The 2012 Garrod Lecture: Discovery of antibacterial drugs in the 21st century

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The discovery and development of antibacterial drugs in the twentieth century were major scientific and medical achievements that have had profound benefits for human society. However, in the twenty-first century the widespread global occurrence of bacteria resistant to the antibiotics and synthetic drugs discovered in the previous century threatens to reverse our ability to treat infectious diseases. Although some new drugs are in development they do not adequately cover growing medical needs. Furthermore, these drugs are mostly derivatives of older classes already in use and therefore prone to existing bacterial resistance mechanisms. Thus, new drug classes are urgently needed. Despite investment in antibacterial drug discovery, no new drug class has been discovered in the past 20 years. In this review, based upon my career as a research scientist in the field of antibacterial drug discovery, I consider some of the technical reasons for the recent failure and look to the future developments that may help to reverse the poor current success rate. Diversification of screening libraries to include new natural products will be important as well as ensuring that the promising drug hits arising from structure-based drug design can achieve effective concentrations at their target sites within the bacterial cell.

Keywords: Antibiotics, screening, structure-based design, targets

Introduction

The development of the sulphonamides and penicillin during the first half of the twentieth century revolutionized the treatment of bacterial infections. The discovery of further drug classes [e.g. aminoglycosides (1944), tetracyclines (1945), cephalosporins (1948), macrolides (1949), glycopeptides (1956), quinolones (1961) and carbapenems (1976)] and derivatives of these drugs during the so-called golden era of antibacterial drug discovery (Figure 1) has led to widespread therapeutic use of antibacterial drugs. Consequently, antibacterial chemotherapy has become an important integral component of medical practice and has contributed significantly to the health of modern society and an increase in life expectancy.

However, as we enter the twenty-first century, alarm bells are ringing owing to the widespread emergence of bacterial resistance to the drugs developed in the twentieth century and the failure to discover new classes to replace them. Indeed, this dire situation has led to predictions of a medical catastrophe and a return to the pre-antibiotic era. We have been aware of the growing deficiency of the antibacterial drug pipeline for a number of years. However, a crisis has now been reached and new initiatives are urgently under way to try to rectify the situation, the first of which was a call from the Infectious Diseases Society of America (IDSA) to improve the infrastructure for research and development and to introduce 10 new systemic antibacterial drugs by 2020. Similar calls for action have recently been launched in Europe by Action on Antibiotic Resistance (ReAct) and by the BSAC through the Urgent Need, Antibiotic Action initiative, which elected me as a member of its initial steering committee. The recent creation of the Innovative Medicines Initiative, which seeks to promote collaborative partnerships between private and public organizations for research and development of new antibacterial drugs, is a further encouraging development.

If these new initiatives are to be successful we must learn lessons from the recent failure to deliver sufficient new antibacterial drugs to meet the growing problems of resistance to established drugs. The reasons for the inadequate flow of new antibacterial drugs into the clinic are complex but are at least in part due to the unfortunate and disappointing failure of industry and academia to identify new suitable drug leads in the past 20 years. Consequently, it will be important to discuss the three principal drug discovery paradigms that are currently in use (Figures 1 and 2). These are whole-cell (non-target-based) antibacterial screening, in vitro high-throughput screening (HTS), now predominantly conducted against isolated biochemical targets that have been identified by genomic approaches, and structure-based drug discovery (SBDD) (Figure 1 and 2a). The last includes both virtual high-throughput screening (VHTS) and fragment-based drug discovery (FBDD), both of which are dependent upon high-resolution
structural data for the target (Figure 1 and 2b). The objective of
all these approaches is the discovery of chemically novel leads
that inhibit new molecular targets, or inhibit established
targets by mechanisms distinct from those exploited by existing
drugs.14,15,18 It is reasoned that such inhibitors are unlikely to be
susceptible to existing mechanisms of bacterial resistance
because of their chemical novelty and unique mode of
action.15,18

In this review, based upon my BSAC Garrod Medal Lecture,
I will examine some of the technical reasons for recent failures
in each of the three drug discovery paradigms and consider
what might be done to improve the prospects for future drug dis-
covery. In part this will involve reinforcing the points recently
made by others in the field.1,14,16,19,20 Nevertheless, I intend to
provide my own insights based upon 43 years of experience in
the field of antibacterial drug research, including periods in
both industry and academia, where I was engaged at the front
end of drug discovery efforts. I also hope to convey some of
the elations and disappointments associated with the difficult
task of discovering new antibacterial drugs.

### Whole-cell (non-target-based) antibacterial screening

Many of the antibacterial drugs currently used in clinical practice,
including those from the golden era, were originally discovered
by empirical whole-cell screening of natural products or synthetic
chemical libraries. More recent empirical whole-cell screening
programmes conducted by industry have, however, focused
primarily on chemical libraries as potential sources of new
drugs.15,19 This reflected a trend by many companies during the
1980s to move away from natural products towards more
readily manipulated synthetic compound libraries1,2,15,19 and a
belief, at the time, that bacterial resistance to synthetic
antimicrobials might occur less readily than to natural products
under clinical conditions.22

The advantages and disadvantages of whole-cell screening
have been extensively discussed in recent reviews by Payne
and colleagues14,15 and these arguments will not be repeated
here. It should, of course, be noted that whole-cell screening
is now accompanied by a number of new methods, derived
from the genomics era, for determining the mode of action of
inhibitors.15,18,22,23 Biosensors that contain promoter–reporter
constructs that are induced by conditions of antibiotic-induced
stress are particularly useful as a supporting technique for
whole-cell-based screening of inhibitors.22,23 Based upon a refer-
ence compendium of antibiotic-triggered microarray experi-
ments, promoters that are induced in response to treatment of
Bacillus subtilis with antibacterials with similar modes of action
have been discovered and manipulated to genetically engineer
five promoter–luciferase reporter fusion strains.22 These biosen-
 sor strains signal the presence of inhibitors of fatty acid (fabHB
promoter), DNA (yorB), cell envelope (ypuA), RNA (yvgS) and
protein (yheI) biosynthesis and therefore represent an excellent
tool for screening of antibacterial agents and potential identifi-
ation of their mechanisms of action. In our laboratory at Leeds
we have expanded the utility of the B. subtilis biosensors by
examining their responses to a wide range of established drugs
and experimental inhibitors.22

A particular problem with current whole-cell screening cam-
aigns has been the high incidence of inhibitors that display
antibacterial activity through non-specific damage to the bacte-
rial cytoplasmic membrane,14 which is a strong indicator that
such inhibitors would have similar activity against mammalian
cells and hence would be cytotoxic.22 The presence of such
inhibitors explains in part why the output from recent
whole-cell antibacterial screening programmes has been so
disappointing.16

Current assays to determine membrane damage caused by
antibacterial agents are costly, or require large amounts of the
test agent. Consequently, new methods are needed for the screening of membrane-damaging agents to process potential chemotherapeutic candidates faster and to eliminate more rapidly compounds with unattractive characteristics. The construction of biosensors responsive to membrane damage has the potential to enable high-throughput detection of membrane-damaging antibacterial agents. However, no such reporter strains have been described to date. To facilitate the generation of such reporters, we have established the transcriptional response of Staphylococcus aureus following exposure to several established membrane-damaging agents by DNA microarray analysis (A. J. O’Neill and I. Chopra, unpublished observations). The objective was to identify up-regulated promoters that could be employed for the future construction of biosensors responsive to the presence of membrane-damaging agents. The transcriptional profiling revealed that genes involved in the maintenance of membrane integrity and cellular energy production were significantly up-regulated in the presence of sub-lethal concentrations of membrane-damaging agents. However, further reverse transcription PCR analysis is needed to verify that these genes are not up-regulated in response to antibacterial agents with other modes of action. This would obviously negate their use in the construction of biosensors specifically induced in response to membrane-damaging inhibitors.

The recent poor success of whole-cell screening campaigns is primarily attributed, with hindsight, to the unsuitable nature of the chemical libraries that were employed for screening. These libraries, which represented compounds synthesized for other therapeutic areas, appear to lack the chemical diversity required for discovering antibacterial leads and were also constrained by conforming to a set of physiochemical parameters (Lipinski’s ‘rule of five’) more likely to result in the identification of compounds with acceptable oral bioavailability and tissue distribution rather than inhibitors able to traverse the complex barriers of the bacterial cell envelope to reach intracellular targets. Indeed, retrospective physiochemical characterization of successful antibacterial drugs demonstrates that they do not conform to the empirical rule of five features observed for drugs in other therapeutic classes. However, there is optimism that whole-cell screening has the potential to deliver new drug leads if the diversity of chemical libraries can be improved, particularly if there is a return to the screening of natural products.
Genomics and in vitro high-throughput screening against isolated biochemical targets

Since the sequencing of the entire *Haemophilus influenzae* genome in 1995, high-throughput genomic and bioinformatic approaches involving the comparison of over 100 genome sequences of significant bacterial pathogens have been increasingly employed in an attempt to identify highly conserved broad-spectrum targets with little mammalian homology.\(^{14,15}\) Approximately 160 essential enzyme targets in bacteria have been identified by such methods and only a small proportion of these targets are exploited by currently developed antibacterial drugs.\(^{14,15}\) The search for inhibitors of many of these new targets by HTS of compound libraries within GlaxoSmithKline has recently been described in detail in the informative reviews of Payne and colleagues.\(^{14,15}\) The experience of GlaxoSmithKline is also typical of that found in other companies.

GlaxoSmithKline undertook a 7 year programme (1995–2001) in which 67 high-throughput in vitro screening programmes on antibacterial targets were run against over half a million compounds. Leads against only five targets were identified, including inhibitors of two aminoacyl-tRNA synthetases, peptide deformylase, and the enoyl-acyl carrier protein reductase (FabI) and 3-ketoacyl carrier protein synthase III (FabH) of fatty acid biosynthesis. However, none of these leads has successfully progressed to clinical trials and the inhibitors identified by HTS generally lacked specificity, or did not possess suitable antibacterial activity or spectrum of action against a range of clinically important bacteria. As in the case of the recent whole-cell screening campaigns discussed above, the lack of success for HTS in identifying antibacterial leads is widely attributed to the unsuitable chemical properties of the libraries used for screening.

Structure-based drug discovery

SBDD, including the component technologies of VHTS and FBDD, is a new *in silico* method of drug discovery that has become possible since the elucidation of the three-dimensional structures of drug targets. These methods have already delivered molecules into the development pipeline in therapeutic areas other than antibacterials\(^ {15,17}\) and are clearly of major interest in the context of antibacterial drugs. The structures of over 600 bacterial proteins are already available\(^ {17}\) and this number will grow in future years, making SBDD an increasingly plausible approach for antibacterial drug discovery. However, there are limitations. For instance, the reliance of SBDD on a single high-resolution crystal structure of a protein target is a restriction, as it only displays the protein in one position, whereas a biologically active protein (typically an enzyme) may adopt multiple conformations. Nevertheless, many of the newer SBDD programmes compensate for this problem by designing flexible ligands which can bind to the protein in a variety of poses.\(^ {17}\)

The results of SBDD approaches, including VHTS and FBDD, for antibacterial drug discovery have been covered in recent reviews.\(^ {17,25}\) Although the number of applications of SBDD to antibacterial drug design is relatively small, it is already evident that attention will be needed to achieve uptake of inhibitors into bacteria and/or to prevent their efflux by the multidrug resistance (MDR) pumps found in a number of Gram-negative bacteria. This is addressed further in the subsequent section of this article entitled ‘The problem of drug accumulation’. Nevertheless, if the issue of poor accumulation of inhibitors can be successfully addressed, SBDD has the potential to deliver new antibacterial drugs into the development pipeline. Here I will discuss some very recent examples of SBDD, particularly FBDD, including a study from our own laboratories at Leeds dealing with the design of bacterial RNA polymerase (RNAP) inhibitors.\(^ {26}\)

FBDD is based upon identifying small chemical fragments that bind to the target, often with weak affinity, which can then be chemically enhanced by further structure-guided manipulation to produce more potent hits (Figure 2b). The recent study from our laboratories clearly illustrates the potential of FBDD for antibacterial drug discovery. For our work we chose to target bacterial RNAP, which catalyses the DNA-dependent synthesis of RNA. This enzyme is essential for the growth and survival of bacteria and is an established drug target since it is inhibited by the ribosomycin family of antibiotics, which are in current clinical use.\(^ {27}\) RNAP is an attractive antibacterial drug target since it is conserved amongst bacteria and exhibits major structural differences from eukaryotic RNAP.\(^ {27}\) Furthermore, new opportunities to design bacterial RNAP inhibitors have recently arisen following the structural elucidation of the myxopyronin binding site on the enzyme.\(^ {28}\) Myxopyronin binds to the switch region of the enzyme, where it interferes with the function of the β′ subunit, leading to an inactive conformation of the enzyme that cannot bind to template DNA. Although myxopyronin itself is not an attractive drug candidate because of unfavourable properties,\(^ {29}\) information on the molecular basis of its interaction with RNAP provided the starting point for our FBDD approach. We were further encouraged to take a structure-based approach since the recent HTS programme conducted by GlaxoSmithKline had failed to identify hits against the enzyme.\(^ {14}\)

Using a co-crystal structure of the *Thermus thermophilus* RNAP–myxopyronin complex, the myxopyronin binding site was analysed by SPROUT, a program for FBDD. Since the myxopyronin binding cavity is large, we concentrated on a region around the enecarbamate side chain of the antibiotic close to residues

Figure 3. Myxopyronin binding region within the β′ subunit of *Thermus thermophilus* RNA polymerase. Desmethyl myxopyronin B is shown in dark yellow with key residues of RNAP labelled. Reproduced from reference 26 with permission from the American Chemical Society.
Trp1039 and Glu1041 in the β′ subunit (Figure 3), since this provided a narrow cavity with the opportunity to identify fragments that could make hydrogen-bonding interactions with these amino acid residues. Indeed, a substituted pyridyl-benzamide (compound 7) was predicted by SPROUT to fill the cavity and to interact with Trp1039 and Glu1041 as well as Gln611 (Figure 4). Compound 7 was synthesized in four steps and was found to be a weak inhibitor of E. coli RNAP in vitro (IC_{50} 151 μM). However, further docking studies led to the prediction that substitution of the picolyl group of compound 7 by nitrogen-containing heterocycles to produce compounds 8 and 9 (Figure 5) would increase potency against RNAP. Compounds 8 and 9 were synthesized and indeed were more active inhibitors of RNAP than compound 7 (Figure 5). To explore structure–activity relationships in further detail, a small group of compounds (compounds 10–13) was also synthesized in which the sulphonamide group in compound 7 was varied. These were all found to be improved inhibitors of RNAP compared with compound 7 (Figure 5). Further docking studies suggested that compounds 8–13 now made hydrogen-bonding interactions with Lys621 and that compounds 8, 10, 12 and 13 were now also able to make a hydrogen bond with the carbonyl residue of Phe1032 also in the vicinity of Lys621 (Figure 6).

Encouraged by these results, we examined the specificity of the inhibitors by determining their ability to inhibit a eukaryotic (yeast) RNAP (RNA polymerase 2; Pol II) and two unrelated mammalian enzymes, malate dehydrogenase and chymotrypsin (yeast) RNAP (RNA polymerase 2; Pol II) and two unrelated mammalian enzymes, malate dehydrogenase and chymotrypsin (yeast) RNAP (RNA polymerase 2; Pol II) and two unrelated mammalian enzymes, malate dehydrogenase and chymotrypsin (yeast) RNAP (RNA polymerase 2; Pol II) and two unrelated mammalian enzymes, malate dehydrogenase and chymotrypsin (yeast) RNAP (RNA polymerase 2; Pol II) and two unrelated mammalian enzymes, malate dehydrogenase and chymotrypsin (yeast) RNAP (RNA polymerase 2; Pol II) and two unrelated mammalian enzymes, malate dehydrogenase and chymotrypsin (yeast) RNAP (RNA polymerase 2; Pol II) and two unrelated mammalian enzymes, malate dehydrogenase and chymotrypsin (yeast) RNAP (RNA polymerase 2; Pol II) and two unrelated mammalian enzymes, malate dehydrogenase and chymotrypsin.

The problem of drug accumulation

As noted in the section dealing with FBDD, new inhibitors of intracellular bacterial enzymes can certainly be designed, but, disappointingly, most appear to be unable to cross the bacterial cell envelope to reach their targets or are not concentrated in the cell because they are removed by efflux pumps. Unfortunately this is also a problem with VHTS, i.e. the identification of inhibitors with no, or poor, antibacterial activity.4,5,31,32 (C. W. G. Fishwick, A. J. O’Neill and I. Chopra, unpublished observations). Lack of antibacterial activity has also been an issue with inhibitors identified by HTS.15,20 Although such results, without further studies, do not prove that lack of whole-cell activity is due to poor inhibitor penetration (i.e. failed uptake or efflux, or a combination of both mechanisms), it is highly suggestive of penetration problems.

What approaches might be possible to address these problems of bacterial cell penetration? Altering the physiochemical properties of inhibitors, such as the introduction of chemical groupings to create zwitterions, should enhance uptake across the bacterial cytoplasmic membrane and also render inhibitors less susceptible to efflux.1,5,31 Although this is an appealing strategy, altering the physical properties of an inhibitor may reduce affinity for binding to the molecular target, giving a counter-productive end result. Nevertheless, the use of increasingly sophisticated docking methodologies to check the ability of modified inhibitors to fit within the binding site and in vitro assays using artificial membranes to study inhibitor permeation means that this is a feasible approach. Indeed, using such methods Venturelli et al.33 have been able to generate derivatives of a β-lactamase inhibitor with improved penetration across the outer membrane of E. coli and improved cellular activity without substantially compromising the binding efficacy for the target.

Another approach to the delivery of inhibitors could involve a ‘Trojan horse’ strategy whereby siderophores normally involved in the uptake of iron by bacteria are utilized for drug delivery (Figure 7).34,35 Although this is a very elegant concept, the technology is still in its infancy and not all inhibitors may be

Figure 4. Compound 7 showing predicted H-bonding interactions with RNA polymerase. Reproduced from reference 26 with permission from the American Chemical Society.
chemically amenable to coupling with siderophores. It is also not certain whether drug release will be necessary within the bacterial cytoplasm for interaction with the target (Figure 7). However, several siderophore conjugates have already been made with existing drug classes, such as β-lactam antibiotics. In several cases the antibacterial activity of the siderophore complexes was greater than that of the unmodified drugs under conditions where siderophore transport was optimal (i.e. under conditions of iron limitation). Nevertheless, if this drug delivery strategy is to be successful it will be important to establish that siderophore–drug conjugates are stable in body fluids to potentially permit oral and systemic application. Furthermore, it will also be necessary to determine whether binding of iron by the siderophores, when administered to the host, could present toxicological problems.

Choice of targets

Much has been written in recent years about the selection of new drug targets in bacteria and genomic methods have undoubtedly improved our understanding of some of the pitfalls of target selection by identifying blind spots such as genetic redundancy and, in some cases, lack of conservation of potential targets across a range of important pathogens. I will therefore restrict my comments to discussion of some biochemical targets with which I have had personal experience.

The MurC to MurF ATP-dependent ligases are intracellular enzymes involved in the early stages of peptidoglycan synthesis in bacteria. They are highly conserved, essential enzymes that are specific to bacteria and much is now known about their structure and function. Since MurC to MurF share similarities in structure and function it was initially considered that all four enzymes might be amenable to multiple inhibition by a single inhibitor. This, in principle, would have advantages in minimizing selection of resistance as mutations conferring high-level

Figure 5. Structures of compounds 7–13 and their activities as enzyme inhibitors. Data from reference 26. MDH, malate dehydrogenase; CHM, chymotrypsin.
resistance would likely need to arise simultaneously in more than one target gene.\textsuperscript{36} This concept was later refined on the basis of improved structural information for the enzymes to include the possibility of discovering single inhibitors of the MurC/MurD and MurE/MurF enzyme pairs.\textsuperscript{37} Nevertheless, such opportunities would still be advantageous from the perspective of reducing mutational resistance since at least two gene targets would still be involved.

The credibility of such concepts appeared to be strengthened by the discovery of several compounds by different research groups that inhibited more than one of the Mur enzymes in vitro.\textsuperscript{1} However, one compound set comprised rhodanine derivatives, which as a group are now known to contain promiscuous enzyme inhibitors.\textsuperscript{1,39} Indeed, in careful re-evaluations of the data supporting claims of the discovery of MurC–MurF inhibitors, Silver\textsuperscript{1,40} came to the conclusion that there is no compelling evidence that the antibacterial activity of any of the MurC–MurF enzyme inhibitors can be ascribed to inhibition of these targets within the bacterial cell. Furthermore, it now seems that these enzymes may well be refractory to inhibition in vivo since they appear to perform as a multi-enzyme complex with possible channelling of reaction intermediates so that individual active sites are inaccessible to inhibitors.\textsuperscript{40,41} Unfortunately, therefore, the recent claim that structure-based and library screening approaches are starting to produce active leads against MurC–MurF enzymes with encouraging antibacterial activity\textsuperscript{38} cannot be sustained.

**Conclusions**

Compared with our scientific predecessors, who were involved in the discovery of antibacterial drugs both before and during the golden era, we have a wealth of molecular information concerning the pathogens we are hoping to control and a massive array of new biological, structural and chemical methods to assist antibacterial drug discovery. Why, therefore, have we been so unsuccessful in recent years in identifying new inhibitors that have the potential to enter the development pipeline and become new therapeutic agents for the treatment of bacterial infections? This question has also been repeatedly raised by many others.\textsuperscript{1,14–16,19,20} Undoubtedly, mistakes have been made in concentrating upon unsuitable chemical libraries for whole-cell screening and HTS. Diversification of libraries for future screening will be essential, including a return to natural product screening, which after all, has been the source of many of the important antibacterial drugs in use today.\textsuperscript{1,2,42} In my opinion and that of others, accessing new natural product sources will be essential and the growing field of metagenomics is particularly exciting, whereby new antibiotics synthesized by the large collections of bacteria present in the environment, but currently non-culturable, can potentially be identified.\textsuperscript{43,44} When new hits are identified, from whatever source, it will be vital to determine their mode of antibacterial action and to dismiss promiscuous inhibitors.

Prospects for the use of totally different technologies such as ‘antisense’ (or ‘antigene’) strategies, although intellectually appealing, are probably too distant to have immediate credibility as methods for delivering the antibacterial drugs so urgently required.\textsuperscript{45}

**Figure 6.** Predicted conformation of compounds 8 (yellow) and 10 (orange) within the β′ subunit of RNA polymerase (grey). Reproduced from reference\textsuperscript{26} with permission from the American Chemical Society.

**Table 1.** Comparison of physiochemical parameters of various drug sets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comprehensive medicinal chemistry data set\textsuperscript{a}</th>
<th>Gram-positive antibacterials\textsuperscript{a}</th>
<th>Gram-negative antibacterials\textsuperscript{a}</th>
<th>FBDD-derived RNAP inhibitors\textsuperscript{a}</th>
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<tr>
<td>Molecular weight</td>
<td>338</td>
<td>813</td>
<td>414</td>
<td>290–344</td>
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<tr>
<td>clogP\textsuperscript{c}</td>
<td>2.7</td>
<td>2.1</td>
<td>−0.1</td>
<td>0.35–1.7</td>
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<td>243</td>
<td>165</td>
<td>84–141</td>
</tr>
<tr>
<td>H-donor</td>
<td>1.6</td>
<td>7.1</td>
<td>5.1</td>
<td>1–3</td>
</tr>
<tr>
<td>H-acceptor</td>
<td>4.9</td>
<td>16.3</td>
<td>9.4</td>
<td>5–9</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Data from reference\textsuperscript{24}.

\textsuperscript{b}M. J. McPhillie, C. W. G. Fishwick and I. Chopra, unpublished data.

\textsuperscript{c}Calculated log of the oil–water partition coefficient of a neutral form of the compound.

\textsuperscript{d}Polar surface area.
Structure-based (FBDD and VHTS) approaches have the potential to deliver specific and potent inhibitors. However, if they are to be successful much more attention will be needed to ensure adequate accumulation of inhibitors by bacteria, paying particular attention to the physiochemical properties of the compounds. Since structure-based methods of drug design are focused upon the discovery of single molecular target inhibitors, we are faced with the intrinsic difficulty that resistance to these agents may arise in the clinical setting due to point mutations affecting the drug binding site. Consequently, it has been appreciated for some time that synthetic agents able to inhibit multiple targets would be desirable, but probably unattainable. Indeed, this is exemplified by the experience with MurC–MurF inhibitors. Therefore we are faced with the prospect that new synthetic single-target antimicrobial drugs may need to be used in combination to minimize the emergence of target-based resistance in the clinical setting. Unfortunately, this will undoubtedly raise the cost and complexity of introducing the new drugs into clinical practice.

Many lessons have been learned in the past 20 years and the wisdom gained must now be applied to new drug discovery programmes. It will not be an easy task. In addition to recruiting the next generation of researchers and adequately funding them, it will take time to implement the insights we have gained from

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Figure 7. The concept of utilizing siderophore (Sid)-mediated iron acquisition in bacteria for the delivery of antibacterial drugs. (a) Model of Sid synthesis, efflux, capture of iron (Fe^{3+}) by Sid, transport of Sid–iron complex into the cell and release of iron (Fe^{2+}) from Sid by reduction. (b) Model of Sid-mediated drug delivery in bacteria. The inability of a drug to achieve accumulation within the bacterium as a consequence of either poor uptake or efflux is depicted on the right. Chemical coupling of the drug via a linker to Sid may facilitate uptake into the cell and also avoid drug efflux systems. Whether Sid–linker–drug complexes can interact with drug targets or will require release of free drug is currently unknown. Reproduced from reference 34 with permission from Springer Science and Business Media.
the past 20–30 years of fallow research on antibacterials. However, this will be essential since the few new drugs in development do not adequately cover growing medical needs. Furthermore, they are mostly derivatives of older classes already in use and are therefore prone to existing resistance mechanisms. We urgently need new drug classes that can also provide the chemical skeletons for future derivatives in much the same way that analogues of the present classes were developed in the past 60 years. If we do not achieve our goal of discovering new classes, there is the possibility of returning to a pre-antibiotic era. Indeed, in some areas of clinical medicine there is the imminent prospect of untreatable infections, including community-acquired diseases such as gonorrhoea. Most of us did not live in the period before antibacterial drugs were introduced. However, a graphic reminder of what a pre-antibiotic era means can be gained from reading the older literature. A research scientist who has devoted much of his career to antibacterial drug discovery, I am confident that we will eventually succeed in delivering new antibacterial drugs into the pipeline. Nevertheless, this will take time, and some believe that new research successes will be too late to meet the current therapeutic challenges. We cannot predict the future of drug discovery. However, I remain optimistic that we have the ability and motivation to reach our goal.

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