The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Rebecca Lawrence, News & Features Editor, *Drug Discovery Today*, e-mail: Rebecca.Lawrence@drugdiscoverytoday.com

'This is your captain speaking'

The enjoyable and thought-provoking article by Beresford *et al.* [1] ends with the somewhat unfair challenge that 'to seek the ultimate scenario one needs vision, drive and determination to overcome inherent conservatism, break silos and generally change the pharmaceutical industry'. By challenging the viewpoint portrayed, one is, by definition, lacking vision, drive and determination, and is content to live in a conservative silo. So, condemning myself to being at risk of being a visionless, un-driven, conservative silo dweller, I feel compelled to comment.

The first impression on reading the article is how revolutionary a certain then-Seattle-based (WA, USA) aeroplane manufacturer is, and why the pharmaceutical industry is unable to move beyond the concept of structure-based drug design (SBDD) to embrace *in silico* in all its forms. Structure-based drug design is the use of X-ray structural information of the protein target to design drugs, but should really be called structure-based ligand design because, as the authors point out, drug-like properties do not need to be considered in affinity seeking. The analogy chosen, that of an aeronautics company designing an aeroplane, is interesting but does not really mirror progress in the way explained. While computer systems have undoubtedly enabled more complex simulations and predictions to be made more rapidly, buildings, trains, boats and planes have been made in the 'prototype as finished article' fashion, many years (centuries) before the advent of the modern computer. It is a great shame that the starting point of many projects is not a biological target with the corresponding X-ray crystallography data. Here, technology still has gaps: that of readily obtaining crystals of membrane-bound membrane-spanning proteins for structural determination. Many of the most attractive and druggable targets are seven-transmembrane (7TM) receptors (particularly aminergic) and ion channels, which are integral to the membrane, thus rendering SBDD problematic. Although greatly advancing our knowledge and stimulating creative chemistry, SBDD is often not as predictive as we would like it to be.

A simple example is how to respond to a hydrogen-bonding pocket in the protein. Is binding of the ligand enhanced by incorporating corresponding H-bonding into the drug molecule, or should lipophilicity be incorporated to displace water? Both opposite approaches can be hugely rewarding or disappointing; both also give surprises, sometimes in causing the molecule to re-orientate in the active site–binding pocket, thus picking up a new set of interactions. The exploration of these types of results can really only proceed in a sequential, rather than parallel, process. Of course, it can be argued that all that is needed is more data, more modelling and more computational power. This argument invariably leads to *in silico* lagging behind screening. A state like this has arguably existed for many systems over the past decade. Is this because the industry has not warmly embraced the technology or that the technology seldom fulfils its promises? Perhaps, in reality, it takes time to find out how best to use the technology in a focused manner. Even our aeroplane manufacturer eventually only built a plane that was incrementally different from all the others.

So, if the 'blue riband' of *in silico* drug design still conjures up a maybe–maybe not response in drug discoverers, what price the computational future that Beresford *et al.* fly us towards?

In fact, the above should not undermine the central message of the authors – that drug disposition is vitally important. We know more about this from a structural and physicochemical viewpoint and we should be aiding drug discovery more, whether by simple face-to-face knowledge exchange or sophisticated computer models. Clearly, having chemistry operating within 'desirable property space', and being able to test chemistry plans in a virtual manner is an excellent goal. A quick scan of the articles in leading journals publishing medicinal chemistry illustrates that there are probably as many examples of chemistry programmes resulting in molecules with many (often obvious) ADME faults as

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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

1 Beresford, A.P. *et al.* (2002) The emerging importance of predictive ADME simulation in drug discovery. *Drug Discov. Today* 7, 109–116

Dennis A. Smith
Pharmacokinetics, Dynamics and Metabolism
Pfizer Global Research and Development
Sandwich, Kent
UK CT13 9NJ

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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