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Can biotech deliver new antibiotics?

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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?'.

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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 heath 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 ([6•]; 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 daptomycin). In 2002, no new antibacterials were approved by the FDA, and in 2003 just two antibacterials were approved ([6•]; 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 $27 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://igweb.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.

Drug name (designation; company name)	Delivery route (class)	Target	Status
Garenoxacin (BMS-284756; Schering-Plough/Toyoma)	IV/PO (Quinolone)	DNA gyrase and topo IV	Phase III
CS-023 (Ro-4908463; Sankyo/Roche)	IV (Carbapenem)	Call wall	Phase II
Tigecycline (GAR936; Wyeth)	IV (Tetracycline; glycylcycline)	Protein synthesis	Phase III/NDA filed

IV, intravenous; NDA, new drug application; PO, oral.