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## 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.

## References

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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<sup>2</sup> 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