

# Cancer Theranostics: An Introduction

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## CANCER THERANOSTICS: A DEFINITION

Theranostics is a portmanteau of therapeutics and diagnostics. It can be diagnosis followed by therapy to stratify patients who will likely respond to a given treatment. It can also be therapy followed by diagnosis to monitor early response to treatment and predict treatment efficacy. It is also possible that diagnostics and therapeutics are codeveloped. For example, nano-platforms can be designed to codeliver imaging and therapy components; antibodies can be labeled for imaging and conjugated with payload as antibody-drug conjugate (ADC) for therapy. Cancer theranostics, as the name implies, represents a combinatorial diagnosis and therapeutic approach to cancer disease and aims to reduce delays in treatment and ease patient care, and appears to be essential for personalized cancer treatment.

Note that in some cases theranostics is also spelled as theragnostics. A keyword search of PubMed on January 7, 2011, right before the launch of new SCI journal *Theranostics*, only found 95 items for “theranostic,” 63 items for “theranostics,” 29 items for “theragnostic,”

and 21 items for “theragnostics.” In the past two years, literature related to theranostics grew exponentially. As of October 18, 2013, a PubMed search found 587 items for “theranostic,” 562 items for “theranostics,” 85 items for “theragnostic,” and 48 items for “theragnostics.”

There are pieces of information related to theranostics in the literature. A dedicated journal named *Theranostics* ([www.thno.org/](http://www.thno.org/)) was launched to open up a forum to exchange clinical and scientific information for the diagnostic and therapeutic molecular and nanomedicine community and allied professions involved in the efforts of integrating molecular imaging and molecular therapy [1]. As an evolving multidisciplinary field catering to the unmet needs of the medical world, cancer theranostics include but are not limited to the following:

- Identification of novel biomarkers to advance molecular diagnostics of cancer
- New molecular imaging probes and techniques for early detection of cancer
- Molecular imaging guided cancer therapy
- Nanoplatfroms incorporating both cancer imaging and therapeutic components

## THERANOSTIC CANCER BIOMARKERS

Sequencing the human genome has the potential to transform the treatment of disease and the practice of medicine. One of the most profound changes to medicine is the movement toward predictive, preventive, personalized, and participatory (P4) medicine [2]. As defined by the President's Council of Advisors on Science and Technology (PCAST), personalized medicine is the tailoring of medical treatments to the individual characteristics of each patient, and the ability to classify individuals into subpopulations based on their susceptibility to a particular disease or their responses to a specific treatment [3]. Personalized medicine therefore has the potential to optimize targeted delivery and dosing of treatments so patients can receive the most benefit with the least amount of risk, cutting out the difficulties of the current trial-and-error process many patients endure to find the correct drug and dose to treat a condition.

Human genome, epigenome, transcriptome, proteome, and metabolome analysis, high-throughput phenotypic assays, and powerful computational methods allow for delineating relevant biological networks underlying the cellular and molecular origins of cancer [4]. Efforts have been spent to develop simple, noninvasive tests that indicate disease risk, regression, and recurrence, and allow early detection to monitor disease progression and to classify patients so that they can receive the most appropriate therapy at the right time.

Early detection and definitive treatment of cancer have been shown to decrease death and suffering in epidemiologic and intervention studies. Application of genomic approaches in many malignancies has produced thousands of candidate biomarkers for detection and prognostication, yet very few have become established in clinical practice. Fundamental issues related to tumor heterogeneity, cancer progression, natural history, and biomarker performance have provided challenges to biomarker development [5]. Technical issues in biomarker assay detection limits, specificity, clinical deployment, and regulation have also slowed progress. The recent emergence of biomarkers and molecular imaging strategies for treatment selection and monitoring demonstrates the promise of cancer biomarkers. Organized efforts by interdisciplinary teams will spur progress in cancer diagnostics.

Similar to the Human Genome Project, the Human Proteome Project aims to map the entire human protein set, with respect to protein abundance, distribution, and subcellular localization, as well as protein interactions with other biomolecules and protein functions at specific time points [6]. Specific post-translational modifications (e.g., phosphorylation) and/or the status (e.g., nuclear localization) of particular proteins in cancer

cells may be meaningful as potential cancer biomarkers for early detection of cancer and personalized therapeutic strategies in clinical settings.

Metabolomics can be broadly defined as the study of all metabolites produced in the body [7]. Cancer metabolome refers to low molecular weight metabolites (MW <1500 Da), including peptides, oligonucleotides, sugars, nucleosides, organic acids, ketones, aldehydes, amines, amino acids, lipids, steroids, and in some cases drugs or xenobiotics, that are germane to cancer and their changes relative to normal tissue. In general, metabolic requirements of cancer cells are quite different from those of most normal differentiated cells. Tumor cells often have a high proliferation rate, thus needing additional nutrients, and ultimately directing the nutrients into the synthesis of new biomass. With the use of metabolomics, various metabolic pathways between cancer and noncancerous tissue can be differentiated. Metabolomics is often combined with other omics disciplines for the confirmation of data from one omics by another. Currently, most of the targeted cancer therapies are based on genetic, or in some cases proteomic, analyses of human tumors. The same strategy can be applied to metabolomic analysis, evaluating the response of an individual patient to a given drug on the basis of the patient's metabolomic status.

## MOLECULAR IMAGING IN CANCER THERANOSTICS

Although *in vitro* diagnostic tests (genomic, transcriptomic, proteomic, and metabolomic) can identify patients who will likely respond to a particular therapy, or fail to respond to a given drug or treatment regimen, *in vivo* molecular imaging is a technique that uses sophisticated diagnostic imaging equipment and systems to visualize, characterize, and measure biological processes at the molecular and cellular levels in humans and other living systems [8]. In the clinic, molecular imaging enables physicians to peer into the living body to identify diseases, monitor their progression, or treat medical conditions at a molecular level. It is quite different from *in vitro* diagnostics, which typically require laboratory analysis of a sample, such as blood or a biopsy, as molecular imaging can study biological processes in their own physiological environment instead of by *in vitro* or *ex vivo* biopsy/cell culture laboratory techniques.

There are many different modalities that can be used for noninvasive molecular imaging, such as molecular magnetic resonance imaging (mMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), ultrasound (US), photoacoustic imaging (PAI), and optical imaging (OI).

Each has its different strengths and weaknesses, and some are more adept at imaging multiple targets than others.

Through the exploration of specific molecular probes instead of conventional anatomical and functional imaging, cancer molecular imaging allows characterization of tumor-related abnormalities and adoption of innovative targeted therapeutics. The advancement of molecular imaging is expected to be able to diagnose cancer early, measure the pharmacokinetics and pharmacodynamics of newly developed drugs, and to monitor cancer therapy response, predicting the effectiveness of a given therapy, preceding the anatomical size change measured by conventional diagnostic modalities such as computed tomography (CT) and MRI.

## IMAGING-GUIDED CANCER THERAPY

Interventional radiology (IR) uses X-rays and other imaging techniques to “see” inside the body while guiding catheters and other very small instruments through the body to the site of a problem, treating a variety of medical disorders without surgery. In the last two decades, interventional radiology has experienced unprecedented growth [9]. Advances in imaging equipment and tracking technology have facilitated the development of new effective and efficient diagnosis and treatment options. Minimally invasive interventions are replacing more costly open surgery, and this trend is seen particularly in the field of oncology. Advantages of such interventions include shortened patients’ recovery time, improved patient comfort, and lowered risk of complications.

During minimally invasive procedures, clinicians rely on combined information from different sources to build up a mental picture for their actions. Typically, a source of static anatomical information obtained before a procedure, such as a CT scan or a magnetic resonance (MR) scan, is combined with real-time devices such as ultrasound scanner and interventional device tracker. The central idea around image-guided intervention is how position of the interventional device can be detected in real time and be superimposed on the patient’s anatomic image and visualized simultaneously for guiding the procedures.

An array of localized, minimally invasive procedures include:

- Radio frequency ablation (RFA): Localized destruction of tissue (tumors) by radio frequency waves or heating
- Microwave ablation: A newer ablation technology that uses electromagnetic waves in the microwave

energy spectrum to produce a larger and faster volume of tissue heating

- Cryoablation: Localized destruction of tissue (tumors) by freezing
- Chemo-embolization: Image-guided treatment delivering cancer treatment (chemotherapy) directly to the tumor through its blood supply
- Selective internal radiation therapy (SIRT): Image-guided treatments to target and treat malignant tumors (e.g., liver cancer) that cannot be removed by surgery
- Dose painting: Nonuniform radiation dose delivery within the tumor volume by targeting radioresistant areas defined by functional imaging

## THERANOSTIC PLATFORMS

There have been many platforms that can combine imaging and therapy for optimizing efficacy and safety of therapeutic regimes. Here we will discuss platforms related to light, magnetism, and sound as examples to illustrate the potential of cancer theranostics.

The use of light as a remote-activation mechanism for drug delivery has received increased attention due to its advantages in highly specific spatial and temporal control of compound release. Phototriggered cancer theranostic constructs may include photodynamic, photothermal, or phototriggered chemotherapy [10].

Photodynamic therapy (PDT) is a treatment that uses a photosensitizer (PS), or photosensitizing agent, and a light of appropriate wavelength, which in the presence of oxygen, will lead to the generation of cytotoxic species and consequently to cell death and tissue destruction.

Photothermal therapy (PTT) of cancer involves irradiation of cancerous tissue with electromagnetic radiation (VIS-NIR light) to cause thermal damage. Unlike PDT, where reactive oxygen species (ROS) are generated by excitation of a PS, in PTT the laser energy is absorbed by the photoabsorbers and is converted to heat. PTT can cause biological changes ranging from protein structural changes to carbonization of the tissue. Similar to PDT, PTT has spatial specificity and minimal invasiveness, which allows only the diseased tissue to be irradiated while the surrounding benign tissue is minimally damaged.

Phototriggered drug release is an intelligent design of drug conjugates that have light responsiveness. It is expected that light (UV, visible, and NIR) can trigger the release of a drug molecule at the right dose, proper timing, and the exact location. The controlled release is often controlled by the wavelength, duration, intensity, and location of the light.

Different microscopic to whole-body optical imaging techniques based on absorption, scattering, fluorescence, transmission, and reflection properties of tissue constituents are available for various biomedical applications. Commonly used optical imaging modalities include but are not limited to phosphorescence, bioluminescence, fluorescence, Raman, and photoacoustic imaging. Light responsiveness is attractive as a cancer theranostic method for its sensitive and specific diagnosis, precise external modulation of the site, and rate of delivery of heat, photosensitizer, or drug of interest.

Conventional widefield microscope-based optical imaging techniques are unsuitable for imaging thick tissue and often restricted to open surface or exposed areas of the body such as skins and eyes, despite their high spatial resolution at the  $\mu\text{m}$  range, owing to the limited depth penetration of light into tissues and blurred, out-of-focus background signal [11]. Endomicroscope imaging techniques are thus developed to achieve optical sectioning by removal of the background intensity using the confocal principle to obtain high-resolution histology-like images from inside the human body in real time. The design of an endomicroscope either includes a miniaturized scanning head at the distal tip of the optical imaging probe or performs the scanning outside of the patient and uses a fiber bundle to transfer the scan pattern to the tissue [12].

Magnetic resonance imaging (MRI) has a critically important role in molecular imaging and clinical diagnosis because it is noninvasive and is capable of producing images with high spatial and temporal resolution. Approximately 35% of clinical MR scans need contrast agents to improve their sensitivity and diagnostic accuracy. For example, superparamagnetic iron oxide (SPIO) nanoparticles are the prevailing  $T_2$  contrast agents, especially for lesion detection.

It is also known that in the presence of time-varying magnetic field, magnetic nanoparticles can realign their magnetic moments to the applied field [13]. As the excitation frequency of the magnetic field increases, magnetic moments of nanoparticles lag the applied field at a given angle. The resulting power dissipation process associated with this misalignment can increase bulk temperature of magnetic nanoparticles and their surroundings. This phenomenon can be used as a method of hyperthermia, suitable for cancer treatment in low-perfusion tissue. In so-called magnetic fluid thermotherapy, magnetic fluids containing magnetic nanoparticles (e.g., iron oxide) are delivered to the cancer and then heated by an external alternating magnetic field, resulting in hyperthermia or thermoablation of cancer tissue.

Magnetic nanoparticles can also be used for site-specific magnetic targeting, and as carriers for

chemotherapeutics or bioactive molecules (double-stranded DNA, small interfering RNA, miRNA, and proteins).

Reported theranostic applications of magnetic nanoparticles include: imaging (serving as contrast agents for MRI); therapy (chemotherapy via controlled drug release and hyperthermia via heat generation in an alternating magnetic field); and cell separation (cell labeling/tracking and isolation using magnetic force).

Ultrasound is an oscillating sound pressure wave with a frequency greater than the upper limit of the human hearing range. Ultrasound contrast agents are mostly gas-filled microbubbles with a high degree of echogenicity. Contrast-enhanced ultrasound can enhance the ultrasound backscatter, or reflection of the ultrasound waves, to produce a unique sonogram with increased contrast due to the high echogenicity difference [14]. Contrast-enhanced ultrasound can be used to image blood perfusion, blood flow, and receptor density in tumors and organs.

High-intensity focused ultrasound (HIFU, or sometimes FUS for focused ultrasound) is a modality of therapeutic ultrasound that applies high-intensity focused ultrasound energy to locally heat and destroy diseased or damaged tissue through ablation [15]. In addition to HIFU, other modalities include ultrasound-assisted drug delivery, ultrasound hemostasis, ultrasound lithotripsy, and ultrasound-assisted thrombolysis.

If the biophysiology of ultrasound is carefully used and the biophysics of ultrasound is under control, it can help move drugs into cells by enhancing extravasation and interstitial transportation, increase the permeability of cell membranes, and help drugs and genes escape from the endosome within the cytoplasm.

Ultrasound-responsive nanoparticles are drug-loaded ultrasound contrast agents that contain a small amount of gas. Coencapsulation of a pharmaceutical along with a gas renders the particles acoustically active, allowing contraction and expansion in response to ultrasound compression and rarefaction [16]. If the oscillating bubble grows to a certain point exceeding the strength of the vesicle, it will rupture and release its payloads. A number of ultrasound-responsive nanoparticles have been developed, with average diameters of 0.8 to 10  $\mu\text{m}$ , including microbubbles, micelles, liposomes, metallic nanoparticles, polymeric nanoparticles, dendrimers, carbon nanotubes, and quantum dots. Many therapeutic agents such as chemotherapeutics, antiangiogenics, and genes can be simultaneously delivered by these nanocarriers to tumor sites to enhance therapeutic effectiveness. Additionally, an agent containing both imaging and therapeutic materials can be utilized as a

multifunctional platform for cancer theranostics. In addition, multiple therapeutic modalities such as a combination chemotherapy and hyperthermia can be coadministered to take advantage of the synergistic effects of combined therapies.

## CHALLENGES AND FUTURE PERSPECTIVES

Personalized oncology is evidence-based, individualized medicine that delivers the right care to the right cancer patient at the right time and results in measurable improvements in outcomes and a reduction in healthcare costs.

The essence of personalized oncology lies in the smart use of theranostic biomarkers. These biomarkers can be from tissue, serum, urine, or imaging and must be validated rigorously. Advances in genome sequencing and other omics technologies have progressed at a rapid pace and provide large amounts of big data for identification of more reliable and novel molecular biomarkers and for delineation of underlying disease pathways and crosstalks for early prediction, detection, diagnosis, prognosis, and monitoring of diseases. Tools for implementing preemptive medicine based on molecular diagnostics and interventions will have the potential to improve cancer prevention. Molecular imaging technologies that truthfully visualize and quantify hallmarks of cancer are already influencing the early detection and management of cancer patients. Combination of *in vitro* molecular diagnostics and whole-body molecular imaging readouts is expected to grow significantly in the future and will be integrated into new cancer therapies as an integrated package, which will provide greater efficiency, value, and cost savings.

A wide variety of nanoplatfoms that are based on diverse nanostructures showed great potential as cancer theranostics. However, although considerable efforts have been directed to the development of theranostic nanoplatfoms and approaches, theranostic nanoparticles have yet to be employed in a clinical setting. We have to bear in mind the following challenges:

- Scaled up synthesis: Many complicated nanoplatfoms with composite structures synthesized in one lab can be difficult to reproduce in another lab and to manufacture in large-scale quantities. Sterility of nanoformulas is another issue.
- Rationale for combined imaging and therapy components within one nanoformula: Imaging and therapy have different requirements for tumor targeting and pharmacokinetics. Codelivery of imaging and therapy may not have significant synergistic effect for clinical application.

- Regulatory hurdles: There is a lack of clear FDA rules to provide adequate oversight of nanotheranostics.
- Nanotoxicity: A variety of nanoparticles have been shown to induce cytotoxicity, genotoxicity, and immunotoxicity related to their nanometer size. The potential benefits and the possible adverse health effects of nanotheranostics need to be considered.
- Economy: Although the “value” of nanomedicine appears to be growing, there is probably still a long way to go for emerging blockbuster nanotheranostic formulas for ultrasensitive marker detection, *in vivo* imaging of cancer targets, and tumor-specific delivery of therapeutics. Nevertheless, coupling therapy with diagnosis together into a single platform now provides industrial vendors and pharmaceutical companies more incentive than conventional diagnostic molecular imaging agents alone to push for clinical trials for higher perceived values of the final products.

In summary, it is increasingly clear that a better understanding of the underlying mechanisms of cancer, identification of new definitive biomarkers, development of tools for ultrasensitive and quantitative measurement of theranostic biomarkers, ability to visualize cancer at its earliest stage with high resolution and in a quantitative manner, prediction of early response to cancer therapy preceding anatomical size change and metastasis dissemination, and new interventional and molecular targeted treatments, especially nanotherapeutics, will all be critical for future individualized cancer treatment. The integration of all these together as cancer theranostics is poised to revolutionize our future healthcare delivery and promises to satisfy the unmet needs in ultimate eradication of cancer.

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