there are clearly incorporating ADME learning. Based on this superficial (and I am sure flawed) analysis, ~50% of the world's medicinal chemistry is employed making 'non-drugs' deliberately. Therefore, it would seem that, following our superficial analysis, with a willingness to change our synthetic ways we could double the pharmaceutical industry's productivity. This is even more compelling when it is known that the ADME faults are obvious to the (jaundiced?) eye (e.g. molecular weight, excess H-bonding, toxicophores, metabolically labile functionality, and so on). It doesn't need the vision, drive and determination of Beresford *et al.* to make the proposal that a computer could do even better or have more impact on the world's medicinal chemists than one (jaundiced) eye's view. Where a diversion in direction could occur in future between the authors' view and my own view is that drug discovery in its final stages looks for the exceptions to the rules, rather than the compounds that comply. Building models and algorithms that are based on a large number of compounds invariably produces an 'average' prediction. The combination of new properties in an unexpected or super-additive way, or the unexpected quirk (magic methyl phenomena), will be present in drug discovery programmes probably forever: I do not foresee computational methods being fully capable of these steps. The magic methyl is a single addition that disrupts a crystal lattice, breaks a hydration sphere, modulates metabolism, enhances chemical stability and displaces a water molecule in a binding site. The compound series is now more water soluble, absorbable, metabolically and chemically stable and potent than its companions that lie on the eternal straight line of more lipophilicity, more potency, less solubility, more rapid metabolism. Nothing in science can replace the excitement of seeing the non-linear incremental improvement in all the drug property data after weeks of toil. The synthetic choices that lead to these molecules are likely to still follow traditional patterns of insight, hunch and, dare one say it in the earshot of Beresford *et al.*, luck.

Luck actually seems a good way to summarize. Using the analogy of luck and gambling, the technology outlined by Beresford *et al.* and other forms of it – even now being piloted in the dark conservative silos of the pharmaceutical industry – will guide the discovery gambler to the right game (target do-ability in terms of chemistry space and interactions) and possibly the right table in the casino (potent and selective lead chemical series). The choice of which specific hands of cards or numbers (final candidate selection) to back once in the game will probably still reside with the discovery scientist for the foreseeable future. As parallel synthetic methods begin to impact increasingly on the early medicinal chemistry stages of discovery programmes, more guidance is needed. Modern developments in chemistry could lead to a bright future for drug discovery: being able to rapidly advance programmes to patent selective drug-like molecules by shear well-directed chemistry fire-power. Remove the ADME guidance and revert to the analysis of frequency of ADME faults, referred to previously in the analysis of medicinal chemistry journals, and the industry has the power to swamp its compound libraries with non-drug like molecules, becoming perhaps future museums of automated futility.

Reference

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The use of imaging to accelerate drug development

A large number of lead compounds are emerging through the use of new technologies such as genomics, proteomics, *in silico* screening and combinatorial chemistry. It is expected that the new paradigm of drug development – 'gene-to-target-to-drug' – will continue to produce more leads for specific diseases. A rather sobering observation is that, despite improved drug discovery technologies, only modest progress has been made in the number of drug approvals or new chemical entities since 1996 (http://www.fda.gov/cber/products.htm). What are we doing wrong? The missing link could be the lack of a parallel improvement in the efficiency of lead optimization methodologies, in particular animal testing.

In a recent issue of *Drug Discovery Today*, Patricia Contag describes how transgenic animals and molecular imaging technologies can be used to optimize new leads early in drug development [1]. This review is timely, in view of the increasing interest by both the pharmaceutical industry and academia to provide proof of mechanism-of-action for investigational new drugs early in drug development, to avoid the high costs of drug failure. The imaging methods proposed by Contag could be used to define the magnitude of target expression, to study drug pharmacokinetics and kinetics of receptor occupancy, and to evaluate target modulation, safety and efficacy of promising leads. The lead optimization paradigm will involve:

- Appropriate selection of *in vivo* disease model. The availability of transgenic animals that express particular human genes or have specific genes 'knocked-out' or 'knocked-down' should enable drug developers to select appropriate

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models for proof-of-principle studies.
- Phenotype analysis. Whole-animal cellular and molecular imaging methods can be used to assess the phenotype (structural and functional) of various tissues and organs in the selected animal models.
- Drug pharmacology. The same imaging methods can be used to investigate the pharmacology of promising leads. Pharmacokinetics, pharmacodynamic and pharmacogenomic studies can be performed at this stage.

Several imaging modalities are now available for conducting these phenotype analyses, some of which were reviewed by Contag. These include, but are not limited to, optical imaging, positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI) and spectroscopy (MRS), computed tomography (CT) and ultrasound imaging (US) [1–3]. These imaging technologies are finding application in several fields, including oncology, neuroscience and cardiology. For a given application, each technique has intrinsic potentials and limitations and, thus, selection of the appropriate technique is important. Overall, the use of imaging is likely to provide high quality phenotype, and in some cases genotype, information that are difficult to obtain otherwise. Of importance is the ability to use the same animal as its own control. This improves statistical quality and leads to a reduction in the number of experimental animals used in biomedical research. It is almost certain that small-animal cellular and molecular imaging will replace traditional lead optimization technologies in the future. For this to happen, acquisition and analysis interfaces need to be simplified and more efficient data storage (gigabytes), reconstruction and resolution recovery algorithms need to be developed. The challenge then, according to Contag, will be that such data generated from molecular imaging will define a 'value proposition' to the industry [1].

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High throughput in drug discovery

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Research and development costs in the pharma industry are steadily increasing, from ~US$20 billion in 1990 to ~US$50 billion in 2000; however, there is no corresponding increase in success rate. In the past two decades, the output remained constant, at 30–50 new chemical entities (NCEs) per year. To what extent can new drug discovery technologies improve this ratio? Where are the bottlenecks? How can organizations speed up and industrialize their R&D process? These questions were discussed at the recent IBC Life Sciences conference *Drug Discovery Technology Europe 2002. Where Science Meets Business*, 15–19 April 2002 in Stuttgart, Germany (www.drugdisc.com/europe).

The topics of the *Science Stream* section of the conference concentrated on better approaches for target discovery, prioritization and validation, and on dedicated methods for lead discovery and optimization. Introductory lectures presented overviews on current practices in big-pharma. Martin Mackay (Pfizer, Groton, CT, USA) discussed strategies to reduce costs, in this manner increasing productivity. Of importance are an integration of technologies, the 'industrialization' of the drug discovery process, a focus on chemistry, the investigation of target families, mining of dense arrays of data, information networks with data sharing and real time access to all data. Pfizer, as well as Novartis, heavily rely on research alliances (e.g. the Novartis–Vertex US$800 million research collaboration; ~30% of the Novartis research budget is spent in external collaborations). Target validation is a highly time-consuming process and Jutta Heim, from Novartis (Basel, Switzerland), emphasized the importance of a strict prioritization of many potential targets. In her company, the process of target validation runs parallel to the lead discovery, optimization and candidate selection process.

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