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

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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assessed without the need to impose blocking doses of cold drugs, which are rarely specific at the doses needed to saturate the binding site. In addition, although the target has been genetically dissected out of the tissue, physical access of the tracer molecule to such binding sites is kept the same as in the wild type. Examples include the use of knockout models for the muscarinic M2 subtype receptor, glycogen storage disease and multidrug resistance.

The use of knockout technology, holds much promise with well-categorized tissues, but caution is advised for pathological tissues, which are inevitably in structural and functional disarray. For example, knockout technology might not be applicable or might cause distortions to function in infarcted, remodelled or neoplastic tissues. When considering the strategies reviewed by Eckelman, one must be aware of the major challenge that remains: *in vitro* screening of potential tracer molecules for their degree of nonspecific binding within the tissue of interest. This is a fundamental issue, because the kinetics of this binding need to be assayed to determine the time course of washout of the nonspecific component in comparison with that from the specific binding site [2]. An additional tool for this streamlining is the use of modelling techniques and bioinformatics, to help derive a library of molecular structures that make for tracers with good signal:background ratio for *in vivo* molecular imaging [3]

Eckelman points out that the main use of PET is for binding-site occupancy studies. However, in addition to this unique application, there are other areas where PET can assist in drug development. These include the *in vivo* measurements in diseased tissue of: (i) the level of expression of a given molecular therapeutic target, (ii) the pharmacodynamic response to a drug and (iii) drug pharmokinetics.

Finally, following validation from the knockout mouse, there is still the need to validate the new molecular probe and the method of analysis of the PET scan data in diseased human tissue. This stage continues to prove challenging in its demand for a multidisciplinary clinical research-led environment [2].

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2 Price, P. and Jones, T. (2002) Molecular imaging: what picture does it paint for future oncology? *Drug Discov. Today* 7, 741–743

3 Abrunhosa, A.J. *et al.* (2000) Preliminary studies of computer aided ligand design for PET. In *Physiological Imaging of the Brain with PET* (Gjedde, A. *et al.*, eds), pp. 51–56, Academic Press

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The future of drugs from plants

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Plant Made Pharmaceuticals was the subject of a three-day conference held in Quebec City, Quebec, Canada, 17–21 March 2003 (see http://www.cpmp2003.org/). Our world needs better production systems for protein-based drugs, especially edible vaccines to increase health, especially in the third world – pharmaceuticals from plants could be the answer.

The first speaker, Paul Arnison of the FAAR Biotechnology Group (http://infoweb.magi.com/~faarbio1/index.htm), pointed out that the use of 'plant factories' is called 'farming' to most people in the world! The DNA code was elucidated 50 years ago, hence the birth of genes, and the birth of plant molecules stemmed from the discovery of the causal agent of Crown Gall Disease in plants – *Agrobacterium tumefacianens*. This is contained in a large plasmid that was involved in the transfer of genes into plant cells, leading to the birth of plant molecules.

The crucial need for plant made pharmaceuticals

Halla Thorsteinsdttir from the University of Toronto (http://www.utoronto.ca) said that biotech products will have an impact on improving health in years to come, especially on communicable diseases in third world countries, but the drugs have to be robust, affordable and acceptable. Recombinant vaccines will be safer than those of present and could be produced from plants. Recombinant drugs are now

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