Pharmaceutical Research, Vol. 24, No. 6, June 2007 (© 2007)
DOI: 10.1007/s11095-007-9281-9

Editorial

Application of Biomedical Imaging in Drug Discovery and Development

Received February 14, 2007; accepted February 22, 2007; published online March 23, 2007

Drug discovery and development is a time-consuming and costly process, which may take approximately 15 years to advance from laboratory discovery to FDA approval and require over a billion dollars. Once a drug candidate is identified in the discovery stage, it goes through preclinical studies in a variety of experimental animals and different phases of clinical trials before the drug's developers apply for FDA approval. Due to the rigorous approval process, many drug compounds often fail after expensive preclinical and clinical studies. Consequently, there is a need for more efficient and accurate processes to reduce the exceedingly high cost of drug development.

Non-invasive biomedical imaging technologies are believed to be the transforming tools that can reduce the high cost of drug discovery and development. Recent revolutionary advances in biomedical imaging have expanded anatomy-based diagnostic imaging into functional and molecular imaging. Modern biomedical imaging, including anatomical, functional and molecular imaging, provides high-quality and high-resolution tissue images, and allows non-invasive visualization and measurement of molecular markers, *in vivo* interaction of molecular probes, and biological, metabolic and physiological processes with high sensitivity and specificity. These advancements have made it possible to use imaging technologies for non-invasive and longitudinal evaluation of the real-time pharmacokinetics and pharmacodynamics of drug candidates in both preclinical and clinical development phases. Biomedical imaging can provide accurate, timely and quantitative pharmacokinetic and pharmacodynamic information of the drug candidates in a relatively small group of subjects as compared to conventional biopsy-based pharmacokinetic methods. Any drug candidate with poor pharmacokinetics and pharmacodynamics can be readily identified and eliminated earlier in the drug development process. Accurate identification of the right drug candidates will certainly eliminate any unnecessary costs and facilitate the process of drug development.

A variety of currently available biomedical imaging modalities can be used throughout the process of drug discovery and development. These imaging modalities include computerized tomography (CT), ultrasound, single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI) and optical imaging. CT is an anatomical imaging modality for tissues and organs of high densities and has low sensitivity for molecular imaging. Ultrasound is the most economic imaging modality, showing real-time structure and movement of the body's internal organs. It can generate high-resolution anatomical and functional images and has a relatively high sensitivity for molecular imaging when a contrast agent is administered. SPECT and PET use short-lived radioactive tracers to generate images and are the most sensitive modalities for functional and molecular imaging. MRI produces high-resolution anatomical images for soft tissues. Its sensitivity for molecular imaging is in between those of CT and nuclear medicine. Optical imaging measures fluorescence or luminescence emission and has a high sensitivity for functional and molecular imaging. Its application largely depends on the depth of light tissue penetration. Combined imaging modalities, such as PET-CT, SPECT-CT and PET-MRI, have been developed to complement each other's strengths. These major imaging technologies have been modified for small animal imaging and are available for preclinical evaluation of drug candidates in rodents.

These imaging modalities can play an important role in drug discovery and development. Pharmacokinetics and biodistribution of drug candidates can be non-invasively and longitudinally measured with PET after proper labeling of the drug with a positron emitter, such as C-11 ($t_{1/2} = 20.4$ min), N-13 ($t_{1/2} = 9.96$ min) or O-15 ($t_{1/2} = 2.07$ min), in both preclinical and clinical studies. Pharmacodynamics and therapeutic responses can be monitored by functional imaging with PET and dynamic contrast enhanced MRI, which reveals metabolic and physiological changes of target tissues towards therapies. Morphological changes can also be spontaneously measured by anatomical imaging with CT, ultrasound or MRI. Molecular biomarkers of diseases can be readily evaluated by molecular imaging with PET or SPECT with specific imaging probes. Magnetic resonance spectroscopy also has a potential to study tumor microenvironment and its response to therapies. Optical imaging is suitable for functional and molecular imaging and evaluation of therapeutic response, which is ideal for small animal imaging with high sensitivity.

In this theme issue, Stephen and Gillies present a comprehensive review on functional and molecular imaging of responses to targeted therapies. They also give valuable insights on how non-invasive imaging can transform the

process of drug development and beyond. Lee *et al.* demonstrate the use of FDG-PET in monitoring pharmacodynamics of a new drug based on tumor glucose metabolism in a rodent tumor model. FDG-PET can be a timely and quantitative endpoint in drug development and can also provide valuable information for more efficacious dosing design. Bogdanov *et al.* use fluorochrome labeled monoclonal antibodies for specific imaging of molecular biomarkers in mice with optical imaging. It is shown that optical imaging with molecular probes can specifically measure molecular biomarkers in small animals. Melancon *et al.* visualize *in vivo* degradation of a poly(*L*-glutamic acid) drug carrier with optical imaging, which also has a potential to non-invasively evaluate *in vivo* enzymatic activities in small animals. Zheng *et al.* non-invasively evaluate pharmacokinetics of a liposomal formulation containing a CT contrast agent and an MRI contrast agent in rabbits with CT and MRI, which visualize the long circulation of the nanosized liposomal formulation. The multimodal system is promising for non-invasive evaluation of liposomal drug delivery systems in preclinical and clinical phases. Wang *et al.* use contrast enhanced MRI to non-invasively study the pharmacokinetics and tumor distribution of a paramagnetically labeled polymer drug carrier and the structure effect of the polymeric drug carrier on drug delivery efficiency in an animal tumor model.

The articles in the theme issue are examples of the applications of biomedical imaging in various phases of drug development or the development of efficient drug delivery systems. Biomedical imaging has demonstrated many advantageous features for non-invasive and longitudinal evaluation of real-time pharmacokinetics and pharmacodynamics of drug candidates as compared to conventional biopsy-based methods in both preclinical and clinical development. The FDA is currently considering use of imaging biomarkers and endpoints in drug discovery and development. The continued development of biomedical imaging technologies will have a revolutionary impact on more efficient and cost-effective drug discovery and development processes.

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