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Molecular imaging comes of Age: applications and impacts in molecular medicine

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ABSTRACT

Molecular imaging is a relatively new discipline that rapidly developed over the past decade. It pursues visual representation, characterization, and quantification of biological processes at the cellular and subcellular levels within living organisms. In this novel field, multidisciplinary efforts from molecular and cellular biology, chemistry, bioinformatics, physics, engineering, and many clinical areas are united. Whereas conventional imaging have mostly relied on nonspecific macroscopic anatomical changes to detect pathological tissues, molecular imaging allows for identification of specific molecular events by exploiting molecular probes as the source of image contrast. This is a significant change in imaging paradigm and molecular imaging is expected to provide early detection, characterization, and monitoring of treatment procedures. One of the apparent goals of molecular imaging is to translate expanding knowledge of molecular sciences into good patient care by integrating the various principles of imaging sciences with the power of molecular biology. Although much of molecular imaging is still largely experimental and only limited clinical success has been achieved, it is anticipated that molecular imaging will move increasingly out of the research laboratory and enter the clinic over the next decade. Molecular imaging, in combination with nanotechnology, biotechnology and new forms of computational hardware and software, is expected to enhance existing imaging modalities. This review provides a brief overview of the current state of molecular imaging and its future directions in biomedical arena.

Key words : molecular imaging, molecular medicine, multidisciplinary, early detection, molecular biology, nanotechnology

Introduction

Advances in molecular science and biology have laid the groundwork for the development of molecular medicine that aims at identification and correction of molecular errors that underlie disease. This, coupled with rapid innovations in imaging and computing technology, has resulted in a new scientific discipline called "molecular imaging". The emerging field of molecular imaging may be envisioned as the *in vivo* diagnosis of complex pathological processes by detection of unique biochemical signatures. Molecular imaging is pushing the temporal detection horizon of medical diagnosis and therapy back from the anatomical sequellae of disease to its earliest physiological and biochemical manifestations. Indeed, it can facilitate the understanding of the molecular basis of disease and provides a mechanism for rapid translation of developments in cellular and molecular biology and other basic sciences into improvements in patient care.

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Definition of Molecular Imaging

Molecular imaging can be defined as the visual representation, characterization, and quantification of biological

processes at the cellular and subcellular levels within intact living organisms (1). Alternatively, it can be defined as the minimally invasive *in vivo* sensing, depiction, and characterization of spatially localized biologic processes at the cellular and molecular levels (2). In a broader sense, molecular imaging encompasses non-invasive visualization of the molecular processes of life in organisms ranging in complexity from individual cells to human beings. Defined from a different perspective, molecular imaging is the combination of new molecular agents with traditional imaging tools to capture pictures of specific molecular pathways in the body, particularly those that are key targets in the disease process.

Interdisciplinary Nature of Molecular Imaging

Still largely in an active preclinical stage, molecular imaging now represents the convergence of multiple image-capture techniques, basic molecular and cellular biology, chemistry, medicine, pharmacology, medical physics, biomathematics, and bioinformatics into a new imaging paradigm (1, 3). These days, biomedical research is becoming ever more interdisciplinary, as it depends increasingly on cross fertilization between the physico-chemical sciences and engineering on the one hand and biology and clinical medicine on the other. Examples of the fruits of such collaboration are recent developments in molecular imaging, biomedical informatics, nanobiotechnology, computer-aided detection and diagnosis, and the merging of diagnosis and therapy.

Development of Molecular Imaging

The development of molecular imaging is largely due to the synthesis of novel molecular agents that can attach with high specificity to genes, proteins, or other biomolecular tar-

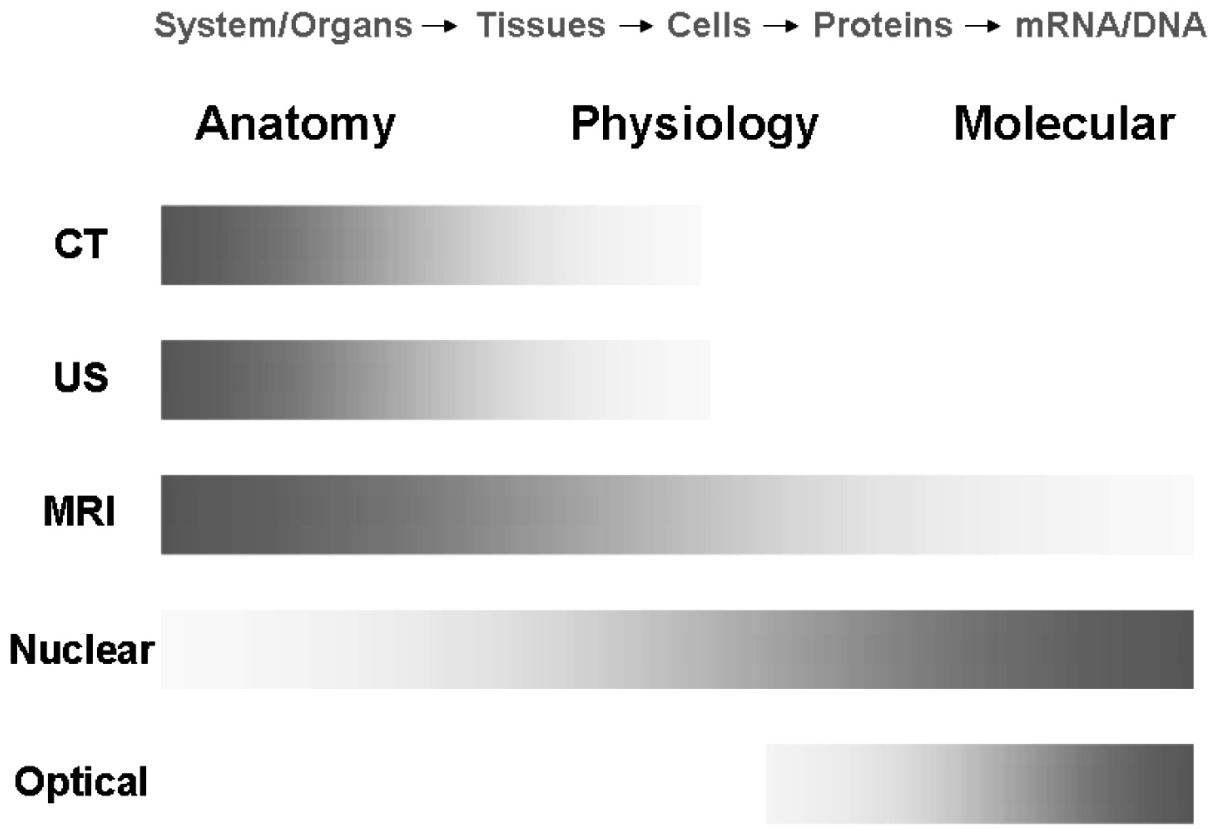

Fig 1. Imaging paradigm shift from anatomical to molecular imaging (modified from Weissleder R and Mahmood U, Radiology 2001;219:316-333)

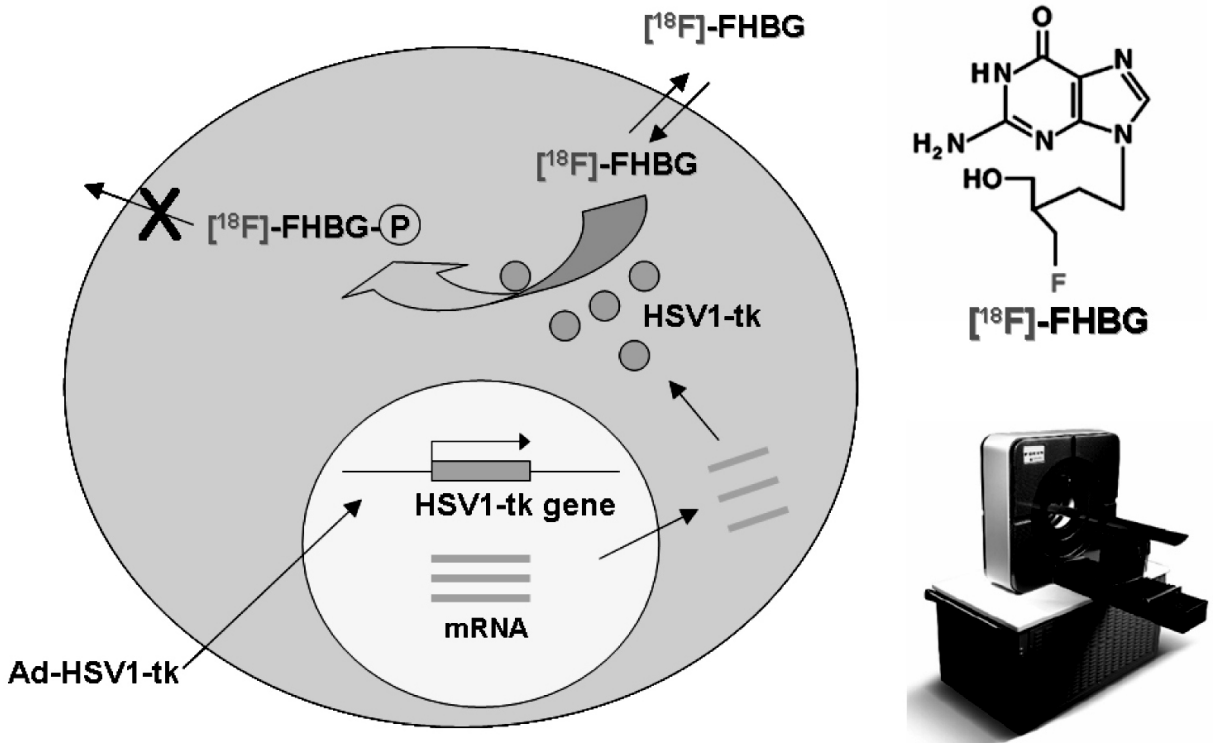

Fig 2. Reporter gene imaging using microPET. The [^{18}F]-FHBG radioprobe, upon phosphorylation by HSV1 thymidine kinase, remains trapped inside the cell and generates signal in microPET. The right bottom panel shows the microPET device dedicated for small animal imaging.

gets and that can then be detected with various imaging modalities. Among these are agents that are activated only in response to particular changes in the local biochemical environment, such as specific gene expression or enzyme activity (1, 4). This change in emphasis from a non-specific to a specific approach represents a significant paradigm shift (Fig 1). The impact of such transition is that molecular imaging can now provide the potential for understanding of integrative biology, earlier detection, better risk stratification, characterization of disease, and evaluation of treatment efficacy.

The growth in the field of imaging devices was also crucial for the development of molecular imaging. Imaging technologies currently employed include radionuclear imaging (Positron Emission Tomography [PET], Single Photon Emission Tomography [SPECT], autoradiography), magnetic resonance imaging (MRI, magnetic resonance spectroscopy [MRS] and smart contrast agents), and spectroscopy, X-ray computed tomography (CT) and optical imaging (*in vivo* bioluminescence and fluorescence, confocal fluorescence microscopy). Especially the field of biophotonics is undergoing leaps in sophistication.

Applications of Molecular Imaging

Application of molecular imaging includes visualization of tissue metabolism and biochemistry using labeled or tagged biologically active compounds, adjunct to diagnosis and staging of diseases in the absence of anatomic findings, determination of biological response to specific therapeutic agents, understanding of the pharmacology of new drugs (pharmacokinetics and pharmacodynamics) using labeled analogues, and exploring the efficacy of new therapies and treatments. More recent applications of molecular imaging include non-invasive visualization and measurement of cell trafficking, tumor growth and spread in the absence or presence of treatment, expression of endogenous as well as exogenously implanted genes, enzyme activity, receptor density,

and protein-protein interactions.

Molecular imaging probes can now be developed by taking advantage of the rapidly increasing knowledge of available cellular/molecular targets. Examples of endogenous gene expression includes p53, NFAT, HIF-1, E2F, FOXO, SMAD4, HSP70, and DEVD. Also there are reports on the imaging of apoptosis as a predictor of therapeutic response (5). In addition to these growing list of endogenous genes and metabolism, numerous studies are being performed on the monitoring or imaging of exogenous gene delivery and expression. This trend is in line with the assumption that a non-invasive method for measurement of *in vivo* transduction and transgene expression is required for successful gene therapy. As a proof-of-principle study, reporter gene constructs (e.g. luciferase or HSV1-tk gene) can be driven by constitutive promoter elements and used to monitor expression of gene therapy vectors, the efficacy of gene targeting, and transduction efficiency. For example, one can genetically modify cells that will accumulate an imaging probe to act as a marker for localizing and tracking the cells (Fig 2). This current molecular-genetic imaging strategies are indirect, because they couple a reporter gene with a complementary reporter probe. In addition to the constitutive promoter approach, inducible promoters can be used as sensors to regulate the magnitude of reporter gene expression. Reporter systems can also be constructed to monitor mRNA stabilization and specific protein-protein interactions. Moreover, tissue-specific promoters can be used to restrict transgene expression to certain tissue types and organs.

Gene marking may be used to follow the behavior of cells in animals. There are numerous examples of molecular imaging of the cells that are marked by *ex vivo* gene transfer procedure and subsequently placed in living rodents. In one example, embryonic rat H9c2 cardiomyoblasts were transduced with adenoviral vector containing HSV1-sr39tk or Fluc reporter gene and injected into the myocardium (6). This *in vivo* imaging of cell transplantation provides obvious advantages over traditional techniques, such as rapid evaluation of clinical parameters and determination of the efficacy of repeated transplantations. With further refinement, molecular imaging will contribute to the goal of clinical transplantation protocols that are reproducible, beneficial, and quantifiable (6).

Multimodality Imaging

The convergence of molecular and genetic disciplines and non-invasive imaging modalities has provided the opportunity for new researches. For example, multi-modality imaging - the coupling of nuclear and optical reporter genes - represents the beginning of a far wider application of this technology in molecular genetic studies being performed in small animals. Optical imaging and optical reporter systems are cost-effective and time-efficient. They require less resources and space than PET or MRI and they are particularly well suited for small animal imaging and for *in vitro* assays to validate different reporter systems. However, optical imaging techniques are limited by depth of light penetration and scatter, and do not yet provide optimal quantitative or tomographic information. However, these issues are not limiting for PET- or MRI-based reporter systems, and PET- and MRI-based animal studies are more easily generalized to human applications.

Many of the shortcomings of each modality alone (Table 1) can be overcome by the use of dual- or triple-modality reporter constructs that incorporate the opportunity for PET, fluorescence and bioluminescence imaging. It is expected that some form of tomographic, small animal optical imaging capability will be developed in the near future, and that this will provide the opportunity for the co-localization of optical signals to anatomical structures provided by tomographic CT and MR imaging. Integration of multiple modalities will be increasingly sought for small animal imaging (Fig 3).

Table 1. Comparison of Imaging Modalities

Method	Sensitivity	Resolution	Cost
CT	+	+++	++
US	++	++	+
MRI	++	+++	+++
PET	+++	++	+++
SPECT	++	++	++
Luminescence	+++	++	++
Fluorescence	+++	++	+

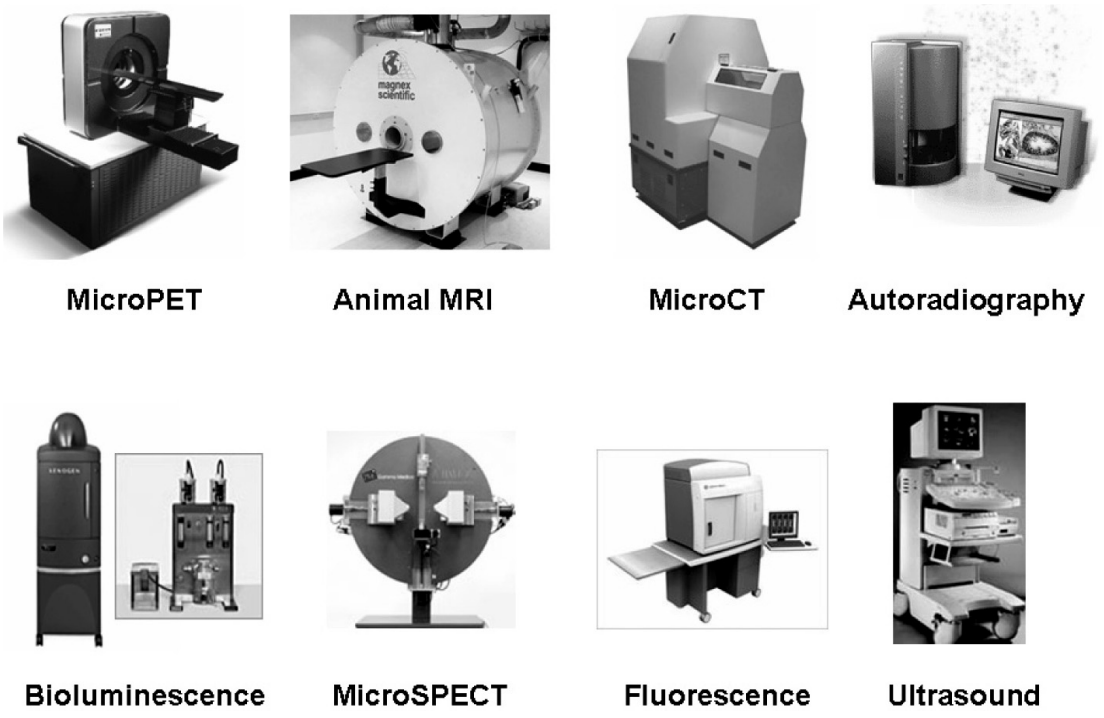

Fig 3. Small animal imaging modalities that can be used for molecular imaging

Impact of Preclinical and Translational Molecular Imaging

Preclinical molecular imaging is a rapidly evolving technology that is revolutionizing the ability to drive medical research from the laboratory bench to the patient's bedside. Ongoing studies involving mouse models of human diseases illustrate the significant impact that preclinical molecular imaging is having on translational research. In the case of cancer, people are investigating animal models of cancer to learn how healthy cells are transformed into tumor cells and how intermediate precancerous cells respond to various types of therapeutic approaches. As studies are growing more sophisticated, more precise markers are needed to study more subtle forms of cancer progression and diseases. Although several molecular imaging technologies are currently available for use in clinical practice, anatomic localization will become increasingly important as more biologically-targeted tracers are introduced. Thus, there will be an increasing need for hybrid or fusion imaging. Moreover, use of radio-, optical, and other forms of biological tracers or contrast agents to diagnose disease and assess efficacy of novel therapeutics will grow.

Conclusion and Future Perspectives

Considerable numbers and varieties of molecular imaging modalities are being investigated these days. Although basic science investigations will continue to dominate for the time being, an eye towards design of clinical translational research will be necessary to ensure successful integration and practical use of molecular imaging. More importantly, increased collaborative efforts between basic scientists, clinicians, and industry will be necessary to optimize device design and to identify new applications. In conclusion, molecular imaging will change many clinical paradigms in future medicine in conjunction with rational targeted therapies.

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