Advanced Drug Delivery Reviews 76 (2014) 60–78

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Targeted multimodal imaging modalities ☆

Seung Yong Lee [1], Seong Ik Jeon [1], Seulhee Jung, In Jae Chung, Cheol-Hee Ahn *

Research Institute of Advanced Materials (RIAM), Department of Materials Science and Engineering, Seoul National University, Gwanak-ro 1, Gwanak, Seoul 151-744, Republic of Korea

ARTICLE INFO

Available online 24 July 2014

Keywords:
Multimodality
Active targeting
Molecular imaging
Targeting moieties
Imaging probes

ABSTRACT

Molecular imaging non-invasively visualizes and characterizes the biologic functions and mechanisms in living organisms at a molecular level. In recent years, advances in imaging instruments, imaging probes, assay methods, and quantification techniques have enabled more refined and reliable images for more accurate diagnoses. Multimodal imaging combines two or more imaging modalities into one system to produce details in clinical diagnostic imaging that are more precise than conventional imaging. Multimodal imaging offers complementary advantages: high spatial resolution, soft tissue contrast, and biological information on the molecular level with high sensitivity. However, combining all modalities into a single imaging probe involves problems yet to be solved due to the requirement of high dose contrast agents for a component of imaging modality with low sensitivity. The introduction of targeting moieties into the probes enhances the specific binding of targeted multimodal imaging modalities and selective accumulation of the imaging agents at a disease site to provide more accurate diagnoses. An extensive list of prior reports on the targeted multimodal imaging probes categorized by each modality is presented and discussed. In addition to accurate diagnosis, targeted multimodal imaging agents carrying therapeutic medications make it possible to visualize the theranostic effect and the progress of disease. This will facilitate the development of an imaging-guided therapy, which will widen the application of the targeted multimodal imaging field to experiments in vivo.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Targeted Imaging".

* Corresponding author.
E-mail address: chahn@snu.ac.kr (C.-H. Ahn).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.addr.2014.07.009
0169-409X/

1. Introduction

1.1. Molecular imaging

Molecular imaging, which has been developed since the early 1990's, non-invasively visualizes and characterizes the biologic functions and mechanisms in living organism at a molecular level. Molecular imaging therefore facilitates better understanding of diseases and the detailed application of personalized treatments for patients. Molecular imaging differs from conventional medical imaging, in that it creates images of the body for the clinical purpose of examining or diagnosing diseases based on both visual and quantitative information. Detecting progress of various diseases, biodistribution of drugs, assessing metabolic changes, and molecular events in vivo now become more feasible in real time by molecular imaging techniques [1]. With the rapid development of imaging instruments, imaging probes, assay methods, and quantification techniques, more refined and vivid images are being obtained [2].

Representative imaging modalities include magnetic resonance imaging (MRI), X-ray computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), optical microscopy, ultrasound and photoacoustic imaging. Table 1 lists the characteristics of each modality. Modalities can be largely divided into two categories, anatomic imaging and functional imaging [3]. Anatomic imaging, also defined as structural imaging, produces information on the exact location inside the body and region of interest with characteristic sensitivity, spatial resolution, and soft tissue contrast, depending on the employed imaging modality. Functional imaging depicts the spatial distribution of biological or metabolic activities and provides information on molecular events within a certain tissue or organ by employing proper probes or tracers. CT and MRI provide three-dimensional anatomic information without penetration depth issues; CT with high spatial resolution and MRI with excellent soft tissue contrast. PET, SPECT and optical imaging visualize the biological functions on molecular level [4–7].

1.2. Multimodal imaging

Multimodal imaging combines two or more imaging modalities into one system to produce details in clinical diagnostic imaging that are more precise than those of conventional imaging. Each imaging modality offers complementary advantages and not only has unique assets, but also has problems of insufficient sensitivity or spatial resolution, which limit its ability to obtain reliable and accurate information at a disease site. While merging one modality from anatomic imaging and another from functional imaging is not always required, multimodal imaging is usually designed to fuse anatomical information with better spatial resolution and biological information at the molecular level with high sensitivity [8].

Table 1
Characteristics of each imaging technique.

Technique	Physical basis	Resolution	Sensitivity[a]	Characteristics
MRI	Magnetic resonance intensity contrast	50 μm	10^{-9}–10^{-6}	- High resolution of soft tissues - No tissue penetrating limit - High cost - Long imaging time
CT	X-ray attenuation, computed image reconstitution	50 μm	10^{-6}	- Fast, cross-sectional images - High spatial resolution - No tissue penetrating limit - Poor resolution of soft tissues - Radiation risk - Not quantitative
PET	Positron annihilation (β^+-decay), detection of γ rays	1–2 mm	10^{-15}	- High sensitivity & quantitative - No tissue penetrating limit - Whole-body scanning - High cost & radiation risk - Can detect only one radionuclide
SPECT	γ-Decay, detection of γ rays	1–2 mm	10^{-14}	- High sensitivity - No tissue penetrating limit - Can distinguish between radionuclides - Radiation risk - Low spatial resolution - Requires radioactivity
Optical imaging	Detection of emitted visible or NIR photons	1–2 mm	10^{-12}	- High sensitivity with multicolor imaging - Activatable - Easy, non-damaging imaging technique - Low spatial resolution - Poor depth penetration
Photoacoustic	Photo-acoustic effect	50 μm	10^{-12}	- Better depth resolution than light - Needs for optimization processes
Ultrasound	Reflection of sound waves	50 μm	10^{-8}	- Real-time imaging - Low cost - Poor image contrast - Poor working in air-containing organs - Operator dependent analysis

[a] Moles of label detected.