nuclear localization. Combinations of targeting ligands, polyethylene glycol, and compacting lipids with plasmid DNA could present considerable manufacturing challenges, including characterization and reproducibility. In other words, systems that are effective at a laboratory scale are not necessarily practical at a production or commercial scale.

One other lesson from immunology might be worth noting when considering the commercial prospects for gene delivery. In 1975, Georges Kohler and Cesar Milstein devised a strategy for the production of monoclonal antibodies. The enthusiastic rush to clinic was stalled by barriers of immunogenicity – the mouse sequences in the first generation of monoclonal antibodies induced a neutralizing immune response. Therapeutic applications had to wait for the development of new techniques of humanization, deimmunization and immunoglobulin-transgenic mice. With one exception, the first monoclonal antibodies were approved nearly 25 years after the initial scientific breakthrough.

Currently, immune barriers to DNA delivery vectors have limited the application of gene therapies. Perhaps the development pathway of gene therapy will parallel the development of monoclonal antibodies, with a renaissance of clinical applications following new solutions to the barriers of immunogenicity. In the meantime, there might be opportunities to harness the immunostimulatory properties of lipid–DNA formulations to develop novel cancer therapies if applied with caution.

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The importance of predictive ADME simulation ▼

In their article on computational modelling and prediction of ADME properties that recently appeared in *Drug Discovery Today* [1], Beresford *et al*. compared the design of aircraft with the design of new drugs. However, the simulation process for new aircraft is far more advanced than that of drug design – we still have to synthesize a large number of drugs and investigate their ADME properties before identifying a marketable drug. We do not have sufficient confidence in current *in silico* models to back our predictions against experimental measurements. Fortunately, the authors of the ADME simulation article all come from an experimental background, and so they recognize the limitations of the *in silico* methodology.

In silico systems are most useful in library design (before compounds are synthesized) to filter out compounds with clear-cut undesirable properties. At this stage the accuracy of the models (currently ~80%) is sufficient to provide a cut-off for lead molecules to pass through the computational screens. In a few cases before the project starts (i.e. before compound synthesis), undesirable properties based on physicochemical characteristics [2] could become apparent using these *in silico* methods. In these cases, project teams could prioritize their approaches to check these undesirable ADME properties.

However, for molecules that have already been synthesized, the chemists like to see some effort expended in the laboratory rather than rely totally on these *in silico* predictions. This usually entails some *in vitro* experimentation using human material (e.g. for inhibition of cytochrome P450s) or animal models (e.g for absorption, clearance, bioavailability, and so on). The *in silico* simulations can be useful in prioritizing this *in vivo* work using a funnel approach to reduce the numbers of compounds, as described in Figure 5 of Beresford *et al*. [1]. The chemists would usually prefer to use an *in silico* approach after *in vitro* data has been generated, so that they gain confidence in the predictions on the specific series of their interest. However, if there is an ADME issue based on experimental data, then the chemists are quite happy to use these *in silico* approaches as guidance for lead optimization.

In silico models for all aspects governing ADME are needed [3], for example, the concerted efforts of CYP3A4 and P-glycoprotein (P-gp) need to be addressed as a primary barrier to absorption in the gut, and P-gp plays an important role in protecting the brain. Computational models might have an important role to play in terms of generating binding affinity data, but it should be recognized that most approaches fail to predict activity within a single order of magnitude.

It should also be acknowledged that *in silico* technology has only been in existence for a relatively short time and

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hence it is not realistic to expect good predictions in every case. Such forecasts are mostly better within a chemical series, and predictions tend to fail when comparing across several chemical templates. Although *in vitro* technology has had a much longer life-span, this still cannot provide all the answers and often fails to predict *in vivo* observations. It is important that *in vitro* and *in vivo* data are constantly fed back into the *in silico* models , which can be helpful for their improvement. Thus, it is still early days for *in silico* technology, but there is no doubt that it will continue to play a key role in drug discovery and development. We look forward to a day when drugs can be designed on a computer in the way aircraft are today!

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Aggressive outsourcing yields therapeutic breadth

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The business stream of IBC's *Drug Discovery Technology Europe* conference (16–18 April 2002, Stuttgart, Germany) covered a wide range of issues, from the strategic management of drug discovery through to partnering and outsourcing, and was supplemented by a session on licensing.

Of lasting concern here was the observation made by many speakers that despite the cost and effort involved in introducing new technologies over the past few years, there has been no apparent impact on the number of new chemical entities (NCEs) entering the market. Some speakers ascribed this problem to a lag phase between the implementation of technology and the effects of its use. Others argued that the whole process does not seem to have been shortened as many more targets need work-up and validation, and that there is an inherently increased risk of failure in development with less validated targets. Efforts are being made to improve the backlog of targets by partnering and outsourcing, and it is hoped that organizational improvements will aid this process.

Failing R&D

There is also an interesting split developing in the management philosophies being employed to tackle the apparently failing output from R&D (diminishing returns). In a keynote address John McKearn (Pharmacia Discovery Research, Peapack, NJ, USA) argued for the need to consolidate research into a few therapeutic areas and to pay attention to the organization. During mergers the focus is always on the development pipeline, but over 50% of mergers fail to achieve their promise in this respect and the future lies in discovery research. Pharmacia was formerly faced with a relatively complex situation with some anomalies of focus. For example, at the time of their merger Pharmacia and Upjohn had dropped inflammatory research and invested in anti-infective research, whereas Searle did the opposite. In the new merged company both areas have prominence, thus concentrating expertise in research alongside marketing and leading to their interests in metabolic disorders being directed into a new company, Biovitrum, in order to maximize value.

McKearn admitted to a personal disappointment at losing a good research group and thus to a lower headcount in research, but also felt satisfaction in the production of a company with a good pipeline and prospects. This was underlined later in the conference when, in a talk on outsourcing, Johan Kördel (Biovitrum, Stockholm, Sweden) disclosed

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