Can biotech deliver new antibiotics?

John F Barrett

The evolution of support for the discovery and development of antibacterial (or antibiotic) agents from the larger pharmaceutical companies to the entrepreneur-like small biotechnology companies has been an experiment in the making for the past 15 years. The word ‘experiment’ is precisely chosen as the outcome is not certain. Many of the antibiotic biotech organizations that were most likely to undertake the task of picking up where large pharmaceutical companies left off have failed to survive, despite their use of outstanding science and their novel approaches to the development of discovery platforms. So this leaves one with the question of ‘can biotech deliver the new antibiotics?’.

Addresses
Department of Infectious Diseases, Merck Research Laboratories, Rahway, NJ 07065, USA

Corresponding author: Barrett, John F (john_barrett2@merck.com)

Current Opinion in Microbiology 2005, 8:498–503

This review comes from a themed issue on Antimicrobials
Edited by Christopher Walsh and Malcolm GP Page
Available online 24th August 2005
1369-5274/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
DOI 10.1016/j.mib.2005.08.007

Introduction
In the late 1960s, the need for new antibiotics began to be questioned on the basis of their medical need. Subsequently, the industrial emphasis on antibacterial (synthetic) and antibiotic (natural product-derived) agents changed from being a therapeutic mainstay in most pharmaceutical companies to becoming a low priority area of research [1–3]. Large pharmaceutical companies had other ideas for internal research efforts and as the next generation of ‘me-too’ drugs (modified mimics of existing medications; i.e. more β-lactams, cephalosporins, tetracyclines, macrolides and quinolones) continued to saturate a slow-growing market, the drive for maintenance of antibiotic research lessened and the age of the chronic care blockbusters was borne [4]. These evolving pharmaceutical industry priorities, which were based on a combination of scientific, medical, marketing and business reasons, accounted for the exit of larger pharmaceutical companies from the area of antibacterial research [1–4]. However, unlike other non-infectious therapeutic areas, the decline in antibacterial research coupled with the increase in antibiotic resistance represents an emerging, if not currently existing, public health threat [5,6,7,8].

This overview examines the evolution in sponsorship of antibacterial research and development (R&D), and investigates whether the current funding model will enable a pipeline of compounds to address the medical needs.

The medical need
Multiple drug resistant pathogenic bacteria are on the increase [8–10]. In July 2004, the Infectious Disease Society of America reported that within hospitals of the United States, ~2 million people become infected with bacteria annually and ~90 000 die as a result of these hospital-based infections (http://www.idsociety.org/pa/IDSA_paper4_final_web.pdf). More than 70% of the bacteria that cause these infections have been reported to be resistant to at least one of the drugs commonly used in routine antibiotic treatment (http://www.idsociety.org/pa/IDSA_paper4_final_web.pdf). Today the antibiotic resistance problem has grown to include all of the major bacterial pathogens and all classes of antibiotic compounds [11,12]. Beyond the US borders, the need for novel antimicrobial agents to combat evolving resistance among human bacterial pathogens is clear and imminent [5,6,13,14].

Big pharma disappears as the driver of antibiotic research
Efforts by the pharmaceutical industry to support basic drug discovery efforts for the identification of new classes of antibiotic agents dropped off quickly. This is owing to several business concerns and competing priorities from other therapeutic areas as the wave of chronic disease research opportunities provided the pharmaceutical industry with other disciplines to invest in [1–4]. It is only within the past decade that the increasingly serious nature of resistance has been recognized [5,13–16], and consensus has emerged that it is essential that novel antibiotic classes are developed as part of the strategy to control the emerging drug-resistant pathogens [17–19]. Currently there is uncertainty as to the types of organizations that will accomplish this.

Many large pharmaceutical companies have reprioritized their R&D efforts so that they no longer support antibacterials and/or antifungals [1–4,17]. In just the past five years, companies such as Wyeth, Aventis, Eli Lilly, GlaxoSmithKline, Bristol-Myers Squibb, Abbott Laboratories and Proctor and Gamble have deemphasized their efforts.
in antimicrobials, whereas others including Novartis, Astra-Zeneca, Merck, Pfizer and Johnson and Johnson continue to support internal antibacterial discovery efforts. A large number of biotech organizations continue to support antimicrobial R&D, but are faced with increasing financial pressures [1].

The past 50 years of chemical modifications of approximately a dozen antibacterial structural scaffolds that are used as chemical building blocks to optimize an antibiotic candidate (mostly natural product sourced) has resulted in the development of analogs and the marketing of several hundred antibacterial agents [8,17]. Only two novel chemotype scaffolds have emerged — the oxazolidinone core (e.g. Zyvox®) and the lipopeptides (e.g. Cubicin®) [20,21]. A modified macrolide class series called the ketolides has emerged, with one representative (telithromycin: Ketek®) being put on the market. These are the only novel antibiotics to reach the market in 30 years [22].

There is just a short list of potential drugs in development from internal efforts at large pharmaceutical companies (Table 1), with the majority of developmental candidates coming from the smaller biotech companies (Table 2) [4,18,19]. Between 1983 and 2001, 47 new antibiotics won approval of the US Food and Drug Administration (FDA) or of the Canada Health Ministry (I6*; http://www.fda.gov/cder/approval/index.htm), but only nine new antibiotics have been approved since 1998, of which just two have a truly novel mechanism of action (i.e. linezolid and dapptomycin). In 2002, no new antibacterials were approved by the FDA, and in 2003 just two antibacterials were approved (I6*; http://www.fda.gov/cder/approval/index.htm). Of the almost 600 drugs in clinical development, only a dozen are novel antibiotics and of these only about three are truly novel scaffolds; all are being produced by smaller biotech organizations (see Table 2) [4].

Antibiotics become recognized as a business
In 2002 the total worldwide revenue of the antibiotic market was just under $22 billion, and was estimated to grow to over $30 billion by 2007 [23]. Despite this market, in which ~80% of sales remain ‘branded’, two-thirds of the top 15 pharmaceutical companies that were active in antibiotic R&D in 1999–2000 have decreased or ceased research on antibiotics [1,3,24]. In the present environment, many scientists and consultants within the pharmaceutical industry argue that the risks of research, development and marketing of an antibiotic are higher than for other drugs [1,25,26].

Together with the 2001 cost estimate from the Tufts University Center for the Study of Drug Development, the average R&D cost of a therapeutic compound (including screening, chemistry, pre-clinical development and clinical testing) is $800 million [26]. However, whereas large pharmaceutical companies generally project that minimum peak sales of $500–800 million are required to recoup R&D investment costs, for a biotech company, annual peak sales of $100–200 million could represent a satisfactory opportunity to recoup the R&D investment.

But business, both in large pharmaceutical companies and in biotech organizations, remains afloat by watching the bottom-line, and the seemingly unending stream of monetary support for the antibiotic biotech start-ups began to drop-off in the late 1990s and continues into the middle of this decade as the biotech ‘experiment’ continues. The difference today is that there is a pipeline of products emerging from the biotech organizations; these are mostly partnered with larger pharmaceutical companies that can fund the expensive Phase II and III clinical trials as well as their launch and initial marketing (Table 2).

The lure of genomics as an end upon itself
Following the publication in 1995 of the first whole genome sequences of two bacterial pathogens — Haemophilus influenzae and Mycoplasma genitalium — both academic and industrial laboratories launched a wave of ‘genomics’ efforts towards the identification of novel bacterial targets [27,28]. Ten years on, genome sequences are known for more than 500 pathogens (http://ligweb.integratedgenomics.com/ERGO_supplement/genomes.html; http://www.ncbi.nlm.nih.gov; http://www.tigr.org/tigr-scripts/CMR2/CMRGenomes; http://www.tigr.org/tigr-scripts/CMR2/CMRGenomes.spl). The initial goal was to identify and to characterize all genes that are essential for bacteria. Both the large pharmaceutical and smaller biotech companies constructed plans that aimed to sequence the genome of bacterial pathogens, identify all essential genes, and advance the ‘best’ targets to high-throughput screens to identify a novel chemotype as a medicinal chemical starting point that could be optimized for use as an antibacterial [29*,30,31,32].

### Table 1

Large pharma antibacterials in clinical development.

<table>
<thead>
<tr>
<th>Drug name (designation; company name)</th>
<th>Delivery route (class)</th>
<th>Target</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garenoxacin (BMS-284756; Schering-Plough/Toyoma) CS-003 (Ro-4008463; Sankyo/Roche)</td>
<td>IV/PO (Quinolone)</td>
<td>DNA gyrase and topo IV</td>
<td>Phase III</td>
</tr>
<tr>
<td>Tigecycline (GAR936; Wyeth)</td>
<td>IV (Carbapenem)</td>
<td>Call wall</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>IV (Tetracycline; glyyclyclcline)</td>
<td>Protein synthesis</td>
<td>Phase III/NDA filed</td>
</tr>
</tbody>
</table>

| IV, intravenous; NDA, new drug application; PO, oral. |
The effort was typically an outstanding scientific accomplishment — usually paired with a DNA sequence-based genomic patent position on certain unique or proprietary targets — but no quality drug candidate emerged from these efforts. It is often as difficult to gauge the ‘quality’ of a lead in small biotech companies as it is in any big pharmaceutical antibacterial drug discovery program. Often this is a point of uncertainty and controversy as short of a drug making it to the market, there is no assurance of its quality. This is because the subjective evaluation of a lead’s quality is full of data, opinion, personal experience and a priori knowledge. However, to date, no genome-associated target has been successfully exploited to the point of having a genomic target inhibitor advanced to the marketplace; the dozens of biotech organizations that built their R&D platform on the identification and partnership of novel genes are now non-existent or are part of a paradigm of the past. Both big pharma and biotech made the same mistakes as they were seduced by the lure of genomics.

The evolution of the discovery and development platform in biotech

Sadly, no biotech organization in the antibacterial arena has survived on the basis of their own internal discovery R&D program. Those that have survived have done so by ‘buying into’ (licensing) a product or a big pharma discontinued or cast-off antibacterial agent. Although not the primary goal of the start-up, this appears to be a viable scenario for the biotech organization as it provides a required ‘asset’ for either an initial public offering or acquisition. The four case studies cited below are examples of this.

The first case study is Cubist Pharmaceuticals, which was formed in 1992 and markets Cubicin® — the first lipo-peptide antibiotic to reach the market. Cubicin® (daptomycin) is an Eli Lilly out-licensed agent that was discontinued in Phase II owing to adverse events, which are now understood to be caused by the suboptimal dose and dosing interval in the clinic [20]. This was salvaged by Cubist in 1997; the subsequent approval of Cubicin® occurred in 2003 and its launch in 2004. This was used for the treatment of complicated skin and soft tissue infections, specifically those caused by susceptible strains of the following Gram-positive microorganisms: Staphylococcus aureus (including methicillin-resistant strains), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae subsp. equisimilis and Enterococcus faecalis (vancomycin-susceptible strains only). Combination therapy can be used if the documented or presumed pathogens include Gram-negative or anaerobic organisms. Daptomycin is not used for the treatment of pneumonia (www.cubicin.com/home.htm).

But Cubist was founded on the discovery platform of exploiting the battery of tRNA-synthases; despite several big pharmaceutical alliances, Cubist was never able to advance a lead into the clinic. Not necessarily owing to the quality of science or failure to execute, Cubist demonstrates the difficulty of having a short rope and a finite timeline for success as defined by a funding source (usually by capital venture groups and small governmental support grants) that anticipate a return in their investment within years rather than decades. History will show that this model is unsustainable, and antibacterial biotech can anticipate a different model of research for the future — the partnership with larger pharmaceutical companies. The return on investment must occur in less than a decade based on capital venture funding models. On the basis of metrics of progress and success in larger pharmaceutical companies, historical data predicts that this is almost impossible. It is thought that there is only one approach that can lead the success — to build the

### Table 2

<table>
<thead>
<tr>
<th>Drug name (designation; company name)</th>
<th>Delivery route (class)</th>
<th>Target</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iclaprim (Arpida/Roche)</td>
<td>IV/PO (Diaminopyridine)</td>
<td>DHFR inhibitor</td>
<td>Phase III</td>
</tr>
<tr>
<td>Faropenem (Replidyne/Suntory)</td>
<td>PO (Carbenem)</td>
<td>Cell wall</td>
<td>Phase II</td>
</tr>
<tr>
<td>Teibipenem (Meiji Seika Kaishar/Wyeth)</td>
<td>PO (Carbenem)</td>
<td>Cell wall</td>
<td>Phase II</td>
</tr>
<tr>
<td>(EP-013420; Enanta/Shionig)</td>
<td>PO (Ketolide)</td>
<td>Protein synthesis</td>
<td>Phase I inhibitor</td>
</tr>
<tr>
<td>(PP-0983M and TAK-589; Takeda/Peninsula)</td>
<td>IV (Cephalosporin)</td>
<td>Membrane disruption</td>
<td>Phase II</td>
</tr>
<tr>
<td>(MBI 594AN; Migenix)</td>
<td>Topical indolicidin peptide</td>
<td>Membrane disruption</td>
<td>Phase II</td>
</tr>
<tr>
<td>Doripenem (JandJ/Peninsula Pharma/Shionogi)</td>
<td>IV (Carbenem)</td>
<td>Cell wall</td>
<td>Phase III</td>
</tr>
<tr>
<td>(RWJ-333441; Essential Therapeutics/JandJ)</td>
<td>IV (Cephalosporin)</td>
<td>Cell wall; transpeptidation</td>
<td>Phase I</td>
</tr>
<tr>
<td>(VRG-4887 and LB415; Vicuron/Novartis)</td>
<td>PO (Hydroxamate)</td>
<td>Peptide deformylase</td>
<td>Phase I</td>
</tr>
<tr>
<td>Ramoplanin (Oscient/Vicuron)</td>
<td>PO (Glycolipo-depsipeptide)</td>
<td>Transglycosylation and Lipid II</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Oritavancin (LY333328; InterMune/Lilly)</td>
<td>IV (Glycopeptide)</td>
<td>Cell wall</td>
<td>Phase III</td>
</tr>
<tr>
<td>Rifalazil (Activbiotics)</td>
<td>IV/PO (4-Aminobenz-oxazine)</td>
<td>RNA polymerase</td>
<td>Phase II</td>
</tr>
<tr>
<td>BAL-5788 (Ceftibiprole) (JandJ/Basilea)</td>
<td>IV (Carbenem)</td>
<td>Cell wall</td>
<td>Phase III</td>
</tr>
<tr>
<td>MC-207110 (Essential Therapeutics/DAichi)</td>
<td>IV (Peptide)</td>
<td>Efflux pump inhibitor</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Dalbavancin (Vicuron/Aventis)</td>
<td>IV (Glycopeptide)</td>
<td>Cell wall</td>
<td>Phase II; NDA filed</td>
</tr>
<tr>
<td>TD-6424 (Theravance)</td>
<td>IV (Glycopeptide)</td>
<td>Cell wall</td>
<td>Phase III</td>
</tr>
<tr>
<td>PTK-0796 (Paratek)</td>
<td>(Tetracycline)</td>
<td>Protein synthesis</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

...
Can biotech deliver new antibiotics? Barrett 501

biotech R&D model on the premise of having a revenue stream in the near future (i.e. 7–10 years). But is this sustainable?

Case study number two is Oscient Pharmaceuticals (Waltham, MA). Formed in a merger of Genome Therapeutics Corp. (Waltham, MA) and GeneSoft Pharmaceuticals (San Francisco, CA), Oscient built an organization on the basis of a platform of a high-throughput DNA sequencing method. They evolved to become a drug discovery house, and subsequently to a development organization with the in-licensing of both ramoplanin (Aventis) and gemifloxacin (Factive®) that Oscient acquired by the merger with GeneSoft Pharmaceuticals (which had previously acquired an out-licensed quinolone [gemifloxacin] from GlaxoSmithKline).

The third case study is Microcide Pharmaceuticals (Mountain View, CA). Formed in the early 1990s on the platform of designing, optimizing and developing a novel cephalosporin with anti-methicillin-resistant Staphylococcus aureus activity, Microcide came close to the generation of an antibiotic, with at least two candidates reaching Phase I in partnership with Ortho-McNeil (Raritan, NJ) and the advancement of a novel class of a non-antibiotic called efflux inhibitors that were designed to potentiate antibacterials subject to drug efflux (in partnership with Daiichi Pharmaceuticals; Daiichi, Japan). However, the technical difficulties of both molecules led to the merger (of Microcide Pharmaceuticals and Altheisis Pharmaceuticals to become Essential Therapeutics) followed by consolidation and then discontinuance of operations in 2003.

The final case study to be discussed is Paratek Pharmaceuticals — a small biotech organization in Boston, MA, which hopes to be the first to break through the development ‘glass ceiling’ with an internal candidate going into development and onto the market. Based on Stuart Levy’s 30 year study of bacterial resistance [16], Paratek has built a discovery platform based on a novel tetracycline backbone designed to resist efflux, which was the major resistance determinant of the classical tetracycline molecules that led to their discontinuation. Similar to the Wyeth approach for a novel tetracycline (i.e. Tigacil®), but as a distinctly different and proprietary molecule, Paratek initially partnered with GlaxoSmithKline and subsequently with Bayer — both of these pharmaceutical companies pulled support for antibacterial R&D and discontinued their collaboration with Paratek. This leaves Paratek seeking a new large pharmaceutical partner as it moves forward with their Phase I clinical studies with their candidate PTK 0796 (www.paratek.com).

All four organizations discussed have several features in common: a solid and well-defined work-plan; excellent scientific leadership; a unique platform for an ascertainment product; well-funded seed money at the company launch; and limited income. All four also have or had an almost unreachable goal of taking an internal candidate to market. At least two dozen less visible and commercially unsuccessful case studies could be documented here, but the point of all is the same — no truly successful model has been developed to compensate for the decrease in big pharma’s support for antibacterial R&D in biotech to date. Something needs to change as biotech can’t fund the necessary clinical trials and remain intact as a drug discovery incubator by itself.

**Biotech becomes a business (just like big pharma)**

A major problem in the existing biotech model is the high capital outlay that is necessary for a company to mount large clinical trials. This is frequently more than $150–200 million, and as such most biotech companies can’t support the costs of these clinical trials. One needs to merely look at the pipeline of drug candidates on the horizon (Table 2) to recognize the potential for success in the biotech arena. None have successfully exploited the novel target approaches that have been attempted by the larger pharmaceutical companies since the onset of ‘genomics’ technology in the mid- to late-1990s, and only two biotech companies have had drugs advanced to the market.

As a business group, the pharmaceutical industry has failed in several aspects of the R&D of antibacterials [4]. The industry has failed to renew the clinical arsenal with novel, high-quality, efficacious, safe ‘products’ since the early 1980s. We have failed at several tactical processes (i.e. hits-to-leads and lead optimization); we have erred in strategically choosing synthetics over natural products as the source for most new leads; and we have been seduced by the lure of genomics, and wasted many years chasing sub-optimal leads against ill-defined targets because they were ‘novel’. Lastly, we have under-estimated the hardiness of serious pathogens to survive and to adapt resistance mechanisms against our best antibacterials, while continuing to exposure normal flora and opportunistic pathogens to existing drug classes resulting in underlying resistance in the emerging pathogens [4]. The ‘we’ used here refers to both large pharmaceutical companies and biotech pharmaceutical companies.

As antibacterial R&D efforts have shifted away from many large pharmaceutical companies to a big contingent of biotech companies, the entrepreneur approach to discovery in the biotechnology arena has led to an explosion of creativity in strategies, selection of targets, genomics, molecular techniques, proteomics and other enabling technologies. Baselia, Oscient, Peninsula and Vicuron are four of the more visible biotech–large pharmaceutical partnership deals underway in the industry; these deals range from licensing back the drug rights to whole com-
pany acquisition. More alliances will follow (see partial listing in Table 2), which will result in a crippled biotech industry with fewer players.

A survey of the most visible R&D efforts by biotech (Table 2) shows that there is an impressive collection of antibiotics in development. It is aimed that these compounds (nearly two dozen) will be launched within the next 6–7 years (Figure 1), and that truly novel genomics targets will follow in the next decade. However, the fall-out rate for drugs in development predicts that no more than 2–4 of these candidates will reach the marketplace, and none are predicted to be blockbusters. But these do suggest that biotech can deliver such products, regardless of the R&D paradigm, and it is this anticipated success that will drive continued investment. In short, biotech can deliver antibiotics, but it must be in collaboration with big pharma to support the downstream clinical trials.

Conclusions
Whereas the emphasis of multiple large pharmaceutical companies has shifted away from antibacterial R&D, the continuing hope for relief of emerging drug resistance in the clinic is in the biotech pipeline. Unfortunately, in the pool of bacterial pathogens that make up the majority of infections there are numerous resistance emergence issues for each therapy setting that involves multiple pathogens. It is clear that something must be done to expand the option for treatment of bacterial infections in light of the increased resistance that is emerging. Although the emerging biotech pipeline will provide some novelty in niche markets, these successes could also spur larger pharmaceutical companies to reinvest in antibiotic R&D as increased antibiotic resistance is recognized as a major medical concern and the commercial paradigm changes to entice increased industrial support.

Although some of the products in the biotech pipeline that will soon be approved represent breakthrough therapy (Figure 1), their niche market nature of treatment options could limit their wider use, which is anticipated to be required to combat widespread resistance emergence. Broad-spectrum, well-tolerated agents will continue to be the focus of the large pharmaceutical companies, but partnerships with biotech will fill big pharma’s pipeline gaps until larger pharmaceutical companies reinvest in their internal antibiotic R&D, which is inevitable with the surge of resistance emergence.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


An excellent overview of the role of resistance emergence in driving the medical need for new, novel antibiotics.
   A well-written synopsis that reviews the molecular and epidemiological levels of the science of resistance emergence.


A thorough review of the science and application of natural products in drug discovery.

