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 Steve Carney, Features Editor, *Drug Discovery Today*, e-mail: S.Carney@elsevier.com

PET and knockout mice in drug discovery

A recent review in *Drug Discovery Today* [1] gives illustrative examples for the use of two powerful tools in the drug discovery process. The first, positron emission tomography (PET), is an established technique in drug development, although the author claims that its use is 'anecdotal'. One reason for the lack of evidence might be that pharmaceutical companies are not willing to publish their results until the end of the drug development process. A recent example is the use of PET in the development of NK1 antagonists for the treatment of depression [2].

Many of the major academic PET centres have an intensive collaboration with pharmaceutical companies, mainly on a contract basis: these contracts are often 30–70% of the total budget of such a centre. Recently, some of the major pharmaceutical companies have built their own PET centres, either within the pharmaceutical research plant or in close vicinity to a hospital. Some of the major radiopharmaceutical companies have started to build up networks of PET centres. These actions clearly demonstrate the value of this technique in drug development.

The author correctly concludes that the majority of the PET studies performed to date have used standard PET radiopharmaceuticals. The increased awareness of the value of PET and the actions mentioned previously enables the use of PET earlier in the drug development process, and in many cases this will generate new radiopharmaceuticals for both old and new drug targets.

The second, more recently introduced, tool is knockout mice. These are extremely valuable for the understanding of the physiological function of receptors and can also, as illustrated in the Eckelman review [1], be used to demonstrate specificity for receptor subtypes when there is a lack of specific antagonists for these subtypes.

A variety of devices for the study of small animals (rodents) with PET have been introduced during the past few years, enabling quantification of the distribution of PET radiopharmaceuticals with a resolution in the order of 1 mm, which are often referred to as micro-PET devices [3]. Animal PET will mainly be used in the early Phases (I and II) of drug development, while human PET will still be applied in Phases III and IV [4].

Although the combination of PET and knockout mice is not a prerequisite for drug development, both techniques clearly have an impact by themselves. In the example given by the Eckelman review, this combination was the only rational means to obtain proof-of-action for the new M2 radiopharmaceutical.

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A 'Rule of Three' for fragment-based lead discovery?

Recent literature has addressed the properties of small molecules that are required to produce good lead compounds [1,2]. Lipinski's Rule of Five, as discussed recently in *Drug Discovery Today* [3], provided the original framework for the development of orally bioavailable drug candidates [4]. These rules have been enhanced by others, such as Veber and co-workers, who discovered that the number of rotatable bonds (NROT) is an important parameter, a maximum of seven seeming to be optimal for oral bioavailability [5]. Literature also indicates that polar surface area (PSA) is another key property [6]; passively absorbed molecules with a PSA of 110–140 $Å^2$ are thought to have low oral bioavailabilities. Recently, the term 'lead-like' was introduced for molecules identified from HTS campaigns that were suitable for optimization and that have properties relatively 'scaled-down' in comparison to the Lipinski values [2,7]. The body of literature is addressing the issues facing compounds that are discovered by screening of

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drug-size compound libraries. A novel, alternative approach has recently emerged and is referred to as 'fragment-based' discovery [8–10]. Using this approach, the hits identified generally obey a 'Rule of Three' and this could be a useful rule for the construction of fragment libraries for lead generation.

This approach begins with fragment libraries (MW 100–250 Da) that are screened using high-throughput X-ray crystallography. These fragments probe key binding interactions in the protein, but are small enough to minimize the chances of unfavourable interactions (electronic or steric) that would prevent them from binding efficiently [1]. The binding modes of these small ligands in the protein are then defined by interpretation of electron density maps. As X-ray crystallography is very effective at identifying weak interactions (μM–mM), fragment hits can be identified that have no measurable activity in a biological assay. Fragment libraries can be constructed to sample chemical diversity or target specific interactions on the protein. Screening of both types of fragment libraries against kinases and proteases, and the subsequent optimization of hits into potent lead compounds indicates that successful hits exhibit particular physico-chemical properties.

We carried out an analysis of a diverse set of fragment hits that were identified against a range of targets. The study indicated that such hits seem to obey, on average, a 'Rule of Three', in which molecular weight is <300, the number of hydrogen bond donors is ≤3, the number of hydrogen bond acceptors is ≤3 and ClogP is ≤3. In addition, the results suggested NROT (≤3) and PSA (≤60) might also be useful criteria for fragment selection. These data imply that a 'Rule of Three' could be useful when constructing fragment libraries for efficient lead discovery.

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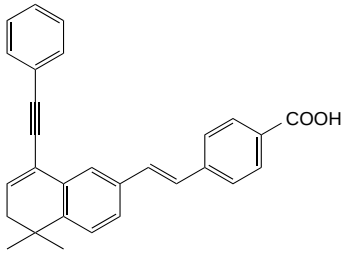
Corrigendum

Please note a correction to the article *Selective retinoids and rexinoids in cancer therapy and chemoprevention* by F. Christopher Zusi, Matthew V. Lorenzi and Valerie Vivat-Hannah, published in *Drug Discovery Today*, 1st December 2002, Volume 7, No. 23, 1165–1174.

In Figure 4 on page 1170, the chemical structure presented for BMS-204493 was incorrect. The accurate structure is shown opposite. The authors apologize for any confusion that this might have caused.



BMS-204493

Figure 4. Chemical structure of the retinoic acid receptor (RAR)-selective pan-antagonist BMS-204493

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