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MACROSCOPY

In Vivo Molecular Imaging Biomarkers: Clinical Pharmacology's new "PET"?

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Medicine, including the pharmaceutical and biotechnology industries as well as many clinical practitioners, has recognized the importance of using molecular imaging biomarkers, including those labeled in such a way as to be imaged by positron emission tomography (PET), as tools for predicting outcomes in drug development and creating opportunities for "personalized" medicine, for diagnosing early-stage disease, and for the follow-up of the effectiveness of treatment. However, only one PET biomarker is currently approved by the Food and Drug Administration (FDA). If the technology is so important, we can ask why there is such a limitation to the availability of these biomarkers.

The FDA, the National Institutes of Health (NIH), and many international organizations have recognized the importance of using biomarkers and expanding their use in medicine. It has now been approximately 6 years since the sequencing of the human genome was completed, and many new insights have been gained from this monumental accomplishment; however, modern systems biology has taught us that genotypic understanding must be expanded to include phenotypic information about disease. This "translational" requirement is part of what has been defined as the "critical path" for clinical pharmacology to influence and accelerate the development of useful therapeutics. As a result of the need for new tools and approaches, a hasten-

ing in the development of new treatment drugs has not occurred. Instead, there has been a recognized deceleration in the drug development process with the advent of the possibility of more personalized drugs. Although the development cost of a new drug has now exceeded US \$1 billion and is predicted to exceed \$2 billion by 2010, the new molecular entity output has decreased by more than 40% in the same period of time. There are several possible solutions, including *in vivo* molecular imaging, but these solutions come with significant challenges, such as a further evaluation of their predictive and therapeutic significance if shown to be as valuable as they appear at this early stage, and how soon these new tools will be available for use.¹

The concept, definition, and importance of biomarkers in general have been discussed at length as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.² They clearly offer a potential pathway from our current model of "one size fits all" to a predictive and personalized approach.

There are several classes of biomarkers, including *in vitro* and *in vivo* markers. Although a biomarker can be as simple as the measurement of blood pressure, much more sophisticated and targeted approaches are being developed. Just as a sphygmomanometer was invented years

Key points

Why PET labeled biomarkers are not yet integrated further into the diagnosis and treatment of patients clinically:

1. Challenges in producing radioactive isotope
2. Laborious process of labeling the biologically active compound to the isotope
3. Cost of production
4. High levels of radioactivity associated with their production
5. Regulatory impediment

ago to measure blood pressure, so must tools be developed today to measure more sophisticated biomarkers. One such tool is PET. PET biomarkers are labeled with positron (a positively charged electron)-emitting radioisotopes, primarily nitrogen, oxygen, carbon, and fluorine, which are short-lived elements (2–110 minutes). PET distinguishes itself from other imaging modalities such as computed tomography (CT) and magnetic resonance imaging in that it allows for metabolic data to be measured, as opposed to merely anatomic measurements.

Six critical paths are emerging to form a cohesive method to improve the effectiveness of drug development. Molecular imaging of biomarkers will contribute significantly to three of these pathways, specifically in the realms of diagnosis, optimal drug dosing, and therapeutic drug monitoring.³ Indeed, in the very

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near future the inability to use molecular imaging in drug development, diagnosis, and treatment follow-up will probably be considered even substandard care in the optimized individualized treatment of a patient.⁴

Clinically, PET can be used to diagnose, stage, or monitor many common cancers, and more than 2 million scans will be performed in the United States this year alone. Depending on the cancer type, PET changes the choice and modality of therapy instituted from 30% to as high as 60% of the cases in which it is used.^{5,6} This is critical, in that the improved prognosis and reduced mortality of patients with cancer in the United States in the past several years have been attributed to the optimization of therapy.⁷ **Figure 1** shows a PET image of a patient with cervical cancer. The CT image showed no anatomical abnormalities, whereas the PET image showed high uptake of fluorodeoxyglucose ($[^{18}\text{F}]\text{FDG}$), indicative of malignancy.

Several PET biomarkers have been developed to measure important biological and cellular functions in humans. **Figure 2** illustrates a few of these important biomarkers, their molecular structure, measured physiological parameters, as well as an example of their clinical applicability.

The question remains: why are PET labeled biomarkers not yet integrated

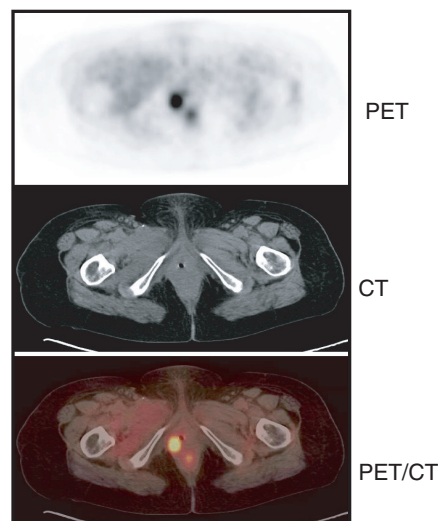


Figure 1 PET, CT, and PET/CT images of a patient with cervical cancer, undetected except on the PET images.

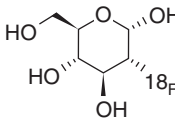
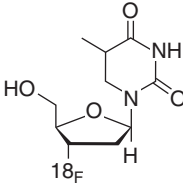
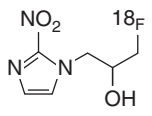
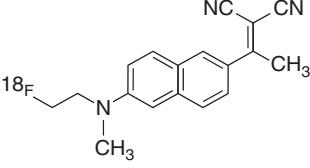
Radio labeled tag	Molecular structure	Physiological parameter	Example of clinical use
^{18}F FDG		Glucose utilization	Possible malignancy
^{18}F FLT		Cell proliferation	Possible malignancy
^{18}F MISO		Cell proliferation	Possible malignancy
^{18}F FDDNP		Amyloid plaque binding agent	Alzheimer's disease marker

Figure 2 Some important PET biomarkers, their molecular structures, physiological parameters for their use, and examples of clinical use.⁶

further into diagnosis and treatment of patients clinically? There are at least five challenges: (i) difficulty in producing radioactive isotope, (ii) the labeling of the biologically active compound with the isotope, (iii) the cost of their production, (iv) the considerable radioactivity associated with their production, and (v) regulatory impediments.

Producing PET labeled biomarkers is challenging in two significant ways. First, a typical process—for example, to produce FDG—requires 1–2 hours of irradiation in a cyclotron accelerator to produce a batch of fluorine-18 (^{18}F) and then 30–45 minutes for conventional chemical techniques to attach the ^{18}F tag to the glucose molecule and another 30 to 45 minutes to perform the required quality control.

Typically FDG is produced in large batches that contain curies of radioactivity. A typical example is the production of 2 Ci of FDG activity at a distribution site that would result in approximately

20 doses at 10 mCi per dose. Only one-tenth of the original activity reaches the patient. A typical dose of these biomarkers contains a few millicuries of radioactivity and only picomolar quantities of the compound. In most cases the radiation exposure to the patient is reasonably low and the quantity of the biomarker injected in the human is orders of magnitude less than for a therapeutic drug. Patient exposure to diagnostic radiation has become a major concern recently, with new data suggesting that one CT scan can increase the risk of cancer (primarily lymphoma, leukemia, and breast cancer) by 1 in 1,000, with the dose being cumulative (*i.e.*, the more scans, the higher the risk).⁸ This product must then be distributed to the end user by automobile or airplane. This entire process can take as long as 3–5 hours, requires human exposure to large amounts of radioactivity, and is very inefficient because of the decay (half-life of 110 minutes) of the ^{18}F isotope. When the compound arrives for use, the subjects or

patients are imaged in sequence, thereby usually requiring hours of additional time and further loss of active isotope due to continuing half-life decay, wasting even more of the compound. Exceptions to this process are found in large research universities that can afford their own nuclear accelerator and a staff of physicists and radiochemists to operate the accelerator and produce the compounds.

The second challenge is attaching the radioactive isotope to the biological agent. Conventional chemical processes require almost 1 hour to perform this task, and with limited effective yield. There is newer technology, however, referred to as microfluidic chemistry,⁹ that markedly shortens the time for labeling the compounds and increases the chemical yields as shown in **Figure 2**.⁴ The production of the FDG compound therefore can be reduced to less than 2 minutes as compared with a typical time of 45 minutes for conventional chemistry, and the yield can be improved from 50% to 98% (unpublished report, Molecular Imaging and Probe Development Group, University of Tennessee Graduate School of Medicine). Another major improvement resulting from the use of microchemistry is that it requires as much as 1,000 times less precursor. Using much smaller quantities of initial reagent potentially simplifies the quality-control process primarily to passing the final product through a separation column to meet the standard purification requirements.

With the labeling process considerably improved, the issue turns to cost effectiveness of the production of the isotope. **Figure 3** shows the design of a cyclotron that is dramatically simplified as compared with the typical cyclotron currently used for production of PET isotopes. The proposed self-shielded cyclotron normally operates at 1 μA of positive ion beam current, as compared with the 100 μA typical of the PET cyclotrons in current use. Additionally, this “microcyclotron”, which is physically about one-fifth the size,⁵ is designed to be integrated with the microchemistry process described above to produce a single human dose of a desired biomarker in approximately 15–20 minutes. The new cyclotron could be designed so as to be installed with-

out building modification in a 12 by 12 ft (3.66 by 3.66 m) room, be operated without additional personnel, and cost four to five times less than conventional accelerators. Coupled with the microchemistry labeling, the new biomarker generator could have “kits” supplied by a manufacturer containing all required precursors and the purification columns necessary to produce approved imaging biomarkers under the clinical Good Medical Practices guidelines enforced by the

The FDA approval process for imaging biomarkers should differ from that for therapeutic drugs.

FDA. Any such “biomarker generator” will, of course, need to undergo the FDA approval process for medical devices.

Ultimately, given the need for smaller amounts of starting reagent, a smaller and less costly cyclotron, on-site cyclotron installation requiring less radiolabeled product due to decreased transport time, and faster labeling of isotope to a biological agent could lead to a marked reduction in cost and bring this capability to the community medical setting where it can have the greatest impact. For example, current capital expenditure for installing a conventional cyclotron alone is in the range of \$4 to 5 million. In comparison, the new biomarker generator installed

with all necessary quality-control equipment is expected to cost less than \$1 million and require no additional staff to operate.

The last remaining challenge is regulatory hurdles. [¹⁸F]FDG is the only important clinical biomarker currently approved for human use by the FDA. One of the significant issues with biomarkers is that, from a process viewpoint, they are treated by the FDA in the same way as a therapeutic drug. This would not be significantly detrimental to the medical community except that financial justification cannot be made for the investment comparable to the investment the pharmaceutical industry makes to obtain FDA approval for a single drug. The result is that important biomarkers cannot be used to measure critical human cellular functions except under research protocol, and in many cases this can be very difficult and time-consuming in itself. Therefore, these important *in vivo* biomarkers are limited in use to a very small number of research programs instead of being potentially available for clinical practice. The reasonably low radiation dose to the patient and the extremely small amounts of the biomarker injected into humans are two fundamental reasons that the FDA process for approval of imaging biomarkers should differ from that for therapeutic drugs. When the FDA's regulatory processes are simplified and shortened to a point more in keeping with investi-



Figure 3 New MicroCyclotron with shield (right) is five times smaller than conventional cyclotron (left).

gational new drug applications and the medical device approval guidelines that are in place when similar devices have been approved (*e.g.*, 510K applications) a very significant hurdle will be eliminated.

This simplification could make these important biomarkers available for clinical trials for therapeutic drugs and for use by physicians to diagnose, optimize, and personalize treatment of numerous diseases, resulting in reduced morbidity and mortality, as well as improve the cost effectiveness of health care with a demonstrable return on investment. *In vivo* molecular imaging with PET biomarkers is therefore a significant public health issue that requires urgent dialogue and

action that result in a timely resolution to the challenges discussed.

CONFLICT OF INTEREST

R. Nutt is the Chief Executive Officer of Advanced Biomarker Technologies, LLC, a company engaged in developing technologies for imaging biomarkers. L.J. Vento has no conflicts. M.H.T. Ridinger has no conflicts.

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1. Food and Drug Administration. Innovation Stagnation, Challenges and Opportunities on the Critical Path to New Medical Products, March 2004.
2. Biomarker Definitions Working Group. Biomarker and surrogate endpoints: preferred definitions and conceptual framework. *Clin. Pharmacol. Ther.* **69**, 89–95 (2001).
3. Lesko, L.J. Paving the critical path: how can clinical pharmacology help achieve the vision? *Clin. Pharmacol. Ther.* **81**, 170–177 (2007).
4. McLarty, K. & Reilly, R.M. Molecular imaging as a tool for personalized and targeted anticancer therapy. *Clin. Pharmacol. Ther.* **81**, 420–424 (2007).
5. Bunyaviroch, T. & Coleman, R.E. PET evaluation of lung cancer. *J. Nucl. Med.* **47**, 451–469 (2006).
6. Hicks, R.J., *et al.* The utility of F-18 FDG PET for suspected recurrent non-small cell lung cancer after potentially curative therapy: impact on management and prognostic satisfaction. *J. Nucl. Med.* **43**, 752–756 (2002).
7. Annual Report to the Nation on the Status of Cancer, 1973–1999. *Cancer* **94**, 2766–2792 (2002).
8. National Research Council. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII. Phase 2, Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation (2006).
9. Lee, C.C., *et al.* Multistep synthesis of a radiolabeled imaging probe using integrated microfluidics. *Science* **310**, 1793–1796 (2005).