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REVIEW ARTICLE

Stimuli-Responsive Carbon Nanotubes for On-Demand Cancer Therapy: A Review

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Abstract
Stimuli-responsive carbon nanotubes (CNTs) have emerged as transformative nanocarriers in precision oncology due to their unique physicochemical, optical, and mechanical properties, enabling controlled, targeted drug delivery. This review presents a comprehensive analysis of CNT-based systems engineered to respond to specific internal (pH, redox, and enzymatic) and external (light, temperature, magnetic, and ultrasound) stimuli for on-demand cancer therapy. The discussion covers synthesis methods, structural differences between single- and multi-walled CNTs, and diverse functionalization strategies that enhance solubility, biocompatibility, and stimuli responsiveness. The crucial advances in CNT-based delivery systems demonstrate their ability to achieve spatiotemporal control over drug release, improve tumour penetration, and minimize systemic toxicity through mechanisms such as pH-triggered drug detachment, GSH-mediated redox cleavage, and NIR-induced photothermal ablation. Integrating CNTs with polymers, peptides, and metal nanoparticles further enables multimodal applications, including chemo-photothermal, chemo-immuno, and gene therapies. Despite remarkable progress, challenges remain in understanding long-term pharmacokinetics, immunogenicity, and biodistribution, as well as in establishing standardized synthesis and regulatory frameworks. The review highlights emerging trends such as AI-driven CNT design, predictive pharmacokinetic modelling, and personalized nanomedicine, emphasizing their potential to revolutionize cancer treatment by achieving precise, adaptive, and patient-specific therapy.

Keywords Stimuli-responsive nanocarriers · Carbon nanotubes (CNTs) · Targeted drug delivery · Photothermal therapy (PTT) · Cancer nanomedicine

Introduction

Cancer represents a significant global health burden, with an estimated 19.96 million new cases and 9.74 million deaths reported in 2022[1]. The Global Cancer Observatory (GCO) projects that about 30 million cancer deaths will occur annually by 2030[2]. The tumour microenvironment (TME) plays a crucial role in cancer progression, metastasis, and therapeutic resistance. It is characterized by abnormal vasculature, hypoxia, elevated interstitial pressure, and distinct biochemical features, including acidic pH, elevated levels of reducing agents such as glutathione (GSH), and overexpression of matrix metalloproteinases (MMPs). These pathological hallmarks distinguish tumour tissues from normal ones and provide exploitable biological cues for designing smart nanocarriers[3–5]. Conventional therapies such as chemotherapy, radiotherapy, and surgery have shown substantial success in cancer management; however, their clinical efficacy is often limited in some instances by issues such as systemic toxicity, non-specific targeting, and the development of therapeutic resistance [6, 7]. These challenges underscore the critical need for precision drug delivery systems that selectively target tumour sites while minimizing off-target effects. Nanomedicine, operating at the nanoscale (1–100 nm), offers transformative potential to overcome the limitations of conventional cancer therapies by enabling engineered nanocarriers with improved pharmacokinetics, selective tumour accumulation, and controlled drug release [8–10]. These nanosystems provide precise spatiotemporal control over therapeutic delivery, enhancing efficacy and biocompatibility while reducing systemic toxicity [11, 12]. A wide range of nanocarriers has been developed to overcome the limitations of conventional cancer therapies. These include liposomes, polymeric nanoparticles, dendrimers, metallic nanoparticles (Au, Fe_2O_3), silica

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nanoparticles, and carbon-based nanomaterials such as CNTs and graphene [13, 14]. Several NCs have already achieved clinical success; for instance, liposomal doxorubicin (Doxil®) and albumin-bound paclitaxel (Abraxane®) have demonstrated improved pharmacokinetics, enhanced tumour accumulation, and reduced systemic toxicity [15–17]. CNTs stand out among these due to their high drug-loading capacity, photothermal properties, and tunable surface chemistry, enabling multifunctional applications in targeted drug delivery, imaging, and combined chemo-photothermal therapy [18, 19]. These clinically relevant advancements highlight the translational potential of CNT-based nanocarriers in precision oncology.

In recent years, the paradigm of stimuli-responsive nanocarriers has transformed cancer nanomedicine. These systems are designed to release their therapeutic payloads in response to specific internal or external triggers such as pH, redox potential, enzymes, temperature, magnetic fields, or near-infrared (NIR) light. This responsiveness allows precise spatial and temporal control over drug delivery, enabling on-demand therapy that enhances therapeutic efficacy while minimizing adverse side effects [20–23]. Stimuli-responsive CNTs represent a convergent innovation that combines the inherent advantages of CNTs with advanced delivery functions. When appropriately functionalized, CNTs can serve as both carriers and stimuli-responsive actuators, enabling real-time control of drug bioavailability within the TME [24, 25]. Furthermore, CNTs are uniquely suited to mediate combination therapies that harness multiple treatment modalities, due to their ability to act as photothermal or photodynamic agents [26–28]. Despite significant progress, several research gaps hinder the clinical translation of stimuli-responsive CNT-based systems. Current studies are primarily limited to preclinical models, with insufficient data on long-term toxicity, biodegradation, and clearance mechanisms [29, 30]. Moreover, the heterogeneity of the tumour microenvironment and the lack of standardized synthesis and functionalization protocols make it difficult to achieve reproducible therapeutic outcomes [31, 32]. A deeper understanding of CNT–cellular interactions, immune responses, and scalability constraints is essential to bridge laboratory success with clinical applicability [33]. Addressing these gaps will be critical for advancing CNT-based nanomedicine toward safe and effective cancer therapy. This review offers a comprehensive overview of the design principles, functionalization strategies, and therapeutic applications of stimuli-responsive CNTs in cancer therapy.

CNT: Structure, Types, and Functionalization

Single-walled Carbon Nanotubes (SWCNTs) vs. Multi-walled Carbon Nanotubes (MWCNTs)

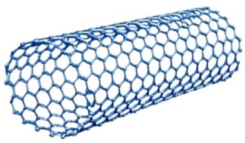
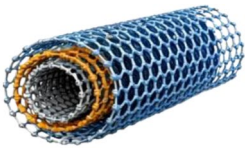
CNTs are cylindrical allotropes of carbon composed of rolled graphene sheets with sp^2-hybridized carbon atoms arranged in a hexagonal lattice. Based on their wall structure, CNTs are broadly categorized into SWCNTs and MWCNTs. SWCNTs consist of a single graphene sheet rolled into a cylindrical form. In contrast, MWCNTs comprise multiple concentric graphene cylinders separated by van der Waals gaps, resulting in enhanced strength and greater drug-loading capacity. Table I shows that SWCNTs and MWCNTs exhibit pronounced differences in their structural, physicochemical, and functional properties, which in turn influence their biomedical applications.

SWCNTs consist of a single graphene sheet rolled into a cylinder, typically with diameters ranging from 0.4 to 2 nm. They possess exceptional electronic and optical properties due to their defined chirality and high aspect ratio (length-to-diameter ratio). Their smaller size and surface area make them more suitable for surface functionalization and applications such as biosensing, drug delivery, and imaging. These properties enhance their sensitivity to external and internal stimuli, including pH changes, redox gradients, and NIR irradiation [34, 35]. In contrast, MWCNTs are composed of multiple concentric graphene cylinders, resulting in larger diameters and greater structural strength, making them useful for bulk drug loading, mechanical reinforcement, and pH-sensitive release systems. Although both types can load drugs effectively through π–π stacking and covalent modifications, SWCNTs generally offer better dispersibility and cellular uptake, while MWCNTs provide enhanced stability and drug retention. The multi-walled structure can hinder uniform functionalization and increase the risk of aggregation, thereby prolonging tissue retention and potentially inducing oxidative stress. Functionalization with PEG, chitosan, or folic acid significantly mitigates these effects, improving both dispersibility and biocompatibility. This highlights the importance of selecting the appropriate nanotube type based on specific therapeutic objectives [36–38].

Synthesis Methods and Materials for CNT Production

CNTs are synthesized from carbon-rich precursors such as methane, ethylene, acetylene, ethanol, benzene, and camphor oil using transition-metal catalysts such as Fe, Co,

Table I A comparative analysis of the key differences between SWCNTs and MWCNTs

Property	SWCNTs 	MWCNTs 	Ref.
Structure	Single layer of rolled graphene	Multiple concentric graphene layers	[39]
Diameter	~0.4–2 nm	~2–100 nm	[40]
Surface Area	Higher due to a thinner diameter	Lower per unit mass	[26]
Functionalization Potential	Easier to functionalize, better dispersibility in biological media	More challenging due to multiple walls	[40]
Mechanical Strength	Good, but lower than MWCNTs	Higher due to nested structure	[39]
Drug Loading Capacity	Moderate (better for molecular drugs)	Higher (suitable for bulkier compounds)	[41]
Stimuli-Responsiveness	High sensitivity to functional stimuli (e.g., pH, NIR)	Effective pH-triggered release, good structural retention	[27]
Cellular Uptake	More efficient due to smaller size and flexibility	Less efficient, but can be enhanced with surface modifications	[40]

Ni, and Mo, typically supported on substrates such as SiO_2 or Al_2O_3 [41]. The main synthesis techniques (Figure 1) include arc discharge, laser ablation, and chemical vapor deposition (CVD). In the arc-discharge method, high-temperature plasma (3,000–4,000°C) vaporizes graphite electrodes in an inert atmosphere, producing high-crystallinity CNTs; however, post-purification is required to remove amorphous carbon and residual metals [42]. The laser ablation technique uses a pulsed laser to ablate a graphite target containing metal catalysts, such as Co/Ni, at approximately 1,200°C, yielding uniform SWCNTs with controlled diameters and low defect densities [43]. Among all methods, CVD is the most scalable and cost-effective. It involves the catalytic decomposition of hydrocarbons on metal nanoparticles at 600–900°C, leading to the formation of CNTs on the substrate [44, 45]. Variants such as plasma-enhanced and floating-catalyst CVD enable control over CNT alignment, length, and purity, making them particularly suitable for biomedical-grade CNT synthesis [46]. Process optimization—including adjustments in temperature, catalyst composition, and gas flow—strongly influences CNT crystallinity, defect density, and surface reactivity, all of which affect drug adsorption and functionalization efficiency [47]. Purification through acid washing or oxidation enhances CNT biocompatibility by eliminating metallic impurities and introducing oxygen-containing functional groups that serve as anchoring sites for drug molecules and ligands [48].

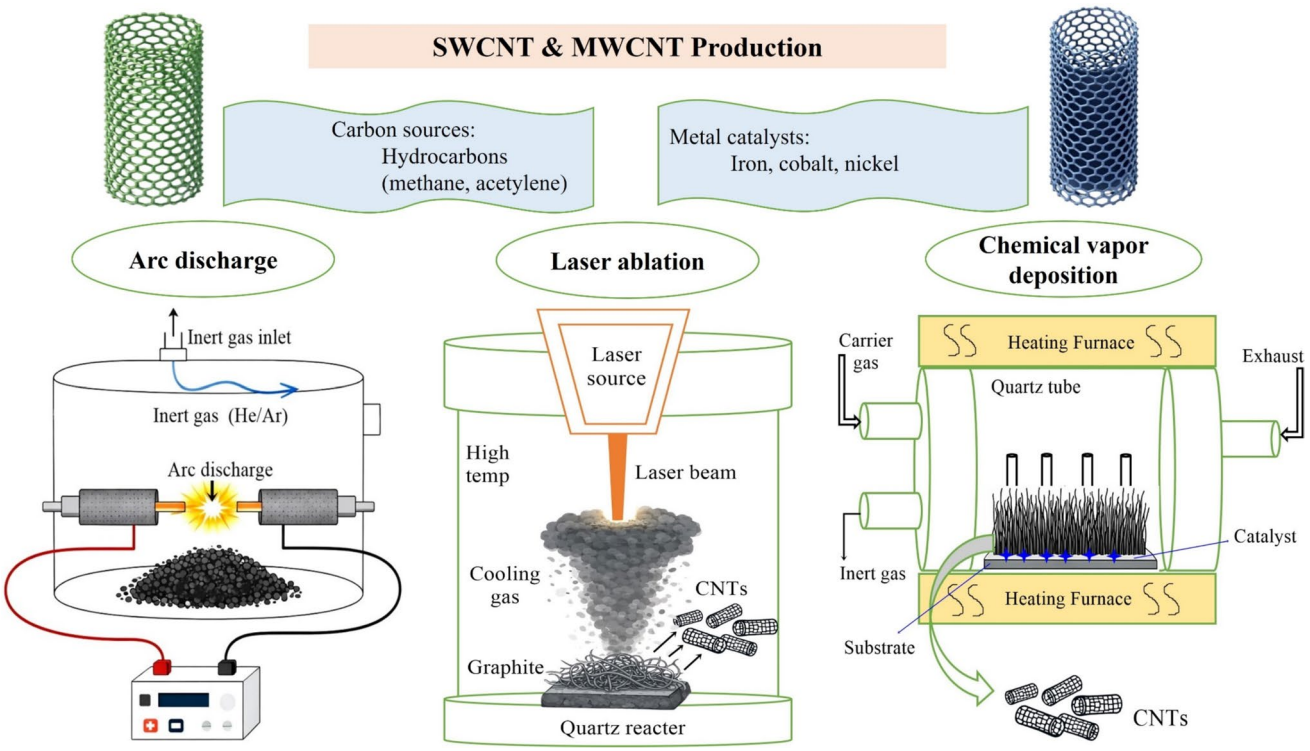


Fig. 1 Synthesis methods and materials for SWCNT & MWCNT production

Surface Modification and Functionalization

Surface modification and functionalization of CNTs are crucial strategies for improving their solubility, biocompatibility, and targeting ability for biomedical applications [39]. Table II summarizes the functionalization techniques and their biomedical uses. These processes involve changing the CNT surface chemistry, either covalently or non-covalently (see Figure 2), to improve their interaction with other materials or to add new functions [40]. Covalent modification involves chemically attaching functional groups (e.g., –COOH, –OH, or $–NH_2$) to the sidewalls or tips of CNTs through oxidation (HNO_3/H_2SO_4) and amination reactions to improve dispersibility. These functional groups enable attachment of therapeutic agents, targeting ligands, or imaging molecules [28, 36]. For instance, acid treatment adds carboxylic groups, increasing the reactivity of CNTs. Groups such as dodecylamine or 3-aminopropyl triethoxysilane can then be covalently bonded, enabling applications in nanocomposites, biomedicine, and energy systems [40]. *Hwang and Park* reviewed how carboxylation and amidation strategies enable precise coupling of anticancer drugs, such as DOX and cisplatin, via covalent attachment to CNTs, thereby achieving controlled release kinetics and improved tumour penetration. This method also facilitates the integration of targeting ligands, such as folic acid and monoclonal antibodies, enabling receptor-specific uptake in cancer cells [49]. Similarly, *Tang et al.* demonstrated that folic-acid- and peptide-functionalized CNTs selectively targeted tumour cells through receptor-mediated uptake while maintaining structural integrity for photothermal and chemotherapeutic co-delivery [50]. Non-covalent approaches, such as π–π stacking interactions with aromatic molecules or polymer coatings, maintain the electronic structure of CNTs while allowing functional improvements. For example, chitosan and polyethylene glycol (PEG) have been used to coat CNTs, enhancing water solubility and reducing immune responses [37, 39]. Additionally, nucleophilic anionic addition (e.g., alkyllithium reactions) enables the grafting of polymers or the attachment of molecular groups to CNTs, thereby improving compatibility with polymer matrices [38].

Hybrid nanocomposites have further advanced CNT surface engineering. For example, metallic nanoparticle–CNT hybrids and polymeric CNT composites exhibit multifunctionality for imaging, sensing, and hyperthermia. *Saliev* highlighted the use of CNT–gold and CNT–iron oxide hybrids, which enable magnetic targeting and combined chemo-photothermal therapy [51]. Moreover, antibody-functionalized CNTs have been successfully employed for selective tumour cell recognition and enhanced photothermal efficacy, providing an emerging platform for precision oncology [24]. In addition, new surface strategies such as "click chemistry" and AI-assisted functionalization have enabled controlled ligand density and reproducibility in

Table II Functionalization techniques and their biomedical roles

Category	Sub-Type/Method	Representative Chemical Agents or Materials	Functional Benefit	Examples in Cancer Therapy	Ref
Covalent Functionalization	Direct chemical modification	–COOH, $–NH_2$, PEG, APTES	Improves solubility, dispersibility, and enables drug conjugation	Doxorubicin (DOX)-loaded COOH-CNTs for enhanced solubility and pH-responsive release	[21] [26] [40]
	Ligand conjugation (subset)	Folic acid, CD44-binding ligands, antibodies, peptides	Enables active tumor targeting through receptor-mediated endocytosis	FA-MWCNTs for selective breast cancer targeting	[53] [54] [55]
Non-Covalent Modification	π–π stacking/supramolecular adsorption	Aromatic drugs, tryptophan, surfactants	Preserves CNT electronic properties and allows reversible drug loading	Topotecan-tryptophan-CNT conjugates showing pH-triggered release	[27] [56]
	Polymeric coating (subset)	Chitosan, Dextran, PEG, PVP	Enhances biocompatibility, reduces immune recognition, prolongs circulation time	PEG-SWCNTs for reduced clearance and improved tumor accumulation	[37] [39] [57]

CNT-based nanocarriers [29]. These surface engineering techniques turn CNTs into highly versatile platforms suitable for targeted drug delivery, imaging, and combined therapies in cancer treatment [52]. Their surface chemistry and architecture directly influence CNTs' ability to respond selectively to biological or external stimuli; thus, understanding their functionalization provides a crucial foundation for exploring the mechanisms that govern controlled drug release.

Functionalization Strategies for Reducing CNT Toxicity

Surface functionalization is a primary determinant of CNT biocompatibility and has been widely shown to mitigate toxic effects associated with pristine CNTs by enhancing solubility, dispersion, and favourable biological interactions. Pristine CNTs are hydrophobic and tend to agglomerate in biological media, leading to membrane disruption, oxidative stress, and inflammatory responses. Functionalization, through chemical or physical attachment of biocompatible moieties, improves aqueous dispersibility, reduces nonspecific protein adsorption, and alters cellular uptake pathways, collectively decreasing cytotoxicity [58, 59]. One of the most extensively studied approaches is PEGylation, which significantly enhances water solubility and biocompatibility. PEG-functionalized CNTs exhibit reduced aggregation and diminished cytotoxic responses *in vitro*, and improved tolerability *in vivo*, compared to non-functionalized CNTs. For instance, PEGylated CNTs have shown enhanced cell viability and lower inflammatory responses, attributed to better dispersion stability and reduced nonspecific cellular uptake [60].

Similarly, covalent attachment of carboxyl and hydroxyl groups increases hydrophilicity and reduces toxicity by promoting dispersion and reducing direct hydrophobic interactions with cell membranes. Carboxylated CNTs have been reported to have lower toxicity and improved drug absorption, supporting their suitability for biomedical applications [61]. Non-covalent functionalization with biopolymers and surfactants (e.g., phospholipid–PEG, chitosan, proteins) also reduces CNT toxicity. These coatings stabilize CNTs in biological media, reduce reactive oxygen species (ROS) generation, and lower immune activation by masking the hydrophobic CNT surface, thereby improving cytocompatibility [62]. Clinical relevance of functionalization is further underscored by recent work showing that high-molecular-weight biomolecule coatings (e.g., hyaluronan) significantly reduce pulmonary injury and inflammatory responses *in vivo*, demonstrating that thoughtful design of surface chemistry can translate into meaningful reductions in organ-level toxicity [63]. Overall, functionalization, whether covalent or non-covalent, is critical for optimizing CNT safety profiles

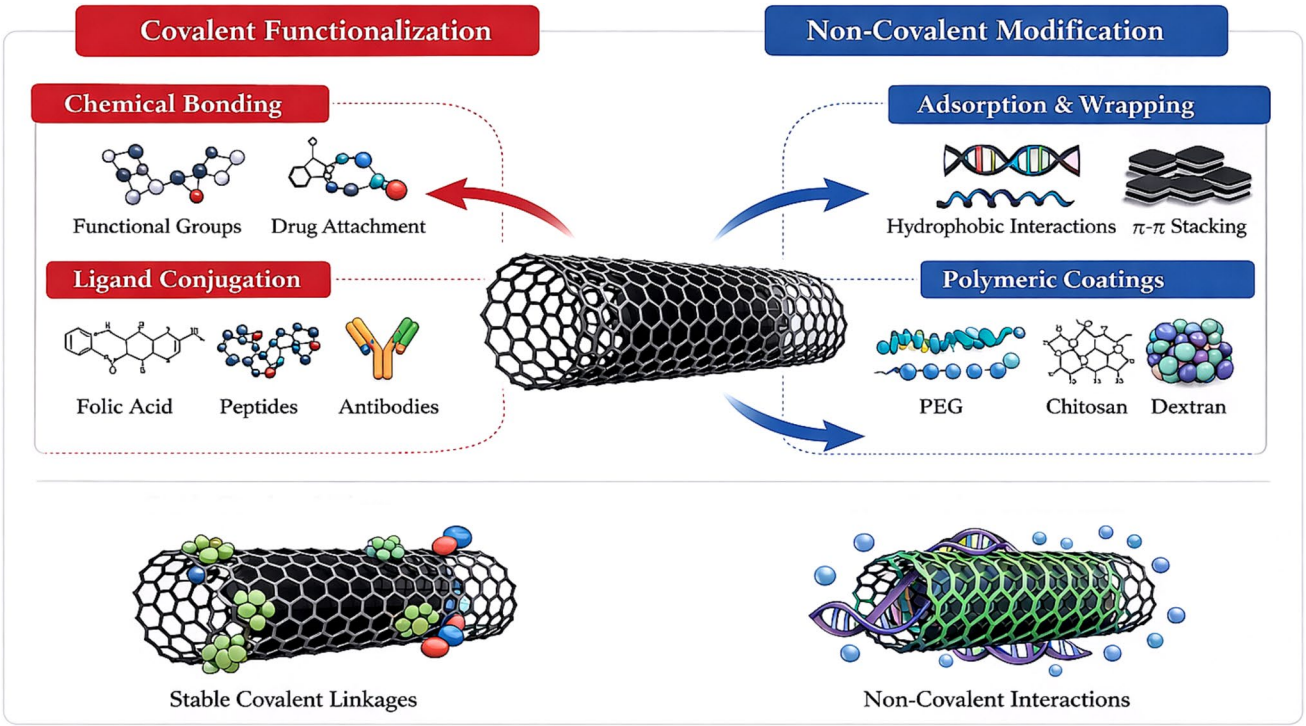


Fig. 2 Surface functionalization pathways of CNTs: covalent and non-covalent approaches

and is routinely employed in drug delivery designs to balance efficacy with biocompatibility. While functionalization substantially improves biocompatibility and reduces CNT-associated toxicity, it also influences stimuli-responsive behavior and drug loading efficiency, as discussed in the subsequent section.

Stimuli-Responsive Mechanisms in CNT-Based Systems pH-sensitive Release in the Tumour Microenvironment

CNT-based systems leverage the unique physicochemical properties of CNTs, such as high surface area and facile surface modification, to create innovative, pH-sensitive platforms for tumour-targeted chemotherapy with improved therapeutic index [64]. pH-sensitive CNT-based drug delivery systems exploit the acidic TME (pH 6.5–6.8 extracellularly; pH 5.0–5.5 in endosomes/lysosomes), which arises from lactic acid accumulation due to hypoxia and the Warburg effect. This difference from the neutral physiological pH (~7.4) enables pH-responsive nanocarriers to release their therapeutic payloads selectively [65]. CNT-based pH-sensitive carriers typically incorporate acid-labile linkers or protonatable functional groups that trigger drug detachment under acidic conditions. The mechanism is schematically illustrated in Figure 3, where acidic pH cleaves pH-labile linkers, resulting in localized drug release within tumour tissues. Functionalized CNTs, particularly those coated with pH-sensitive molecules such as tryptophan or linked via acid-labile bonds (e.g., π-π stacking or hydrazone linkages), have demonstrated enhanced drug retention at physiological pH and accelerated release in acidic conditions. For instance, tryptophan-functionalized CNTs exhibited strong van der Waals interactions with topotecan at neutral pH. In contrast, under acidic conditions, electrostatic repulsion triggered drug release by protonating surface groups [27]. In addition, a CNT-based hybrid nanogel with chitosan exhibited enhanced pH sensitivity and greater DOX release in acidic conditions, effectively suppressing tumour cell proliferation. Specifically, *Seyfoori et al.* reported a 3.5-fold increase in DOX release at pH 5.5 compared to pH 7.4, with approximately a 65% reduction in cancer cell viability, highlighting the advantage of pH-triggered selectivity[56]. Likewise, *Anbarasan et al.* found that DOX-loaded MWCNTs released 75–80% of the drug at pH 5.0, compared with <20% at pH 7.4, leading to a 2.3-fold increase in cytotoxicity against MCF-7 cells[40]. Similarly, *Kordzadeh et al.* functionalized CNTs with carboxyl and folic acid groups, enhancing DOX release near cancer cells via combined pH and receptor-targeted mechanisms. Molecular dynamics confirmed stronger interactions and uptake by cancer cell membranes [66]. Functionalized multi-walled CNTs showed stronger drug binding at pH 7.4 and released more 5-FU

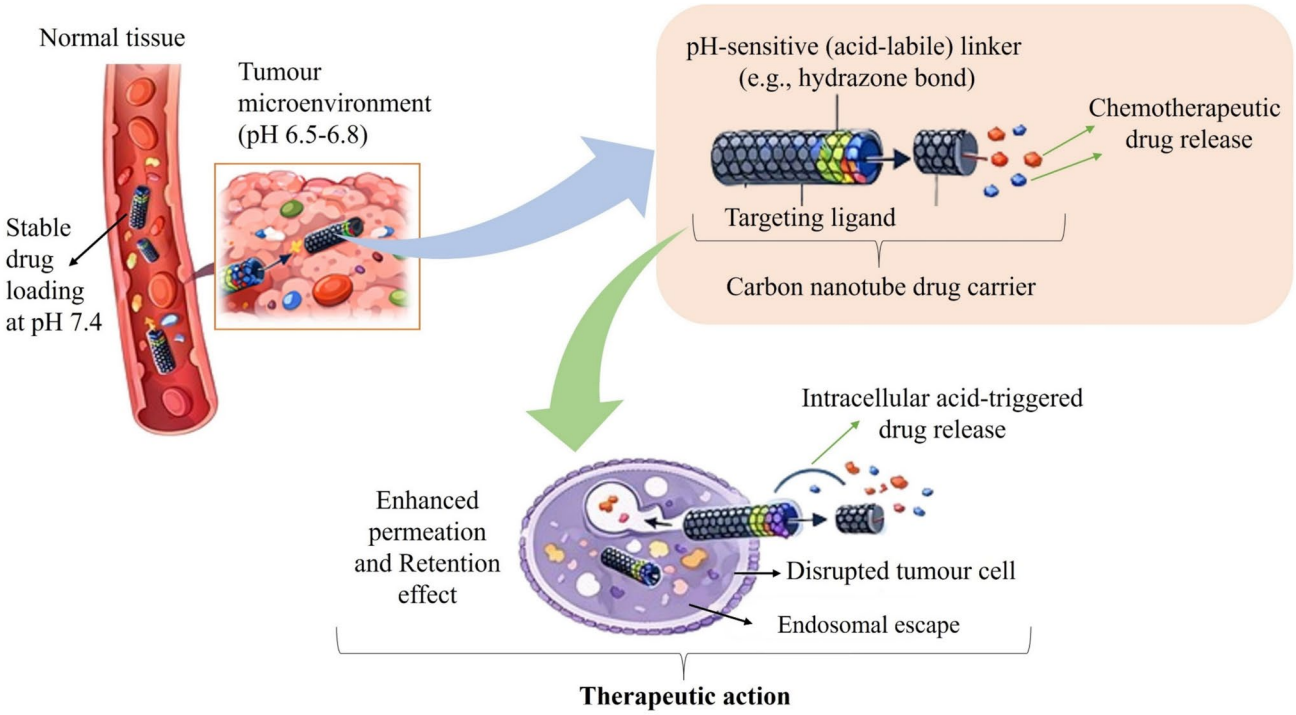


Fig. 3 pH-sensitive release mechanisms in tumour-specific CNT delivery systems

at pH 5.0, making them ideal for tumour-targeted delivery[67]. For instance, polyethyleneimine-coated multiwall magnetic carbon nanotubes (Mag-CNTs) released naproxen efficiently at acidic pH mimicking inflamed tissues, showing enhanced stability at neutral pH [68]. However, long-term toxicity, non-biodegradability, and immune response are active research concerns, particularly in biomedical fields [69]. Beyond pH-triggered systems, redox-responsive CNTs exploit intracellular GSH gradients to achieve selective drug release within tumour cells, providing a complementary internal stimulus for precision therapy.

Redox-responsive Systems (GSH-sensitive bonds)

Tumour cells exhibit intracellular GSH concentrations up to 1–10 mM, 1000 times higher than in the extracellular environment, due to redox imbalance in rapidly proliferating cells. Redox-responsive CNT systems employ disulfide linkages or thiol–exchange reactions that are cleaved by elevated GSH levels inside tumour cells, triggering localized drug release [70]. These systems often employ disulfide bonds as cleavable linkers between the CNTs and drug molecules or surface coatings. This redox-triggered release process is depicted in Figure 4, highlighting disulfide bond cleavage in high-GSH tumour environments. In the reductive environment within cancer cells, elevated GSH levels cleave disulfide bonds, resulting in rapid, localized drug release [26]. Recent studies validate this concept both *in vitro* and *in vivo*. *Jia et al.* engineered disulfide-bridged CNT nanocarriers, achieving 80 % DOX release within 24 h at 10 mM GSH and ~3-fold enhanced cytotoxicity in HeLa cells [71]. *Burkert et al.* reported nitrogen-doped CNT "cups" that produced >60 % tumour reduction in mice via redox-triggered DOX release (70%) at 5 mM GSH without organ toxicity [28]. *Dai et al.* developed a smart redox and pH-responsive GSH/pH degradable nanosponge which releases DOX (~77.0%) in acidic (pH5.0) and cytosolic reduction (10 mM GSH) conditions with low cytotoxicity up to a concentration of 1000 µg/mL [72]. Likewise, disulfide-bridged nanocarriers based on CNT scaffolds have demonstrated efficient intracellular delivery of chemotherapeutics, thereby increasing cytotoxicity in cancer cells with minimal impact on healthy tissues [71, 73]. Similarly, redox-sensitive linkers incorporated into CNT-drug conjugates have enabled precise intracellular drug release, thereby improving therapeutic outcomes and minimizing off-target toxicity [28]. These systems capitalize on the redox gradient between tumour and normal tissues, offering a highly selective mechanism to achieve spatially controlled chemotherapy using CNT-based nanocarriers [74]. While redox sensitivity relies on intracellular reducing environments, enzyme-responsive systems capitalize on protease overexpression in tumour tissues, further enhancing site-specific selectivity.

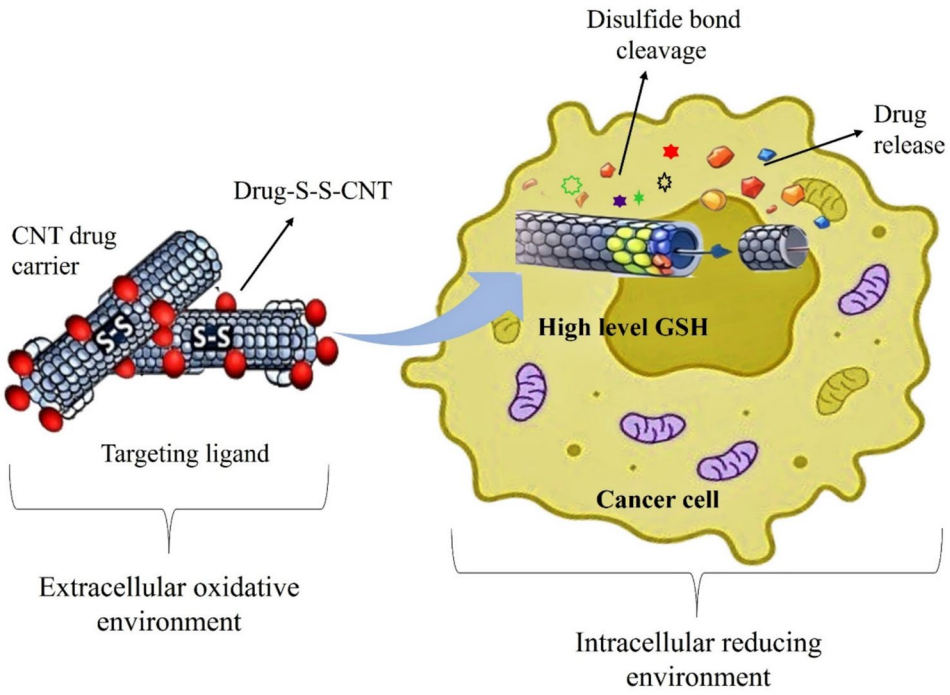


Fig. 4 Redox-responsive drug release from CNT nanocarriers triggered by intracellular GSH-mediated disulfide bond cleavage

Enzyme-responsive Release (Matrix metalloproteinases, proteases)

Tumour tissues exhibit elevated levels of proteolytic enzymes, including MMP-2, MMP-9, cathepsins B and L, and esterases. These enzymes degrade extracellular matrix components, facilitating invasion and metastasis. Their pathological overexpression creates a biochemical cue for engineering CNT systems that release therapeutic agents selectively in enzymatically active tumour sites [75]. CNTs can be functionalized with enzyme-cleavable peptide linkers that remain stable in circulation but are selectively degraded by target enzymes, thereby triggering the release of conjugated drugs directly at the disease site. This approach enhances spatial control, reduces systemic toxicity, and improves the therapeutic index. For instance, Ding *et al.* designed MWCNTs conjugated with a gelatinase-cleavable peptide (GPLGVRGDK) and loaded with DOX. *In vitro*, MMP-2 exposure accelerated DOX release (≈80% in 12 h) compared with 20% in enzyme-free media. Cytotoxicity assays on MDA-MB-231 breast cancer cells showed 2.6-fold higher apoptosis, whereas negligible release was observed in normal fibroblasts [76]. Recent advancements have incorporated enzyme responsiveness into more complex, multi-functional delivery systems. Gangrade *et al.* embedded CNTs into a photo-electroactive silk fibroin hydrogel crosslinked with MMP-degradable peptides. Upon NIR irradiation and MMP exposure, the system produced controlled DOX release (≈70 % over 24 h) and achieved complete tumour growth suppression in a murine melanoma model, with no systemic toxicity [77]. *Li et al.* fabricated CNTs encapsulated in large-pore mesoporous silica and coated with enzyme layers (MMP-2 & trypsin) to create an NIR-responsive nanocomposite hydrogel. The hybrid released >75 % of DOX only when both MMP activity and NIR irradiation were present. *In vivo* imaging confirmed tumour-specific activation and 4× tumour growth inhibition compared with control [78]. Tang *et al.* reported CNTs functionalized with cathepsin B-cleavable dipeptide linkers (Gly-Phe-Leu-Gly) for paclitaxel delivery. The system exhibited rapid intracellular degradation in cathepsin-rich lysosomes, resulting in ~70% drug release within 8 h and significant apoptosis in HeLa cells; *in vivo*, tumour volume was reduced by >60% compared with free paclitaxel [50]. Figure 5 shows tumour-specific drug release from functionalized carbon nanotubes (CNTs). (A) MMP-2/9 enzymes cleave peptide linkers on drug-loaded CNTs, triggering DOX release and tumour cell apoptosis. (B) Cathepsin B cleaves Gly-Phe-Leu-Gly linkers in CNT–paclitaxel conjugates, enabling intracellular drug release. (C) Dual NIR/enzyme-responsive CNT hydrogels combine enzymatic degradation and laser activation for enhanced, localized drug release and tumour suppression. In addition to biochemical cues, thermal triggers provide an externally controllable means to induce drug release, offering spatiotemporal precision through local hyperthermia or photothermal conversion.

Temperature-triggered (thermo-responsive systems)

Solid tumours typically exhibit mild hyperthermia (39–42 °C) due to elevated metabolic activity, hypoxia, and impaired heat dissipation. This localized temperature difference can

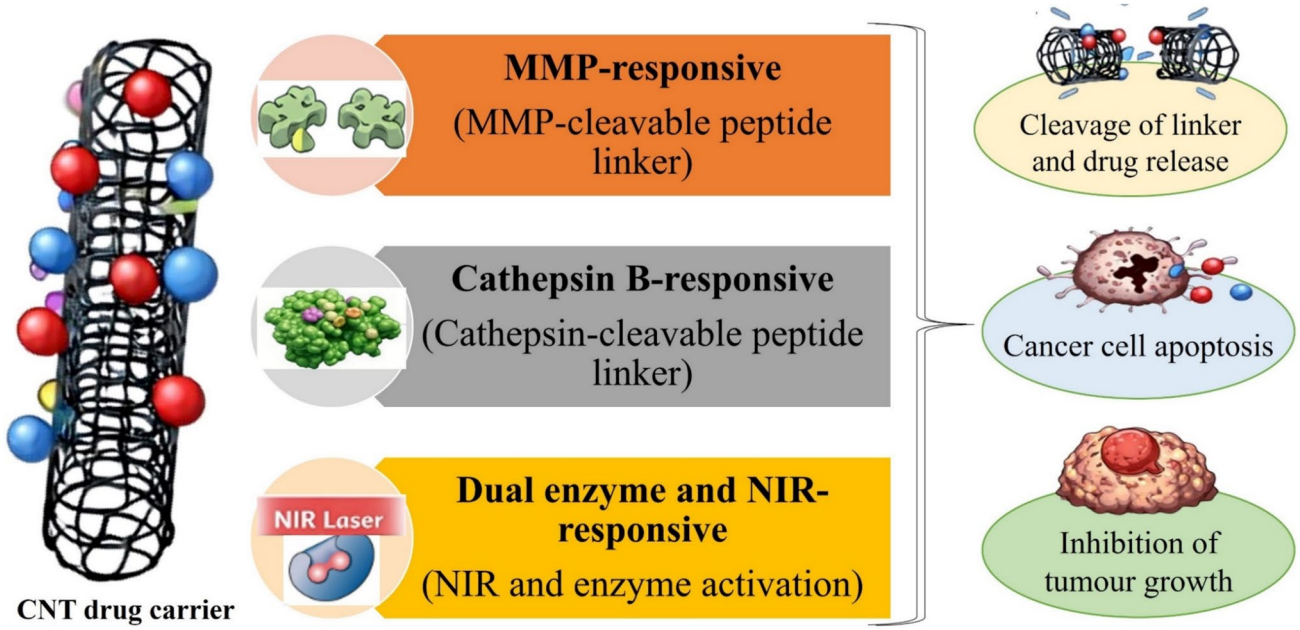


Fig. 5 Enzyme-responsive mechanisms governing drug release from CNT-based nanocarriers in the TME

be externally amplified via photothermal or magnetic stimulation, creating a controllable thermal gradient ideal for on-demand therapeutic activation. Exploiting this feature, thermo-responsive CNT systems release their payload only when the temperature in the tumour region rises beyond a specific threshold, thereby minimizing premature release in normal tissues [79, 80]. Thermo-responsive CNTs are generally fabricated by integrating CNTs with thermo-sensitive polymers such as poly(N-isopropylacrylamide) (PNIPAM) or poly(N-cyclopropylacrylamide) (PNCPA). These polymers undergo a reversible phase transition around their lower critical solution temperature (LCST ≈ 40 °C) [81, 82]. Similarly, thermo-responsive polymer-gated CNT systems use reversible hydrogen bonding to release drugs only when a thermal threshold is reached [83]. For instance, Qin *et al.* designed a thermo-/pH-dual-responsive CNT–hydrogel nanovehicle that encapsulates DOX. The system released 2.5 times more DOX at 40 °C than at 25 °C and exhibited enhanced cytotoxicity under NIR irradiation, driven by localized hyperthermia. In *in vitro* assays, the formulation achieved a 70% reduction in tumour cell viability, while *in vivo* mouse studies confirmed controlled release and reduced systemic toxicity [84]. Dong *et al.* reported a chitosan-CNT composite hydrogel that combined temperature and NIR responsiveness. When irradiated at 808 nm, CNTs converted light to heat, triggering DOX release. The system produced nearly complete drug release within 10 min at 42 °C, resulting in >80% tumour cell apoptosis in *in vitro* models [82]. Similarly, Kang *et al.* fabricated CNT-framed thermally conductive membranes for transdermal drug

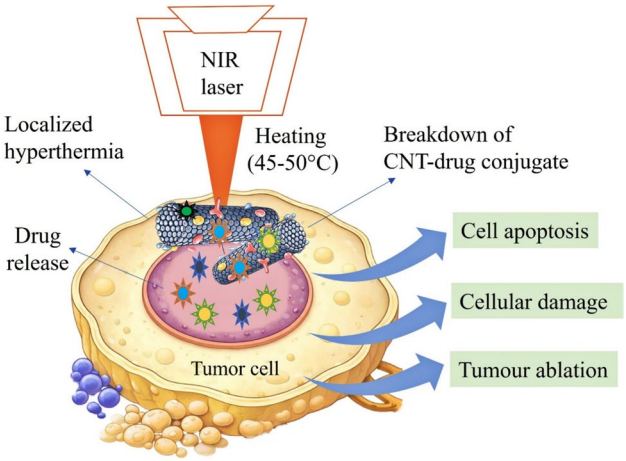


Fig. 6 Thermo-responsive CNT-based drug delivery systems for cancer therapy

delivery, responsive to body and skin temperature changes. The membranes exhibited temperature-dependent diffusion, with maximum permeability observed between 36.5 °C and 40 °C, demonstrating their suitability for externally triggered or fever-responsive drug delivery applications [81]. Moreover, CNT-filled phase change materials exhibit dramatic changes in conductivity during thermal transitions, making them particularly suitable for thermal switching and memory devices [85]. In contrast, shape memory CNT-polyurethane composites enable temperature-tuned shape recovery for responsive tagging or actuation systems [86]. Figure 6

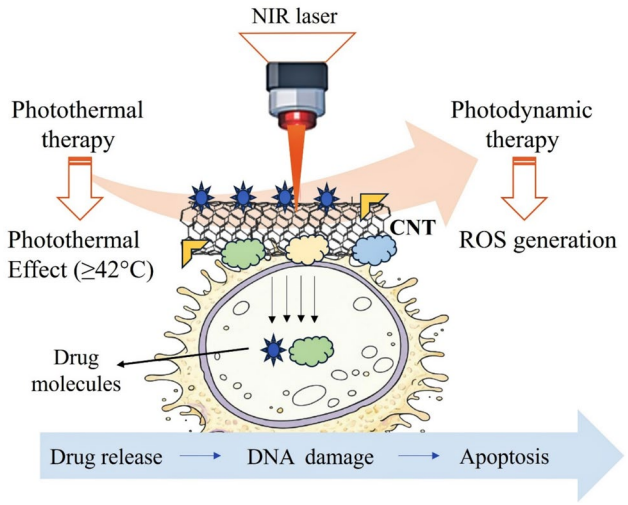


Fig. 7 Light (NIR)-triggered CNT-based therapeutic platforms for cancer treatment

illustrates the working principle of thermo-responsive CNT nanocarriers in a hyperthermic TME. The schematic highlights temperature-dependent structural changes, on-demand drug release at the tumour site, and resultant therapeutic outcomes, including enhanced cancer cell death, tumour reduction *in vivo*, reduced systemic toxicity, and synergistic chemo-photothermal therapy. Light, particularly in the NIR range, serves as a non-invasive, highly tunable external stimulus that complements thermoresponsive mechanisms for controlled drug activation.

Light-triggered (especially NIR for photothermal therapy)

Within the TME, regions of hypoxia and high vascular permeability enable deeper penetration of NIR light, which can be harnessed as a non-invasive external trigger. SWCNTs and MWCNTs exhibit strong NIR absorption in both NIR-I (700–950 nm) and NIR-II (1000–1350 nm) windows, enabling them to convert light into localized heat and induce cancer cell death with high spatial precision [87]. When CNTs absorb NIR radiation, excited electrons relax through non-radiative decay, producing localized heat. This process can directly induce tumour cell apoptosis via hyperthermia (>42 °C) or facilitate the disruption of thermo- or pH-sensitive coatings for controlled drug release [88, 89]. Figure 7 schematically illustrates the design and therapeutic mechanisms of NIR-responsive CNT systems within the TME. The Figure highlights crucial TME features (hypoxia, leaky vasculature, poor lymphatic drainage), underlying mechanisms of action, and representative applications including chemo-photothermal therapy, pH/NIR dual-responsive delivery, RNA interference, and hydrogel-based on-demand drug release, emphasizing the spatiotemporal control and translational potential of light-responsive CNT nanoplatforms. Moon *et al.* intravenously injected PEG-functionalized SWCNTs into nude mice bearing human colon carcinoma. Under 808 nm laser irradiation (1.4 W cm^{-2}, 10 min), intratumoural temperatures rose above 50 °C, resulting in complete tumour destruction with no recurrence for >3 months and no observable hepatic or renal toxicity [90]. Similarly, Han *et al.* synthesized phenoxylated dextran-coated MWCNTs that exhibit excellent aqueous dispersion and tumour accumulation. Upon 808 nm NIR exposure (2 W cm^{-2}, 5 min), tumour temperature increased by >18 °C, producing >90 % cancer-cell death *in vitro* and complete regression of xenograft tumours in mice, while normal fibroblasts remained unaffected [91]. Likewise, Ren *et al.* designed SWCNTs carrying siRNA against oncogenic KRAS. Under NIR irradiation at 980 nm, local heating triggered spatially controlled siRNA release, resulting in ≈ 80% gene-silencing efficiency and significant tumour-volume reduction in A549 lung-cancer-bearing mice [92]. Further innovations integrated CNTs into bilayer hydrogel systems, enabling mechanical deformation in response to NIR light. Such systems demonstrated robust, reversible actuation, with CNT-laden hydrogels achieving over 100° bending within 10 minutes of irradiation, opening new applications in soft robotics and biomedical microactuation [93]. Tang *et al.* developed a dual-network hydrogel incorporating MWCNT-COOH and iron–tannic nanoparticles that achieved 90° bending within 330 s of NIR exposure and recovered its original shape within 35 min. The study highlighted reversible deformation and efficient photothermal conversion, suggesting potential for biomedical actuation systems [94]. Additionally, CNTs were also incorporated into thermosensitive hydrogels and lipid carriers for controlled, on-demand drug release triggered by NIR irradiation [82, 95]. Finally, CNT-based systems demonstrated dual-mode cancer therapy by integrating chemotherapeutic agents, such as DOX, with NIR-triggered thermal ablation, thereby achieving enhanced cancer cell apoptosis through localized heating and controlled drug release. For instance, CNT-containing hydrogels demonstrated significantly improved therapeutic efficacy through this combinational approach, minimizing systemic toxicity while maximizing localized treatment outcomes [96]. Together, these advancements illustrate the versatile functionality of CNT-based NIR-responsive systems, providing thermal ablation, targeted delivery, and combinational therapies with minimal invasiveness in cancer treatment. Expanding beyond optical stimuli, magnetic- and ultrasound-responsive CNT systems introduce physical-field-based control, enabling deep-tissue targeting and enhanced intratumoural penetration.

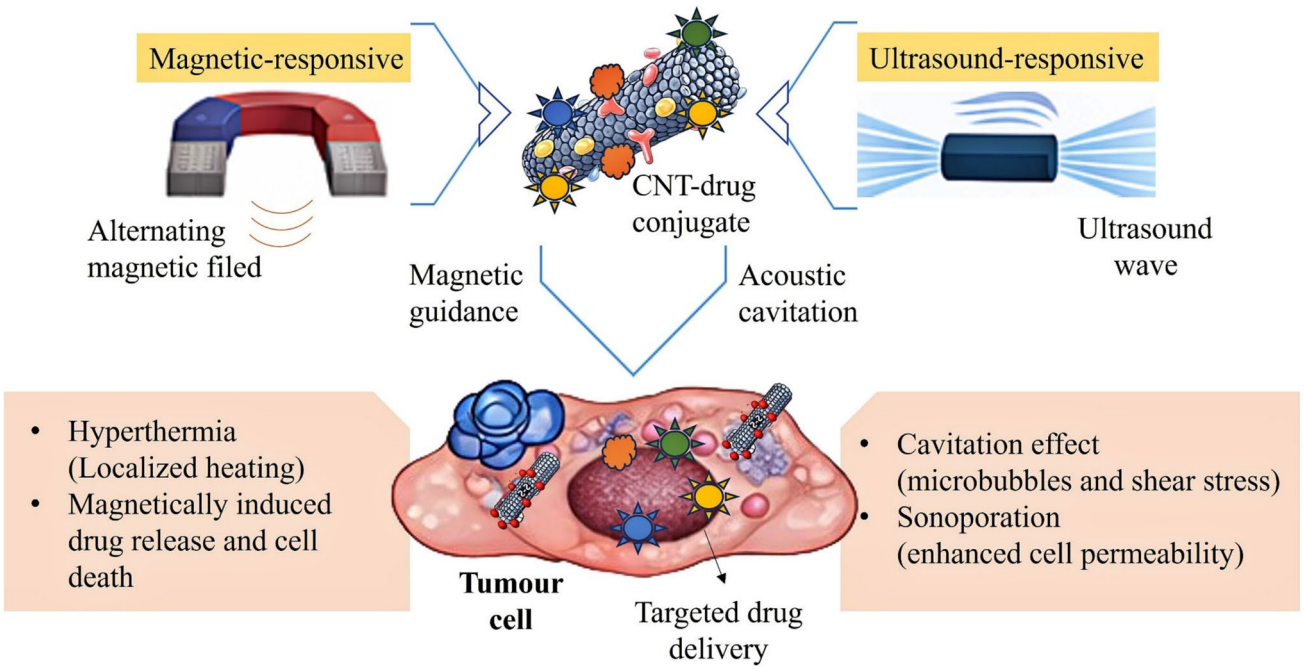


Fig. 8 Schematic representation of magnetic and ultrasound-triggered CNT behaviours

Magnetic and ultrasound-responsive CNTs

The TME's abnormal vasculature and poor perfusion often limit uniform drug distribution [97]. External physical fields, particularly magnetic and ultrasonic stimuli, offer non-invasive ways to overcome these barriers. Both stimuli can penetrate deep tissue without damaging healthy cells and can be precisely focused at tumour sites. CNTs can be magnetically activated by embedding or filling them with ferromagnetic nanoparticles (Fe, Fe_3O_4, Gd^{3+}). Under an alternating magnetic field (AMF) (100–500 kHz, 10–30 kA m^{-1}), these hybrid structures generate localized heat via Néel and Brownian relaxation, producing magnetothermal therapy, or they can be steered by a static field for guided drug delivery [79, 98]. Ultrasound waves produce mechanical oscillations and acoustic cavitation, generating transient pores in cell membranes (sonoporation) and disrupting CNT coatings to trigger drug diffusion. Ultrasound-responsive systems operate at frequencies between 0.8 and 3 MHz and intensities of 0.5–2 W cm^{-2}. Functionalized CNTs exposed to 1 MHz ultrasound exhibited 80–90 % drug release efficiency and a twofold increase in intracellular uptake compared with passive diffusion [99, 100].

Magnetic and ultrasound-responsive CNT-based systems operate via external stimuli that modulate CNT behaviour for applications like targeted delivery, separation, or material alignment (Figure 8). For instance, *Winkless* reviewed *in vivo* studies showing that Fe-filled CNTs achieved a specific absorption rate of ≈ 50 W g^{-1} Fe under AMF, raising tumour temperatures above 45 °C and destroying cancer xenografts without damaging surrounding tissue [101]. Likewise, Aydın *et al.* synthesized Fmoc-amino-acid-coated magnetic CNTs loaded with mitoxantrone. The nanocarriers exhibited excellent dispersibility and stability, with magnetically enhanced cellular uptake and controlled drug release under combined pH- and magnetic-trigger control. Cytotoxicity against MCF-7 cells increased by ~70% compared with the free drug [102]. Additionally, ultrasonic waves are used to modulate drug release or enhance cellular uptake. Early studies showed that CNTs exhibit strong ultrasonic emission, making them suitable candidates for ultrasound-mediated therapies. Hwang *et al.* engineered functionalized CNTs capable of releasing chemotherapeutic cargo upon low-intensity ultrasound exposure (1 MHz, 1 W cm^{-2}). The system produced on-demand release bursts with > 85 % drug recovery and a > 2-fold increase in cancer-cell uptake compared with passive diffusion [49]. Bafkary and Khoee developed CNT–porphyrin nanoconjugates that acted as sonosensitizers. Upon ultrasound irradiation, they generated ROS, leading to ~80% cell death in HeLa cells while maintaining negligible toxicity in the absence of ultrasound [103]. Furthermore, *Zhang and Tian* reported that ultrasound pretreatment of tumours increased CNT penetration by ~60%, facilitating higher intratumoural drug concentrations and improving therapeutic response in murine models [104]. Despite these advancements, the mechanistic understanding and application of ultrasound in CNT systems have been less extensively studied compared to magnetic manipulation.

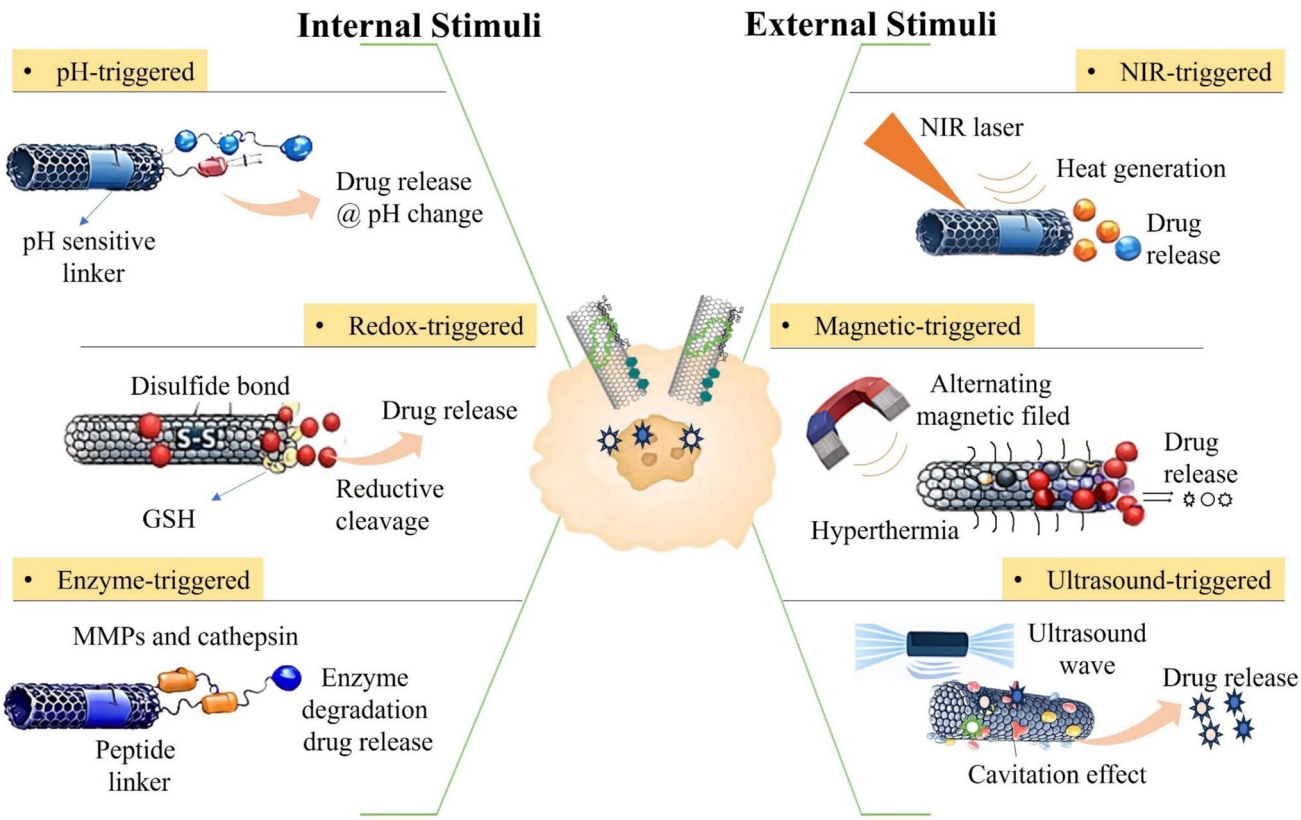


Fig. 9 Schematic illustration of stimuli-responsive drug release mechanisms from CNTs (internal vs external stimuli)

However, the tunable surface chemistry and structure of CNTs allow them to be tailored for sonodynamic therapy applications. These adaptations enable CNTs to synergize with ultrasound-enhanced membrane permeability, facilitating increased cellular uptake and improving the therapeutic efficacy of the delivered agents [103, 104]. While individual stimulus-responsive behaviours demonstrate the versatility of CNTs, integrating these mechanisms into unified, on-demand systems offers a more comprehensive approach to achieving precise spatial and temporal control of therapeutic delivery.

The overall mechanisms of internal and external stimuli-responsive drug release from CNTs are illustrated in Figure 9, which schematically depicts how endogenous cues, such as acidic pH, GSH levels, and enzyme activity, and exogenous triggers, such as NIR light, temperature, magnetic fields, and ultrasound, act on CNT surfaces to induce drug liberation through bond cleavage, structural deformation, or photothermal conversion.

CNT-Based On-Demand Drug Delivery Systems

On-demand drug delivery systems are engineered to release therapeutic agents at precise locations and times in response to specific physiological or externally applied stimuli. Unlike conventional stimuli-responsive systems that passively react to biological conditions, on-demand platforms offer programmable responsiveness and even real-time adaptability, thereby enhancing therapeutic precision and minimizing systemic toxicity [105–107]. Within this paradigm, CNTs were shown to load large amounts of therapeutic molecules, particularly aromatic drugs such as DOX, via π–π stacking interactions. These interactions enabled stable drug encapsulation with controlled unloading triggered by specific stimuli, such as acidic pH in TME, or external cues, such as NIR irradiation and magnetic fields [108, 109]. Further refinements introduced stimuli-responsive linkers and tailored surface modifications that enabled CNTs to remain stable in circulation but rapidly release their drug payload upon encountering tumour-specific conditions or external activators [110]. Depending on the source of activation, CNT-based on-demand delivery systems can be broadly categorized as either endogenously or exogenously triggered. Endogenous triggers leverage the unique biochemical

conditions of diseased tissues, such as acidic pH, elevated GSH concentrations, and overexpression of enzymes like MMP, to induce site-specific release. These designs minimize premature drug leakage and ensure maximal activity within tumour cells. Exogenous triggers, on the other hand, employ controllable physical cues such as NIR light, temperature shifts, magnetic fields, or ultrasound waves [99, 111, 112].

For example, CNTs modified to respond to acidic pH exploit the lower pH in tumour tissues and lysosomes to promote intracellular drug release, thereby enhancing selectivity and uptake by cancer cells while sparing normal tissues [113]. Additionally, their high aspect ratio facilitates endocytosis and intracellular accumulation, enabling efficient drug delivery even in hard-to-reach tumour regions. Importantly, CNTs can be co-functionalized with targeting ligands (e.g., folic acid or antibodies) and imaging agents, creating theranostic platforms that integrate diagnosis and therapy into a single nanostructure [114]. Moreover, computational and molecular dynamics simulations have enabled fine-tuning of system design to optimise cell membrane penetration and intracellular drug trafficking, demonstrating that magnetically guided CNTs can traverse membranes within minutes, offering real-time, spatially controlled delivery [115]. Furthermore, multifunctional CNT systems are being developed to combine chemotherapy with photothermal and photodynamic therapies, enhancing cytotoxicity while minimizing collateral damage to healthy tissues [116]. Despite their vast promise, long-term safety, immunogenicity, and biodegradation of CNTs remain key challenges that must be addressed through ongoing *in vivo* studies and rigorous toxicological assessments before widespread clinical translation can be achieved [117]. Table III provides a comparative overview of different stimulus-responsive mechanisms in CNT-based drug delivery systems.

An emerging frontier in on-demand CNT-based systems is integration with artificial intelligence (AI) and sensor networks. AI-guided modelling enables predictive optimization of CNT configurations for patient-specific tumour environments [118]. At the same time, embedded nanosensors can provide real-time feedback on drug concentration, temperature, or redox status, enabling autonomous release regulation [119, 120]. Such closed-loop CNT delivery platforms could revolutionize personalized medicine by allowing adaptive therapeutic control based on physiological cues. Despite these advances, several challenges remain before clinical translation can be realized. The biodegradability, long-term biosafety, and reproducibility of CNT formulations require further investigation, alongside regulatory frameworks tailored to hybrid nanodevices combining biological and electronic functionality [121]. Nonetheless, the integration of stimuli-responsive chemistry, external-field activation, and intelligent control positions CNT-based on-demand drug delivery systems as a transformative approach for precision oncology. Building upon these mechanistic insights, the following section illustrates how stimuli-responsive CNTs have been translated into practical therapeutic platforms, demonstrating enhanced efficacy and reduced toxicity in diverse cancer models.

Applications in Cancer Therapy

Chemotherapy: Enhanced Tumour Accumulation and Reduced Systemic Toxicity

Stimuli-responsive CNTs represent a new generation of intelligent drug-delivery systems that address the two fundamental challenges of conventional chemotherapy—non-specific drug distribution and systemic toxicity. By incorporating molecular linkers, polymeric coatings, or hybrid composites that react to biological or externally applied stimuli, CNTs enable spatiotemporally controlled drug release precisely within the tumour microenvironment [113]. This design ensures that anticancer agents such as DOX, paclitaxel, or cisplatin are released only when the carrier encounters the intended trigger, such as acidic pH, elevated GSH, specific enzymes, or physical cues like NIR light or heat. The therapeutic performance of these systems depends on their ability to integrate targeting and responsiveness simultaneously [123–126]. Functionalization with ligands such as folic acid, CD44-binding peptides, or antibodies enables receptor-mediated tumour uptake, while stimuli-sensitive linkers ensure that drug release occurs exclusively within tumour cells [127, 128]. For instance, Yan *et al.* developed pH-responsive folic acid modified MWCNTs conjugated with DOX via hydrazone bonds that remained stable at physiological pH but released 70% of the payload at pH 5.0, resulting in over two-fold higher cytotoxicity against tumour cells compared to free DOX [54]. Similarly, Yang *et al.* developed a CNTs-PFI/T@DOX composite that showed improved monodispersity, stability, and biocompatibility, with excellent photothermal conversion efficiency under 808 nm NIR irradiation. *In vitro*, CNTs-PFI/T@DOX effectively induced apoptosis and cell cycle arrest in MCF-7 cells, showing enhanced therapeutic efficacy through combined chemotherapy and hyperthermia. *In vivo*, CNTs-PFI/T@DOX exhibited the most potent antitumor activity among all tested formulations, indicating its strong potential as a dual-function drug delivery platform for synergistic chemo-photothermal cancer therapy [129]. Zhang et al. examined the Fe3O4–CNTs–DOX complex, which demonstrated efficient DOX loading (17.02%) and was further encapsulated in Span-PEG microbubbles via acoustic cavitation. The resulting microbubbles exhibited high safety (tolerating up to 450× concentration), strong inhibitory effects

Table III Summary of stimulus-responsive CNT drug delivery systems, underlying principles, and representative applications

Stimulus Category	Triggering Environment	Mechanism of Drug Release	Representative CNT Systems	Therapeutic Outcomes	Advantages	Limitations	Ref
pH-responsive	Tumor extracellular pH (6.5–6.8); endosomal pH (5.0–5.5)	Protonation-induced weakening of π–π stacking; cleavage of acid-labile bonds (hydrazone)	Tryptophan-functionalized CNT–topotecan; Chitosan–CNT–DOX nanogel; Acid-sensitive DOX–MWCNT	3–3.5 × higher drug release at pH 5.5 vs 7.4; ~ 75–80% release in acidic media; enhanced cytotoxicity in MCF-7 cells	Passive tumor selectivity; endogenous activation	Mild acidity in non-tumor tissues may trigger premature release	[37, 53, 63]
Redox-responsive (GSH)	High intracellular glutathione (1–10 mM; ~ 1000 × extracellular)	Disulfide bond cleavage; thiol–exchange reactions	Disulfide-bridged DOX–CNT conjugates; Nitrogen-doped CNT nanocups	~ 70–80% release at 5–10 mM GSH; > 60% tumor reduction *in vivo*	High intracellular specificity; reduced extracellular leakage	GSH variability among tumor types	[26] [68, 69]
Enzyme-responsive	Overexpression of MMP-2/9, cathepsin B in tumor microenvironment	Enzyme-cleavable peptide linkers	MMP-sensitive peptide–MWCNT–DOX; Cathepsin B-responsive CNT–paclitaxel	~ 80% release in enzyme-rich media; 2–3 × higher apoptosis; significant *in vivo* tumor inhibition	High biological specificity	Enzyme heterogeneity between tumors	[46, 71, 73]
Thermo-responsive	Hyperthermia (39–42 °C) or NIR-induced heating	LCST polymer phase transition (e.g., PNIPAM shrinkage)	CNT–PNIPAM dual-responsive hydrogels; CNT–chitosan composites	~ 2.5 × increased drug release at 40 °C; > 80% tumor apoptosis under NIR-triggered heating	On-demand release; synergistic with PTT	Risk of overheating; limited heat diffusion	[79, 81]
Light-responsive (NIR)	808–980 nm irradiation	Photothermal conversion → localized hyperthermia → drug diffusion	PEG–SWCNTs; Dextran-coated MWCNTs	Tumor temperature > 50 °C; near-complete tumor regression in xenografts; > 90% in vitro cancer cell death	Precise spatial control; non-invasive	Limited light penetration depth	[87–89]
Magnetic-responsive	Alternating magnetic field	Magnetothermal heating; magnetic targeting	Fe-filled CNTs; Magnetic CNT–mitoxantrone hybrids	Tumor heating > 45 °C; enhanced cellular uptake (~ 70% increase)	Deep tissue applicability; MRI compatibility	Requires specialized magnetic setup	[98, 99]
Ultrasound-responsive	0.8–3 MHz ultrasound	Sonoporation; mechanical disruption of CNT coatings	Ultrasound-triggered CNT–drug systems; CNT–porphyrin sonosensitizers	80–90% triggered release; ~ 2 × increased uptake; significant cancer cell death	Non-invasive; adjustable depth	Requires optimization of acoustic parameters	[46, 100]
Dual-responsive systems (e.g., pH/NIR; Redox/pH)	Combination of endogenous + external triggers	Sequential bond cleavage + photothermal activation	pH/NIR-responsive CNT hydrogels; Redox/pH degradable CNT nanocarriers	~ 77% release under acidic + GSH conditions; superior tumor suppression vs single stimulus	Improved spatiotemporal precision	Increased structural complexity	[69, 79]

Table III (continued)

Stimulus Category	Triggering Environment	Mechanism of Drug Release	Representative CNT Systems	Therapeutic Outcomes	Advantages	Limitations	Ref
Tri-responsive systems (pH/Redox/Thermal)	Multiple TME cues + heat	Multi-layered polymer conformational changes + disulfide cleavage	Poly(NIPAM-HEMA-SS)/MWCNT composites; CNT–mesoporous silica hybrids	Controlled multi-stage release; strong *in vivo* tumor inhibition	Highest targeting precision	Fabrication complexity; reproducibility challenges	[99, 122]

on liver cancer SMMC-7721 cells (48.3%), and excellent magnetic targeting and ultrasound imaging performance [130]. These systems exhibit superior tumour accumulation, controlled release, and minimal systemic exposure compared with conventional chemotherapy. However, clinical translation remains limited by concerns about long-term toxicity, surface heterogeneity, and reproducibility under GMP conditions. Some patent databases also show growing interest in such platforms, for instance, recent filings describe pH/NIR dual-responsive CNT–hydrogel composites and redox-cleavable CNT conjugates designed for selective tumour therapy, reflecting increasing commercial and regulatory attention to stimuli-responsive CNT nanomedicines [76, 131–133]. In contrast, chemotherapy benefits from controlled release and tumour selectivity; combining CNTs with photothermal therapy enables synergistic cancer ablation through localized hyperthermia.

PTT: CNTs as heat-generating Agents

PTT employs photoabsorbing nanomaterials to convert NIR light into localized heat, thereby enabling selective tumour ablation via hyperthermia. In contrast to PDT, which relies on photosensitizer-mediated generation of ROS upon light exposure, PTT primarily functions through non-radiative thermal energy conversion, independent of oxygen concentration or photochemical intermediates. This distinction is significant in the context of hypoxic TME, where oxygen deficiency often limits PDT efficacy but does not affect PTT performance [134–136]. CNTs are highly efficient photothermal agents due to their strong NIR-I and NIR-II absorption, enabling deep tissue penetration with minimal damage to healthy cells. Under NIR irradiation, CNTs convert light into heat through non-radiative relaxation, elevating tumour temperatures above 42 °C to induce protein denaturation, membrane disruption, and cell death. Their high aspect ratio and customizable surface allow functionalization with polymers, metals, or ligands to enhance photothermal efficiency and tumour targeting [122, 137–139].

Stimuli-responsive CNT-based PTT enables localized tumour ablation with minimal damage, leveraging CNTs' strong NIR absorption (700–1,100 nm) for deep tissue penetration and efficient heat generation. Upon NIR irradiation, CNTs convert light to heat, elevating tumour temperatures above 42 °C to trigger cancer cell apoptosis or necrosis. Functionalizing CNTs with responsive polymers or targeting ligands enables on-demand thermal activation and controlled drug release, achieving synergistic chemo-photothermal therapy [140–142]. Recent studies have demonstrated the high efficacy and precision of NIR-responsive CNT systems in both *in vitro* and *in vivo* cancer models. Han *et al.* synthesized dextran-coated multi-walled CNTs (MWCNT@Dex) that exhibited excellent

aqueous stability and strong photothermal conversion under 808 nm irradiation (2 W cm^{-2}). The system achieved an 18 °C rise in local temperature within 5 min, resulting in > 90 % cell death in HeLa cells and complete tumour regression in xenograft-bearing mice, with no adverse effects on surrounding tissues [143]. Similarly, Moon *et al.* reported PEG-functionalized single-walled CNTs (PEG–SWCNTs) for colon carcinoma therapy, achieving total tumour ablation in nude mice after 10 min of 808 nm NIR exposure (1.4 W cm^{-2}), with no recurrence for 90 days and no hepatic or renal toxicity [144].

Further, the high aspect ratio and surface area of CNTs also enable hybridization with metallic or polymeric materials to enhance photothermal conversion and responsiveness. Wang *et al.* designed gold nanoparticle-coated MWCNTs functionalized with PEG and folic acid that exhibited exceptional light-to-heat conversion efficiency (~ 45 %) and improved spatial confinement of thermal energy, resulting in complete tumour suppression *in vivo* [145]. Similarly, Choi *et al.* developed multi-stimuli-responsive mesoporous organo-silica nanocomposites activated by GSH, hyaluronidase, and hydrogen peroxide, integrating chemo-, photothermal-, and photodynamic therapy. The system loaded indocyanine green (ICG) and DOX and demonstrated efficient NIR-triggered hyperthermia and enzyme-controlled drug release, achieving synergistic tumour suppression in B16F10 melanoma models [146]. Wand *et al.* designed a pH- and temperature-responsive mesoporous silica–gold nanorod hybrid (PDA-AuNRs@MSN) with dual-drug loading (DOX and bortezomib). The nanocarrier exhibited enhanced NIR absorption (808 nm), on-demand DOX release, and synergistic chemo-photothermal tumour ablation with real-time imaging capability [147]. Translationally, Mocan *et al.* showed that PEG–MWCNTs under 808 nm laser irradiation induced mitochondrial membrane depolarization, leading to ROS generation, oxidative stress, and apoptosis in pancreatic cancer cells, confirming a mitochondrial-mediated apoptotic pathway [148]. Despite these promising findings, clinical translation remains limited due to challenges in balancing photothermal efficiency, biocompatibility, and reproducibility. However, early preclinical data from CNT–DOX hybrids and polymer-coated CNT hydrogels indicate significant potential for near-term clinical advancement. The integration of artificial intelligence to optimize CNT geometry, NIR absorption, and surface modification is expected to accelerate the development of safe, patient-specific, and stimuli-tunable PTT platforms [19, 149]. The integration of multiple therapeutic modalities within CNT platforms, such as chemo-photothermal, chemo-gene, and chemo-immunotherapy, demonstrates the full potential of stimuli-responsive nanomedicine to achieve enhanced efficacy through multimodal synergy.

Combined therapies: Chemo-PTT, Chemo-immuno, Chemo-gene

CNTs have redefined the landscape of multimodal cancer therapy by serving as multifunctional nanoplatforms that integrate chemotherapy, PTT, immunotherapy, and gene therapy within a single construct. The intrinsic NIR absorbance, high surface area, and chemical tunability of CNTs enable the combination of therapeutic payloads and external stimuli to achieve synergistic tumour ablation while minimizing systemic toxicity. These systems typically exploit dual or triple responsiveness, such as pH/NIR, redox/NIR, or pH/redox/temperature triggers, to ensure spatially confined and temporally controlled therapeutic activation[122, 142, 150]. The crucial examples of such combinational platforms are shown in Table IV. Among combination modalities, chemo–PTT using CNT-based carriers is the most extensively studied. CNTs act simultaneously as drug reservoirs and photothermal converters, enabling synergistic tumour eradication via combined chemotherapy and heat-induced apoptosis[19, 140]. Grześkowiak *et al.* developed FA-functionalized, DOX-loaded nanoparticles that combined photothermal conversion with targeted chemotherapy. The FA–DOX conjugates exhibited efficient tumour-specific uptake, pH-sensitive drug release, and >90% tumour cell death under NIR irradiation (808 nm). *In vivo* experiments confirmed near-complete tumour regression with minimal off-target toxicity, paralleling the performance of FA–MWCNT–DOX hybrids. [151]. Similarly, Tan *et al.* developed a temperature-sensitive chitosan hydrogel (CS/GP@CNT) incorporating carbon nanomaterials for dual-temperature–NIR-responsive chemo-photothermal therapy. The hydrogel gelled at 37 °C, enabled controlled DOX release, and under 808 nm irradiation induced rapid heating (~42 °C), resulting in >80% tumour apoptosis, significant melanoma suppression, and low systemic toxicity [152]. Moreover, Wang *et al.* developed SWCNT-PEI/DOX/NGR systems functionalized with polyethyleneimine and NGR peptide. These CNTs showed pH- and NIR-triggered DOX release, with accelerated drug liberation under 808 nm irradiation or acidic tumour conditions. The platform achieved enhanced antitumor efficacy and reduced systemic toxicity, demonstrating strong potential for synergistic chemo-photothermal therapy [153].

In chemo-immunotherapy, CNT-based photothermal ablation has been shown to stimulate strong adaptive immune responses, which, when combined with immune checkpoint inhibitors like anti-CTLA-4 antibodies, can suppress metastasis and enhance long-term tumour control [154]. CNTs functionalized with temperature-sensitive lipids have enabled the co-delivery of siRNA and chemotherapeutic drugs, achieving potent tumour suppression through gene silencing and photothermal

Table IV Comparative evaluation of CNT-based combined therapies

Combination Type	Therapeutic Agents/CNT Type	Stimuli Type	Advantages	*In vivo*/*In vitro* Evidence	Ref
Chemo–PTT	DOX-loaded PEGylated SWCNTs exposed to NIR laser	Light (NIR)/Temperature	Synergistic cell killing, controlled drug release under NIR irradiation	Enhanced tumour ablation and reduced systemic toxicity *in vitro* and *in vivo*	[110, 161–163]
	DOX + Folic acid-conjugated MWCNTs@Poly(N-vinyl pyrrole)	pH/NIR (Light)	Targeted tumour accumulation, acid-triggered release, heat-enhanced cytotoxicity	Significant tumour regression in mouse models	[54, 162]
Chemo–Immuno	DOX + Anti-CTLA-4 antibody + SWCNTs	Light (NIR)/Thermal	Immune activation, antimetastatic response following photothermal ablation	Improved systemic tumour control and reduced recurrence	[108, 164]
Chemo–Gene	siRNA + DOX + Lipid-coated CNTs	Temperature/Light (NIR)	Dual therapy combining gene silencing with photothermal-induced apoptosis	Marked tumour regression with minimal off-target toxicity	[82, 155]
Chemo–Redox	DOX-loaded disulfide-linked CNTs	Redox (GSH-sensitive)	Controlled intracellular release in tumour cells with elevated GSH levels	Enhanced cytotoxicity in tumour cells; minimal impact on normal cells	[26, 71]
Chemo–pH Responsive	DOX-functionalized COOH–MWCNTs	pH-sensitive	Selective drug release in acidic tumour microenvironment	3–4 × higher cytotoxicity at pH 5.5 compared to pH 7.4	[56, 66, 165]
Tri-Stimuli (Chemo–PTT–Redox)	DOX + Mesoporous silica-grafted CNT copolymer	pH/Temperature/Redox	Precise spatiotemporal drug release, improved selectivity and therapeutic index	Strong tumour inhibition under combined stimuli	[166]

activation [155]. Furthermore, Li *et al.* developed glycated chitosan–modified SWCNTs (SWNT–GC) as immunoactive photothermal agents. In tumour-bearing mice, NIR irradiation (1064 nm) of intratumorally injected SWNT–GC induced local ablation, and when combined with anti-CTLA-4 therapy, produced synergistic tumour regression, metastasis inhibition, and systemic antitumor immunity through a dual light–immune activation mechanism [156]. Moreover, Suo *et al.* engineered anti-Pgp antibody–functionalized, PEG-coated MWCNTs for particular PTT of multidrug-resistant (MDR) cancers. The nanocarriers exhibited minimal nonspecific interactions, efficient intratumor diffusion, and selective uptake by Pgp-expressing cells. Upon NIR irradiation, they induced strong, targeted cytotoxicity in MDR tumour cells and spheroids, with no toxicity to normal cells, demonstrating their potential as an effective, selective treatment for resistant cancers [157].

Stimuli-responsive CNTs have also been engineered for the co-delivery of chemotherapeutic drugs and genetic materials, such as siRNA, miRNA, or plasmids, enabling simultaneous gene silencing and cytotoxicity. Chen *et al.* created amylose-derivative-modified SWCNTs (ADP@SWNTs) capable of co-delivering plasmid DNA or siRNA and performing NIR photothermal ablation. The platform demonstrated high transfection efficiency, excellent dispersion, and enhanced tumour inhibition under NIR irradiation. *In vivo*, ADP@SWNT/TNF-α significantly reduced tumour growth and metastasis, with synergistic gene silencing and photothermal apoptosis [158]. Yang et al. developed biodegradable CNT–polyester composites for co-delivery of siRNA and gemcitabine, achieving simultaneous K-ras and Notch1 gene silencing and reversal of chemoresistance. This dual-action platform produced potent synergistic inhibition of pancreatic cancer cell growth, highlighting its promise for overcoming multidrug resistance in gene–chemo combination therapy [159]. Moreover, *Kumar and Ansari* reported thermoresponsive lipid–CNT hybrids that enable spatially controlled NIR heating and co-release of genetic material and chemotherapeutic drugs. The system achieved precise hyperthermic activation at tumour sites, resulting in enhanced bioavailability, efficient gene silencing, and synergistic tumour regression (>80%) with minimal off-target toxicity. This demonstrates the strong therapeutic potential of lipid-coated CNTs as multifunctional, stimuli-responsive nanoplatforms for combined chemo-gene-photothermal therapy [160]. Although significant progress has been made in developing CNT-based therapeutic systems, several biological, manufacturing, and regulatory challenges continue to limit their clinical translation, warranting a critical discussion of current obstacles and future opportunities.

Challenges

Biological Obstacles and Stability Challenges

The most significant biological obstacles include immunogenicity, toxic accumulation, and non-specific biodistribution. CNTs tend to adsorb plasma proteins upon systemic administration, leading to opsonization and subsequent clearance by the mononuclear phagocyte system (MPS), particularly in the liver and spleen [167]. Moreover, due to their fibrous morphology and high aspect ratio, CNTs may elicit inflammatory or fibrotic responses in pulmonary and hepatic tissues. Surface functionalization with biocompatible coatings such as PEG or chitosan has been shown to reduce these effects, yet reproducibility and long-term safety remain concerns [168].

Stability challenges are equally critical for maintaining CNT functionality in biological environments. Pristine CNTs exhibit strong van der Waals interactions that promote aggregation in aqueous media, reducing dispersibility and limiting bioavailability. This aggregation not only diminishes the active surface area but also alters pharmacokinetics and cellular interactions. Chemical oxidation or polymer grafting can improve solubility and stability, though these modifications may alter the intrinsic electronic or mechanical properties that underpin CNT responsiveness [169, 170]. Additionally, exposure to oxidative or enzymatic degradation *in vivo* can lead to structural instability, releasing potentially toxic fragments and metal catalysts used during CNT synthesis [171].

Another concern is batch-to-batch inconsistency and surface heterogeneity, which affect reproducibility and safety evaluation. Variations in CNT length, diameter, chirality, and residual metal content significantly influence toxicity, biodistribution, and degradation profiles. These factors complicate regulatory approval and standardization of CNT-based therapeutics. Recent studies emphasize the need for advanced characterization protocols and computational modelling to predict CNT-biological interactions and optimize design parameters for clinical use [172].

Toxicity and Clearance Issues

Despite remarkable progress in CNT functionalization and targeted delivery, toxicity and biodegradability remain significant challenges for safe clinical translation. The toxicological profile of CNTs is primarily determined by length, purity, aggregation state, and surface chemistry. Pristine CNTs tend to induce inflammation, oxidative stress, and genotoxicity, particularly in pulmonary and immune tissues, due to their fibrous morphology and high

aspect ratio, which can mimic asbestos-like responses [173]. These effects vary widely across studies because of inconsistencies in synthesis methods and the presence of metal catalyst residues, highlighting the need for standardized toxicological assessment protocols [168, 174]. Functionalization significantly mitigates toxicity by enhancing dispersion, reducing nonspecific protein adsorption, and promoting renal excretion. For instance, PEGylation and carboxylation improve hydrophilicity, minimize hepatic accumulation, and minimise macrophage activation, thereby improving systemic tolerability [64, 175]. Nevertheless, the long-term fate of CNTs depends heavily on their interaction with the mononuclear phagocyte system (MPS), particularly macrophages. Upon internalization, macrophages initiate oxidative degradation through reactive oxygen and nitrogen species (ROS/RNS) generated by NADPH oxidase and myeloperoxidase (MPO). These reactive intermediates attack the graphitic sidewalls of CNTs, introducing oxygenated defects that promote structural fragmentation and shortening [176, 177]. Enzymatic oxidation further contributes to CNT biodegradation. Peroxidase enzymes such as MPO, eosinophil peroxidase (EPO), and horseradish peroxidase (HRP) catalyze the oxidative cleavage of CNTs into smaller carbonaceous fragments and soluble oxidized residues. Functionalized CNTs are particularly susceptible to enzymatic degradation because of increased defect density and improved enzyme accessibility [178, 179]. Over time, macrophages fragment oxidized CNT residues into smaller, hydrophilic carbon clusters, which are excreted via renal and biliary pathways [69]. However, biopersistence remains a concern, especially for MWCNTs, which are more resistant to enzymatic degradation because of their multiple concentric graphene layers and lower defect density. Persistent MWCNTs may cause chronic inflammation, fibrosis, or granuloma formation if not efficiently cleared [180].

Pharmacokinetics, Immunogenicity, and Long-Term Biodistribution

The pharmacokinetic and immunological behaviour of CNTs (see Table V) is a critical determinant of their clinical viability. CNT pharmacokinetics are strongly influenced by size, surface charge, and functionalization, which dictate absorption, biodistribution, and clearance pathways. Functionalization profoundly alters CNT pharmacokinetics by improving solubility, stability, and circulation time. For example, PEGylated MWCNTs demonstrated favourable pharmacokinetics in murine models, with extended blood circulation and enhanced tumour accumulation compared to pristine CNTs. These PEGylated variants modulated DOX pharmacokinetics, enhancing antitumor efficacy while mitigating systemic toxicity [181]. Similarly, SWCNT–paclitaxel conjugates achieved a tenfold increase in tumour uptake and prolonged systemic retention via the enhanced permeability and retention (EPR) effect, confirming efficient drug transport and controlled release kinetics [182]. These pharmacokinetic improvements depend largely on functionalization density, linker chemistry, and CNT dimensions, underscoring the need for design optimization to achieve clinical consistency.

While pristine CNTs can trigger inflammatory and immune activation pathways due to hydrophobicity and residual catalysts, functionalization minimizes immunogenicity. Surface coatings such as PEG, chitosan, or glycated chitosan reduce macrophage recognition and complement activation, improving systemic tolerance. Immuno-functionalized CNTs incorporating adjuvants like glycated chitosan (SWNT–GC) not only reduced inflammatory toxicity but also induced adaptive antitumor immunity by enhancing antigen presentation and T-cell activation following photothermal therapy [183]. Similarly, recent analyses confirm that CNT-based immunomodulatory systems can balance immune activation with tolerability, suggesting their potential in combination chemo-immunotherapy[184].

Long-term biodistribution studies reveal that CNT clearance primarily occurs through hepatic and biliary routes, with limited renal excretion for longer nanotubes. *In vivo* analyses show preferential accumulation in the liver, spleen, and lungs, correlating with macrophage uptake and reticuloendothelial system sequestration [185]. Functionalization improves biodistribution homogeneity and reduces aggregation; for instance, polymer-coated CNTs (PLA-PEG) exhibited minimal pulmonary inflammation, enhanced brain uptake, and lower spleen deposition over extended durations compared to uncoated controls [186]. Long-term retention studies indicate that enzymatic oxidation by peroxidases and macrophage-mediated degradation can progressively fragment CNTs into soluble carbon species, though multi-walled CNTs show higher persistence and slower clearance rates [187]. Understanding and controlling these pharmacokinetic, immunogenic, and biodistribution parameters are critical for regulatory approval. Developing standardized testing protocols and predictive in silico models will accelerate translation by enabling rational design of clinically safe CNT-based nanotherapeutics.

Scalability and Reproducibility

Despite the promising biomedical potential of CNTs, large-scale manufacturing of CNT-based nanotherapeutics faces significant challenges that impede clinical translation. The foremost issue lies in scalable synthesis with consistent quality. While CVD remains the most adaptable route for large-scale production, achieving uniform control over CNT diameter, length, and defect density across batches is difficult because synthesis parameters, such as catalyst composition,

Table V Pharmacokinetics and toxicology summary of CNT variants

CNT Variant	Functionalization/Composition	Experimental Model/Study Design	Pharmacokinetic Behavior	Stability Characteristics	Toxicity and Biological Response	Ref
Pristine SWCNTs	Unmodified, synthesized via CVD	*In vivo* rat model; biodistribution via Raman spectroscopy	Rapid hepatic and splenic accumulation; minimal renal excretion; long-term tissue persistence	Aggregation observed; low dispersion stability in physiological fluids	Induced oxidative stress and mild nephrotoxicity after chronic exposure	[188]
PEGylated SWCNTs (SWCNT-PEG)	Covalently functionalized with PEG (MW ≈ 5000)	*In vivo* rat model; intravenous administration; biodistribution evaluated via Raman spectroscopy; histological and behavioral assessment	Detected in blood, liver, spleen, and specifically in the brain cortex, demonstrating the ability to cross biological membranes	High colloidal stability in serum and physiological media; no aggregation or precipitation	No acute toxicity, inflammation, or behavioral impairment observed; No hepatotoxicity or neurotoxicity	[189]
Oxidized MWCNTs (COOH-MWCNTs)	Acid oxidation (H_2SO_4/HNO_3) introducing carboxyl groups	*In vitro* cytotoxicity assay with human fibroblasts	Moderate cellular uptake; improved dispersion	Enhanced solubility and surface charge stability	Low cytotoxicity at < 50 µg/mL; dose-dependent ROS production	[190]
PEG–MWCNTs–DOX Nanocarriers	Polyethylene glycol modification with DOX loading	Controlled release, pH 5.5 vs 7.4; factorial design optimization	pH-dependent release kinetics (faster at acidic pH); sustained release over 48 h	High colloidal stability under physiological pH	Minimal cytotoxicity to normal cells; effective anticancer action in HeLa lines	[191]
CuO–MWCNT Composite	Green-synthesized CuO nanoparticles integrated into MWCNTs	Electrochemical and cytotoxicity studies	High surface interaction enhances conductivity; controlled adsorption	Stable nanocomposite with minimal aggregation	No significant cytotoxicity; mild oxidative activity observed	[192]
Chitosan–cMWCNT–UiO-66 Hybrid	Carboxylated MWCNTs integrated with metal–organic framework and chitosan	Electrochemical and biointerface stability test	Improved molecular adsorption and electron transfer	High physicochemical and thermal stability	Excellent biocompatibility and reusability; negligible cell toxicity	[193]

temperature profiles, and gas flow rates, must be precisely regulated to avoid structural heterogeneity and impurity formation. Such variability directly affects CNT physicochemical properties and, by extension, biological performance and therapeutic outcomes, complicating reproducibility and regulatory compliance [47, 194].

Post-synthesis purification further exacerbates scalability issues. Traditional purification techniques, such as acid oxidation, high-temperature annealing, or surfactant-assisted treatments, aim to remove metal catalysts and amorphous carbon residues but often introduce structural defects or alter surface chemistry, reducing yield and material integrity. Impurities from catalysts and carbonaceous by-products not only compromise biocompatibility but also lead to inconsistent functionalization efficiency, making standardized surface modification across large batches difficult [195].

Batch-to-batch consistency is also hindered by surface functionalization processes that are essential for enhancing dispersion, biocompatibility, and targeting capabilities. Even minor deviations in reaction conditions during functionalization can result in uneven ligand densities or unstable conjugates, leading to variable pharmacokinetics and therapeutic efficacy. This lack of reproducibility remains a critical barrier in ensuring predictable biological behaviour and satisfying stringent quality standards for clinical applications [175, 195].

Addressing these challenges will require advances in real-time process monitoring and quality control, such as *in situ* characterization techniques and automated synthesis platforms that can enforce narrow tolerances in CNT growth and functionalization. Emerging strategies—such as combining machine learning and process automation to optimize reaction parameters—are showing promise for improving consistency and yield, but further research and integration with GMP frameworks will be essential for reliable industrial-scale production of biomedical CNTs [196, 197].

Regulatory and Clinical Translation Barriers

Regulatory frameworks in the United States and the European Union acknowledge the unique challenges posed by nanomaterials but do not yet provide CNT-specific approval pathways, resulting in case-by-case evaluations rather than standardized classification rules. The U.S. Food and Drug Administration (FDA) has issued a suite of nanotechnology guidance documents, notably, which outline how nanomaterials should be characterized and evaluated within existing drug approval pathways and emphasize rigorous physicochemical, safety, and quality assessment for products containing engineered nanoscale components (e.g., those with dimensions up to ~100 nm and exhibiting nanoscale-related properties) [198]. Parallel efforts by the European Medicines Agency (EMA), provide early guidance on the pre-authorization evaluation of nanomedicines but similarly stop short of defining formal CNT-specific criteria or regulatory categories, instead advocating quality-by-design and comprehensive risk assessment tailored to each product's characteristics [199, 200]. This lack of clear classification is compounded by broader regulatory ambiguities in nanomedicine, where materials may be variably designated as drugs, devices, or combination products depending on their intended use and properties, and where traditional bulk material data may not predict nanoscale behavior, complicating safety and efficacy assessments [201].

Furthermore, the lack of standardized protocols for *in vivo* and *in vitro* testing leads to variability in safety assessments, making it challenging for regulators to compare studies or establish clear safety thresholds. Limited human data and the lack of large-scale clinical trials also hinder risk-benefit evaluations, which are critical for regulatory approval. Additionally, the high cost and technical complexity of producing GMP-grade CNTs suitable for clinical use pose significant logistical and economic barriers. Overcoming these challenges requires coordinated efforts to establish CNT-specific regulatory guidelines, validated testing methodologies, and comprehensive safety databases that support predictable, evidence-based clinical decision-making [202–204]. Despite promising preclinical outcomes, the clinical and regulatory progress of CNT-based drug delivery systems remains limited. For instance, PEG-SWCNT-DOX systems face unresolved long-term toxicity and biodistribution concerns [116]; FA-MWCNT-DOX conjugates encounter regulatory framework and safety standardization gaps due to surface heterogeneity [205]; and CNT-PNIPAAm hydrogels demonstrate challenges in ensuring scalable, GMP-compliant synthesis and batch reproducibility [163]. To overcome these challenges and accelerate clinical progress, emerging approaches such as artificial intelligence-driven design and personalized nanomedicine are being explored to optimize CNT properties and tailor therapies to individual patient profiles.

Emerging trends: AI in CNT Design, Personalized Nanomedicine

AI-driven computational modelling and predictive analytics have accelerated CNT design, enhanced biocompatibility, and enabled patient-specific nanotherapeutic strategies. These intelligent systems analyze vast physicochemical and biological datasets to optimize CNT configurations for targeted applications, thereby improving treatment specificity and safety [206]. Recent advances demonstrate that machine learning (ML) and deep learning (DL) algorithms can accurately predict CNT behaviour in biological systems, including toxicity, dispersion stability, drug-loading efficiency, and pharmacokinetics. ML-based quantitative structure–toxicity relationship

(QSTR) models now correlate CNT dimensions, chirality, and functional group density with immune compatibility and cellular uptake, supporting the rational design of biocompatible CNTs with reduced systemic toxicity [160, 207]. Likewise, deep neural networks (DNNs) can simulate CNT–drug interactions, predicting π–π stacking affinities and optimizing functionalization to enhance binding and control release within the tumour microenvironment, thereby reducing the experimental trial-and-error cycle [208]. Beyond single-parameter tuning, AI-assisted multi-objective optimization frameworks simultaneously balance CNT length, ligand density, NIR absorption, and hydrophilicity, facilitating the development of dual- and multi-responsive CNT nanoplatforms for combined chemo-photothermal and redox-triggered therapies [209]. Complementarily, AI-guided digital twin and physiologically based pharmacokinetic (PBPK) models provide in silico simulations of CNT biodistribution, clearance, and tumour accumulation, effectively creating "virtual patients" that predict treatment responses and refine dosage regimens before clinical trials, reducing reliance on animal testing [210]. Parallel advances in AI-integrated CNT biosensors enable real-time monitoring of tumour microenvironmental parameters, such as pH, temperature, and redox potential. These closed-loop nanosystems use AI algorithms to regulate drug release based on physiological feedback autonomously, transforming CNTs into active, self-adaptive therapeutic systems rather than passive carriers [211]. Similarly, AI-enhanced imaging and biosensing platforms integrate CNTs with multimodal image-guided systems for feedback-based precision therapy [212]. Finally, the integration of AI with multi-omics data, including genomics, proteomics, and metabolomics, is pushing personalized nanomedicine toward clinical translation. AI-driven algorithms can process multi-layered tumour data to design CNT formulations matched to each patient's tumour profile, tailoring drug type, dosage, and release kinetics accordingly [213]. This AI–omics convergence enables adaptive, patient-tailored treatment strategies that dynamically respond to molecular feedback during therapy [214]. Collectively, these innovations demonstrate that AI-guided CNT nanomedicine is transitioning from empirical design to a predictive, self-optimizing system that integrates diagnostics, drug delivery, and feedback control within a personalized framework. Collectively, these advancements mark a paradigm shift in the evolution of CNT-based nanomedicine, paving the way for next-generation, adaptive, and patient-specific therapeutic strategies, which are summarized in the concluding section.

Future Directions

AI and Machine Learning Applications in CNT Design

AI and ML are poised to revolutionise the rational design and optimisation of CNT-based drug delivery systems. AI-driven algorithms can predict optimal CNT geometries, surface functionalisation patterns, and stimulus responsiveness with unprecedented precision. Recent developments in QSAR and QSTR models enable accurate prediction of CNT–biomolecule interactions, toxicity profiles, and pharmacokinetic behaviour before laboratory synthesis. By integrating large datasets from *in vitro* and *in vivo* studies, ML can identify key design parameters, such as length, chirality, aspect ratio, and surface charge, that influence biodistribution and cellular uptake. Deep learning models can further optimise multi-stimuli-responsive designs by correlating material properties with drug release kinetics and therapeutic outcomes [215–219]. In the future, AI-enabled digital twin simulations could be used to model patient-specific tumour microenvironments, predict drug release dynamics, and virtually pre-screen CNT formulations before clinical trials. Such tools will substantially reduce experimental costs, accelerate discovery, and enhance safety by minimizing empirical testing.

Personalized Nanomedicine and Oncology

The integration of CNT-based systems with personalised oncology represents a key step towards precision nanotherapy. Tumour heterogeneity, characterised by spatial variations in pH, enzyme expression, and redox gradients, requires adaptive, patient-tailored platforms capable of dynamic responses. Stimuli-responsive CNTs, when combined with biosensors, wearable devices, and microfluidic feedback systems, can form real-time therapeutic loops that monitor biomarkers (e.g., GSH levels, temperature, or oxygen concentration) and regulate drug release accordingly [220, 221]. Such closed-loop nanosystems offer unparalleled control over dosage and timing, reducing systemic toxicity while improving efficacy. Personalised CNT systems could also be designed based on genomic and proteomic profiles, ensuring compatibility with individual tumour phenotypes and immune environments. Integration with imaging modalities such as NIR fluorescence and MRI further supports image-guided therapy and treatment monitoring [137, 222]. Future CNT-based personalised nanoplatforms are envisioned to function as "intelligent therapeutic nodes"—sensing, responding, and adapting in real time to the patient's physiological conditions.

Regulatory Pathways and Translational Frameworks

Despite their remarkable potential, CNT-based nanomedicines face substantial regulatory and translational hurdles. The absence of CNT-specific regulatory guidelines from agencies such as the FDA or EMA remains a significant bottleneck. Current assessments rely on general nanomaterial safety frameworks that fail to address the unique physicochemical and biological complexities of CNTs. The key challenges include batch-to-batch variability, a lack of standardised toxicological protocols, and limited biodegradation data. Long-term studies on CNT clearance, metabolic fate, and immunogenicity are essential for establishing comprehensive safety profiles. Moreover, the scalable manufacturing of CNTs under GMP conditions is still in its infancy, necessitating advances in purification, defect control, and reproducibility [69, 201, 223, 224].

Conclusion

Stimuli-responsive CNTs have emerged as highly versatile nanocarriers with tremendous potential for controlled and on-demand cancer therapy. Their unique physicochemical properties, such as high surface area, mechanical strength, and tunable electronic and optical characteristics, allow precise drug loading, targeted delivery, and controlled release in response to specific stimuli. By functionalizing CNTs with appropriate chemical linkers and responsive moieties, researchers have engineered systems capable of responding to internal biological triggers, such as pH, redox gradients, and enzymatic activity, as well as to external physical stimuli, including NIR light, magnetic fields, temperature, and ultrasound. These intelligent nanocarriers enable spatiotemporal regulation of therapeutic release, improving treatment precision and minimizing systemic toxicity. Furthermore, CNTs facilitate multimodal approaches such as chemo-photothermal and chemo-immunotherapeutic strategies, offering synergistic effects and enhanced therapeutic outcomes.

Despite significant advancements, the clinical translation of CNT-based drug delivery systems remains a major challenge. Critical gaps persist in understanding their biocompatibility, biodegradation, biodistribution, and long-term toxicity. Inconsistencies in CNT synthesis, purification, and surface functionalization have led to variability in physicochemical and biological behaviours, limiting reproducibility and scalability. Moreover, the absence of standardized evaluation protocols and regulatory frameworks for CNT-based nanomedicines complicates their assessment and approval for clinical use. The establishment of uniform guidelines for material characterization, biosafety testing, and pharmacokinetic evaluation is essential to ensure consistent performance and regulatory compliance. Addressing these limitations will require comprehensive interdisciplinary research integrating materials science, biology, and regulatory science.

Looking ahead, several research directions can accelerate the advancement of CNT-based on-demand systems. Detailed mechanistic studies on CNT–cell and CNT–immune system interactions are needed to clarify their degradation and clearance pathways and to mitigate toxicity concerns. The development of biodegradable or hybrid CNT analogues could improve biological safety and enable controlled degradation. Moreover, integrating multi-stimuli and feedback-responsive mechanisms may enable precise, autonomous regulation of drug release under dynamic biological conditions. Advances in AI and computational modelling also offer new opportunities for optimizing CNT design, predicting biological interactions, and tailoring drug delivery to individual patient profiles. In parallel, the formulation of standardized manufacturing and safety protocols will be vital to ensure scalability, reproducibility, and regulatory acceptance.

In conclusion, stimuli-responsive CNTs represent a transformative platform for next-generation precision oncology. Their capacity for targeted, controllable, and multifunctional drug delivery provides an innovative route toward safer and more effective cancer treatments. However, realizing their full clinical potential will depend on resolving existing challenges through collaborative, multidisciplinary efforts that combine advanced nanomaterial engineering, computational intelligence, and translational biomedical research. As these fields converge, CNT-based intelligent drug delivery systems are poised to play a central role in the future of personalized and adaptive cancer therapy.

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Declarations

The authors declare that they used Grammarly Premium to enhance the linguistic clarity and readability of this manuscript. They carefully reviewed and edited all generated text to ensure accuracy and alignment with the research's intended meaning.

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