nature. The fluoroquinolones are an important example of exceptionally useful antibacterials having (for the most part) origins in the synthetic realm.^{53,54} The second realm is the antibiotics discovered by Nature, as exemplified by the incredible array of natural products found during the “Golden Age” of antibiotic isolation and thereafter.⁵⁵ The interface between the two realms comprises the structures synthetically elaborated from the antibiotics of Nature. This transformation is robustly exemplified by the structure-activity development of the sub-classes (including the penicillins, cephalosporins, carbapenems, monobactams, monocarbams, and monosulfactams) of the β -lactam antibacterials.⁵⁶ The challenge with respect to the chemistry of antibiotic discovery thus coincides with two inquiries. Is there opportunity for structural development within the “golden age” antibiotic structures? Are there unrecognized compounds with antibacterial activity in the synthetic structures found in chemical libraries, or to be found in Nature?

The answer to both questions is “yes”, notwithstanding the daunting difficulty of realizing chemical answers.^{51,52} A sense of the answer to the first question is given by Scheme 1, where recent structures represent some of the key structural and mechanistic frontiers for the grand classes of the antibacterials of the golden age of discovery (the aminoglycosides, the β -lactams, the tetracyclines, the macrolides, and the quinolones). The focus of the remainder of this review is the answer to the second question: finding new antibacterials from chemical libraries and from Nature.

Part of the reason for the perception of a scarceness of antibacterial matter in chemical libraries is the poor alignment between the desirable chemical properties of drugs that address bacterial, compared to eukaryotic, targets, in such libraries.^{76–78} Recognition of this difference has led to the design of chemical libraries that are biased toward the generally more polar character of known antibacterials. These efforts have attained promising results.⁷⁹ Aligning yet further the libraries to coincide with the different antibacterial sub-classes (such as attention to the requirements for optimal inhibition of cell wall targets compared to the ribosome as a target) may improve success.⁸⁰ Nonetheless—and notwithstanding the reality that successful antibacterial discovery requires more than optimization of the physicochemical properties of the chemical library⁸¹—there are antibacterials waiting to be found in chemical libraries. For example, the interplay of library screening, synthesis, and the use of reverse genomics identified the spiropyrimidinetrione inhibitors of the bacterial topoisomerases.^{82, 83} Subsequent structure-activity effort yielded a lead structure (EXT-0914) with excellent *in vitro* activity, and promising *in vivo* activity,⁸⁴ against *inter alia* *Neisseria gonorrhoeae*.^{85–87} Likewise, library screening has had exceptional success in identifying potential antibacterials targeting *Mycobacterium tuberculosis*, as evidenced by both the imidazopyrimidine^{88–95} and benzothiazinone^{96–103} classes. As with any such structure, whether natural or synthetic, it remains to be seen whether it has the robustness (most emphatically, with respect to resistance development) needed to progress. But the structures are there. The new Community for Open Antimicrobial Drug Discovery effort is an opportunity to identify these structures.^{104,105} This objective of this effort is to expand the chemical diversity of antibacterial (and antifungal) compositions of matter through a free screening program (<http://www.co-add.org>), requiring submission of only 1 mg of a pure, water- or DMSO-soluble compound for the purpose of screening. The results of the screening are “free” (ownership is retained by the submitters).

Virtual chemical libraries in principle should not have the limitation of (for example) mismatched physical properties, but in fact virtual screening shares this same encumbrance since every virtual structure must have a physical counterpart. The treatment of disease (alas) will never be virtual. Nonetheless, the dramatically improved structural understanding of validated bacterial targets has provided examples of successful virtual screening.¹⁰⁶ A recent example of successful virtual screening include the identification of inhibitors of the Penicillin-Binding Proteins having promising *in vitro* Gram-positive activity.^{107–109} Other examples include efforts directed toward the cytoskeletal protein FtsZ;^{110,111} the sortase transpeptidases;^{112,113} the GlmU uridyltransferase (from a lead identified by high-throughput screening);^{114,115} and the Mur enzymes of peptidoglycan biosynthesis.^{116–118} The qualification of “promising” for all of these structures (again) refers to the momentous difficulty of taking a structure from *in vitro* activity to clinical efficacy. But this is a difficulty that is universal for all of drug discovery. A chemist’s reflection on the ungainly heterocyclic structures that are approved inhibitors against the kinases of human cancer¹¹⁹ leads to the conclusion that however momentous the difficulty, the difficulty can be surmounted if the resources and incentives are in place. Antibiotic discovery is challenging. But it is not evident that its requirements for resources and incentives are any greater than

for any other target, or any other disease. Rather, it is simply that neither the correct resources nor the correct incentives are fully in place.

The conclusion that antibacterial drug discovery is a surmountable challenge also stands on the ingenuity of Nature. If the golden age of antibiotic discovery has passed, a new era of natural product discovery is dawning.^{120–123} The antibiotics identified in the “golden age” of discovery originated from extraordinary scientific perspicacity. While this requirement has not lessened with time—the challenge of finding and then isolating (or replicating by total synthesis) a natural product, on the mass scale required for antibiotic activity, cannot be understated—the chemist today has an unprecedented ability not just to manipulate secondary biosynthesis, but also to interrogate a vastly greater diversity of bacterial and fungal species.^{124–137} Many of the genes for secondary metabolism are under epigenetic control.^{138–140} One can now pair the sequencing of a genome in order to identify the genes dedicated to secondary metabolite biosynthesis, with epigenetic activation of what often are silent biosynthetic pathways. For example, application of this strategy to a filamentous fungus, exploiting histone deacetylase inhibition to alter gene expression, activated 75% of the genes involved in secondary biosynthesis and resulted in the expression of ten secondary metabolites, four of which were new.¹⁴¹ There is no reason to believe that this strategy is not general. It is a strategy that could diversify access to both exploratory antibacterials, such as the nybomycin class of gyrase inhibitors^{142,143} as well as proven antibiotics such as the glycopeptides.^{144–149} Nor will it necessarily require a small molecule epigenetic modifier: interspecies communication within the microbial “interactome” has the same ability.^{150–153} Future natural product discovery will not be limited to the particular proteins encoded by the genes of an organism.¹²⁴ We now have such a grasp on the modular organization of polyketide assembly that manipulation of the modules is feasible.^{55, 154–156} Future natural-product discovery will not be limited to the genome of a single organism,^{132,133,157–160} nor to the multimodular synthases they may encode, as evidenced by the emerging ability to reprogram the biosynthetic function of these synthases.^{161,162} A compelling example of the future possibilities for the discovery of antibiotics that were previously hidden, is the use of microbial co-culture to elicit antibiotic expression by the so-called “dark” or “uncultivable” bacteria.^{145,163–166} This strategy culminated in the discovery of the Gram-positive active, cell-wall biosynthesis-targeting depsipeptide, teixobactin.¹⁶⁷

The transformation of a new structure from Nature into a clinically useful antibiotic follows in many cases combined empirical synthetic tailoring with property-based and structure-based design.^{69,168,169} Recent exemplifications (from among many) include structural development of the tetracyclines,⁶⁹ the glycopeptides,^{170,171} and the antifolates.^{172–175} The selection of a clinical candidate among chemical structures with similar *in vitro* characteristics will be facilitated by an emerging new pharmacological criterion, a long residence time for drug engagement of its target.^{176–182} Structures that possess this ability achieve an advantageous kinetic selectivity, wherein off-target interactions are minimized. The relevance of this criterion was exemplified recently during the assessment of inhibitors of LpxC, a key enzyme in the biosynthetic pathway to the lipopolysaccharides of the outer membrane of the Gram-negative bacteria. LpxC is a validated antibacterial target. However, its conformational mobility as a protein enables it to accommodate resistance mutations.^{183,184} Incorporation of kinetic performance, measured as the on-rate for

formation and off-rate for breakdown within a series of LpxC inhibitors, yielded a pharmacodynamic model wherein the dose-response curves for these inhibitors in a *Pseudomonas aeruginosa* animal model of infection was predicted.¹⁸⁵ The use of comparative kinetic data in compound evaluation will facilitate the pre-clinical assessment of exploratory antibacterial structures.

Endless antibiotics: a biological perspective

Notwithstanding the fact that antibiotic resistance in Nature coincided with the discovery of the antibiotics, the conceptualization of “resistance” continues to evolve.^{186–188} This evolution is multi-dimensional. Its directions include not just the mechanism(s) of the resistance against a particular antibacterial, but the spectrum of thought ranging from reflection on the ecological purpose of the antibiotics, to the criteria necessary to attain the multi-agent synergy against infectious disease that the future may demand. Here we offer a concise perspective on the eclectic breadth of the conceptualization of bacterial resistance, with emphasis on (and acknowledgement of) the most recent contributions defining its directions.

The emerging methodologies to probe the relationships among bacterial pathways and antibacterial structures will prove transformative for antibacterial discovery.^{189,190} Both the “Comprehensive Antibiotic Resistance Database” (“CARD”: <http://arpcard.mcmaster.ca>)^{191,192} and the NCBI National Database for Antimicrobial Resistant Organisms (<http://www.ncbi.nlm.nih.gov/projects/pathogens/>) address the bioinformatic aspects of these relationships. One example of a new methodology to complement bioinformatics analysis is the use of sub- μm fluorescence to attain resolution within the dimensions of the bacterial cell. With this resolution, an immediate visual assignment of the antibacterial mechanism by examination of the cytological profile of fluorescent reporters as a result of the presence of the antibacterial.^{193,194} A second example is the use of imaging mass spectrometry to evaluate specialized metabolite synthesis by *Streptomyces coelicolor* as the result of interspecies interaction.^{150,151} This methodology has the promise of improving our understanding of bacterial communication, especially as it relates to antibiotic synthesis, mechanism, and resistance responses. With respect to these mechanistic aspects, it is prudent for us to appreciate how poor is our understanding, even for the “golden age” antibiotics. The venerable class of β -lactam antibiotics exemplifies our ignorance. We are reminded that there is an enormous breadth of structure around the β -lactam core among the sub-families of this class. Individual β -lactam structures show differential affinity for their Penicillin-Binding Protein (PBP) enzyme targets. Each bacterium has a family of PBPs, and each of these PBPs uniquely contributes—some essentially, others much less so—to the growth and shape of the bacterium. Hence, each β -lactam structure uniquely profiles the PBP family of a bacterium.^{195,196} This uniqueness explains why particular β -lactams are clinically efficacious for infections by particular bacteria, but does not reveal the mechanistic interconnection between PBP inactivation and subsequent bactericidal cell lysis. While recent profiling of the relationship among β -lactam structure, PBP inactivation, and MIC value confirms the importance of selective PBP inactivation, it also identifies particular β -lactams for which the MIC does not coincide with

PBP inactivation. The answer to the “bactericidal mechanism of the β -lactams” is remarkably incomplete.^{197–199}

A further context around this incompleteness is our equally rudimentary understanding of the ecological purpose in Nature for the antibiotics. The conception that many natural products produced by microbes are messengers, a molecular realm termed by Davies as the “parvome”,^{200–204} is now well accepted. But what is their message? The traditional explanation for the antibiotics as defensive molecules to secure and preserve an ecological niche is supported by recent experiments.^{205,206} Nonetheless, the antibiotic concentrations used in chemotherapy vastly exceed the concentrations attained in ecological niches, and accordingly we must be mindful of understanding the bacterial responses to sub-MIC (sub-lethal) antibiotic exposure.^{207,208} The proven relationships among quorum sensing,^{209–212} biofilm formation,^{213,214} and virulence establish communication as a key role for the antibiotics of Nature.^{215–217} Antibiotics, even if simplistically conceptualized as weaponry, communicate. Their communication ability is intimate to the complexity of bacterial tolerance²¹⁸ and persistence^{219–227} within the diversity of the ecological microbiomes.^{5,228–231} Chemical communication among bacteria is understandably an evolutionary force for genetic transformation^{19,208,232–234} and thus is one and the same with resistance.

Here we return to the mysterious depth of the resistome, and the underestimated ability of bacteria to adapt to what we naively might believe to be an even more than decimating assault by the antibacterial concentrations attained during clinical use. We cannot be surprised that while we know that antibiotics are powerful evolutionary forces, we do not understand the relative pressure of these forces in particular ecological niches^{235–237} and within the universe of resistance mechanisms.^{238–241} Both new mechanisms for antibacterial invention (such as the discovery that the allosteric regulation of the essential PBP2a enzyme of methicillin-resistant *Staphylococcus aureus* can be disrupted)^{109,242–244} and new mechanisms to secure resistance (as just demonstrated for the tetracyclines)^{245,246} will be found. We face the dilemma that while the microbiome is heterogeneous²⁴⁷ and the natural state for bacteria is a surface-bound community,²⁴⁸ there are compelling arguments to study the behavior of individual bacteria,^{249,250} even for the determination of the MIC for an antibacterial.²⁵¹

How is this labyrinth to be confronted for antibacterial discovery? The obvious answer is the use of the antibiotics themselves, as superlative chemical probes, to provide both understanding and opportunity with respect to the confluence of targets and pathways. Two complementary themes exemplify efforts toward such identification. One is the relationship of antibiotic activity to metabolism (defined in the broadest sense). The second is the ability of antibacterial pairs to synergize their respective antibiotic activities. A direct relationship between metabolism and antibiotic activity is well recognized.^{252–257} Less understood is why the relationship directly correlates for some antibiotics, but indirectly for others.²⁵⁸ The ability to correlate the mechanism of ribosome-directed antibiotics, their antibiotic efficacy, and the rate of growth of *E. coli* provides promise that an understanding of the key aspects of this relationship, in terms of clinical strategies, will be forthcoming.²⁵⁹ A more demanding question is for which bacteria, and for which circumstances, the generation of

reactive-oxygen species²⁶⁰ contributes^{253, 261–265} or does not contribute^{266–268} to antibacterial efficacy. An answer to this question may contribute (for example) to a mechanistic understanding of how the new antibiotic lysocin acts through interference with the menaquinone of the bacterial membrane;²⁶⁹ and whether the role of glutamate dehydrogenase activity in coordinating FtsZ-dependent cell division in *Caulobacter crescentus*²⁷⁰ represents a potentially synergistic pathway confluence in bacteria that have FtsZ-dependent bacterial division. Such synergism—collateral sensitivity—is a central theme to the future discovery of antibiotics.^{271–281} Exploration of this concept with respect to the β -lactam antibiotics in *S. aureus* has identified synergistic confluence with inhibitors of its cell division pathway,²⁸² of its peptidoglycan biosynthesis pathway,^{283,284} and of its wall-teichoic acid biosynthesis pathway.^{285–290} This latter correlation is especially interesting, as the wall-teichoic acids are important contributors to colonization.^{291,292} Collateral synergy is now also demonstrated between the teichoic acids and the undecaprenyl lipid biosynthesis pathway.²⁰⁵ The undecaprenyl lipids are attractive targets as bacteria have a small pool of these lipids to support cell-wall biosynthesis.^{293–296} Understanding just how to achieve this sensitivity is incomplete,^{281,297,298} as evidenced by other studies on the undecaprenyl pathway. Incomplete inhibition of undecaprenyl biosynthesis in *B. subtilis* induced a stress response that resulted in increased resistance to other cell-wall-active antibiotics.²⁹⁹ Lastly, even when the outcome for the pairing of an antibiotic with a synergistic inhibitor is decisively advantageous in pharmacological models, validating this outcome in the clinic is especially challenging. Not only must safety be proven for the pairing of the both entities, but for optimal efficacy for the structures of the pair, and dosing choices for the pair, should correspond to matched pharmacokinetics of the two entities. The current cluster of β -lactam/ β -lactamase inhibitors in clinical evaluation for Gram-negative bacterial infection reflects not just their promise of efficacy as a pairing, but the ability to bring to the clinical design the established clinical experience of the β -lactam partner. The task is simpler when one of the entities is known.

Conclusion

The title of this perspective pairs a declaration with a question. The declaration is irrefutable. This perspective has addressed the question, but without separation of the question into its two very different contexts. New antibiotics will be discovered. In this context of the question, our answer is resoundingly positive. Indeed, the basis for this opinion is the central theme of this perspective. There is, however, a second context for this same question. Will these new antibiotics achieve clinical impact? The answer to this question is less positive. The enthusiastic optimism and resoundingly positive answer to the question in the first context, and reserved (even deeply reserved) pessimism for the answer in the second context, is not cognizant dissonance. At this time good progress is being made with respect to the 10 \times 20 initiative of the Infectious Diseases Society of America.^{300,301} New antibiotics (especially new β -lactamase-inhibitor combinations)^{65,302–310} are reaching the clinic. Yet over this same decade a fundamental transition has occurred with respect to early antibiotic discovery. This task has transitioned from major pharma companies to smaller biotechnology companies, and to academic centers. An excellent example of success from such collaboration is SMT-19969, now in Phase II clinical trials for *Clostridium difficile*

infection.^{311,312} SMT-19969 is a member of the synthetic, DNA-interacting bis-benzimidazole class of structures. Its mechanism is not gyrase inhibition, as is the case for other members of this class.³¹¹ SMT-19969 shows good selectivity for *C. difficile*. As it is less active against other Gram-positive anaerobes and the Gram-negative anaerobes, and only weakly active against both Gram-positive aerobes it has potential as a selective, microbiome-sparing entity. Although the transition of early discovery away from major pharma certainly does not itself mean that antibacterial discovery and development will falter, there is reason for concern. The urgency for the preservation of existing antibacterials, and the discovery of new antibacterials, is such that Nathan has argued for an open discovery initiative embracing academic, industrial, foundational, and governmental collaboration.³¹³ Given the present requirements for the size and scope of clinical evaluation (although these requirements are changing for the better) within the unchanging cost structure for the antibiotic market, there are credible reasons for such a proposal. Absolute ownership of intellectual property is a necessity for all new drug entities. Acquisition of this ownership requires tight integration of the timing of the patent prosecution with clinical development. The financial return on the investment required to bring an antibacterial to market, even using optimistic estimates, is predicted to occur only in the final years of the patent life. This sobering reality is illustrated (Figure 1). The necessity for a fundamental change in how the necessary investment in the discovery and development of anti-infective drugs is made appears inescapable.^{28,47,313,314} As we stated emphatically a decade ago, bringing a new drug to market (nor even the discovery of a new antibiotic) is not an instantaneous event.³¹⁵ Achieving intellectual property ownership while sustaining credible progression to the return on investment, in a development model where early discovery does not tightly transition to clinical development, is a profound challenge. The financial incentives for antibiotic discovery must change if clinically relevant antibiotic discovery is to be sustainable. The interim solutions of reconsidering old antibiotics^{316,317} or synergistic pairing of existing antibacterials (as we have just discussed) are essential. But neither solution, alone or together, offers the prospect of endless antibiotics.

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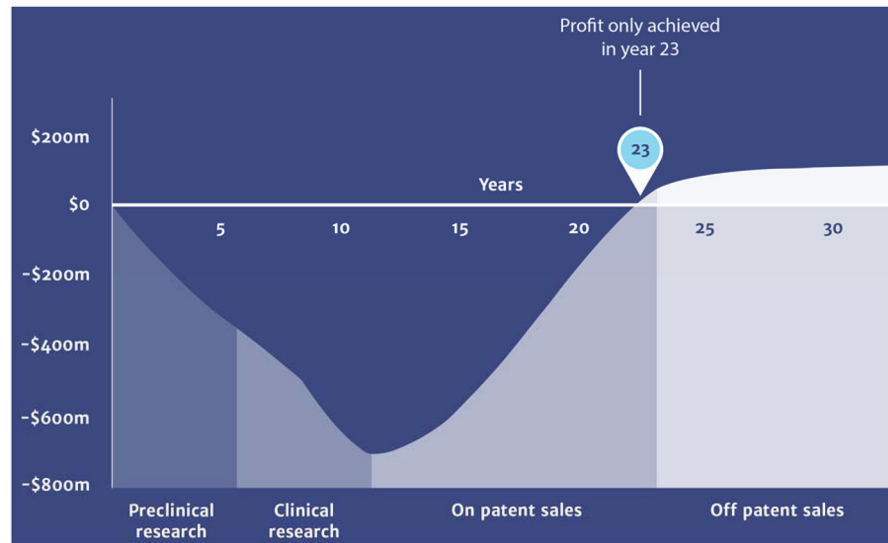
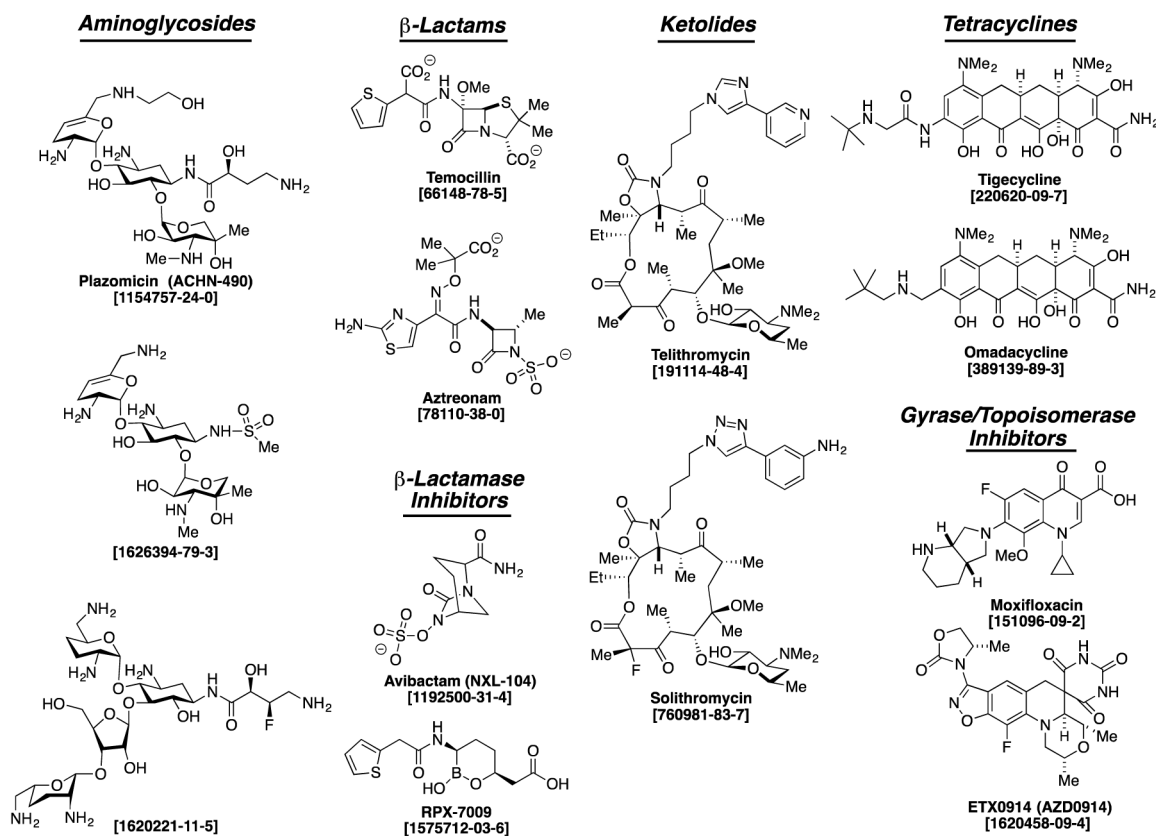


Figure 1.

A simulation of the cost to discover and develop an antibacterial (preclinical and clinical research) compared to the return on the cost of the investment (on-patent and off-patent sales). This Figure is taken from p. 11 of the 2015 document “Securing new drugs for future generations: The pipeline of antibiotics” of the Wellcome Trust.⁴⁸ The factual basis for this figure is provided in the appendix to this document. (Acknowledgement: ‘Review on Antimicrobial Resistance. Securing new drugs for future generations: the pipeline of antibiotics. 2015’).

**Scheme 1.**

Structure–activity development within the “Golden Age” classes of the antibiotics continues, and certainly will address the future need for new antibacterials. This Scheme displays structures (identified by their generic name and/or their registry number) that exemplify (but by no means define) the research frontiers for these classes. The *Aminoglycoside* class (Column 1) is represented by the late-stage clinical candidate plazomicin,⁵⁷ having broad-spectrum activity, low toxicity, and good evasion of the aminoglycoside-modifying enzymes of resistance.^{58,59} Structure [1626394-79-3] is an exploratory monosulfonamide-modified derivative of sisomicin with excellent Gram-negative activity and (in mice) exceptionally reduced ototoxicity.⁶⁰ Structure [1620221-11-5], a second exploratory aminoglycoside, combines selective deletion of alcohol functional groups (to avoid resistance enzyme modification) with a fluoro-dependent reduction of the basicity of the neighboring amine with a consequent reduction in toxicity.⁶¹ Among the recent developments in the *β -Lactam* antibiotics (Column 2) is the reevaluation of older β -lactam structures such as temocillin⁶² and aztreonam. These latter two structures were perceived at time of their entry into the clinic as undesirably narrow-spectrum. With the proliferation of β -lactamase resistance enzymes over the past two decades, the ability of these older structures to resist hydrolysis by many β -lactamases is now regarded as advantageous. The antibacterial spectrum of aztreonam is further improved upon combination with β -lactamase inhibitors.⁶³ The new *β -Lactamase Inhibitor* class (Column 2) includes the diazabicyclooctane avibactam.^{64,65} Other members of the diazabicyclooctane class under active investigation include the MK-7615 structure⁶⁶ and the OP-0595 structure.⁶⁷ A second new exploratory β -lactamase

inhibitor, the cyclic boronic acid RPX-7009, restores carbapenem activity to bacteria expressing the KPC β -lactamase.⁶⁸ Macrolides within the new ***Ketolide*** class (Column 3) are represented by telithromycin and by the newer fluoro-substituted solithromycin.⁶⁹ The characterization of the rRNA methylase that confers ketolide resistance to the producing *Streptomyces* strains will facilitate the structure-activity development of this class, given the probable eventual transition of this activity as a resistance mechanism.⁷⁰ New structures within the ***Tetracycline*** class (Column 4) include the clinically-approved tigecycline⁶⁹ and the exploratory structure omadacycline. Although the structural difference between the two is subtle, the latter has oral activity.⁷¹ A second exploratory class of new tetracyclines is the hexacyclines.⁷² Resurgent interest in bacterial ***Gyrase/Topoisomerase Inhibitors*** (Column 4) is driven both by the proven clinical value of the fluoroquinolones and the consequent resistance development.⁷³ A comparison of the structures of moxifloxacin, a recent generation fluoroquinolone, with that of the new exploratory structure ETX-0914 (having both Gram-positive and Gram-negative activity) shows superficial similarity (both have a modified fluoroquinoline core). Notwithstanding this similarity and the shared target, the mechanistic difference between the two is distinct.^{74,75} ETX-0914 is a clinical candidate targeting *Neisseria gonorrhoeae*. It is discussed in this review as an outstanding example of the possible value that synthetic chemical libraries may have for the discovery of new antibacterials.