# *Perspectives and Potential Applications of Nanomedicine in Breast and Prostate Cancer*

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***Abstract:*** Nanomedicine is a branch of nanotechnology that includes the development of nanostructures and nanoanalytical systems for various medical applications. Among these applications, utilization of nanotechnology in oncology has captivated the attention of many research endeavors in recent years. The rapid development of nano-oncology raises new possibilities in cancer diagnosis and treatment. It also holds great promise for realization of point-of-care, theranostics, and personalized medicine. In this article, we review advances in nano-oncology, with an emphasis on breast and prostate cancer because these organs are amenable to the translation of nanomedicine from small animals to humans. As new drugs are developed, the incorporation of nanotechnology approaches into medicinal research becomes critical. Diverse aspects of nano-oncology are discussed, including nanocarriers, targeting strategies, nanodevices, as well as nanomedical diagnostics, therapeutics, and safety. The review concludes by identifying some limitations and future perspectives of nano-oncology in breast and prostate cancer management. 

**Key words:** nanocarriers; nanodevices; diagnostics; therapeutics; imaging; personalized medicine

## *1. INTRODUCTION*

Nanotechnology generally deals with structures and systems with a size less than 100 nm.[1] Owing to the apparent reduction in size, nanostructures possess unique physical, chemical, and biological properties.[2] Technological advances in physics, chemistry, engineering, and molecular biology in the last decade enabled the study and manipulation of these tiny structures for various applications, such as in electronics, optics, and medicine.[3–5] Although nanotechnology is still in the early stages of development, it has already demonstrated

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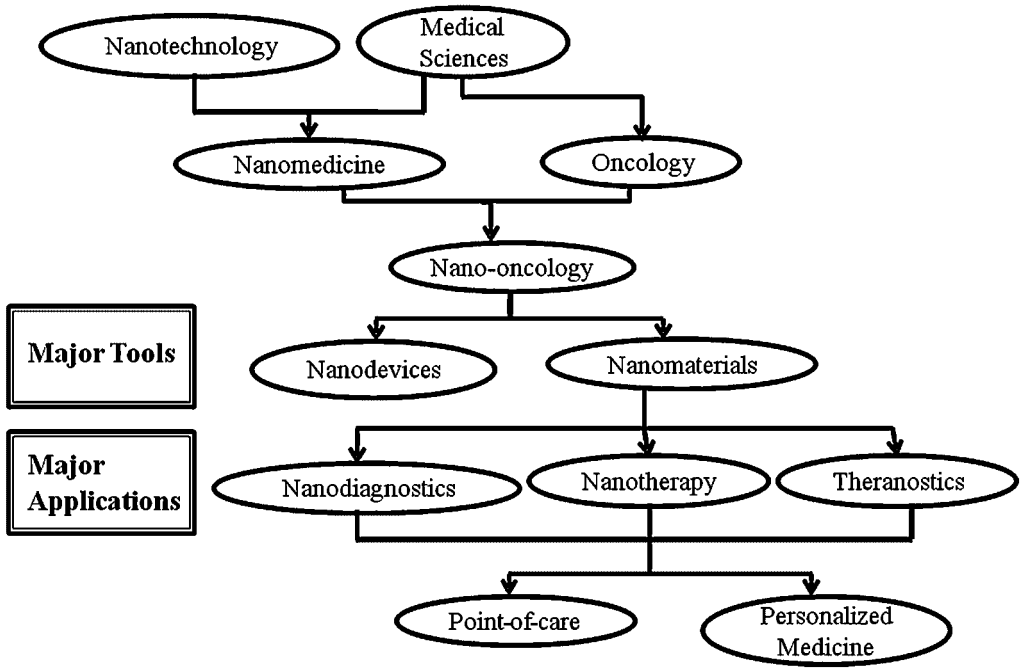


***Figure 1.*** The relationship between nano-oncology and related fields.

enormous potential as a potent platform for future technological development in diverse areas of fundamental research and applications.

Nanomedicine is the application of nanotechnology in the medical field. As physiological processes at cellular and subcellular levels occur on a nanoscale, nanomedicine holds great promise for improving medical diagnostics and therapeutics.[6] Among the numerous medical applications of nanomedicine, its utilization in oncology has received enormous attention in recent years, with an emphasis on breast and prostate cancer, which are among the most common types of cancer.[7] Special efforts have been directed to utilizing nanomedical techniques in cancer diagnosis and treatment to improve the efficiency and safety of conventional anticancer regimens, such as chemotherapy, radiotherapy, and surgery. For instance, nanoparticle-based imaging facilitates the visualization of cancerous tissue[8,9] and nanomedical photodynamic therapy (PDT) has been employed to treat tumors.[10,11] Furthermore, nano-oncology has potential paradigm-shifting impact on theranotics, personalized medicine, and point-of-care. The relationship between nano-oncology and related medical interventions is illustrated in Figure 1. In spite of these advances, nano-oncology for breast and prostate cancer still suffers from several limitations and challenges, and the translation of preclinical research to humans still needs further investigations.

In this review, we surveyed the state of the art in nano-oncology, with an emphasis on breast and prostate cancer. The scope of this review is limited to the major aspects of nano-oncology that include nanocarriers, targeting strategies, nanodevices, and their applications in diagnostics, therapeutics, and human safety. Challenges and perspectives on future directions of nano-oncology are briefly discussed.

## *2. NANOCARRIERS AND TARGETING STRATEGIES*

The development of nanocarriers has become a prominent area of nanomedical research as these nanostructures feature high surface-to-volume ratio, novel functionalities, improved

specificity, and pharmacokinetics. To date, numerous nanocarriers have been employed for nano-oncology applications, including polymeric nanocarriers (e.g. dendrimers, organic polymers, micelles, and liposomes), inorganic carriers (e.g. quantum dots (QDs), carbon nanotubes (CNTs), and gold nanoparticles (AuNPs), and hybrid carriers (e.g. dye-doped inorganic nanoparticles). In addition, the performance of nanocarriers can be further enhanced by various targeting strategies.

### *A. Nanocarriers*

Although nanomedicine is still at its infancy, thousands of nanocarrier-related research articles have already been published.[12] Nanocarriers can be generally categorized into two groups: polymeric and inorganic. Because of the large quantity in nanocarriers' types, comprehensive discussions would be too extensive. Consequently, we will only summarize nanocarriers in brief, with additional discussion of three paradigms in each category.

*1. Polymeric nanocarriers*

Polymeric nanocarriers possess several merits for nano-oncology applications, such as biocompatibility, biodegradability, processability, and high drug-loading capacity, which render them attractive candidates as drug delivery vectors. There are various forms of polymeric nanocarriers, such as dendrimers, micelles, and liposomes (Fig. 2).

Dendrimers are hyperbranched polymers with low polydispersity.[13] These well-defined macromolecules have a globular architecture with several branches reaching out from the core.[14] The concept of dendrimers was first introduced in 1985,[15] and in 1990, a convergent approach to synthesize dendrimers was developed by Frechet et al.[16] The monodispersity and well-defined structures of dendrimers lead to high reproducibility of their functionalities. Moreover, they also offer multivalency that enables grafting of various biological moieties on a

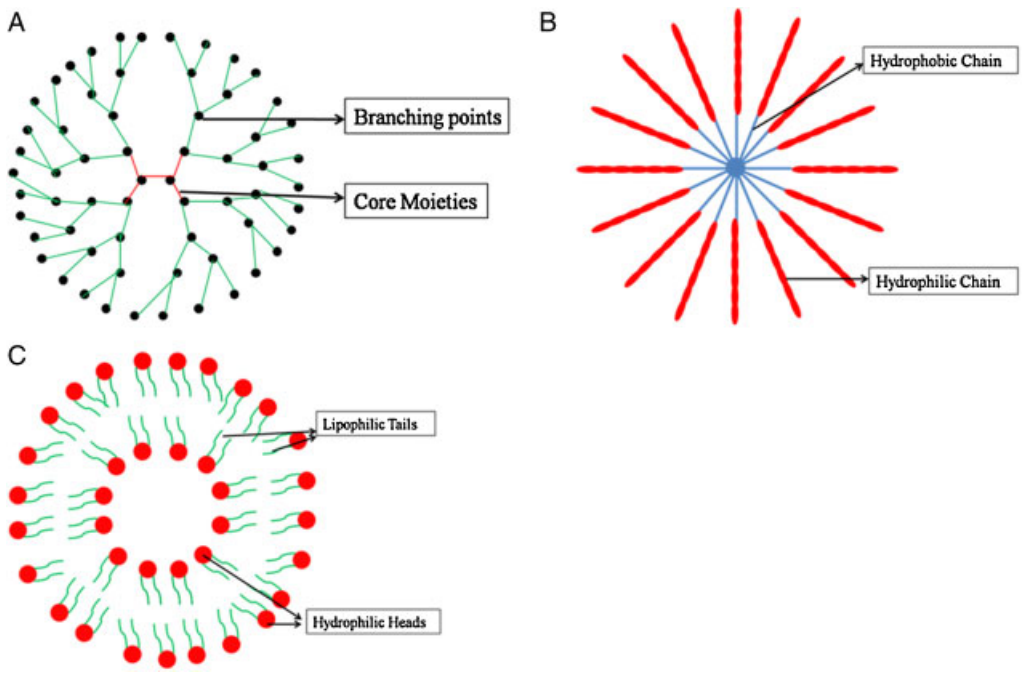


***Figure 2.*** Illustrations of polymeric nanocarriers: (**A**) dendrimers, (**B**) polymeric micelles, and (**C**) liposomes. [Color figures can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

single nanocarrier.[17] Beside dendirmers, other macropolymers, such as poly-L-lysine (PL), have also been employed as carriers for drugs and contrast moieties.[18–21] For instance, Weissleder et al. developed numerous PL-based contrast agents for imaging enzyme activities.[22–25]

Polymeric micelles are nanostructures generated from spontaneous self-assembly of amphiphilic block polymers.[26] They generally possess a hydrophilic outer shell and a hydrophobic core or vice versa. Micelles can only be formed when (1) the temperature of the system exceeds the critical micelle temperature, and (2) the concentration of polymer exceeds the critical micelle concentration.[27] Because the core of these micelles can function as an ideal loading environment for poorly soluble drugs, they are considered to be potent candidates for targeted drug delivery and controlled drug release.[28]

Liposomes are globular nanostructures composed of one or multiple amphiphilic lipid bilayers.[29] They have superior biocompatibility owing to their composition that is similar to the cell membranes. A unique feature of liposomes is that they possess distinct hydrophilic and hydrophobic regions, which enable them to simultaneously encapsulate both water-insoluble and water-soluble materials.[30] For instance, hydrophobic moieties can be entrapped in the lipid bilayers while hydrophilic moieties can be retained within the aqueous core.[31] Many of the liposomes are larger than 100 nm in hydrodynamic diameter, with some approaching 1 μm.

*2. Inorganic nanocarriers*

Inorganic nanocarriers, such as QDs, CNTs, and AuNPs, have also been adopted for nano-oncology use. Compared to polymeric nanocarriers, inorganic nanocarriers offer unique functionality owing to their innate physical, chemical, and biological properties.

QDs are colloidal semiconductor nanoparticles, with size ranging from 2 to 100 nm.[32] They are typically formed by group II-VI elements or III-V elements. Unlike bulk semiconductors, the bandgap between valence and conductance band in nanosize semiconductors is not fixed. Instead, the bandgap depends on their size.[33] Consequently, QDs displays size-dependent fluorescence spectra and size-dependent fluorescent life time.[34] Moreover, QDs enjoy several advantages over conventional fluorescent dyes: they have narrower emission spectra, larger Stokes shift, higher quantum yield, and higher photostability.[35] In addition, the broad excitation spectrum of QDs facilitates their use in multicolor imaging applications. With such broad excitation window, QDs possessing different emission peaks can be excited with the same light source to report diverse molecular processes. These inherent characteristics render QDs promising candidates for oncological imaging applications.

CNTs are cylindrical carbon nanostructures with a high aspect ratio, which are essentially rolled-up tubular structures of sheets of condensed benzene rings (graphene).[36] CNTs can be generally categorized into two classes based on their structures of walls: single-walled nanotubes and multiwalled nanotubes. They are attractive as potential nanocarriers owing to their high anisotropy, high stability, unique optical properties, ease of fabrication, and facile bioconjugation.[37] Moreover, as CNTs have both inner and outer surfaces, they can be functionalized differently, depending on the intended applications.[38] Consequently, CNTs are ideal candidates as multifunctional nanocarriers. However, their utilization in nano-oncology is currently limited by their intrinsic toxicity. For instance, it was reported that CNTs can impose significant oxidative stress on cells, causing apoptosis and necrosis.[39–42]

AuNPs have also been applied to nanomedicine within the last decade. AuNPs are desirable as nanocarriers due to the following reasons: (1) they are relatively bioinert and stable in vivo, (2) they have tunable optical properties through localized surface plasmon resonance,[43] (3) they can be readily conjugated using thiol chemistry, and (4) they are thermally responsive to light, producing photothermal effect.[44] To date, numerous gold nanostructures have been made, such as Au nanospheres, Au nanorods, and Au nanoshells.[45]

These various forms of AuNPs provide another potential solution to significant challenges in oncology.

### *B. Targeting Strategies*

Traditionally, drugs or contrast agents are delivered orally or intravenously with poor specificity and bioavailability.[46] In addition, anticancer drugs can often be toxic to normal tissue and this side effect hinders the use of effective dosage of the therapeutic agents.[47] This effect is most prevalent in traditional chemotherapy.[48] Conceivably, nanocarriers can overcome this obstacle by employing various targeting strategies. In principle, this can be achieved by either tuning physical properties (passive targeting) or biochemical properties (active targeting) of the nanocarriers.

Passive targeting strategy relies on enhanced permeability and retention effect (EPR).[49] EPR is a phenomenon that originates from the histological signature of cancerous tissues. First, tumor tissues are ''leaky'' because cancer cells and extracellular matrix are poorly organized in terms of histology, leading to hyperpermeability. Second, cancerous tissues have poor lymphatic drainage due to rapid uncontrolled growth, which leads to nanocarriers' accumulation in the tumor environment.[50] In addition, EPR is size dependent.[51] Consequently, by fine tuning the size, nanocarriers can be tailored to selectively accumulate at tumor sites.

In contrast, active targeting is achieved by conjugation of targeting ligands to the nanocarriers for binding overexpressed surface molecules or receptors on cancerous cells (cancer biomarkers). Therefore, nanocarriers can be directed to cancerous tissue with higher efficiency. Actively targeted nanocarriers often interact with cancer cells via cell-surface receptors and subsequent receptor-mediated endocytosis.[52,53] In recent years, numerous active targeting strategies have been developed. For breast and prostate cancer, possible targets includes integrin,[54–56] gelatinase,[57] somatostatin receptors,[58] executioner caspases,[59] gastrin-releasing peptide receptor,[60–66] epidermal growth factor receptor (EGFR),[67–69] transferrin receptor,[70,71] folate receptor,[72,73] matrix metalloprotease (MMP),[74] luteinizing hormone releasing hormone (LHRH) receptor,[75] chorionic gonadotropin receptor,[76] urokinasetype plasminogen activator (uPA) receptor,[77,78] and vasoactive intestinal peptide receptor.[79–81]

## *3. NANODEVICES FOR IN VITRO APPLICATIONS*

In vitro analytical devices are crucial in clinical oncology because they can track cancer markers for diagnosis, prognosis, therapy, and personalized medical interventions. Technologically, these devices are fast, accurate, and affordable. In addition, the high throughput analytical capability facilitates rapid screening of samples. Together, these features of nanodevices are needed for early detection and prevention of cancer recurrence. Moreover, owing to their small size and portable nature, nanodevices are ideal for point-of-care applications. Using these devices, tedious, expensive, and resource-wasting procedures that are conventionally performed in hospitals and sophisticated laboratories can be accomplished at the bedside. In addition, only a small quantity of the biological sample is needed. For example, a drop of blood is sufficient for the analysis of multiple biomarkers.

Modern nanodevices for in vitro assays generally stem from microarray and microfluidic technologies. The incorporation of nanotechnology into these existing systems further enhances the performance of conventional micro-size devices while reducing their size and cost. Nanodevices are often based on developed nanoplatforms, such as semiconductor nanowires

(NWs), CNTs, QDs, or AuNPs. The interrelationship between nanodevices and related technologies is depicted in Figure 3.

NWs are particularly useful in nanodevice fabrications. These applications utilize field-effect transistors (FETs), which vary their conductivity in response to changes in their surface electric field.[82] As polar/charged macromolecules alter the electric field distribution of surroundings, electric conductance of nanowire FETs can change upon binding of biomacromolecules to their surface. These transient changes are quantitatively recorded to measure a target molecular process or biological event. In addition, as the nanowires are 1-D structures that have small cross-sections, biomolecules binding can lead to greater changes in conductance as compared to planar FETs. Lieber et al. developed nanowire sensor arrays that could detect multiple cancer markers simultaneously.[83] Prostate specific antigen (PSA; a prostate carcinoma biomarker), carcinoembryonic antigen (CEA; a breast cancer biomarker), and mucin-1 (a breast cancer biomarker) were detected from clinically relevant samples of blood serum and cell extract at femtomolar concentration with high selectivity. They were also able to monitor telomerase activity and inhibition in real-time. In addition, Chen et al. reported the development of GaN nanowire sensor that could detect ''hot spot'' mutations in the p53 tumor-suppressor genome down to picomolar concentration.[84]

CNTs have been utilized to fabricate nanodevices for breast and prostate cancer detection owing to their large surface area and unique electrical and mechanical properties. CNTs can be either a semiconductor or a metallic conductor, depending on their structural

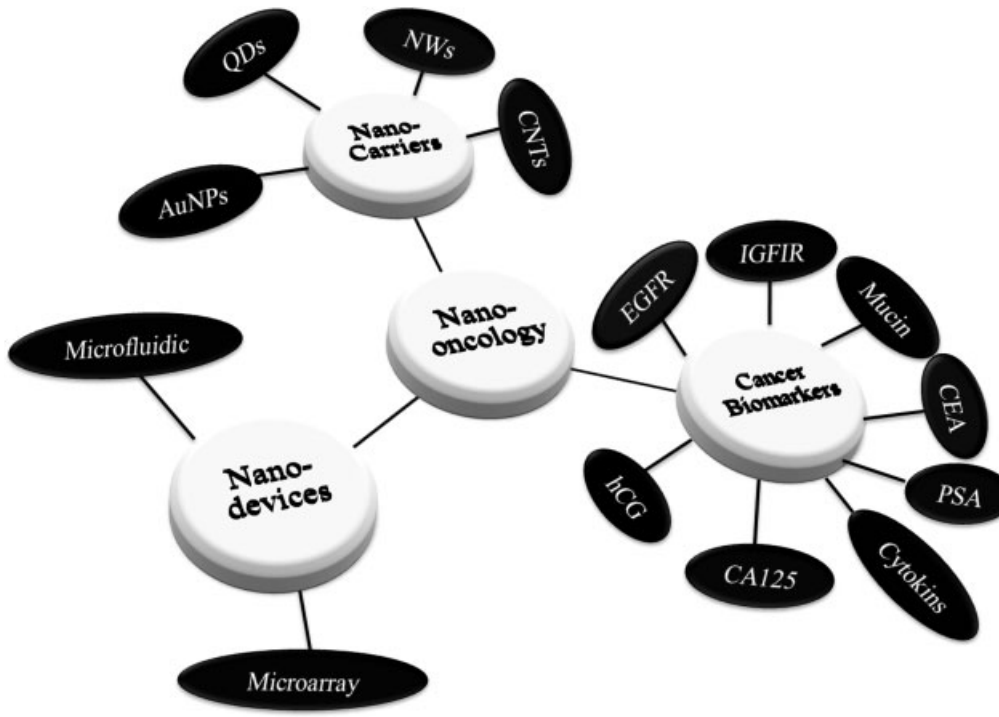


***Figure 3.*** Interrelationships between nanodevices and relevant technologies. NWs, semiconductor nanowires; CNTs, carbon nanotubes; QDs, quantum dots; AuNPs, gold nanoparticles; PSA, prostate specific antigen; CEA, carcinoembryonic antigen; IGF1R, Insulin-like growth factor-1 receptor; EGFR, epidermal growth factor receptor; CA125, cancer antigen 125; hCG, human chorionic gonadotropin.

chirality. Similar to NWs, semiconducting CNTs can also be employed to make FET for biosensing applications. For example, Li et al. demonstrated complementary biosensing of PSA using p-type CNTs and n-type $In_2O_3$ nanowires.[85] Upon PSA binding, reduced conductance in CNTs and enhanced conductance in nanowires were observed. Interestingly, Kim et al. found that introducing spacers to PSA-antibody functionalized CNT-FET surface could effectively lower the detection limit and suppress nonspecific binding.[86] They attributed such phenomena to larger distance between receptors due to the presence of spacers, and consequently charged that PSA could interact with CNTs more easily. Fabrication of biosensor arrays based on CNT-FETs that could detect single cell was reported by Shao et al.[87] These arrays were functionalized with insulin-like growth factor-1 receptor and EGFR-2 (widely known as HER2) specific antibodies. These arrays could sense MCF7 and BT474 human breast cancer cells in human blood. The authors postulated that multiplexed cell–antibody–CNT interactions imposed a stress on the CNTs that reduced their conductance.

Beside FETs, CNTs can be utilized to fabricate nanodevices in the form of CNT forest or electrode components. Yu et al. employed single-wall carbon nanotube (SCNTs) forests combined with CNT-secondary antibody bioconjugates to fabricate cancer immunosenors.[88] PSA was detected in serum and tissue lysates by such sensors, and they achieved $\pm 5\%$ accuracy for human serum samples with reference to an ELISA method. Similarly, Wang et al. showed that CNT-decorated glassy carbon transducers had improved performance in enzyme-based electrochemical detection of DNA hybridization of BRAC1 breast cancer gene segments.[89] In their study, CNT-modified glassy carbon electrodes were utilized as working electrodes, which allowed sensitive detection of targeted DNA. Maehashi et al. used a SCNT-modified platinum electrode to fabricate label-free electrochemical immunosensors.[90] These sensors were able to detect the PSA level as low as the cut-off limit between prostate hyperplasia and cancer. In their follow-up studies, SCNT-arrayed electrodes were integrated with microfluidic devices.[91] Using these devices, PSA and human chorionic gonadotropin (another tumor marker) could be detected simultaneously.

Similarly, QDs have been applied in nanodevices for breast and prostate cancer detection based on their exceptional photostability and brightness. Gokarna et al. fabricated QD-conjugated protein microarrays for PSA detection with reduced nonspecific binding.[92] In addition, they constructed QD-conjugated protein nanoarrays via dip-pen nanolithography. To multiplex the information content, Zajac et al. developed QDs protein microarrays for detecting multiple cancer biomarkers.[93] In the study, six cancer biomarkers, including TNF-$\alpha$, IL-8, IL-6, MIP-1$\beta$, IL-13, and IL-1$\beta$ cytokines, were detected down to picomolar concentration. Moreover, Jokerst et al. demonstrated that a nanobiochip can be fabricated, based on the integration of a microporous agarose bead array, a microfluidic system, and QDs.[94] Such chips could quantify three cancer biomarkers, including CEA, cancer antigen 125 (CA125), and HER-2 from clinical samples of serum and saliva.

AuNPs offer an alternative platform for nanodevices fabrication. Because AuNPs have a large area-to-volume ratio that facilitates surface absorption of protein molecules, they are ideal candidates for antibody immobilization. For instance, Yuan et al. fabricated a CEA immunosensor via layer-by-layer assembly of cationic chitosan and anionic AuNPs on glassy carbon electrodes.[95] The CEA antibody was subsequently immobilized on the electrodes. In their follow-up study, they reported another CEA immunosensor based on AuNPs/Nano-$CaCO_3$/Prussian-blue modified glassy carbon electrodes with a detection limit of 0.1 ng/ml.[96] Moreover, Lin et al. fabricated a disposable CEA immunosenser with a detection limit of 1 ng/ml by immobilizing CEA antibody on AuNPs-chitosan membrane modified indium-tin oxide (ITO) electrodes.[97] ITO electrodes make such sensors significantly cheaper than sensors based on glassy-carbon electrodes.

## 4. IN VIVO NANODIAGNOSTICS

Nanodiagnostics can offer oncologic imaging with high sensitivity, resolution, specificity, and reliability. With recent advances in nanotechnology and imaging technology, it is feasible to monitor cancer biomarkers, cellular events, molecular pathway dynamics, and therapeutic outcomes in vivo at the molecular level. Incorporating nanotechnology into imaging modalities, such as X-Ray, computed tomography (CT), ultrasound imaging, optical imaging, nuclear imaging, and magnetic resonance imaging (MRI), confer enhanced performance in cancer diagnosis. Although nanodiagnostics include a variety of imaging modalities, this section will focus on optical imaging, nuclear imaging and MRI methods as well as multimodal imaging. Nuclear imaging and MRI are well-established and numerous reviews on these methods are available.[98–112] Hence, only a brief discussion is presented. Special attention is given to new optical imaging and multimodal imaging technologies because they hold great promise for molecular imaging of cancer.

### A. Optical Imaging

The rapid developments in biophotonics and nanotechnology within the last two decades have accelerated the emergence of optical imaging for biomedical applications, as a paradigm-shifting method in functional and molecular imaging. Relying on visible and near-infrared (NIR) light, optical imaging is able to detect biological events ranging from molecular and subcellular levels to organ system.[113]

Optical imaging method has several advantages over conventional imaging methods. Optical imaging has numerous contrast mechanisms at its disposal, including absorption, scattering, fluorescence intensity, fluorescence lifetime, photoacoustic, and bioluminescence reporting strategies. Depending on the biological question of interest, optical imaging can reveal fundamental molecular pathways in a noninvasive manner, making it an ideal method for molecular imaging. Beyond cellular studies, where single molecule is attainable, optical imaging can provide structural and functional information with high sensitivity. Of all imaging methods, biomedical optical techniques have the highest spatial resolution, with the ability to resolve individual cells through intravital microscopy[114–119] and organ structures by optical coherence tomography.[120–128] Thus, the method is amenable to all medical interventions where the target tissue is superficial, such as the skin, eye, and the oral cavity. It is also suitable for endoscope- and catheter-accessible organs, such as the gastrointestinal system. Noninvasive applications in deep tissues are also feasible in some organs, such as the breast tissue, where significant lipid content allows NIR light to travel longer distances with reduced attenuation compared to the liver. Unlike nuclear methods, optical imaging utilizes nonionizing radiation. This explains the recent surge in interest to apply the method in intraoperative procedures, where tumor margins, treatment response, and important physiological parameters can be monitored in real-time in a surgical suite. Cost consideration also favors optical imaging technologies. The imaging system is relatively cheap and can be miniaturized into handheld or portable devices that facilitate point-of-care medical interventions. Moreover, integration of optical imaging with therapeutic modalities, such as PDT, has been explored in small animals and humans.[129,130]

Yet, historically optical imaging suffers from sallow penetration depth due to wavelength-dependent absorption of tissues. As a result, their biomedical applications were initially limited to surface-weighted techniques with microscopes and endoscopes. Recently, advances in NIR optical instrumentation and NIR contrast agents have pushed this limit to several centimeters by operating in the biological window (700–900 nm). Consequently, small animal whole-body tomography and deep tissue human imaging have been accomplished by

optical imaging and spectroscopy.[131–133] For example, Patwardhan et. al developed a fluorescence diffusion optical tomography (DOT) system for rapid whole-body scan of mice in approximately 2 min.[134] This DOT system could provide quantitative whole-body biodistribution of targeted fluorescent contrast agents. Mice bearing subcutaneous implanted human breast cancer carcinoma MDA-MB-361 were imaged and the preferential uptake of the targeted molecular probes in the tumor sites was reported quantitatively. Therefore, DOT has enormous potential for real-time study of pharmacokinetics and pharmacodynamics of cancer therapeutic and imaging agents. Furthermore, Nothdurft et al.[135] and Kumar et al.[136] designed fluorescence life time DOT systems (FLT-DOT) for in vivo imaging. Because tissue heterogeneity in vivo leads to variations in fluorophore lifetimes, FLT-DOT is particularly efficient in differentiating tumors from their surrounding tissues. The new instruments are capable of detecting and resolving FLT ranging from 349 ps to 1,340 ps, with $\pm 5$ ps precision and $<100$ ps temporal resolution.[135] Mice bearing 4T1 murine mammary carcinoma were imaged using FLT-DOT system, and accumulation of targeted optical probes at tumor site was revealed (Fig. 4). Another advantage of FLT imaging is its independence on fluorescence intensity. This feature allows the use of both fluorescence intensity and lifetime contrast mechanisms for complementary reporting strategies.[137]

Coupled with advances in instrumentation is the development of biocompatible molecular probes and nanoparticles for use in biological imaging. For in vivo applications, carbocyanine dyes are widely used. A typical example of this class of polymethine dyes is indocyanine green, a US Food and Drug Administration-approved dye for use in humans.[113] Carbocyanines are particularly interesting because their spectral properties can be altered through small structural modifications, thereby generating a series of fluorescent compounds with absorption and emission from visible to the NIR spectral region. This feature renders them particularly suitable for cell, small animal, and human cancer imaging.[132] Some examples of carbocyanine dyes for in vi*vo* imaging are cypate,[138] Cy dyes,[139] and related water-soluble dyes[140,141] (Fig. 5). Yet, upon injection into blood vessels, some of these fluorescent dyes are often opsonized and subsequently destroyed by phagocytes. Additionally, because they are small molecules, they do not enjoy the privilege of EPR effects in tumor imaging. To overcome these obstacles, integration of carbocyanine dyes with nanocarriers is advantageous. For instance, Almutairi et al.[8] encapsulated cypate dye in a biodegradable polyester dendrimer, and subsequently coated them with a protective polyethylene oxide shell (Fig. 6). This configuration sequestered the dye from the biological medium, improving and stabilizing the photophysical properties of the nanoprobes in vivo. Moreover, their blood circulation time increased accordingly because of decreased uptake by the reticuloendothelial

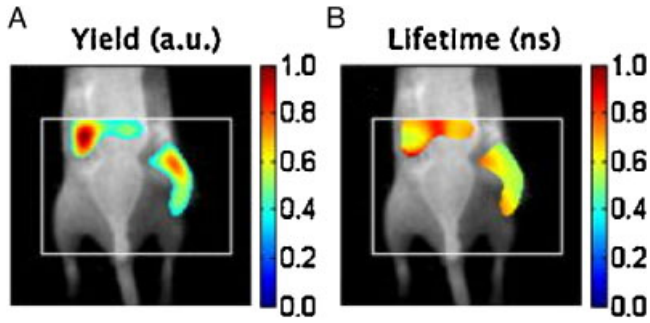


***Figure 4.*** In vivo imaging of tumor using FLT-DOT.[135] (**A**) Fluorescence yield for a tumor-bearing mouse, imaged 24 hr after injection of a targeted contrast agents. The subcutaneous tumor locates on the right flank. (**B**) Coregistered FLT image. Reprinted with permission from reference 135. Copyright 2009 SPIE. [Color figures can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

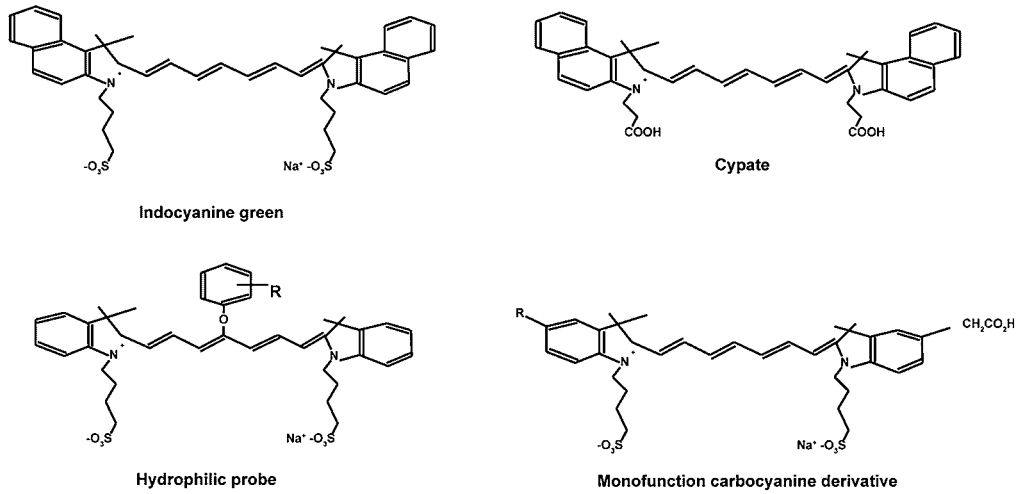


***Figure 5.*** Structures of representative NIR carbocyanine dyes.[113]

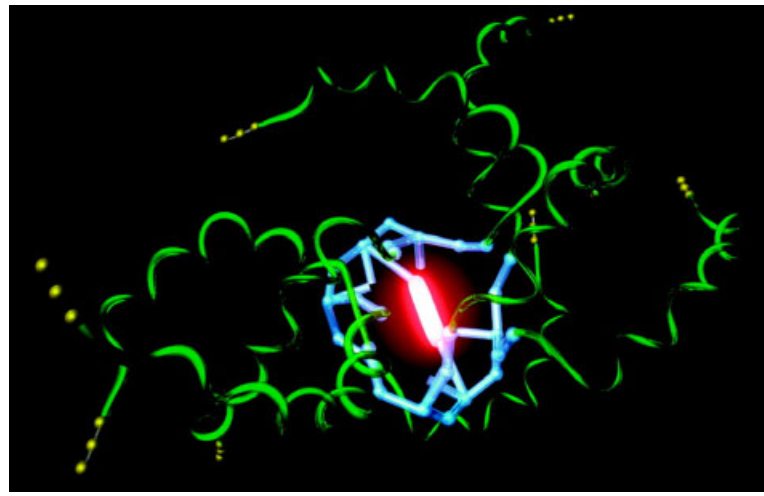

***Figure 6.*** Illustration of dendritic NIR nanoprobes, where cypate is indicated in red, polyester dendrimer in blue, and PEO shell is green.[8] Reprinted with permission from reference 8. Copyright 2008 American Chemical Society. [Color figures can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

system (RES). In addition to using fluorescence intensity measurements to monitor the biodistribution of the nanoprobes, in vivo biodegradation could be monitored by the rate of FLT change using a small animal FLT imaging system. Despite a homogeneous FLT map detected at the first hour, FLT increased in a site-specific manner from day 1 to day 6. The liver and intestines were found to have the highest FLT, indicating a higher biodegradation rate at those sites. Consequently, these nanoprobes hold great promise for early-stage tumor diagnosis via FLT-DOT technology. They also represent a good model for monitoring controlled drug release and bioavailability of polymer-encapsulated drugs.

An important limitation of using conventional fluorescent nanoprobes for in vivo imaging is high background signal generated by circulating nanoprobes. The resulting low signal-to-noise (S/N) ratio compromises imaging contrast, thereby impeding the identification of cancerous tissues when the expression level of targeted biomarker is low. In light of this,

novel "smart nanoprobes" that selectively exhibit fluorescence in response to specific signals at tumor site is highly desirable, because they can achieve a background-free state and improve S/N ratio. Thus, special efforts have been directed to developing smart nanoprobes for optical imaging. The pioneering work of Weissleder et al. centered on this concept.[22–25] Using a polylysine framework, peptide substrates for diagnostic enzymes were attached to the polymer and capped with NIR fluorescent cyanine dyes.[22–25] By virtue of the multiple copies of the dye molecules in close proximity to each other, their fluorescence was effectively quenched. Upon recognition and cleavage of the substrate by the target enzyme, a fragment of the dye-labeled peptide substrate detaches from the polymer, resulting in fluorescence enhancement. Thus, the level of fluorescence increase could be used to localize pathologic sites and report the functional status of enzyme biomarkers. Similarly, Almutairi et al. reported biocompatible and biodegradable polymers that selectively enhanced NIR fluorescence intensity and altered the dye's FLT under acidic microenvironment.[9] In this nanoprobe construct, cypate dye molecules were covalently attached to a dendrimer through acid-cleavable linkages. To improve in vivo circulation in blood, PEG groups were attached to the dye–dendrimer nanoprobes (Fig. 7). At neutral pH ("off" state), both fluorescence intensity and FLT were suppressed by nonradiative decay, minimizing the background signal. At acidic pH ("on" state), cypate was released, which enhanced the dye's fluorescence intensity and increased the FLT. Such pH-sensitive nanoprobes are particularly promising in cancer diagnosis, because they can detect the local acidic environment caused by high metabolic activity of malignant tumors and provide valuable molecular information.

"Smart nanoprobes" can also be designed based on the intrinsic fluorescence quenching capability of AuNPs. For instance, Lee et al. reported AuNP-quenched NIR nanoprobes that were responsive to MMP activity.[74] MMP is a critical factor in cancer progression that plays an important role in cancer diagnosis. When the nanoprobes encounter MMPs, Cy5.5 dyes were cleaved from the linkers that connect them to the AuNPs, leading to an enhanced fluorescence yield. They imaged tumor-bearing mice with these nanoprobes and observed an enhanced fluorescence at the tumor region. In another study, Oishi et al. developed caspase-3-responsive nanoprobes for apoptosis monitoring based on AuNP quenching of fluorescein isothiocyanate.[142] Fluorescence signal was activated when the nanoprobes were in contact with cells undergoing apoptosis (high caspase-3 activity), while background fluorescent signal is minimal. These caspase-3-responsive nanoprobes are potential candidates to monitor patients' responses to treatments.

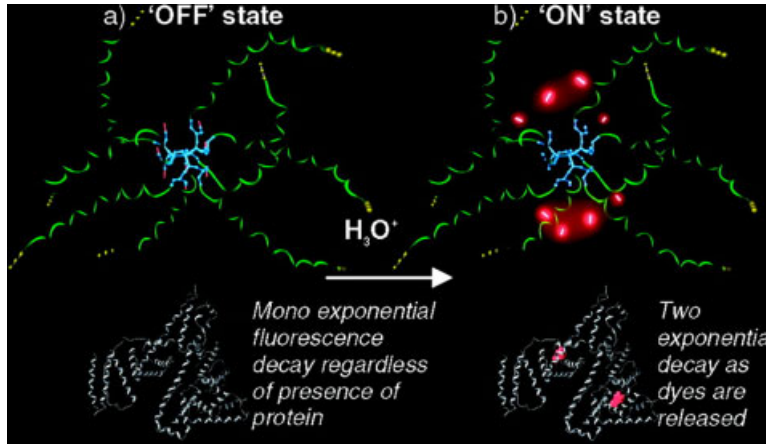


***Figure 7.*** Illustrations of pH-sensing nanoprobes, where cypate is indicated in red, polyester dendrimer in blue, and PEG shell in green.[9] Reprinted with permission from reference 9. Copyright 2008 American Chemical Society. [Color figures can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In addition to "smart nanoprobes," various optical nanoprobes based on other types of nanocarriers, such as QDs and CNTs, have also been developed. For example, Gao et al. reported polymer-encapsulated NIR QDs for prostate cancer detection in vivo.[143] They discovered that QDs could be targeted to tumor sites either via passive targeting or via active targeting. Welsher et al. conducted whole-animal imaging of tumor-bearing mice using single-walled semiconducting CNTs that exhibited NIR fluorescence.[144] They were able to resolve small vessels in tumors by this method. Despite these successes, concerns about the inherent toxicity of these particles need to be addressed before human use of nanoprobes based on QDs or CNTs.

### *B. Nuclear Imaging*

Nuclear imaging modalities can be generally classified into two categories: positron emission tomography (PET) and single photon emission computed tomography (SPECT).[145] Unlike CT or MRI, which provides anatomical information, PET and SPECT generate 3-D functional/metabolic images of tissues.[104] Nuclear imaging methods are of great clinical significance for the early detection of cancer as functional changes precede noticeable anatomical changes.[146] In PET imaging, tracers labeled with positron emitting radionuclides are injected into the body before imaging. As the radionuclides decay, positrons are generated and subsequently annihilate upon contact with electrons after traveling a short distance from the source. The annihilation leads to emission of two photons in forms of gamma rays, which travel in opposite directions. PET scanner can detect these photons, and thereby reconstruct the functional images of the body.[147] In SPECT, gamma rays are also detected. However, unlike PET that measures the photons generated from positron annihilation, SPECT detects the gamma rays emitted directly from the tracer.[148] In modern practice, PET and SPECT images are often fused with other modalities, such as CT or MRI, to correlate functional with anatomical information. The high potential impact of multimodal imaging has resulted in the development of commercial SPECT/CT and PET/CT systems for human use.[149]

Radiolabeled colloids, such as $^{99m}$Tc-labeled colloidal particles, are widely used as lymphatic mapping agents in breast and prostate cancer patients.[150] These macroparticles can guide sentinel lymph node localization, which is used in tumor staging.[151] More recently, nanocarriers have been employed to deliver radionuclides, augment circulation time, and enhance targeting efficiency of radiopharmaceuticals. For instance, Rossin et al. developed $^{64}$Cu-labeled folate-conjugated shell cross-linked nanoparticles (SCKs) for PET imaging of tumor-bearing mice.[152] The SCKs achieved prolonged blood circulation time. Their accumulation in tumors was mainly driven by EPR effect, as demonstrated by comparable tumor uptake for both folated and nonfolated SCKs. However, in small tumors, folate-mediated cellular uptake was observed, which provided a promising route to treat early-stage tumors. Liu et al. conducted PET imaging of tumor-bearing mice using $^{64}$Cu-labeled arginine–glycine–aspartic acid (RGD) conjugated single-walled CNTs.[153] They confirmed in vivo stability of CNT nanoprobes and achieved high targeting efficiency in integrin overexpressed tumors. In addition, Kobayashi et al. developed immunoglobulin G conjugated polyamidoamine dendrimers (PAMAM) labeled with either $^{111}$In or $^{153}$Gd.[154] They found preferential accumulation of $^{153}$Gd-labeled nanoprobes in tumors and concluded that $^{153}$Gd-labeled nanoprobes had better biodistribution profile than $^{111}$In labeled nanoprobes.

### *C. Magnetic Resonance Imaging*

MRI is a medical imaging modality widely used in clinics to examine the anatomical structures of the body and provide some physiological information. As MRI offers high spatial resolution of different tissues (especially soft tissues) than other imaging modalities, it

has been applied in clinical practices for various purposes, including oncologic imaging.[155,156] Moreover, in contrast to conventional oncologic imaging techniques, such as PET, SPECT, and CT, MRI does not utilize harmful ionizing radiation for imaging. Instead, MRI generates contrast by employing external magnetic fields to manipulate the nuclear spins of atoms.[157]

However, the sensitivity of MRI for molecular imaging is far from satisfactory for accurate oncologic diagnosis, when relying on endogenous contrast of tissues.[98] Also, functional information that differentiates cancerous tissues from normal ones is not readily extracted from MRI. Hence, magnetic contrast agents are required to enhance tumor contrast. Despite the fact that gadolinium diethylenetriaminopentaacetic acid (Gd-DTPA) is well accepted in medical communities, Gd-DTPA does not have sufficient contrast and circulation time for early cancer diagnosis.[158,159] For these reasons, magnetic nanoprobes has emerged as promising candidates because they offer fine-tuned magnetic properties, longer blood retention time, and improved specificity to cancer biomarkers.[160]

The most widely used MRI nanoprobes are iron oxide (IO) nanoparticles owing to their unique paramagnetic properties that lead to a strong T2 contrast.[161] Chen et al. developed herceptin-conjugated superparamagnetic IO nanoparticles (SPIONs) to target HER-2 in breast cancer cells.[162] They found that the contrast enhancement was proportional to expression level of HER-2 via in vitro studies. The MRI imaging of human breast cancer-bearing mice with SPIONs revealed a high specificity and contrast at tumor sites (45% enhancement drop in $T_2$). Similarly, Leuschner et al. fabricated SPIONs that were conjugated with either LHRH or β chorionic gonadotropin, which could target breast cancer cells.[163] They reported that LHRH-SPIONs traced breast tumors and metastases effectively in a mouse model. Furthermore, Lee et al. demonstrated that Mn-doped IO nanoparticles conjugated with herceptin greatly enhanced MRI sensitivity for small tumor detection in a mouse model.[164] In addition, other researchers, such as Rodriguez et al. and Yang et al., have developed MRI nanoprobes for improved breast and prostate cancer diagnosis.[165,166] Specific active targeting of MRI nanoprobes to tumors is still controversial because of the amount of materials needed to generate contrast. Clearly, a combination EPR effects and cell-surface receptor binding of the nanoparticles contribute to the observed tumor uptake.

### *D. Multimodal Imaging*

Ideally, a single oncologic imaging modality should possess the capacity to provide 3-D anatomical, molecular, and metabolic information with high sensitivity, resolution, specificity, speed, and low cost. Unfortunately, every imaging modality to date can only offer a portion of these virtues. To acquire versatile functionalities, multiple imaging technologies are fused or combined to harness the advantages of each system. In reality, multimodal integration has already been adopted for some years. A paragon is the coregistration of nuclear imaging and CT. In clinical settings, it is now rare to use PET or SPECT scanners without coregistration with CT. The combination of PET/CT and SPECT/CT scanners allows CT to provide anatomical information, while PET and SPECT offer functional information.

Recently, optical imaging has emerged as novel functional/molecular imaging candidate modality with high detection sensitivity and low cost without the use of ionizing radiation. Hence, incorporation of other imaging modalities with optical technologies is an attractive and viable option. An elegant strategy to implement the integration of multimodal imaging is the development of contrast agents that simultaneously carry multiple signaling moieties for the different imaging systems. Using multimodal contrast agents instead of multiple monomodal probes, researchers can simplify data processing, improve coregistration accuracy and minimize toxicity.[167] Utilization of nanocarriers in multimodal imaging is particularly promising owing to the polyvalent nature of nanocarriers. On each nanocarrier, one can

incorporate multiple copies of contrast moieties. Thus, one can normalize the differences in the detection sensitivities for each modality, thereby facilitating coregistration of images.[167] This approach has captivated the interest of many research laboratories. One of the earliest demonstrations of this approach is the use of dye-labeled IO nanoparticles for MRI and optical imaging of enzyme activities.[168] In this platform, optical imaging provides molecular information about the functional status of diagnostic proteases and MRI reports the requisite anatomical landscape for the detected fluorescence signal. In more recent studies, Yang et al. developed uPA-conjugated IO NPs that were grafted with Cy5.5 NIR dye.[169] These NPs could selectively accumulate in mammary tumors and metastasis, as revealed by MRI-optical imaging in a mouse model. In addition, Lee et al. developed $^{64}$Cu-labeled RGD-IO nanoprobes for MRI-PET imaging and integrin-specific targeting of tumors were achieved.[170]

In some cases, imaging modalities with similar detection sensitivities have been combined.[167] For example, optical–nuclear multimodal imaging platforms have been developed to provide complementary information.[55,171–174] On the basis of these probes, multimodal imaging of tumor using bioluminescence, fluorescence, gamma scintigraphy, and SPECT were made possible.[55] Furthermore, caspase-3 activity can be monitored in vivo, where the always "on" nuclear signal reports probe distribution, "switchable" optical signal provides functional information of caspase-3.[172] Using these probes, the spatial limitation of penetration depth in optical imaging can be overcome, while the temporal limitation of short radionuclide half-life in nuclear imaging can be compensated as well. Several studies on optical–nuclear nanoprobes have been conducted. For example, Yang et al. developed micelles encapsulating Cy-7 NIR fluorescence dye, which were labeled with $^{111}$In radionuclides as well.[175] These micelles featured prolonged blood circulation time and excellent breast tumor targeting efficiency in a mice model. In another study, Cai et al. reported PET-optical dual imaging of tumor-bearing mice using $^{64}$Cu-labeled RGD-QDs.[176] They concluded tumor targeting effect primarily originated from RGD–integrin interactions.

Without doubt, there will be more elegant nanoprobe designs in the future, based on the need for structural information provided by CT or MRI and molecular information from nuclear or optical imaging. It is, therefore, expected that applications of multimodal imaging in breast and prostate cancer will have an even greater impact on clinical diagnostics and therapeutics.

## 5. NANOTHERAPEUTICS

In the field of oncology research, massive efforts have been devoted to applying newly developed nanotechnology to cancer therapeutics. Augmented by nanomedical platforms, conventional therapeutic modalities, such as chemotherapy, radiotherapy, surgery, PDT, targeted therapy, and hormone therapy are now capable of fighting cancer at the molecular level. Below, we briefly review the status of nanotherapeutics, with a focus on targeted drug delivery, PDT, and radiotherapy.

### A. Targeted Drug Delivery

Chemotherapy is an anticancer method that uses chemicals to inhibit or kill rapidly dividing cells in cancerous tissue.[177] Continuous refinement of chemotherapeutic methods has increased long-term survival rate of cancer patients. Yet, most drugs used in whole-body chemotherapy have poor selectivity for tumor tissue, which results in serious and sometimes life-threatening side effects. A few examples of common side effects are nausea, vomiting, anemia, infection, fatigue, hair loss, and diarrhea.[178] These side effects not only compromise the quality of life,

but also limit the use of effective dosage of chemotherapeutic agents.[179] Nanomedicine offers an elegant solution to this problem through targeted drug delivery, where chemotherapeutic drugs are encapsulated or conjugated into nanocarriers. As with imaging nanoprobes, the selective uptake of drug-loaded nanocarriers in tumors can be improved by either passive or active targeting mechanism.

There are numerous advantages for targeted anticancer drug delivery. For example, the release profile of drug from the nanocarriers can be controlled by either tailoring the properties of nanocarriers or modifying the interaction between drugs and nanocarriers. Thus, sustained or controlled release can be achieved. In addition, the poor water solubility of hydrophobic drugs can be overcome by encapsulating them in a hydrophobic core of water-soluble nanocarriers. Moreover, the nanocarriers can stabilize and shield the drugs either physically (encapsulation) or chemically (conjugation), thereby reducing their possibility of being transformed prematurely by enzymes or degraded in vivo. By tuning properties of nanocarriers, the blood circulation time can be increased and the RES uptake can be decreased. A combination of specific targeting and EPR effect can augment drug uptake in tumors. Finally, complications from multidrug resistance can be solved by utilizing the cellular transport route of nanocarriers rather than that of drugs.[180]

To date, many anticancer drugs have been delivered to tumors via nanocarriers. Abraxane is the earliest FDA-approved nanoformulation in 2005 to treat metastatic breast cancer patients who failed combination therapy.[181–183] In the Abraxane formulation, albumin-based nanoparticles (130 nm nanocarrier) was used to deliver paclitaxel to target tissue. Studies have shown that Abraxane has significantly increased tumor response rate and reduced toxicity. Development of other nanoparticle-based formulations of chemotherapeutic drugs for clinical investigations is in progress, including chlorambucil,[184] doxorubicin,[185] dipyridamloe,[186] daunorubicin,[187] bleomycin,[188] cisplatin,[189] pyrene,[190] methotrexate,[191] and cytarabine.[192] The therapeutic effects of these drugs generally increase while their side effects are reduced.

Furthermore, in pursuit of more efficient delivery methods, various "smart release" methods have been developed. Selective release of the drugs could be mediated by physiological or external stimuli, such as pH,[193–195] temperature,[190,196,197] enzyme activation,[198] and ultrasound stimulation.[199–201] These "smart release" nanocarrier drug systems have shown promising results in cancer therapy and they are anticipated to undergo intensive translational development in the near future.

### *B. Photodynamic Therapy*

PDT is a noninvasive or minimally invasive treatment method for several types of cancer.[202] Initially, PDT was introduced into clinical practice to treat superficial conditions, such as skin cancer. To date, it has been applied to clinical treatment of other cancer types, including breast[203] and prostate[204] cancer. Generally, PDT operates by injecting a photosensitizer (PS) into patients, followed by photo-activating the PS in tumor to generate reactive oxygen species (ROS).[205] ROS (mainly singlet oxygen $^1O_2$) are highly cytotoxic and can induce cell death. In PDT, the production of ROS is modulated by illumination of light at specific wavelengths, and only cells in contact or close to PS will be affected. Consequently, PDT offers high specificity and low systemic toxicity, which makes it a preferred treatment regimen over conventional therapies in some forms of cancer. In addition, since PDT is an optical modality in nature, it can be coupled with optical imaging to facilitate the implementation of theranostics and personalized medicine.

The recent development in nanotechnology has assisted PDT in three ways. First, the efficiency and specificity of PDT were improved by delivering PS to tumors via nanocarriers.

This approach is analogous to "targeted drug delivery" discussed above, where PS is now employed as the photo-activatable drugs. For instance, liposomes have been intensively studied for PS delivery to cancerous tissues, either by passive or active targeting.[206,207] Alternatively, PS was conjugated to QDs that have high absorption coefficient. The PS could then be activated indirectly via Forster resonance energy transfer upon excitation of QDs. Energy transfer to the PS provides flexibility in the choice of excitation wavelengths of PS.[208–211] Finally, new nanoprobes with higher sensitivity to ROS were developed.[212] ROS nanoprobes hold great potential for real-time monitoring of ROS level, which may be useful for PDT dosimetry and quality control.

### *C. Radiotherapy*

Radiotherapy uses ionizing radiation in cancer treatment for curative or palliative purposes.[213] It is commonly applied to the treatment of prostate and breast cancer. Radiotherapy utilizes high-energy radiation to induce DNA damage in the cancer cells that is generally lacking the capacity to repair DNA breakage, and thereby shrinks or eradicates cancerous tissues.[214] There are three major categories of radiotherapy, depending on the position of radiation sources. In external beam radiotherapy, the sources are located outside the body.[215] In contrast, sealed radioactive sources are placed inside or next to the area under treatment during brachytherapy.[216] For radionuclide therapy, radioactive substances are administered directly into the body by intravenous injection or ingestion.[217]

However, radiotherapy for both prostate and breast cancer requires higher accuracy in delivering ionizing radiation to reduce side effects exerted on surrounding normal tissues.

Compared with conventional radiotherapy, nanomedical strategy enhances targeting efficiency and can amplify radiation dose in vivo.[218] Specifically, nanoparticles can augment the therapeutic efficiency of radiotherapy by different pathways. For example, nanocarriers could act as bona fide radiosensitizers. Inorganic nanoparitcles, such as AuNPs and QDs, could preferentially accumulate at tumor sites and enormously enhance the absorption of radiation energy.[219] Several reports have shown that the in vivo efficacy of X-rays and $\gamma$-rays were augmented by AuNPs, and the implementation of such enhancement was feasible by external beam radiotherapy and brachytherapy.[220–224] Furthermore, nanocarriers can also deliver radionuclides for targeted radioisotope therapy. This is a special form of targeted drug delivery where radionuclides are loaded as the drugs. Polymeric nanocarriers, such as liposomes, have been employed as targeted delivery vectors in numerous studies, and improved therapeutic efficiency with reduced toxicity was achieved.[225–230]

## *6. NANOMEDICAL SAFETY*

The application of nanotechnology in oncology is a double-edged sword. On one hand, it leads to a fascinating development of new devices and modalities. On the other hand, it also gives rise to potential toxicity in humans. Among various in vitro and in vivo nanomedical applications, in vitro studies are generally easier to manage because exposure to nanomaterials is external (e.g. inhalation and physical contact). To the contrary, in vivo nanomedical applications are facing much greater challenges because in vivo nanotoxicity is harder to quantify and monitor.

The potential risks of nanomedicine generally stem from the same origin as their functionalities. In a sense, functionality and toxicity are "coupled." For instance, owing to the large surface-to-volume ratio, nanocarriers offer multivalency that is ideal for active targeting. However, the large surface-to-volume ratio also leads to their uncontrollable bioactivity that may cause cytotoxicity. Another example of "coupled" relationship is that the physical and

chemical compositions of QDs and some CNTs confer unique optical properties. However, degradation of their physical and chemical constituents will lead to either toxic remnants (from physical breakdown) or toxic ions (from chemical degradation). A third instance of ''coupled'' functionality–toxicity pairs is active targeting strategies. By conjugating bioactive moieties to the nanocarriers, improved specificity to cancerous tissues can be achieved. However, intensive immune responses may also be triggered due to these ''active'' moieties. Consequently, a critical issue for nano-oncology is how to balance the pros and cons of nanoprobes and nanopharmaceuticals. Instead of integrating all functionalities together to achieve ''universal nanocarriers'' regardless of actual need, which appears to be an emerging trend in nanomedical research, a reasonable trade-off of functionality for biocompatibility may be more crucial for clinical applications.

To better translate nanomedicine to clinics, studies of nanotoxicity should be performed paralleled with studies of nanofunctionality. Unfortunately, many nanomedical research activities tend to emphasize much more on ''gain-of-functionality'' than ''loss-of-biocompatibility.'' In some cases, the claimed ''biocompatibility'' is debatable because the ''biocompatibility'' is generally obtained from in vitro studies while the ''functionality'' has to be realized in vivo. Clearly, in vitro behaviors of nanostructures are considerably different from their in vivo actions. In fact, this ''mismatch'' results in many contradicting reports from different biocompatibility studies. Hence, parallel in vivo studies to access biocompatibility and nanotoxicity are highly encouraged. With more information from in vivo biocompatibility studies in future, issues with nanotoxicity may be systematically addressed by astute nanoparticles formulation strategies.

## *7. CONCLUSION*

With the capability to offer tremendous sensitivity, accuracy, efficiency, versatility, and high throughput, nanotechnology has already exerted significant impact on medicine. As nano-oncology continues to evolve into a central science in oncology research and practices, development of new nanobased analytical devices, diagnostic modalities and therapeutic modalities is highly needed. They can provide insight into carcinogenesis at the molecular level and offer personalized therapies, where each patient is treated according to their own genetic and proteomic traits. Another trend in nano-oncology is the symbiotic integration of therapeutics with diagnostics (theranostics). This area is particularly useful for monitoring patients' response to therapy, providing a mechanism to alter treatment regimen for non-responding patients. Furthermore, the portable features and low cost of nanodevices facilitates seamless integration into existing medical devices or miniaturized standalone systems. Such devices are critical toward the full realization of the high potential of nano-oncology for the implementation of point-of-care paradigm. With continuous translational research endeavors that bring nanomedicine from bench top to bedside, we anticipate that medical interventions in breast and prostate cancer will evolve into an early, fast, accurate, non- or minimally invasive, versatile, affordable, and high throughput practice in the near future.

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