Antibiotics: where did we go wrong?

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In the late 1960s, the medical need for new antibiotics began to be questioned, and the pharmaceutical industry shifted its emphasis of antibacterials from that of a therapeutic leader to a low-priority research area. Although infectious diseases, in particular those caused by bacterial infections, are still among the top causes of mortality in the world, industrial support continues to wane. The shift from this important area of antimicrobial research has been attributed to a combination of science, medical, marketing and business reasons. This decline in antibacterial drug discovery, coupled with increasing risk as a result of infections caused by drug-resistant bacterial pathogens, represents a clear public heath threat.

Historically, the pharmaceutical industry capitalized on the discovery that many microbial secondary metabolites act as antibiotics [1–3]. The *Actinomycetes*, which are isolated from soil, have provided the vast majority of antibacterial compounds. Over 50 years ago, the golden age of antibiotics dawned with considerable achievements in the discovery and development of the sulfonamides, penicillin and streptomycin. This success was followed by the characterization of the tetracyclines, macrolides, glycopeptides, cephalosporins and nalidixic acid [1–3]. Most of these compounds are either derived from natural products or are produced by the synthetic modification of natural products. The compounds from this time period have provided the basic scaffold for medicinal chemistry modifications to expand the spectrum and/or potency of improved analogs in subsequent years [1]. In the past 20 years, over 50 antibacterial drugs have been developed, and large pharmaceutical companies have supplied generation after generation of improved antibiotics characterized by these original classes of drug to meet the existing medical need for novel agents with antibiotic activity [4–10]. However, these numbers are dwarfed by the number of new antibiotics introduced in the preceding 20 years when antibiotics were the mainstay of every large pharmaceutical company.

Antibacterial therapy – a success story

The research and development of antibacterial agents during the past 50 years has been an immense success story. The rate of mortality caused by bacterial infections has dropped precipitously since the pre-penicillin days of the 1930s [11,12]. Although antibacterial agents, improved hygiene, vaccines and an awareness of the bacterial cause of various disease states are all believed to have contributed to a lower morbidity and lower mortality worldwide, the major impact of these factors on morbidity and mortality has been observed in the industrialized world, where drug supplies have been readily available. In 1967 and 1969, the US Surgeon General, William H. Stewart, was reported to have commented: '…that we had essentially defeated infectious diseases and could close the book on them [infectious diseases]…' [13,14], and the popular consensus of the time was that the unmet

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TABLE 1

Antibacterials currently in clinical development by large pharmaceutical companies

Drug name or designation (company)	Class	Target	Status
ABT492 (Wakunaga)	Quinolone	DNA gyrase and topo IV	Phase I[a]
WCK771A (Wockhardt)	Quinolone	DNA gyrase and topo IV	Phase I[a]
PNU288034 [Pfizer (Pharmacia)]	Oxazolidinone	Protein synthesis	Phase I[a]
Garenoxacin [BMS284756 (Schering-Plough and Toyoma)]	Quinolone	DNA gyrase and topo IV	Phase III[a,b]
Doripenem (Shionogi and Pennisula Pharma)	Carbapenem	Cell wall	Phase III[a,b]
CS-023 (Sankyo and Roche)	Carbapenem	Call wall	Phase II[a,b]
Tigecycline [GAR936 (Wyeth)]	Tetracycline	Protein synthesis	Phase III[a,b]

Information acquired from: [a]Investigational Drugs database; and [b]company website, press release or analyst meeting. Abbreviation: Topo, topoisomerase.

medical needs of infectious diseases had been satisfied by existing therapies, thus infectious diseases were of a lower public health priority. Moreover, there was a subsequent decline in broad-based industry support for antibacterial and antibiotic research, which, together with the advent of widespread chronic disease therapy (e.g. cardiovascular, CNS, pain, arthritis and cholesterol-lowering agents), has continued to decrease to its present state of minimal backing from the large pharmaceutical companies. The incidence of multidrug-resistant (or pan-resistant) pathogenic bacteria is on the rise [15–17]. The Infectious Disease Society of America (IDSA) recently reported (July 2004) that in US hospitals alone ~2 million people acquire bacterial infections each year, and in 90,000 cases these infections have fatal outcomes (http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf). In addition, >70% of the bacterial species that cause these infections are likely to be resistant to at least one of the drugs commonly used in the treatment of bacterial infections. All this prompts the question – where did we go wrong?

A snapshot of the antibacterial agents currently available

Examination of the current status of potential novel antibacterial drugs indicates that there are only a few compounds in development by the large pharmaceutical companies (Table 1), with the majority of candidates coming from the smaller biotechnology pharmaceutical companies (Table 2) [18,19]. In the past 30 years, the only truly novel agents that have been launched are linezolid (Pharmacia and Pfizer) and daptomycin (Cubist) [1,19]. Concomitant with the development of these novel agents, there has been a decrease in the number of analogs generated of the classical antibacterials, predominantly penicillins, carbapenems, cephalosporins, tetracyclines, macrolides and quinolones [4,5,11,18,20–25]. Between 1983 and 2001, 47 new antibiotics won approval by the US FDA or the Canada Health Ministry (http://www.fda.gov/cder/approval/index.htm; http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf). Only nine new antibiotics have been approved since 1998, of which just two had a novel mechanism of action. In 2002, there were no new antibacterials in the list of almost 90 drugs approved by the FDA and, in 2003, there were just two antibacterials approved (http://www.fda.gov/cder/approval/index.htm). Of the ~550 drugs currently in development, only six are novel antibiotics (Table 2) [26,27].

What has become of 'big pharma' as the driver of antibacterial research?

Fifty years of medicinal chemistry efforts centered around ~12 antibacterial core chemotype scaffolds have resulted in the development and marketing of >200 antibacterial agents [1,2,28]. Although no new major chemotype scaffolds have emerged, with the possible exception of the oxazolidinone synthetic core (e.g. linezolid), the lipopeptides (i.e. daptomycin) and the ketolides (i.e. telithromycin), which are modified macrolides, have been developed to address emerging resistance problems [29,30]. Many large pharmaceutical companies have reprioritized their R&D efforts to either de-emphasize or to no longer include antibacterials and/or antifungals, while many maintain their support of R&D into antivirals [18–20,27,28]. In the past five years, companies such as Wyeth, GlaxoSmithKline, Bristol-Myers Squibb, Abbott Laboratories, Aventis, Eli Lilly and Proctor and Gamble have de-emphasized or abandoned their endeavors in antimicrobials, whereas Novartis, AstraZeneca, Merck, Pfizer, Johnson and Johnson and others continue to promote internal antibacterial discovery efforts. Meanwhile, a large number of biotechnology organizations continue to support antimicrobial R&D, but are faced with increasing financial pressures, which have led to many companies ceasing operations [19]. This situation raises the question – is this effort enough?

The rise of the biotechnology company

As the emphasis of antibacterial R&D efforts has shifted away from many large pharmaceutical companies to a large contingent of biotechnology companies, the entrepreneur approach to discovery has led to an explosion of creativity in strategies, selection of targets, genomics and development paradigms. The output of this effort is a pipeline of primarily novel, but niche, antibacterials in varying stages of clinical development (Table 2). On examination of the models used by these companies, a

TABLE 2

Antibacterials currently in clinical development by biotechnology companies

Drug name or designation (company)	Class	Target	Status
MC02479 [RWJ54428, RWJ442831[a] (Trine and J&J)]	Cephalosporin	Cell wall and transpeptidation	Phase I[b]
MC04546 [RWJ333441, RWJ333442[a] (Trine and J&J)]	Cephalosporin	Cell wall and transpeptidation	Phase I[b]
VRC4887 [LBM415 (Vicuron and Novartis)]	Hydroxamate	Peptide deformylase	Phase I[b,]
BB83698 (Vernalis, Genesoft and Oscient)	Hydroxamate	Peptide deformylase	Phase I[b,d]
Ramoplanin [GTC (Oscient) and Vicuron]	Glycolipodepsipeptide	Transglycosylation and lipid II	Phase II–III[b,c]
Oritavancin [LY333328 (Intermune and Lilly)]	Glycopeptide	Cell wall	Phase III[b,c]
Rifalazil (Activbiotics)	Benzoxazinorifamycin	RNA polymerase	Phase II[b,c]
BAL5788 (Basilea and Roche)	Cephalosporin	Cell wall	Phase II[b,c]
MC04,124 (Mpex Pharm, Trine and Daiichi)	Peptide	Efflux pump inhibitor	Preclinical[b,c]
MP601,205 (Mpex Pharm and Daiichi)	Peptide	Efflux pump inhibitor	Preclinical[c]
Dalbavancin (Vicuron and Aventis)	Glycopeptide	Cell wall	Phase III[b,c]
TD6424 (Theravance)	Lipoglycopeptide	Cell wall	Phase II[b,c]

[a]Prodrug of active component. Information acquired from: [b]Investigational Drugs database; and [c]company website, press release or analyst meeting. [d]Discontinued development.
Abbreviation: J&J, Johnson & Johnson.

pattern becomes apparent. The observed trend is a combination of the acquisition of niche products that have not been developed by larger pharmaceutical companies, the exploitation of scientific discoveries not successfully applied to drug discovery by larger pharmaceutical companies and an incremental improvement in an existing class of agents. Surprisingly, none of the large pharmaceutical companies have successfully developed the novel targets approach to identifying drug candidates. The premise of this failed novel targets approach is generally based on attempts to exploit the 'genomics' technology that launched after the start of the whole-genome-sequencing era in the mid- to late-1990s. However, two biotechnology companies have managed to progress non-genomics program drugs to the market. These two success stories are the lipopeptide Cubicin®, an intravenous hospital drug for the treatment of serious Gram-positive infections, which was developed by Cubist and approved for therapeutic use in 2003 [22,31], and the quinolone Factive® (gemifloxacin), used for respiratory tract infections, which was developed by Oscient and was also approved in 2003 [31].

Although the drugs that are approved, or are soon-to-be-approved, might represent breakthrough therapy, the overall product profile of the biotechnology organizations developing these novel agents fits more of the niche market treatment options than broader or empirical use. Narrow-spectrum agents are generally not considered to be as commercially attractive by the majority of large pharmaceutical companies when compared with the commercial potential of drugs for the treatment of other therapeutic areas. Because most therapeutic agents are used in empiric therapy, there will need to be a drastic change in treatment paradigms or a major improvement in the diagnostic area to promote increased interest in niche antibacterial markets. Broad-spectrum, well-tolerated agents that address emerging resistance will continue to be the focus of the remaining key pharmaceutical industry players. Another problem that biotechnology companies currently face is the significant capital that is necessary to undertake large-scale clinical trials. Most biotechnology companies cannot undertake the costs of these clinical trials alone, and for many such companies the new business model for survival appears to be to move forward with single, key indications that will provide a steady revenue stream upon first regulatory approval to market their drug. Unfortunately, when the biotechnology company cannot find a development partner to bear the high cost of Phase II–III trials, the result of this plan has frequently been to dispose of discovery assets (including people) to pay the cost for clinical development. This is not a sustainable business model.

The essentials of antibiotic and antibacterial discovery

As with any other therapeutic area, antibiotics requires a novel starting point to spark interest, the perception of do-ability and a sustained commercial value potential in pursuing antibacterial R&D. Historical nomenclature has antibiotics as derivatives of natural products [32] and antibacterials as products of synthetic chemotypes. The process of discovery is similar in all therapeutic areas involving synthetic or semi-synthetic molecules, but is different from biologics (which will not be considered further here). A key distinction between antibacterials and antibiotics and chronic disease therapy has been the reliance on natural products for a chemotype starting point [2,21,26], with several important exceptions such as the natural product-based statins, multiple cancer agents and some immunosuppressive drugs [35]. In the past two decades, the greatest probability of short-term success has come from improving the existing, safe and proven classes of antibacterial agents – but this strategy no longer commands a premium price in the market to justify the investment. With the almost complete

withdrawal of the large pharmaceutical companies from natural product sourcing for antibiotics, the R&D discovery units turned to pre-existing synthetic libraries of compounds made primarily for other purposes; this approach has frequently identified excellent target inhibitors in HTS (and analog programs), but few with antibacterial activity (usually as a result of permeability issues in transporting inhibitors across bacterial cell membranes).

What changed in the 'value' of antibiotics and antibacterials?

There are numerous factors that have an impact on the 'value' of antibiotics in the marketplace, including: (i) increase in antibacterial sales (both percentage increase and overall dollars); (ii) generics; (iii) segmentation (specialization of the market); (iv) increased regulatory hurdles and postlaunch commitments; (v) total R&D cost versus 'return on investment' (ROI); and (vi) the competition for resources within the pharmaceutical industry for R&D areas limited by capital available (i.e. should constrained resources be used to develop antibacterials versus chronic drugs?) [19,20,27,28].

Whereas the recent successes of chronic disease drugs (e.g. statins, CNS agents, pain relief, asthma treatment, arthritis relief and erectile dysfunction drugs) provide a stark contrast in their relatively limited numbers of drug classes (when compared with the history of antibiotics R&D), these chronic disease treatment areas have an advantage in the way in which they are used (i.e. life-long, pill-a-day therapy). By contrast, antibiotics are administered in predominantly acute situations to reduce infection and prevent mortality; thus, the numbers of patients-days (total number of days an individual patient is on drug therapy) for antibiotics is dwarfed by drugs for chronic indications in the same patient population in the industrialized world [19].

There is also a lack of appreciation for the untold cost of bacterial resistance development in the microbial community and its effect on clinical efficacy of antibiotics [12,34–46]. Resistance, which is inherent in the mode-of-action of all antibiotics and antibacterials, poses challenges in the development of new antimicrobial agents by large pharmaceutical companies, as well as biotechnology companies. The majority of antibiotics and antibacterials have an 'inherent obsolescence' because of the emergence of resistance by virtue of the target they attack [34,42–46]. Unlike chronic drug therapy, where an efficacious drug can be used indefinitely without 'resistance' to that drug lowering efficacy, the action of antibiotics facilitates the selection of mutant bacteria, which arise as resistance pathogens during the normal course of therapy [9,45,47,48]. Thus, antibiotics are unique in that their extensive use in clinical therapy will lead to an inevitable decrease in drug benefit, both for the individual drug and the entire class of drugs that act via the same mechanism. Increased resistance usually accompanies the wide use of newly approved antibacterial agents and, typically, resistance has been identified within just four years of FDA approval of the drug [28]; linezolid is the latest example of this pattern, with resistance to this antibiotic initially occurring in clinical trials.

These emerging pathogens represent a real public health threat [2,12,15–18,22]. This can be seen in numerous surveillance programs worldwide, which provide researchers and clinicians with data on the susceptibility trends, as well as presenting drug discovery researchers with an indication of existing problems and a projection of future needs [36–41,49,50].

In the hospital setting, the re-emergence of Gram-negative pathogens is of major concern [2,12,15–17,28]. In one large study, >60% of the sepsis cases were caused by virulent Gram-negative bacteria (e.g. *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli* and *Enterobacter* spp.) [34,38,39]. In addition, emerging resistance among 'newer' pathogens, such as *Acinetobacter baumannii* (once thought to be an environmental contaminant and now seen as a serious opportunistic pathogen in hospitals) also presents significant and growing medical concerns [40], as do older pathogens such as methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Salmonella typhimurium* and *Mycobacterium tuberculosis* [35,37,43,50,51]. In 1993, the World Health Organization (WHO) declared *M. tuberculosis* to be a global emergency [12], the first such designation ever made by the organization. According to the WHO, one individual becomes infected with *M. tuberculosis* every second, and every year eight million people contract the life-threatening disease [12], of which two million die. The WHO predicts that between 2000 and 2020, nearly one billion people will become infected with *M. tuberculosis* and this disease will cost a total of 35 million people their lives. The impact of HIV infection as a co-factor in *M. tuberculosis* prevalence [51] necessitates that efforts be taken now to avoid a catastrophe in the next 20 years.

Antibiotic versus antibacterial scaffolds for drug development

The starting point for virtually all natural products that have become antibiotic scaffolds is that they possess one or more target-inhibition sites, and that the bacterial membranes are permeable to such natural compounds [1,16,21,26,32]. Many of the attempts to identify novel antibacterials have been disadvantaged because the approach has optimized target activity only (i.e. nM K_i values of inhibitors that do not have activity against bacteria). Without a bacteria-permeating lead as a starting point, and no knowledge of the SAR of the ability of the lead to permeate the bacterium, multiple industrial programs have produced nM inhibitors that failed to penetrate into the bacterium. There have been numerous reports of nM levels attained for enzyme inhibitors, for example, alanine racemase, that are precluded from

being engineered to become antimicrobials because of their inability to penetrate the bacterium adequately. [3,21,52].

The manufacture of secondary metabolites by 'producer organisms' in nature is believed to support multiple functions, including the ability to communicate with other microorganisms and to protect the organism from attack [26,33,53,54]. If the microbial strategy is to protect the producer organism, it is logical that antimicrobials would be identified in nature under adverse conditions because their production would assure and/or enhance the survival of the producer organism from environmental insult. Thus, the rich source of antibiotic activities in nature (some that have selectivity over eukaryotes and others that do not) is understandable in terms of structural design from an evolutionary survival standpoint – and represents a great sourcing pool for novel chemotypes. However, the field of industrial natural product sourcing has been eliminated from the best practices of the large pharmaceutical organizations because of: (i) a lack of more-recent successes; (ii) the promise of genomics and HTS screening; (iii) the potential of rational drug design based on structural work; and (iv) the possibilities associated with combinatorial chemistry [1,20,26,32,33,55]. Furthermore, it is now known that conventional techniques for cultivation only enable the isolation and growth of a small subset of all microbial life forms identified in nature [56]. Ironically, natural product scaffolds were used to construct many of the first-generation chronic disease drugs, such as cardiovascular agents (e.g. digoxin, digitoxin and lanosterides), anticancer agents (e.g. bleomycin, doxorubicin, vincristine, mitomycin, paclitaxel and camptothecin), CNS agents (e.g. codeine, morphine, physostigmine and galanthamine), immunomodulatory agents (e.g. cyclosporine and FK506) and cholesterol-lowering agents (e.g. simvastatin, pravastatin and lovastatin) [33].

Where did we go wrong?

Analyses of the synopsis of factors that drive the support of antibacterial R&D now enables consideration of the question at hand – where did we go wrong? Apart from the judgmental nature of the question (i.e. point the finger at other individuals), there are at least eight key aspects that enter into a thorough answer.

Shifting priorities by business

The change in emphasis and/or support of antibiotics is a combination of the changing market potential and a shift away from the guaranteed success of 'me-too' analogs of classic chemotypes to the high-risk, new target and non-natural product-sourced antibacterial leads that have produced few success stories. This has prompted a continuous, serious business review of the value of the only guaranteed renewable research area (i.e. inherent obsolescence as a consequence of resistance emergence), and more pharmaceutical companies could discontinue antibacterial R&D. Undoubtedly, when the first wave of the blockbuster chronic disease drugs lose exclusivity, a repeat of this paradigm will be observed, which might level the playing field in valuing antibacterials.

Under-appreciation of resistance

Resistance evolves in bacteria because of the nature of their high growth rate (i.e. doubling time) and their ability to select for bacterial survivors in a population that have spontaneous mutants. Bacterial mutants with enhanced ability to survive in the presence of the environmental insult (including antibiotics) will constantly be emerging in the microbial ecology. Unlike bacteria, eukaryotic cells rarely evolve within the lifetime of a therapy to a 'resistant state' (with the exception of the lower eukaryotic fungal cells and some cancer resistance mechanisms). Thus, in the drive for originality in the blockbuster areas of 'met medical need', those institutions that cover the consumer cost of drugs will require strong convincing to use a new generation chronic disease agent over the older effective generic chronic drug treatment. By contrast, antibiotic innovation is the definitive solution to the increasingly difficult-to-treat bacterial infections that are caused by antibacterial-resistant pathogens. Therefore, the treatment of drug-resistant pathogens represents a renewable unmet medical need, but does not yet represent a significant commercial opportunity for industry.

Seduction of genomics and forgetting how to 'make' a drug

The seduction of genomics of the mid-1990s has led to unsuccessful industrial efforts to exploit novel bacterial targets. Well-defined, 'classical' targets were replaced overnight with a wave of novel genomic targets, which were subsequently matched to totally new chemotypes as leads, and the new paradigm was predicted to be more successful than classical approaches to antibacterial drug discovery. We were wrong!

Beginning with the delivery of the *Haemophilus influenzae* genome sequence in 1995 [57], numerous pharmaceutical firms quickly understood that this sudden influx of microbial genome data could be mined for sets of novel targets for antibiotic and vaccine development [58–62]. In addition, advanced computational tools and innovative genomic strategies such as DNA microarrays for gene message expression analyses [63,64] and proteomic analyses [65,66] provided 'validation' of several dozen novel, essential, broad-spectrum targets. However, to date, not one 'genomics' target has been exploited to the point of reaching clinical trials. Although the hope of genomics-based drug discovery could offer an alternative strategy in the future, these tools of microbial genomics are just a part of the successful execution of identification and development of novel antibacterials.

Industrial shift from natural product sources for novel chemotypes

The abandonment of natural products by most industrial groups is a mistake, because the leads identified in natural product sourcing for antibiotic scaffolds often provide a starting point for medicinal chemistry. This subsequently leads to the search for the target, the identification of which is typically achievable because the nature of the natural product compound is such that it has a structure that enables it to permeate the bacterium. Medicinal chemistry builds on a SAR with pre-existing antibacterial activity, enabling optimization of other 'drug-like' properties without having to discern how to transport the lead across the bacterial cell wall and/or membrane. Consequently, beginning with an 'antimicrobial' as a lead has proven the most successful approach to date in the discovery of antibiotics [1,26]. Over the past 30 years, only the oxazolidinones have a totally synthetic history, but even the quinolones evolved accidentally from a distinct natural product scaffold for malaria [33,67]. If the path to the discovery of nalidixic acid (the progenitor of the successful fluoroquinolone class) is examined, it can be seen that the major antimalarial drugs (chloroquine, mefloquine and primaquine) were all derivatives of the alkaloid quinine (which can be found in the South American tree *Cinchona succiruba* [68]). This quinine nucleus, which was subsequently synthesized in the laboratory, was the scaffold from which nalidixic acid (a 1,8-naphthyridine) was identified as an unintentional by-product by chemists at the Sterling Drug Company [33], and it was this product that formed the basis for the synthesis of new antimalarials; these agents later formed the synthetic core for the fluoroquinolones [68].

Multivariable problem in need of an integrated, consensus solution

As an 'industry', we have fallen behind the evolving decrease in susceptibility of major pathogens to antibiotics and antibacterials and the foothold they have in the clinic. All 'stakeholders' have a part in this general 'industry' term, including those that discover and develop drugs, those that approve drugs for licensing, prescribe drugs for infections and the administrators and/or payers of the cost expenditures for antimicrobial therapy. The position the industry finds itself in is the 'wrong' of all participants, which will be solved only by significant change in its approach to dealing with bacterial infections. There are multiple initiatives underway to address this problem, including efforts by the IDSA, WHO, National Institutes of Health and regulatory authorities (among others) to convene meetings with key opinion leaders in an attempt to build a consensus solution.

Complacency

Complacency might be a good term to cover several aspects of the 'norm' established in the first 30–40 years of antibacterial R&D. Among these norms were: (i) the belief that there are always other analogs with superior qualities to be sold (i.e. β-lactams and tetracyclines); (ii) the conviction that a 'fast follow-on' was the same as me-too drugs (e.g. the success of Levaquin® argues otherwise – the development of the single L-isomer of the racemic ofloxacin mixture led to increased potency, efficacy, improved dosing and enhanced safety profile); (iii) new analogs will enable antibiotics to stay ahead of the bacterial resistance curve; and (iv) the opinion held by industry, academia, the medical community, regulatory authorities and commercial groups that 'failure' to execute is the same as 'chance of success' (a number calculated by historical metrics to benchmark success rates). That is to say, there has been a repeated failure to deliver new antibacterials to the marketplace, but this factor is only one of many used to prioritize research efforts. There must be a significant improvement in efficacy, safety, cost and/or compliance to command a premium price and deep penetration in the marketplace.

Who can blame be assigned to?

Is the pharmaceutical industry culpable for the current situation? The industry most probably would be deemed a 'success story' for most of its history, but mistakes have been made in underestimating and/or misunderstanding a changing marketplace, failing to appreciate the force of resistance on the erosion of efficacy in particular drug classes and missing the changing paradigm that managed care brought to the marketplace (i.e. facing a satisfied and segmented market and the impact of generics in lowering the perception of 'value' of antibacterials). Lessons have been learned, including that novel disease states (predominantly chronic diseases) offer an easier path to success and that incremental improvements in analogs of existing drugs will be essential with a higher 'quality' bar to compete in a satisfied market. In addition, genomics could identify new targets and disease states, but the identification of a viable, antimicrobial starting pharmacophore is the key factor for success. It appears that the industry as a whole has lost the innovative edge in antimicrobial discovery research that it once had.

Diagnosis

As a business group, the pharmaceutical industry has not succeeded at some key aspects of the discovery of antibacterials and antibiotics. The industry has failed in the continuous production of novel, high-quality, efficacious and safe 'products' since the early-1980s. Furthermore, it has not succeeded at several tactical processes (i.e. hits-to-leads and lead optimization); it has erred in strategically choosing synthetics over natural products as the sole source for the majority of new leads; and it has been seduced by the lure of genomics and has wasted many years chasing sub-optimal leads against ill-defined targets simply because the targets were genomically-identified and/or

validated or 'novel'. The industry has also underestimated the hardiness of serious pathogens to survive and to adapt resistance mechanisms against the best antibacterials, while continuing to expose normal flora and opportunistic pathogens to existing drug classes, resulting in underlying resistance in emerging pathogens. In short, the industry has not got the job done in recent times. This must change.

Conclusions

There is a serious unmet medical need for new antibacterial agents to treat drug-resistant infections [69]. The underlying resistance to antibiotics in emerging pathogens might be selected for by drug exposure in prior rounds of antibiotic therapy; this latent resistance is potentially a major problem to be addressed in the near future. Only the successful identification and development of novel, potent, efficacious antibacterial agents will solve this problem. Reinvigorated, sustained efforts by multiple, large pharmaceutical companies, either directly or in partnership with biotechnology companies, to support clinical trials will drive this situation to a successful paradigm again.

The industry has simply not delivered novel antibacterials, however, the diverted resources have had a major positive impact on the treatment advances for chronic disease states, including both life-threatening (e.g. cardiovascular, lipid-lowering, asthma and cancer) and quality-of-life (e.g. anti-anxiety, anti-depression, anti-emisis and erectile dysfunction) drugs. There has been no clear vision for the importance of antibiotic resistance and the constantly evolving marketplace expects safer and broader spectrum and/or coverage from the new agents. Furthermore, the prioritization of resources has been driven by a lack of commercial 'value' of antibacterials and the lure of treating chronic diseases. In the past 5–10 years, multiple attempts have been made to exploit novel antibacterial targets, and virtually all have been unsuccessful. This could be viewed as '...the drug industry gone wrong...' or it can be seen as a logical shift of resources that will enable the industry to survive as a business entity.

Perhaps our perspective as members of the industry should be one of 'shared success' and 'shared culpability'. The emergence of resistance has brought the industry to the point of requiring severe paradigm shifts in how antibacterials are developed and brought to the marketplace. The 'blame' can be assigned to individuals or all the players involved, but this accomplishes nothing in facilitating a solution. Perhaps the way to move forward is to admit shortcomings (through a process of gleaning 'lessons learned' from past experiences) and to advance towards a joint, universal solution to convince the pharmaceutical industry to reinvest support in antibacterial R&D. A non-judgmental, broad-based consortium of multidisciplinary, multiorganization key opinion leaders must be mounted to forge a sustainable plan for reversing these undesirable trends without pointing the finger at the most convenient partner. To the question – where did we go wrong? – there might not be a consensus answer, but there must be a consensus solution. If a resolution is to be reached, the 'pre-antibiotic' scenario that key infectious disease specialists have warned of for many years might have to be faced.

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