

## Biomedical Imaging: Contrast Agents and Multifunctionality

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### Bioimaging

Bioimaging is one of the major streamlines of comprehensive cancer care in both diagnosis and research with significant advantages of real time monitoring, minimal or no invasive action, and operational over relatively wide ranges of time and size scales involved in biological and pathological processes. Bioimaging plays a great role in different stages of cancer management: Prediction, screening, biopsy for detection, staging, prognosis, therapy planning, therapy guidance and therapy response [1-5]. Biomarkers identified from the genome and proteome can be selectively targeted and chemical binding can improve their imaging signal. Various pharmaceutical therapies that have been developed for cancer are classified as cytotoxic, antihormonal, immunotherapeutic and molecular targeted. Imaging can help the molecular targeted therapies to control their effectiveness and include: signal transduction, angiogenesis, cell cycle inhibitors, apoptosis inducers and epigenetic modulators [6].

The molecular imaging is a combined functional and structural imaging modality, which effectively can be used to achieve the health benefit from understanding the spatial mapping at the whole-body level and molecular processes within cells and tissues [7]. Various targeted agents for cancer markers are for example: epidermal growth factor receptor (EGFR),  $\alpha_v\beta_3$  integrin, vascular endothelial growth factor (VEGF), carcinoembryonic antigen (CEA) and folate receptors (FR). Clearly, the development of minimally invasive targeted therapy and drug delivery should be based on the guided imaging system. Most clinical imaging systems are based on the interaction of electromagnetic radiation with body tissues and fluids except ultrasound which is based on the reflection, scattering and the frequency shifts of acoustic waves (i.e., Doppler effect). Ultrasound also has the capability of imaging tissue elasticity, thus can be employed in differential diagnosis of breast cancer, prostate cancer, and liver fibrosis because cancer tissues are less elastic than normal tissue and ultrasound elastography [8,9]. High frequency electromagnetic radiation such as  $\gamma$ -rays, X-rays or UV light is ionizing, which can cause mutation hence leading to cancer. In contrast, non-ionizing radiation imaging systems including IR spectroscopy, microwave imaging spectroscopy, photoacoustic and thermoacoustic imaging which are readily used for imaging poses no such danger. Imaging systems has one common point; they vary in physical properties including sensitivity, temporal and spatial resolution. In addition, the imaging systems produce images that have differences in contrast. The differences in contrast can be due to changes in physical properties caused by the endogenous nature of the tissue e.g.: radiation absorption, reflection, transmission, magnetic relaxivity, magnetic susceptibility, oxygenation, spectral distribution, electrical impedance, mechanical elasticity, etc. or exogenous mechanisms e.g.: radiation absorption, reflection, emission, magnetic relaxivity, magnetic susceptibility, isotope spectra, fluorescence, perfusion, hypoxia, etc. Finally, it is believed that the sensitivity and specificity of diagnostic systems can be improved by combining the systems as one system known as *multimodal system*.

### Multimodal Strategies

No single imaging system can provide all the required information in biomedical imaging technology. As mentioned above each imaging

modality has its own advantages and limitations in terms of sensitivity, resolution, accuracy and quantitative capabilities. The major problem which is often faced with single-modality imaging is the inability to assure the conformance of diagnosis, which is very important factor in determining the treatment. The problem is solved by multimodal imaging system where a combination of techniques with complementary strengths offer unique benefits which are not met by individual methods. Therefore, utilizing such complementary imaging modes will greatly improve the diagnosis and treatment reliance and render extra comfort to both physicians and patients. Multimodal imaging techniques can be obtained in two different approaches (i) combining the different imaging instruments into one unit, (ii) to develop multimodal imaging agents.

### Examples of combined imaging systems

- PET-CT
- MRI-Optical
- MRI-CT
- MRI-PET
- MRI-PET-NIRF
- MRI/SPECT
- MRI-PA-Raman
- SPECT-CT
- PA-US
- PA-OCT
- PA-Fluorescence
- PA-US-Agents.

### Examples of multimodal imaging agents

Although every individual imaging modality system has its particular contrast agents, multimodal imaging systems also require its customized multimodal contrast agents. Some examples are as follows:

**Iron oxide-Gold nanoparticles (SPION-Au):** has been used in MRI-PAI dual mode imaging [10] where they showed the defined structural characteristics and physical properties of this agent not only

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offer contrast for electron microscopy and MRI but also a new mode of magneto photoacoustic imaging. The (Au-SPION) provides a superior contrast compared to using only single conventional nanoparticles. It was recently shown that the combined imaging system based on interferometric scattering (iSCAT) and AFM enhances the accuracy, temporal resolution and capable of producing high resolution images of individual SPION-Au nanoparticles [11].

**Iron oxide-gold nanoclusters:** Small nanoclusters with optical, magnetic, and therapeutic functionality, designed by assembly of nanoparticle building blocks, offer broad opportunities for targeted cellular imaging, therapy, and combined imaging and therapy [12]. Approximately 30 nm stable uniformly sized near-infrared (NIR) active, superparamagnetic nanoclusters formed by kinetically controlled self-assembly of gold-coated iron oxide nanoparticles. The nanoclusters of approximately 70 nm iron oxide primary particles with thin gold coatings display intense NIR (700-850 nm) absorbance.

**Single-walled carbon nanotubes (SWNTs):** New size-controlled and biocompatible Gd<sub>2</sub>O<sub>3</sub>-DEG-gelatin nanoparticles were fabricated for MRI and PA [13]. Single-walled carbon nanotubes (SWNTs) is another multimodal contrast agent which possess surface properties and biocompatibility similar to plasmonic nanoparticles with wide absorption that can produce strong photoacoustic signals.

**Perfluorocarbon (PFC) droplets:** Phase-change contrast agents transform liquid emulsions into microbubbles (MBs) contrast agents that can have both diagnostic and therapeutic functions. PFC droplets undergo a volumetric expansion when is subject to sufficient acoustic pressures delivered by an ultrasound transducer, called acoustic droplet vaporization (ADV) [14]. Similarly, when it is subject to optical irradiation, vaporization also occurs (ODV) [15]. Thus, when the laser fluence is below the vaporization threshold, the droplets remain in the liquid phase and can be used as a PA contrast agent. However, when the fluence exceeds the threshold, it induces droplet vaporization resulting in MBs which can be used for contrast enhanced ultrasound imaging. MBs can be composed of phospholipids, albumin or polymer. These gas-filled can produce strong acoustic scattering relative to the surrounding tissue. In more advance form, Au MBs comprise of albumin-shelled microbubbles with encapsulated gold nanorods and have been used as PA/US dual modality contrast agent for thermotherapy [16].

**Dye-doped PFC nanoparticles:** These contrast agents have been used as PAI-FI [17]. Spectroscopic characterization of the developed NIR dye-loaded perfluorocarbon-based nanoparticles for combined fluorescence and PA imaging revealed distinct dye-dependent photo physical behavior. They demonstrated that the enhanced contrast allows detection of regional lymph nodes of rats *in-vivo* with time-domain optical and photoacoustic imaging methods. Also, the use of fluorescence lifetime imaging provided a strategic approach to bridge the disparate contrast reporting mechanisms of fluorescence and PA imaging methods.

## Multi-functionality

The progress and advances in nanobiotechnology during the last decade has resulted in significant achievements. On the hand, it seems, the everyday increasing clinical demands has a direct role in shaping, directing and even accelerating part of this progress in specific directions. For example, the heterogeneity of cancers necessitates image-guided therapies, where personalized disease treatments are planned based on individual patients' pathological conditions and

responses to the treatment. Consequently, as a result of such demands, the idea of *multifunctional* (i.e., multimoiety) nanoparticles was formed. Multifunctional nanoparticles are those that are capable of combining various functional features in one package acting as a single multifunctional nanoprobe for different purposes: detection, imaging, therapy or drug delivery [18,19]. Though, the clinical demands provided the necessary motivation it is, however, important to acknowledge the fact that emergence of new advance nanoparticles itself is due to nanofabrication techniques advancement which render various possibilities for biomedical applications. Basically, a nanoparticle outer layer (normally with a suitable coating) can be linked to a specific targeting ligand that only recognizes the unique features of the surface of the target. In addition, other moieties can be attached simultaneously for other purposes including imaging and drug delivery. Therefore, the function of such multifunctional structure depends on the application which in turn governs the type of components that can be used.

## Conclusion

Let us remind that the high surface area-to-volume ratio facilitates surface loading capability with more cargoes such as targeting moieties, imaging and therapeutic agents or other functional molecules. Once such a multifunctional structure is administrated to body, it can be triggered by light excitation (optically and thermally) or by magnetic field for diagnostic and therapeutic applications. However, prior to their use, a number of requirements ought to be satisfied: (a) biocompatibility, (b) non-toxicity, (c) stability in *in-vivo* environment, (d) high selectivity, (e) long circulation time in the bloodstream and (f) efficient clearance by the renal system. The next stage to consider is the synthesis process. The synthesis of nanoparticles has received a great deal of interest and attention because of their potential biomedical applications which in turn are affected by the kind of surface modification. There are broadly two types of modification methods: chemical and physical where the former offers a stronger and robust bonding and stable surface ligand. A proper surface modification determines how well biomolecules are conjugated on the nanoparticles. A wide variety of contrast agents and labels is required for different types of detection and imaging such as MRI, PET, SPECT and fluorescence-based imaging. While the last method is widely used for *in-vitro* imaging, the others are generally applied for *in-vivo* applications. An important class of nanoparticles comprises those made of inorganic materials such as metals, metal oxide, semiconductor, rare earth minerals and silica. These materials possess unique electrical, optical, magnetic and plasmonic properties due to quantum mechanical effects at nanoscale. Most nanocrystals can be fabricated with a great control on size, shape, composition and physical properties. Potential single agents and functional nanoparticles that can be used for both therapy and bioimaging are: Dyes (for example, Indocyanine-green(ICG), Fluorescein isothiocyanate (FITC), Alexa Fluor 750, Evans blue, IR Dye 800CW, Methylene blue,...), gold nanoparticles, gold nanoshells, gold nanorods, nanocages, nanostars, nanobeacons, SPIONS, polymeric NPs (e.g., PLA, PEG, PEO, PPO and PLGA), dendrimers, Silica, QDs and upconversion nanoparticles. Multimodal nanoparticles can often offer better spatial registration of different imaging modality and avoid excessive immune response caused by repeated challenge. A number of multimodal nanoparticles combine the use of a full body scan with an imaging modality that offers local images with higher resolution [20]. This technique allows characterization of disease at multiple spatial scales. For example, SPIONS labeled with Cy5.5, functionalized silica nanoparticles or FITC-conjugated magnetite nanoparticles and many other similar combinations were utilized for biomedical imaging applications [21-23].

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