EMBO reports

analysis

The big and small of drug discovery

Biotech versus pharma: advantages and drawbacks in drug development

In 1999, a small biotech company called Magainin Pharmaceuticals suffered a near-fatal blow when its greatest hope, a small antibacterial peptide for the treatment of diabetic foot ulcers, failed to obtain approval by the US Food and Drug Administration (FDA). The agency rejected the compound, first discovered in the skin of the African clawed frog *Xenopus laevis*, not on the grounds that it was unsafe or inefficient, but solely because it was no more effective than other antibiotics used to treat ulcers. For Michael Zasloff, discoverer of the peptide, and the then president of Magainin Pharmaceuticals, it was the end of an adventure into the ruthless world of biological entrepreneurship; he left the company and returned to an academic position at the University of Georgetown in Washington DC, USA. Speaking from his office as Dean for Research and Translational Science, he remarked "I still have a hole in my chest, and a great deal of sadness about what happened."

This is understandable to any scientist who has made a significant discovery that has fallen on deaf ears. Zasloff's finding, a classic case of curiosity-driven research producing an exploitable result, goes back to his time carrying out basic research at the US National Institutes of Health (NIH), where he worked with *Xenopus* oocytes. Noting that the frogs from which he gathered the oocytes did not develop infections despite being operated on with techniques that cause sepsis, Zasloff suspected that they produced a type of antibiotic. In 1987 he identified the substance, a short positively charged peptide with hydrophobic residues, and named it 'magainin' from the Hebrew word for 'shield'. Magainins, he theorized, worked by binding to the negatively charged membranes of bacterial cells, where they assembled to form transmembrane pores that 'bleed' the bacterium

to death. Zasloff left the NIH, taking the magainins with him and founding the eponymous company to develop them into drug candidates. The final recombinant protein, produced in massive fermenters at Glaxo, now GlaxoSmithKline (Brentford, UK), had "a dream profile with respect to resistance and spectrum" and seemed a dead-ringer for success. Pexiganan, or Locilex™, as the therapeutic cream was named, was specific for bacterial membranes (mammalian membranes do not carry an external negative charge), attacked a large spectrum of bacteria, and bacteria would not easily develop resistance to it because it does not bind to a discrete and mutable bacterial target.

"There's a lot in the biotech environment that hasn't hit the test of reality."

However, the drug's greatest enemy turned out not to be bacteria, but the FDA, which refused approval on grounds of insufficient evidence of efficacy, despite an impressive performance in phase II trials—at which stage only 40% of drugs are approved, and most fail due to low efficacy. This confounded Zasloff, who refers to the verdict as "a total miscarriage of the approval process." The FDA requested a placebo-controlled trial to establish a base-line for efficacy, an intrinsically unethical approach that Magainin Pharmaceuticals was reluctant to consider. Although it may have been more ethical to perform such a trial on less severely affected patients, the difference between treatment and placebo would have been much smaller, hence compromising the study. However, these considerations were purely academic once the news reached Wall Street. The fledgling company's stock was plummeting like a dead duck.

This story is all the sadder because the few new drugs in the fight against antibiotic resistance in bacteria that have been approved by the FDA in recent years are merely variations on old themes. Such disrespect for the cunning of microbes mortifies biologists and public health officials alike. Pexiganan, however, would have been the first truly novel concept to reach the market (Table 1), but obviously the market—and the FDA—was not yet ready for it. With the wisdom and bitterness of hindsight, the Georgetown researcher admits that "there's a lot in the biotech environment that hasn't hit the test of reality." The reality is that the multi-drug-resistant superbug epidemic has not yet hit, and as Zasloff concedes, there are still enough traditional antibiotics that can be tweaked to meet the growing resistance problem. These also have the advantage over newcomers of ease of development and extensive knowledge of their toxicology. "I suspect that when resistance becomes a real problem, there will be no issue", he added.

Table 1 | Antimicrobial peptides in clinical development

Peptide	Company	Application	Development stage
Pexiganan	Magainin (Genaera; Plymouth Meeting, PA, USA)	Infected diabetic foot ulcers	Not approved after phase III completed
MBI-226	Micrologix (Vancouver, Canada)	Catheter infection	Phase III
MBI-594	Micrologix (Vancouver, Canada)	Acne	Phase II
Protegrin analogue	Intrabiotics (Mountain View, USA)	Mucositis	Phase III
Histatin analogue	Demegen (Pittsburgh, PA, USA)	Gingivitis	Phase II
Heliomycin	Entomed (Illkirch, France)	Antifungal	Preclinical
Human lactoferricin	AM Pharma (Bunnik, The Netherlands)	Antibacterial	Preclinical
BPI (bactericidal permeability increasing protein)	Xoma (Berkeley, CA, USA)	Meningococcal meningitis	Phase III

Source: Zasloff, M. (2002) Antimicrobial peptides of multicellular organisms. *Nature*, **415**, 389–395.

It is difficult to apportion the blame to any party in this saga as many aspects are typical of the interplay between a small biotech company, large pharmaceuticals companies and the regulatory agencies. Clearly, the FDA has an important role, and is becoming increasingly strict in judging the apparent efficacy of new drugs compared with their undesirable side-effects. Instead of increasing, the rate of FDA approvals per year is dropping, whereas EU (European Union) approvals are on the rise (Fig. 1). Many people question whether some of the most widely used drugs would now pass the FDA's increasingly discerning requirements; aspirin, for one, would struggle. But efficacy and tolerability, the main prerequisites of any drug (Fig. 2), are merely two of a series of obstacles to be negotiated by new drug candidates, of which 90% fail between identification and being put on the market.

Another common reason for a new drug to fail is the lack of a comprehensive knowledge of the patients and the market. This might have been a factor for pexiganan, because diabetics' foot ulcers can vary considerably in their propensity to heal without antibiotic intervention. Large pharma would go a step further, and argue that their big advantage over small biotech is their unparalleled knowledge of the drug development process from start to finish, as Christine Debouck, Senior Vice President of Worldwide Genomic & Proteomic Science at GlaxoSmithKline, explained. This, she argued, makes them better able to make the right decisions early in the research phase. Indeed, large pharma companies know well that a drug's value cannot be predicted in the laboratory, and is not related to its novelty. Add to that their sheer size, which allows them to survive the disappointments of the approval process, and you have a winner. Nevertheless, as the history of new drugs in the last decade shows, large companies are often not the ones to have the best ideas in the first place.

According to Shereen El Feki, healthcare correspondent at *The Economist*, the bulk of successful drugs produced by certain pharma giants in the past few years come not from their own research, but from collaborations or licensing agreements with small companies (Table 2). "SMEs (small and medium-sized enterprises) are able to strike much better deals with large pharma, because large pharma needs their wares", she commented. Indeed, in this respect there has been a sea-change since the mid- 1990s, when small firms tried to sell off shaky ideas fresh from the lab. Not surprisingly, most failed in the clinic. In the late 1990s, however, the promise of the human genome allowed many start-ups to raise large sums of money, helping them to fund their own phase II clinical trials, which put a considerably higher value on the drugs that survived. The ensuing success of biotech companies and a slow late-stage pipeline in some large pharma companies have conspired to make the wares of SMEs even more attractive.

Two major deals in the past few months alone demonstrate this phenomenon. GlaxoSmithKline has partnered up with Exelixis (San Francisco, CA, USA), a genomics-based drug-discovery firm, to develop small molecules for vascular biology, inflammatory disease and oncology. The deal gives Exelixis US $30 million upfront, and a further US $90 million over the next six years. In the same vein, Roche (Basel, Switzerland) recently announced a deal with Antisoma, a small UK company in London that specializes in the development of anti-cancer drugs. The "broad strategic alliance, which grants Roche exclusive worldwide rights to the Antisoma pipeline of oncology

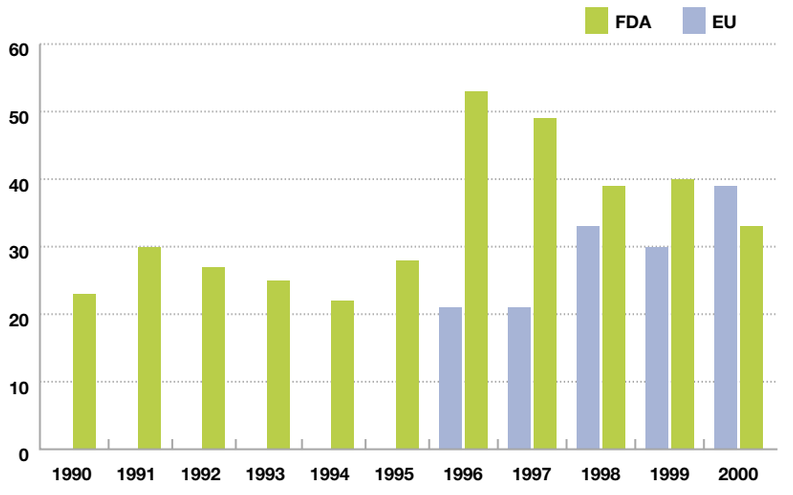

Fig. 1 | US Food and Drug Administration (FDA) and EU (European Union) approvals of new drugs per year. Sources: www.emea.eu.int and www.phrma.org

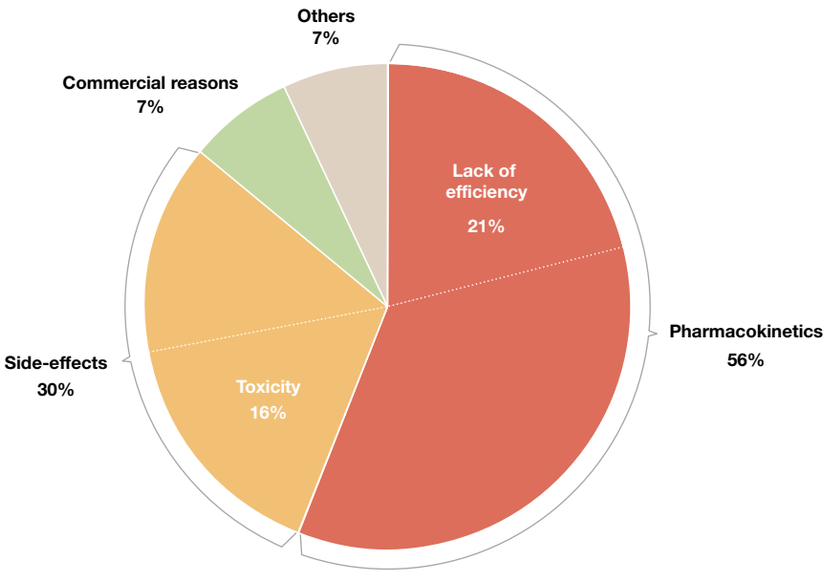

Fig. 2 | Major stumbling blocks for new drugs (industry averages during 1996–2000)

products", according to Antisoma's press release, is initially worth US $6.6 million.

Part of the insatiable desire of large pharma for juicy morsels from the SME table is a direct result of investors' insistence on returns of more than 10% per annum, an increasingly hard task for a large company. "The bigger you are, the more molecules you need to produce," noted El Feki; and so it goes on, *ad infinitum*. And for some, it seems that infinity is the limit. Merger after merger, fuelled by Wall Street expectations, have led to ever-larger giants, an unwise situation in El Feki's opinion. "Mergers were always praised," she remarked, "but it may be that investors need to be re-educated." Indeed, big may not always be beautiful in the pharmaceutical market of the future. After recession, investor fickleness, and reality tests have been overcome, there will still be a broad diversity of small healthy companies, many of them concentrating on niche markets. These companies, not interested in the lure of 'blockbuster' products, may then be the best positioned to capitalize on developments in pharmacogenomics and personalized medicine.

In the meantime, however, the brutal reality is that many small companies are facing closure or cutting large sectors of their workforce. Most can blame the backlash of market over-estimation by investors who had little knowledge of scientific realities. The hype surrounding the human genome, for instance, completely neglected the fact that a new disease gene does not automatically mean a new drug target. This is especially true in the case of small-molecule drugs, which have always been the favourites of large pharma because the combinatorial chemistry and screening are amenable to the heavyweight high-throughput technologies that, until now, only large companies could afford. But small molecules usually bind to pockets in other molecules—mainly enzymes, a handful of ion channels and receptors—and as Jonathan Knowles, head of global pharmaceutical research at Roche, pointed out, "it's not about how many genes there are, but how many pockets there are in biology." It is also about choosing the right target, which, as large pharma also knows, is extremely important in determining the chances of success for a new drug.

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Small companies at the academic interface may therefore win more often in the large-molecule 'biologicals' sector of the market, according to Knowles, where they can make fast progress with their in-depth knowledge of pathology and human biology and by collaborating with clinicians. But it is equally true that the increasing affordability of molecular biology and screening technologies has considerably narrowed the gap between the type of research done in large and small companies. Hence, drug research and development will in future be an increasingly mixed industry, less constrained by the advantages of size that hitherto favoured large pharma. And as recent history shows, there is clearly no single recipe for success, rather many profitable niches. The only prerequisite is good science.

The development of good science into good drugs is an area in which US companies, with skilful support from their government, clearly excel. Ever since the Bayh-Dole Act of 1980 allowed US academics to capitalize on their discoveries, the country's biomedical sector as a whole has flourished. The European biotech industry will need political support if it is to achieve the same highly productive interconnectivity between large companies and academic research that exists in the USA. Consequently, the European Commission (EC) has focused more attention in its 6th Framework Programme on supporting the development of novel drugs. As Alfredo Agilar, head of the Unit for Biotechnology and Applied Genomics of the EC's Directorate-General for Research in Brussels, Belgium, explained, FP6 contains a €2.3 billion funding component over four years that is almost completely geared to health. Moreover, the EC has signalled its realization of the potential value of SMEs by setting aside 15% of this budget for them. "We see it not as a subsidy, but rather as

Table 2 | Where do new drugs come from? Number of phase I–III drugs from biotech versus large pharma (USA, 2000)

Phases	I	I/II	II	II/III	III	Approved	Total
Biotech	115	43	138	10	92	49	447
Large pharma	8	1	13	0	10	27	59
Total	123	44	151	10	112	76	506

Source: 2002 survey 'Medicines in Development–Biotechnology', Pharmaceutical Research and Manufacturers of America (PhRMA); www.phrma.org/newmedicines/surveys.

investment in research," Agilar said. Furthermore, if companies reach the stage of phase I and II clinical trials, the EC will support the generation of 'demonstrative results' to the tune of 35% of the cost of the trials. With help from the EC, Agilar says, the "situation for SMEs is improving dramatically." And it certainly has to if European biotech is to catch up with its counterpart in the USA.

And what of magainin? Not surprisingly, the company has changed its name to Genaera (Plymouth Meeting, USA), but it may be that 'antimicrobial peptides', now precariously near the bottom of Genaera's product list, will be reborn. On 20 November 2002, the company announced an option agreement for "certain antimicrobial peptide intellectual property held by Genaera" with E.I. du Pont de Nemours (Wilmington, USA). Although du Pont sold its pharmaceuticals division to Bristol–Myers Squibb (New York, USA) over a year ago, it still has a sizeable biotechnology interest in agriculture. Whether this will mean the reincarnation of magainins in agriculture is not clear, and Genaera refused to comment on the deal.

…big may not always be beautiful in the pharmaceutical market of the future.

In the meantime, Michael Zasloff is already at the next conceptual stage in the exploitation of antimicrobial peptides. For him, it would merely be logical to see magainins make it to the dispensing chemist; his mind is already busy with the next step. "I think there will be a time when we can stimulate expression of endogenous peptides", he commented. "This is a wonderful area for drug development; we may cure all diseases that are constitutional, but we will always have bugs around us." Although it seems that Zasloff is the victim of powers beyond his control, he may rest assured that one day, when bacterial resistance becomes a larger problem, his magainins will be rediscovered by someone else. As Thomas Edison put it "A good idea is never lost […] Accordingly, my principal business is giving commercial value to the brilliant but misdirected ideas of others."

Andrew Moore

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Government rhetoric and their R&D expenditure

A score-card for governments' investments into science and future technologies

If you want to harvest in the autumn, you need to sow in spring. This ancient wisdom holds true not only for agriculture, but for all economic activities. When nations turned their focus from agriculture to industry, the definition of 'sowing' and 'harvesting' changed. The latter is relatively easy to identify: it is the nation's wealth in terms of economic growth, employment level, *per capita* income, exports, and so on. Such achievements point the way not only to re-election of the politicians who ensure a rich harvest, but also to the well-being of all its citizens.

Slightly harder to define is the 'sowing' part—the public and private investments that guarantee economic growth and high employment in the long term. After the industrial revolution took place, governments needed simply to ensure that the social, political and financial structures were in place to encourage entrepreneurs to start businesses and create new jobs in the emerging industrial sector. Now, at a time of globalization, international corporations move to where they can find the best opportunities in terms of employee salaries and governmental incentives. It follows that robust manufacturing processes are being transferred from their traditional locations in the developed world to areas that offer the best financial projections and the lowest cost structures. As a result, the so-called advanced economies have to find new ways to maintain their privileged status. The common solution is to focus on new discoveries that bring with them ownership of commercially valuable intellectual property and require a phase of development and manufacturing in a highly skilled environment. Thus, the seeds that need to be sown are now investments, from both industry and

Table 1 | Gross domestic product (GDP) and gross domestic expenditure on R&D (GERD) by Japan, the USA and the EU countries

Country	GDP (billion US$)[1]	GERD as % of GDP[2]	GERD estimates (billion US$)
Austria	220	1.89	4.1
Belgium	267.7	1.97	5.2
Denmark	149.8	2.07	3.1
Finland	133.5	3.67	4.9
France	1,510	2.13	32.1
Germany	2,174	2.52	54.8
Greece	189.7	0.67	1.3
Ireland	104.7	1.21	1.3
Italy	1,402	1.04	14.5
Netherlands	413	2.02	8.3
Portugal	174.1	0.76	1.3
Spain	757	0.97	7.3
Sweden	219	3.78	8.3
UK	1,470	1.86	27.3
EU	9,184	1.90	174.0
USA	10,082	2.70	272.2
Japan	3,450	2.98	102.8

[1]Data estimated for 2001. Source: the CIA World Factbook; www.cia.gov/cia/publications/factbook/index.html
[2]Source: Communication from the European Commission (2002) "More Research for Europe – Towards 3% of GDP" COM 499.