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Optical Molecular Imaging Frontiers in Oncology: The Pursuit of Accuracy and Sensitivity

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ABSTRACT Cutting-edge technologies in optical molecular imaging have ushered in new frontiers in cancer research, clinical translation, and medical practice, as evidenced by recent advances in optical multimodality imaging, Cerenkov luminescence imaging (CLI), and optical image-guided surgeries. New abilities allow *in vivo* cancer imaging with sensitivity and accuracy that are unprecedented in conventional imaging approaches. The visualization of cellular and molecular behaviors and events within tumors in living subjects is improving our deeper understanding of tumors at a systems level. These advances are being rapidly used to acquire tumor-to-tumor molecular heterogeneity, both dynamically and quantitatively, as well as to achieve more effective therapeutic interventions with the assistance of real-time imaging. In the era of molecular imaging, optical technologies hold great promise to facilitate the development of highly sensitive cancer diagnoses as well as personalized patient treatment—one of the ultimate goals of precision medicine.

KEYWORDS optical molecular imaging, multimodality molecular imaging, optical multimodality tomography, Cerenkov luminescence imaging, intraoperative image-guided surgery

1 Introduction

Imaging has become an unprecedentedly powerful tool in preclinical cancer research and clinical practice. In the past 15 years, there has been a significant increase in the number of imaging technologies and their applications in the field of oncology [1–4], but perhaps the biggest breakthroughs are in the new developments in optical molecular imaging (OMI). With recent advances in optical multimodality imaging, Cerenkov luminescence imaging (CLI), and intraoperative optical image-guided surgery, the sensitivity and accuracy of tumor diagnoses and therapeutic interventions have moved to a whole new level. Researchers and clinicians are now on the verge of being able to address some of the important questions in oncology that were once impossible to conclusively answer. How do we shift from conventional *in vitro* assay-based findings to non-invasive *in vivo* imaging-based detection? Is it possible to obtain accurate and quantitative biological information (e.g., the receptor density in tumor tissues) on a three-dimensional (3D) cellular or sub-cellular level? How can we better delineate tumor boundaries and guide tumor resection? Can we exceed the sensitivity limitation of conventional imaging methods for effective small tumor foci detection both preoperatively and intraoperatively? How do we translate preclinical OMI into clinical applications for better tumor treatment outcomes?

In this article, we highlight some recent advances of OMI in three categories: optical multimodality imaging, CLI, and optical image-guided surgery. We review cutting-edge optical imaging instruments, the development of optical tomographic imaging models and reconstruction algorithms, and promising optical imaging strategies with smart utilization of multiple molecular probes in both breadth and depth. We also demonstrate specific applications and state-of-the-art *in vivo* imaging examples of OMI in biomedical research and recent clinical translations.

2 *In vivo* optical multimodality molecular imaging

Different imaging modalities have their inherent advantages and disadvantages, and they are complementary. For example, radionuclide imaging has a superb sensitivity to molecular targets but a limited spatial resolution, whereas computed tomography (CT) and magnetic resonance imaging (MRI) can offer good spatial resolution but suffer from low sensitivity in detecting molecular events [5]. Planar optical imaging that adopts photographic principles is the simplest technique for capturing visible and/or near-infrared (NIR) light emitting from optical reporter molecules *in vivo* [6–8]. This planar

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technique can offer good superficial resolution (the resolution of an imaging subject surface), high sensitivity, and high-throughput imaging ability, and it is technically easy to implement preclinically [9]. However, it also has two major limitations. The first limitation is the difficulty in quantification of the *in vivo* distribution of optical probes due to the nonlinear relationship in spatial position and signal strength between the detected surface flux and the light source [10]. The second is the relatively shallow imaging depth due to the significant light scattering and absorption inside the tissue and organs of imaged animals [11]. These features result in the application of this approach primarily to qualitative superficial observation. Although various efforts have been made to develop different algorithms for tomographic reconstruction solely using planar optical images, the process inevitably involves erroneous interpretation of the data collected unless the nonlinear effects are explicitly corrected or accounted for [9]. Therefore, combining planar optical imaging with other modalities is recommended in order to compensate for these limitations while building on its strengths to capitalize on its great potential [12].

2.1 From 2D qualitative to 3D quantitative imaging

Tomographic reconstruction of the biodistribution of optical molecular probes can be traced back to the early 1990s. The first theoretical frameworks were proposed as a way to spatially resolve intrinsic tissue contrast in the context of studying hemodynamics or organelle concentration [13–16]. Visible and NIR photons (from 650 nm to 950 nm) are highly scattered in tissue and start to diffuse within a millimeter of propagation [17]. However, a portion of the light can still penetrate several centimeters and reach a small-animal skin surface because of the low photon absorption in this spectral window [18, 19], which is known as the first NIR window (NIR-I) [20, 21]. At wavelengths shorter than 650 nm, there is an increased absorption by blood (oxygenated and deoxygenated) and skin, whereas at wavelengths longer than 950 nm, water and lipids demonstrate stronger absorption.

In recent optical multimodality tomography (OMT), the diffuse light patterns are collected from a small animal surface at one or multiple angles using photodetector sets or various charge-coupled-device (CCD) cameras. Meanwhile, the anatomical structure of the animal is acquired using CT or MRI (Figure 1) as one of the *a priori* sets of information for helping optical reconstruction. Based on the types of optical molecular probe applied, this 3D non-invasive whole-body small-animal imaging technology is subdivided into three categories: fluorescence molecular tomography (FMT, employing fluorescent probes and external illumination sources) [22, 23], bioluminescence tomography (BLT, employing reporter genes, luciferin substrates, and no external illumination sources) [24, 25], and Cerenkov luminescence tomography (CLT, employing radioactive probes and no external illumination sources) [26, 27]. With the presence of the extra dimension, the combination of sufficient imaging information from different modalities, and appropriate optical molecular probes with specificity to cellular and sub-cellular processes, OMT is able to overcome the first limitation of the conventional planar optical imaging technique mentioned earlier, and offer more accurate and robust quantitative imaging on a cellular and molecular level.

The hardware setup of these multimodality imaging methods may vary in different biomedical applications or when prepared by different research groups (Figure 1). Examples include the hybrid optical-CT imaging system shown in Figure 1(a) and (b), the hybrid optical-MRI system in Figure 1(c)–(e), and the triple-modality optical-CT-MRI system shown in Figure 1(f) and (g). However, there are two generic factors that have significant influence on tomographic performance. First, it is crucial to develop appropriate mathematical imaging models describing photon propagation in tissues—an issue that is known as the forward problem; and second, it is equally important to develop sophisticated algorithms for tomographic reconstruc-

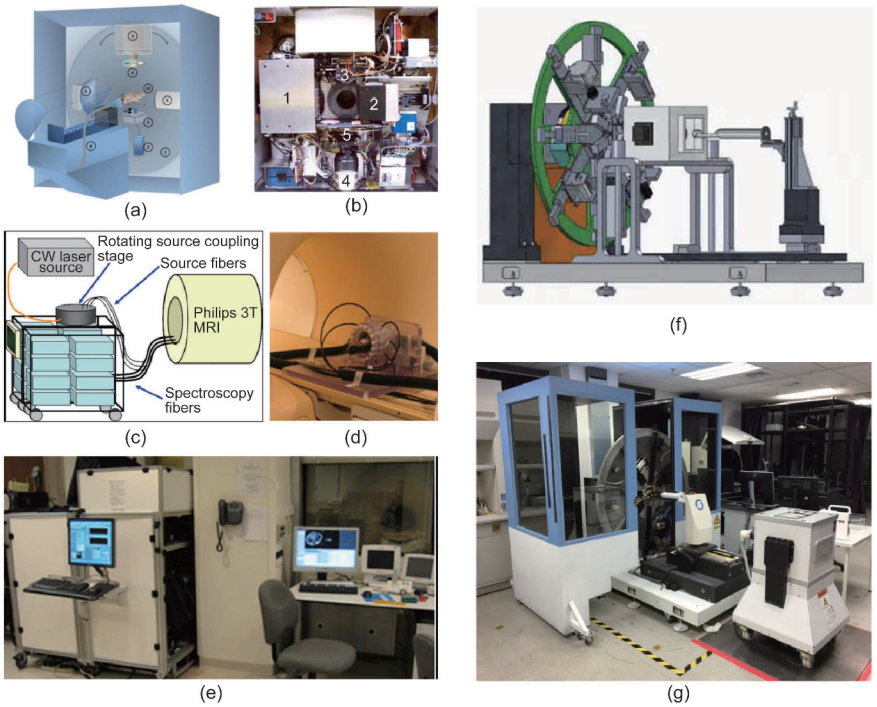

Figure 1. Examples of different OMT systems. (a) The diagram and (b) internal structure of the hybrid FMT-CT system developed by the Vasilis Ntziachristos group, reproduced from Refs. [28, 29]; the optical and CT subsystems are perpendicular to each other, and the mouse lies in the center of the rotating gantry during imaging acquisition. (c)–(e) The FMT-MRI system developed by the Brian Pogue group, reproduced from Ref. [30]. (c) A diagram of the MRI-coupled 16-channel optical system for fluorescence tomography. (d) The mouse with MRI coil and fiber bundles lies inside a clinical 3T MRI system. (e) The optical system is inside the MRI control room. (f) & (g) The triple-modality optical-CT-MRI system developed by the Jie Tian group. (f) The system design diagram shows that the optical and CT subsystems are installed on the rotating gantry, whereas the cubic MRI subsystem (1 T permanent magnet) is installed in the middle of the gantry and the small animal transmit unit. Since the system is still in development, the final position of the MRI subsystem may differ from the original design (g).