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@current-trends.com

More collaboration needed between drug development and imaging communities ▼

The recent article in *Drug Discovery Today* by Aboagye *et al.*[1] nicely summarized the capabilities of positron-emission tomography (PET) that make it a unique tool for drug development. This review of the application of PET to *in vivo* pharmacokinetics and pharmacodynamics comes from a group that has pioneered the use of PET in the evaluation of new drugs. The Aboagye review provides several examples of how PET imaging can enhance the drug development process and should give the reader a great deal of enthusiasm for the potential that PET imaging holds for pharmaceutical scientists.

PET is quickly gaining favor as a clinical tool in the US, Europe and Japan. As a result, the number of PET imaging centers is rapidly increasing around the world. However, current PET imaging studies performed as routine clinical procedures take advantage of only a relatively small proportion of what PET has to offer. Routine clinical PET studies only use a small subset of the PET radiotracers described by Aboagye. Other than the most frequently used compound – the glucose analog [F-18]-fluorodeoxyglucose (FDG) – and tracers to measure cardiac and cerebral blood flow, the radiopharmaceuticals labeled as 'clinical' in the Aboagye review have undergone only limited testing in patients[2].

Routine clinical studies are mostly frequently done for cancer staging[3], with a smaller number of PET procedures applied to coronary artery disease, medically intractable epilepsy and dementia. Clinical studies are interpreted either qualitatively or using relatively simple quantitative tracer uptake measures. Therefore, while many centers can or will soon be able to perform clinical PET studies, very few centers have the capability for radiopharmaceutical design and testing, quantitative image analysis with kinetic modeling, and support for translational research necessary for the kind of drug development applications described by Aboagye and colleagues.

Given expanding capabilities but an increasing clinical demand, how can we encourage the type of research required to make PET more useful for drug development? First, public and private sources, including the pharmaceutical industry, must provide support for individuals and institutions to design and test imaging approaches for drug development. In particular, granting agencies and corporate R&D departments need to appreciate the interdisciplinary nature of this research and must seek approaches that can bring together individuals from a wide range of disciplines, including imaging sciences, pharmacology, radiochemistry and applied mathematics. At our institution, individuals from the Radiology and Pharmaceutics Departments recently joined forces to investigate the use of [C-11]-verapamil PET to quantify the transport of antiviral agents by P-glycoprotein.

Secondly, governmental support is required to assist with the regulatory issues and testing support structure needed to bring new PET radiopharmaceuticals to clinical trials. Recent efforts by the US National Cancer Institute in conjunction with the Food and Drug Administration (FDA) to support radiopharmaceutical development[4] provide an example of the type of support that is required to facilitate the application of PET imaging to early drug testing.

Finally, we need to take advantage of recent developments in computer hardware and software to generate user-friendly tools for quantitative image analysis, including kinetic analysis and parametric imaging[5,6]. Because current clinical PET imaging does not include detailed quantitative image analysis, commercial tomograph manufacturers are unlikely to develop such tools without research support and the encouragement of the medical community. Once developed, software for strong quantitative image analysis will greatly enhance both research and clinical studies.

PET has already demonstrated its unique ability to guide clinical practice and translational medical research, but we have just scratched the surface of what PET imaging can do. Drug development is one of the areas where PET might ultimately have its greatest effect. The drug development and imaging communities need to join forces to support this important work. The type

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of review provided by Aboagye and colleagues is a good early step in this direction.

David A. Mankoff, Jeanne M. Link, Jashvant Unadkat, Janet F. Eary, Kenneth A. Krohn
Division of Nuclear Medicine and Department of Pharmaceutics
University of Washington
Seattle, WA, USA

References

1 Aboagye, E.O. *et al.* (2001) *In vivo* pharmacokinetics and pharmacodynamics in drug development using positron-emission tomography. *Drug Discov. Today* 6, 293–302
2 Tewson, T. and Krohn, K.A. (1998) PET radiopharmaceuticals: state-of-the-art and future prospects. *Semin. Nucl. Med.* 28, 221–234
3 Mankoff, D.A. and Bellon, J.R. (2001) PET imaging of cancer: FDG and beyond. *Semin. Rad. Oncol.* 11, 16–27
4 Hoffman, J.M. (2000) Imaging in cancer: a National Cancer Institute 'extraordinary opportunity'. *Neoplasia* 2, 5–8
5 O'Sullivan, F. (1993) Imaging radiotracer model parameters in PET: a mixture analysis approach. *IEEE Trans. Med. Imag.* 12, 399–412
6 Cunningham, V. and Jones, T. (1993) Spectral analysis of dynamic PET studies. *J. Cereb. Blood Flow Metab.* 13, 15–23

Are drug targets missed due to lack of physical activity? – Reply ▲

Initial letter: Gurwitz, D. (2001) *Drug Discov. Today* 6, 342–343

Response from Brenda Anderson

David Gurwitz provides good justification for testing drug efficacy in exercising rodents. He rightfully points out that the genome is 'fine-tuned' for physical activity, and provides evidence that exercise influences many systems, including transmitter systems[1–3].

Despite the evidence, the use of exercising rats might not be appropriate for all drug testing. Numerous human conditions and disease states are associated with reduced levels of activity. Individuals that develop Alzheimer's disease are reported to lead more sedentary lives prior to disease onset relative to persons that do not go on to develop the disease[4]. Low levels of physical activity are associated with bouts of depression, and activity is reduced with age. Thus, specific conditions exist that might be modeled best with the standard lab cage.

Although it might be true (as Gurwitz points out) that drug efficacy could be better detected in exercising rats, sedentary rats might provide a better model for the detection of side effects. Exercise can be neuroprotective against ischemia[5] and epilepsy[6–7]. Exercising rats have less oxidative damage in the brain[8], and an increased capacity for oxidative metabolism in central motor structures[9]. Therefore, side effects related to excitotoxicity could be detected more easily in sedentary rather than in exercising rodents.

Strong arguments can be made for the use of exercise as a standard laboratory condition. However, the ultimate choice of animal housing should depend on the population being modeled, and the goal of the study.

References

1 Brown, B.S. and Van Huss, W. (1973) Exercise and rat brain catecholamines. *J. Appl. Physiol.* 34, 664–669
2 Fordyce, D.E. and Farrar, R.P. (1991) Physical activity effects on hippocampal and parietal cortical cholinergic function and spatial learning in F344 rats. *Behav. Brain Res.* 43, 115–123
3 MacRae, P.G. *et al.* (1987) Endurance training effects on striatal D_2 dopamine receptor binding and striatal dopamine metabolite levels. *Neurosci. Lett.* 79, 138–144
4 Friedland, R.P. *et al.* (2001) Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc. Natl. Acad. Sci. U. S. A.* 98, 3440–3445
5 Stummer, W. *et al.* (1994) Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia. *Stroke* 25, 1862–1869
6 Arida, R.M. *et al.* (1998) Effect of physical exercise on kindling development. *Epilepsy Res.* 30, 127–132
7 Arida, R.M. *et al.* (1999) Effect of physical exercise on seizure occurrence in a model of temporal lobe epilepsy in rats. *Epilepsy Res.* 37, 45–52
8 Radák, Z. *et al.* (2001) Regular exercise improves cognitive function and decreases oxidative damage in rat brain. *Neurochem. Int.* 38, 17–23
9 McCloskey, D.P. *et al.* (2001) Exercise increases metabolic capacity in the motor cortex and striatum, but not in the hippocampus. *Brain Res.* 891, 168–175

Brenda Anderson
Department of Psychology
State University of New York at Stony Brook
Stony Brook, NY 11794, USA