antisera raised against a recombinant protein show no reaction to laboratory-grown bacteria even though it might actually be a great vaccine candidate if tested in an animal model. To address some of these concerns, other complementary techniques, such as transcription profiling and proteomics, are being employed. Using transcription profiling, Grifantini *et al.* were able to identify *N. meningitidis* ORFs that were expressed only during adherence to human epithelial cells and further study of these ORFs identified potential vaccine targets, some of which were not predicted by genomic mining algorithms [5]. Several extracellular proteins have also been detected by proteomic approaches that, again, were not predicted by *in silico* mining to be surface-exposed or secreted and, hence, might be potential vaccine targets [6].

Genomics and the application of reverse vaccinology have changed the way vaccine discovery research is conducted today. The early-phase timeline to identify vaccine targets has been dramatically reduced but, consequently, many more targets must now be tested. Therefore, rate-limitation in preclinical vaccine discovery research now lies in the immunological screening and animal model testing processes. Although it is too early to be certain, it is probable that a vaccine discovered by genomic methods will make it into the market in the future. Only time will tell.

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Biotechnology discovery productivity: a note of caution

In a recent issue of *Drug Discovery Today* [1], Jurgen Drews makes a case for the future productivity of drug discovery to fall increasingly to the star performers of the biotechnology sector. Drews is a well-known commentator on the strategy of pharmaceutical R&D, and is justified in his focus on the importance of drug discovery output. But while the leading companies have succeeded laudably, the record of the biotechnology sector as a whole is patchy.

First, what is the 'biotechnology' sector? The term arose from the early focus of the first generation 'alternative' pharmaceutical companies on biologically produced therapeutics, rather than chemically manufactured ones. Current trends indicate that the proportion of new products of this kind is increasing (albeit slowly and inconsistently) each year. One of the attributed benefits of this kind of development is the lower attrition rate of biological research in comparison with medicinal chemical approaches. But pharmaceutical R&D on biologicals is not confined to what most people understand to be the 'biotechnology' sector (for example, drotrecogin alfa (Xigris™), a recombinant protein for sepsis from Lilly). Nor is this sector confined to R&D on biotechnological approaches to new drugs. Drews, in his comment that the 'first tier of biotechnology companies is likely to become the most effective segment of the drug industry', comments on a set of now large companies that were established to challenge the status quo. Many such companies, such as Biogen, have a mixed portfolio of developments, some biological and some small molecules. In a sense, Drews' focus on large biotechnology selects for the brightest and the best, whereas, the significant bulk of the biotechnology sector is composed of small innovative pharmaceutical R&D companies, with a mixed set of aims and strategies.

This leads to the second point, concerning whether or not small companies really have been more successful in R&D, and/or are more likely to be so in the future. Here, the evidence is mixed at best. While 'Pharmaprojects' records that the number of compounds in early phases of drug development has increased over the past seven years [2], this increase is concentrated only in Phases I and II. Over a similar period, there has been a tremendous increase in the number of biotechnology sector companies and their R&D expenditure. To date, there has not been a commensurate increase in Phase III investigational compounds. Indeed, evidence from the Centre for Medicines Research suggests that there has been a 71% increase in the time taken in Phase II between 1997 and 2001 (Society for Medicines Research Symposium: Is there a best strategy for drug discovery? 13 March 2003; http://www.prous.com/drugdiscovery). The success rate for compounds in Phases I, II and III have declined over the same period. A more detailed analysis of the time taken for various phases of development by the different sizes of company shows a

concerning trend: small companies take significantly longer to progress through Phase II than large companies. This might be a reflection of the greater drive by entrepreneurial companies to advance compounds into and through the early stages of development, at the cost of creating problems to be solved later. Alternatively, it might reflect the hiatus in biotechnology company developments while collaborative or licensing arrangements are negotiated. Although it is often reported that small companies are able to make decisions faster, owing to reduced bureaucratic encumbrance, these figures tend to dispute the universality of this presumption. Rather than speed, a better foundation for success lies in the quality of decision-making in R&D. With regard to the question of whether or not biotechnology companies are any better than their large company cousins in this regard, it is surely too early to say.

Third, a fundamental point of Drews', concerning large company failure, is that R&D decisions are often marketing-led. This is undoubtedly an increasing trend within the industry. Again, the CMR reports that 23% of projects are abandoned for 'portfolio' reasons. There is heightened concern, however, because, historically, ~70% of products that do reach the market do not recoup their R&D investment [3]. But commercial R&D forecasting is fraught with dangers. Famously, cimetidine was forecast to sell no more than US$60 million annual peak sales. Estimates for Viagra™ were similarly erroneous and there will doubtless be plenty of others that were wrongly abandoned. Marketing departments cannot make reliable predictions on undeveloped markets (and even with developed markets, the results are far from flawless); but it is those same markets that need to be developed if the industry is not to stagnate. Drews has a valid point; without the conviction based on scientific rectitude to advance into uncharted areas in the face of conventional commercial wisdom, medicine will advance little, and the future for the pharmaceutical industry is lacklustre.

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