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The use of radiotracers in drug discovery and development

The recent review by William Eckelman on 'The use of PET and knockout mice in the drug discovery process' [1] gives an excellent overview of the possibilities of combining positron emission tomography (PET) with our knowledge of well-defined biochemical changes in animals. Eckelman highlights PET as an aid to shorten the present drug approval process, which can take as long as 15 years. For the validation of radiotracers, the use of knockout mice in combination with the wild type can isolate the difference in binding resulting from the lack of the specific binding site, with all other variables remaining equal. Unlike pharmacological intervention in mice, which produces a complex spectrum of biological changes, knockout mice, by their nature, possess one clear biochemical alteration and, thus, provide results that are far easier to interpret. Consequently, a relatively small number of experiments are needed, making more rapid drug development possible.

One could also view this discovery process from a broader perspective: what are the possibilities of PET in the fields of drug development and drug evaluation?

In the field of drug development, PET, in combination with radiopharmaceutical chemistry, is unique in being able to measure drug distribution as a function of time in a quantitative way, by using the labelled drug. The label should be chosen as a chemically identical replacement in the molecule, (e.g. replacing a ^{12}C atom with a ^{11}C atom). Ascertainment of drug biodistribution in the early stages of development can be valuable; for example, knowing whether it crosses the blood–brain barrier can be essential information for the further development of the drug. Of course, this means that for every new drug, a PET version must be synthesized and hence, innovative radiopharmaceutical chemistry is mandatory. However, the information subsequently gained is always of value: positive findings mean new information for the validation of the drug and negative findings mean halting development and thus avoiding needless investment.

A second potential use for PET is to assist in drug evaluation, by measuring the effect of a new drug by using existing radiopharmaceuticals able to quantify the effect of the new developed drug.

Looking at the potential of PET in the field of drug discovery, one might raise the following question: should a newly developed drug have to be 'PET approved'? If the answer is 'yes', huge pressure to absorb the necessary PET knowledge will be put on the pharmaceutical industry in the short term. However, in the long term, PET will then be a standard procedure in drug development, resulting in less paperwork (because of PET evaluation) and added marketing value. If the answer is 'no', further testing and paperwork will be necessary, owing to the demand for '100% security' in today's society.

Reference

1 Eckelman, W.C. (2003) The use of PET and knockout mice in the drug discovery process. *Drug Discov. Today* 8, 404–410

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Knocking out radiotracers for molecular imaging with PET

In a recent review in *Drug Discovery Today* [1], Bill Eckelman described the impetus to streamline radiotracer discoveries and developments in accordance with those of the drug itself. To this end, he draws attention to the opportunity to use genetically manipulated knockout mice to accelerate the discovery of specific radiotracers for positron emission tomography (PET)-based *in vivo* assays of the occupancy of specific binding sites. The rationale for this methodology lies in using the difference in tissue binding of the tracer between wild-type and knockout mice. Because knockout mice lack the specific binding site (and assuming all other variables are equal), binding differences can be attributed to the degree of specificity that the molecular probe has for that site. The key advantage of this technology is that specificity can be

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