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Radiation Imagers for Quantitative, Single-particle Digital Autoradiography of Alpha- and Beta-particle Emitters

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Promising therapies are being developed or are in early-stage clinical trials that employ the use of alpha- and beta-emitting radionuclides to cure hematologic malignancies. However, these targeted radionuclide therapies have not yet met their expected potential for cancer treatment. A primary reason is lack of biodistribution, dosimetry, and dose-response information at cellular levels, which are directly related to optimal targeting, achieving a requisite therapeutic dose, and assessing the safety profile in normal organs and tissues. The current set of imaging tools, such as film autoradiography, scintigraphy, and SPECT/CT, available to researchers and clinicians do not allow the effective assessment of radiation absorbed dose distributions at cellular levels because resolutions are poor, measurement and analytical times are long, and the spatial resolutions are low—generally resulting in poor signal-to-noise ratios. Recently, new radiation digital autoradiography imaging tools have been developed that promise to address these challenges. They include scintillation-, gaseous-, and semiconductor-based radiation-detection technologies that localize the emission location of charged particles on an event-by-event basis at resolutions up to 20 μm FWHM for alpha and beta emitters. These imaging systems allow radionuclide activity concentrations to be quantified to unprecedented levels (mBq/μg) and provide real-time imaging and simultaneous imaging capabilities of both high- and low-activity samples without dynamic range limitations that plague traditional autoradiography. Additionally, large-area imagers are available (>20 × 20 cm^2) to accommodate high-throughput imaging studies. This article reviews the various detector classes and their associated performance trade-offs to provide researchers with an overview of the current technologies available for selecting an optimal detector configuration to meet imaging requirement needs.

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Introduction

For many years, alpha and beta particles have been recognized for their potential in cancer therapy. Both preclinical and clinical studies have shown that cell-directed radioimmunotherapy (RIT) can be an effective method for delivering a lethal dose of radiation to metastatic lesions and micrometastases.[1-9] Cell inactivation occurs as a high-energy electron (β) or a helium nucleus (α) imparts ionizations along a path, preferentially at or near the cell nucleus, thereby inducing damage to DNA. The quality of the radiation is characterized by the spatial distribution of the energy imparted and by the density of ionizations per unit path length. This is referred to as the linear energy transfer.[10-12] With their higher energy (2-10 MeV) and short range (40-70 μm in soft tissue), alpha particles have a much higher linear energy transfer (60-110 keV/mm) compared with β-particles (0.1-1 keV/mm), which range in energy from a few keV to MeV, and cause localized, irreparable double-strand DNA breaks that lead to immediate cell death, with minimal radiation to neighboring normal tissues.

Although targeted RIT with alpha emitters has the potential to be highly effective, it can also be quite toxic.[10] This places the utmost importance on knowledge of the spatial distribution of targeted, short-range alpha-emitter immunoconjugates as a function of time at the cellular and intracellular levels.[13] Additionally, an accurate representation of the biodistribution at this level is required to determine targeting efficiency and estimated absorbed dose to nontargeted tissues and organs where alpha-emitters may also accumulate.[10]

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Determining radionuclide activity distributions remains difficult with the current technology, particularly in clinical practice, and dosimetric biodistribution data from pretreatment imaging studies are not possible for most alpha-particle-emitting radionuclides with therapeutic potential.[10] Consequently, greater emphasis is placed on preclinical studies and extrapolation of results for use in human RIT.

Imaging plays a key role for determining the local biodistribution of radioimmunoconjugates. Autoradiography is an important tool as it serves as an ex vivo imaging technique that provides a high-resolution snapshot of the radionuclide activity distribution at a single instance in time.[14,15] Traditional autoradiography involves placing a thin section of tissue, for example, 10 μm thick, in contact with an imaging plate composed of a phosphor screen and a film—all enclosed within a light-tight cartridge. Scintillation light generated by charged-particle interactions in the phosphor exposes the film, which is later developed to obtain a visual representation of the radionuclide distribution. Another technique is the use of a photostimulable phosphor imaging plate that traps electrons during exposure.[16] Image readout is done by scanning a laser across the plate to free trapped electrons followed by detection of recombination photons using a photomultipler tube (PMT), whose output is proportional to the total signal deposited during the exposure. A notable advantage of traditional autoradiography is that large-area plates enable many samples to be simultaneously imaged. Limitations of this approach include a relatively low dynamic range, limited activity quantification capability, and lack of a real-time imaging capability. A low dynamic range presents difficulties in simultaneous imaging of both high- and low-activity samples where sufficient contrast to visualize the low-activity distribution requires long exposures but negatively causes saturation effects for the high-activity samples. Conversely, good contrast for high-activity samples is achieved with shorter exposures, but results in poor image quality for low-activity samples. Additionally, the optimal exposure time for either scenario may be unknown and require trial imaging tests.

Recently, digital autoradiography methods have been developed using a new generation of position-sensitive, charged-particle imagers that can detect individual alpha and beta particles on an event-by-event basis and estimate their emission location at high spatial resolutions. A number of these imagers have been developed for single-photon x-ray or gamma-ray imaging applications including small-animal SPECT and scintigraphy, but can readily be configured for charge-particle digital autoradiography. A variety of detection options exist including scintillation-, gaseous-, and semiconductor-based technologies. Key advantages of these technologies over those used for traditional autoradiography include an unrestricted dynamic range, activity quantification capability, high detection efficiency, and a real-time imaging capability.

In this article, we review these detection technologies and list their features in the application of digital autoradiography of alpha- and beta-emitters in terms of spatial resolution, imaging area, commercial availability and cost, counting-rate capability, sample type, and particle-discrimination capability.

Single-particle Radiation Imagers

Scintillation-based Charge-coupled Device/ Complementary Metal-Oxide Semiconductor Imagers

During the last several years, a number of high-spatial-resolution, scintillation-based radiation detectors have been investigated. These detectors were primarily developed for preclinical gamma-ray imaging applications including small-animal SPECT and gamma-ray scintigraphy. Fine sampling of the scintillation light distribution, which enables location of the event interaction at high spatial resolution, is achieved using a combination of a very thin phosphor screen or a structured scintillator, for example, microcolumnar CsI(Tl),[17] that restricts the lateral spread of scintillation light and a highly pixelated imaging sensor such as a charge-coupled device (CCD) or complementary metal-oxide semiconductor (CMOS). The intrinsic detector spatial resolution for gamma-ray imaging with these detectors is ~100 μm FWHM.[18-20] This imaging approach is in contrast to that employed for traditional, PMT-based gamma cameras in nuclear medicine where scintillation light is spread over large areas and multiple PMT tubes, with intrinsic detector resolutions in the range of 2-3 mm or lower. A variety of imaging configurations exist for these CCD, CMOS-based detectors, each with inherent trade-offs in terms of spatial resolution, detector area, counting-rate capability, and cost. Generalized components and imaging configurations for these detectors are shown in Figure 1.

High-resolution position estimation of the interaction location is achieved by imaging the scintillation light distribution generated by the charged-particle or photon interaction, extracting the pixels associated with the event, which is referred to as a cluster, and then computing a two-dimensional (2D) or three-dimensional estimate of the position using a centroid calculation or maximum-likelihood algorithm.[18] This position estimation algorithm is illustrated in Figure 2 for alpha particles.

One realization of this class of detectors that was developed for beta-particle digital autoradiography, as described by Barthe et al, is called the Micro Imager (BetaImager-DFine) and is composed of a phosphor screen, image intensifier, and CCD camera.[22] Using a similar imaging configuration and the recent advances in CCD/CMOS cameras and the computing capabilities afforded by the latest graphics processing units, Miller et al developed an imager sensitive to alphas, betas, thermal neutrons, and gamma-ray photons.[21] The detector is called the ionizing-radiation quantum imaging detector (iQID) and uses multi-megapixel, high-frame-rate CMOS cameras. Upfront optical amplification by the image intensifier allows for large-area imagers and enables practically any camera sensor to be use for radiation imaging, even cell phone camera sensors. The imager provides a spatial resolution of ~20 μm FWHM for alpha emitters.[23] A cross-sectional schematic of an iQID is shown in Figure 3. Recently, this imaging methodology has gained interest for targeted-alpha therapy applications for quantifying the spatial activity distribution near cellular levels and for microdosimetry of alpha emitters. Imaging alpha particles typically involves placing