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Review

# Toward carbon nanotube-based imaging agents for the clinic

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ABSTRACT

Among the many applications for carbon nanotubes (CNTs), their use in medicine has drawn special attention due to their potential for a variety of therapeutic and diagnostic applications. As progress toward clinical applications continues, monitoring CNTs *in vivo* will be essential to evaluate their biodistribution, potential toxicity, therapeutic activity, and any physiological changes that the material may induce in specific tissues. There are many different imaging modalities to visualize and track CNTs *in vivo*, yet only a few are full-body penetrating, a central characteristic that widens their clinical utility. In order to visualize CNTs, chemical modification is often required for the material to be used as a platform to carry imaging agents compatible with one or more of the clinical imaging techniques. Here, we focus on the most recent work involving the use of CNTs as imaging agents for the non-invasive, full-body penetrating clinical modalities of MRI, PET, SPECT, and X-ray CT. The synthesis and modification of the CNT materials are discussed, as well as relevant preclinical studies.

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## 1. Introduction

Among the many nanoparticles currently under investigation, carbon nanotubes have been and continue to be a key material for their unique properties, cost effectiveness, and extreme diversity of applications. Carbon nanotubes (CNTs) can be described as graphene sheets that are rolled in a cylindrical shape and have different electrical and optical properties depending on the axis about which they are rolled, which is called chirality or the "twist" of the nanotube. The different CNT chiralities include the armchair structure, in which the C–C bonds are perpendicular to the tube axis; the zig-zag structure, in which the C–C bonds are parallel to the tube axis; and the chiral structure, in which the C–C bonds lie at an angle with respect to the tube axis [1,2]. CNTs are either single-walled (SWCNTs) with a diameter around 1–2 nm, or multi-walled (MWCNTs), which are composed of 2–30 concentric SWCNTs with an outer diameter ranging from 10 to 100 nm. Some of the methods that are generally used to produce CNTs are arc-discharge, laser-ablation, and chemical vapor deposition, including the high-pressure carbon monoxide (HiPCO) synthesis. These processes usually occur in the presence of transition metal (Co, Fe, Ni) or rare earth (Gd, Y) catalysts, which remain in the pristine CNT product [3–9]; significant progress has been accomplished in the removal of trace amounts of these catalysts [9–13], although more work is currently underway. Since their discovery [14], CNTs have been of great interest because of their unique structural and chemical properties, such as their high tensile strength, high aspect ratio, and the capability to be chemically functionalized, while remaining relatively inert [15–18]. This interest has led to CNTs being used in a variety of applications in electronics [19,20], material composites [21], energy [22], catalyst supports [23,24], and particularly those in the medical field [25–27]. Within the emerging field of nanomedicine, CNTs have been investigated as drug delivery vectors [28,29], therapeutic agents exploiting microwave-, photo-, or radiofrequency-induced thermal effects [30–33], scaffolds for

*Abbreviations:* acac, acetylacetone; CNTs, carbon nanotubes; CT, computed tomography; CA, contrast agent; DTPA, diethylenetriaminepentaacetic dianhydride; DOX, doxorubicin; EXAFS, extended X-ray absorption fine structure; GNT, Gadonanotube; hfac, hexafluoroacetylacetone; HiPCO, high pressure carbon monoxide; HR-TEM, high resolution transmission electron microscopy; ICP-MS, inductively-coupled plasma mass spectrometry; i.v., intravenous; Ti, inversion time; MRI, magnetic resonance imaging; MWCNTs, multi-walled carbon nanotubes; PCP, p-carboxyphenyldiazonium; %ID/g, percent injected dose per gram of tissue; PBS, phosphate buffered saline; PAH, poly(allylamine hydrochloride); PDDA, poly(-diallydimethylammonium chloride); PEG, polyethylene glycol; PET, positron emission tomography; STEM, scanning transmission electron microscopy; SPECT, single-photon emission computed tomography; SWCNTs, single-walled carbon nanotubes; SPIONs, superparamagnetic iron oxide nanoparticles; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; thd, 2,2,6,6,-tetramethyl-3,5-heptanedione; T, Tesla; TEM, transmission electron microscopy; US-SWCNTs, ultra-short SWCNTs.

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tissue engineering [34], and diagnostic imaging agents [35,36].

For diagnostic and therapeutic applications, it is essential to determine the CNT biodistribution and pharmacokinetic profile to study the biological effects of the material on specific tissues. To this end, researchers have used a wide range of imaging modalities that rely on the intrinsic properties of CNTs. These techniques include Raman scattering [37], high optical and near infrared (NIR) absorbance and photoluminescence [38–40], photoacoustic [41–44], thermoacoustic [45], and echogenic properties [46]. However, some of these imaging techniques suffer from penetration depth limitations, poor spatial resolution, or poor soft-tissue contrast [47,48]. To combat these limitations, CNTs may be employed as a scaffold or capsule for radionuclides or ions that are used for the noninvasive, full-body penetrating clinical modalities, such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and X-ray computed tomography (X-ray CT) (see Fig. 1).

While common imaging contrast agents (CAs) generally are not able to cross the cell membrane, the use of CNTs allows for these agents to be delivered intracellularly for cell tracking and sometimes selectively with the use of biological targeting moieties. Packaging the imaging agents onto or inside the CNTs enables them to be internalized by cells [49] without the need of cytotoxic transfection agents [50,51]. However, the highly hydrophobic nature of CNTs also prohibits their suspension in aqueous media, requiring covalent or non-covalent functionalization techniques to produce biocompatibility and high aqueous suspendability (see Fig. 2). Several reviews discussing extensively the different methods for CNT functionalization have been previously published [52–54], as well as reviews on the use of CNTs for imaging [35,36,55–57]; however, the rapid growth in the field constantly prompts an updated discussion of current findings. For this reason, this review focuses primarily on recent clinically relevant work involving exclusively non-invasive full-body penetrating techniques reported within the past five years.

## 2. CNT-based agents for MRI

Among the imaging techniques used in the clinic, MRI offers the advantage of high-quality anatomical images with high spatial resolution without the use of ionizing radiation. Instead, MRI utilizes a high-intensity magnetic field that aligns the nuclear magnetization of hydrogen atoms in water molecules within the body, taking advantage of the difference in water concentration among tissues to produce images. Common MRI CAs are chemical compounds containing a chelated paramagnetic metal ion (such as $Gd^{3+}$, $Mn^{2+}$, etc.) with larger effects on $T_1$ shortening (spin-lattice relaxation agents), or superparamagnetic materials such as iron oxide nanoparticles with larger effects on $T_2$ shortening (spin-spin relaxation agents), where $T_1$ and $T_2$ are the proton relaxation times. The theoretical basis for the relaxivity of paramagnetic and superparamagnetic agents has been extensively described in the literature [58–62]. In order to produce an MRI-active CNT CA, a paramagnetic or superparamagnetic agent must be conjugated to or encapsulated within the CNT platform.

### 2.1. Gadolinium-based contrast agents

The first CNT-based MRI CA containing $Gd^{3+}$ was reported in 2005 by Sitharaman et al., and was termed the "Gadonanotube" or GNT [63,64]. The CA consisted of ultra-short (20–80 nm) single-walled carbon nanotubes (US-SWCNTs) loaded with $Gd^{3+}$ ion clusters (3–4% Gd by weight, see Fig. 3A and B). GNTs displayed 40–90 times superior relaxivity values compared to the clinically used MRI CA Magnevist®. Furthermore, the $Gd^{3+}$ ion cluster are so tightly contained by the CNT platform that the ions do not leak out of the CNTs under biological conditions [65], which is critical for clinical applications given the high toxicity of free $Gd^{3+}$ [66]. Usually, a 0.17% Pluronic® F-108 solution is used to suspend the GNTs in an aqueous medium for *in vitro* studies. In subsequent reports, GNTs were used to label macrophage cells [67], mesenchymal stem cells (see Fig. 3C and D) [68,69], and HeLa cells [70]. In all cases, GNTs localized in the cytoplasm of the cell, delivering about $10^9$ $Gd^{3+}$ ions per cell. In another study, GNTs were covalently derivatized with D,L-serine amino acid substituents to produce water-suspendable (2 mg/mL) "ser-GNTs," which were then used to label MCF-7 human breast cancer cells with no observable cytotoxic effects or morphologic changes [71].

In a follow-up to the original GNT report, three new Gd-based CAs, derived from confinement of three different gadolinium chelates within the cavities of the same US-SWCNTs were recently reported. The chelates $Gd(acac)_3 \cdot 2H_2O$, $Gd(hfac)_3 \cdot 2H_2O$, and

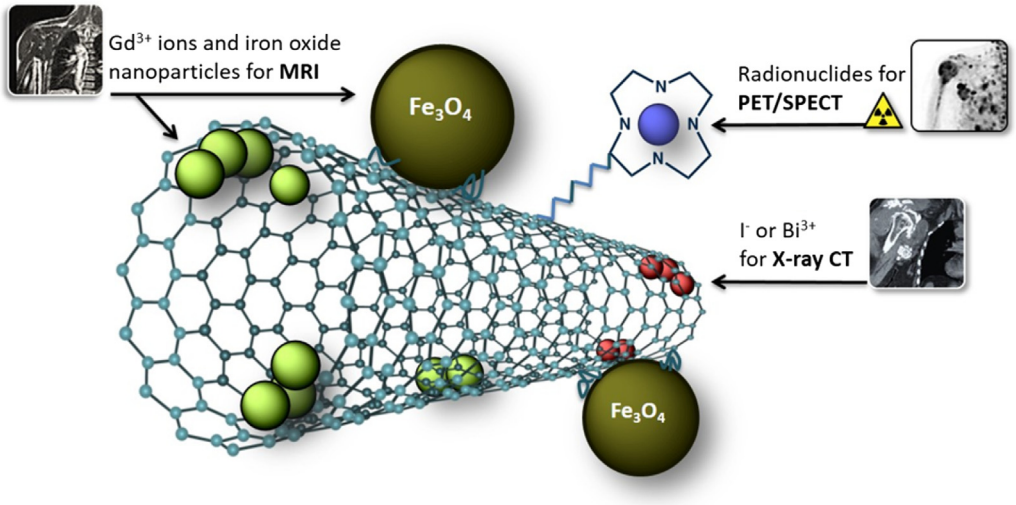


**Fig. 1. Schematic of the versatile CNT platform**. Various ways to modify CNTs: attaching chelated ions or nanoparticles, such as superparamagnetic iron oxide nanoparticles (SPIONs), to the outer surface of the material or loading other agents or ions within the hollow interior of the material.

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