

# Molecular Imaging Technologies and Translational Medicine

Throughout the decade since the National Institute of Biomedical Imaging and Bioengineering was established, molecular imaging has continued gaining acceptance as a successful component of translational research. Before molecular imaging is employed routinely in clinical trials, however, the need remains for biomarker validation and proof-of-concept studies.

Molecular imaging's reach has expanded in parallel with the recognition of its potential role as a biomarker in the drug discovery process. In 2001, the Biomarkers and Surrogate Endpoint Working Group developed a classification system for biomarkers: type 0 (markers of the natural history of disease), type 1 (markers of the mechanism of drug action), and type 2 (markers used as surrogate endpoints when the marker predicts clinical outcome). Molecular imaging plays a role in all these areas.

Molecular imaging has been applied to natural history experiments in atherosclerosis, including the characterization of inflammatory atheroma. Several techniques have been applied, including carotid  $^{18}\text{F}$ -FDG PET. Results suggest cathepsin B and other proteases may serve as type 0 biomarkers for predicting high-risk plaque.

Type 1 biomarker studies include pharmacokinetic evaluation of activity-based probes (ABP) for proteases. Two main techniques to image proteolytic activity *in vivo* have been employed: a reporter substrate that emits a fluorescent signal when processed by a protease, and fluorescently labeled ABPs that indicate active proteases. Potential applications to visualize proteases in intact cells include ABPs to monitor

caspase activity after induction of apoptosis and papain-family cysteine protease in a mouse model for pancreatic cancer.

Finally, molecular imaging elucidates ways to measure the concentration of a drug within the tumor as well as the biological response. The first PET pharmacokinetic study of an antiangiogenic agent illustrated this technique well. The inhibition of vascular endothelial growth factor (VEGF) was assessed using  $^{124}\text{I}$ -HuMV833 PET, visualizing radioligand uptake and subsequent clearance by both normal tissue and dysplastic cells. MR imaging algorithms measured the vascular permeability surface area product, which is controlled by VEGF. The findings suggested tumor response varied by anatomic area, supporting the contention that molecular imaging allows for *in situ* biological response assessments.

The momentum to bring molecular imaging from bench research to the clinical trials arena must continue. Success with this integration will require flexibility of regulatory agencies and collaboration among sites, drug sponsors, and imaging laboratories.



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completed in the past year include: *Retooling for an Aging America: Building the Health Care Workforce*, which calls for bold initiatives to ensure the availability of sufficient adequately trained health care workers to tend to the expanding population of older patients; *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*, a blueprint for ways in which cancer care providers can address patients' psychological, emotional, and social needs in addition to their physical ailments; *Treatment*

*of Posttraumatic Stress Disorder: An Assessment of the Evidence*, which found that research to determine the effectiveness of various treatments is urgently needed in light of uncertainties about most therapies and growing patient needs; and *Knowing What Works in Health Care: A Roadmap for the Nation*, which provides a vision and roadmap for improving the ways in which the nation uses scientific evidence to identify the most effective clinical services.

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