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# Advances in photoactivated carbon-based nanostructured materials for targeted cancer therapy☆

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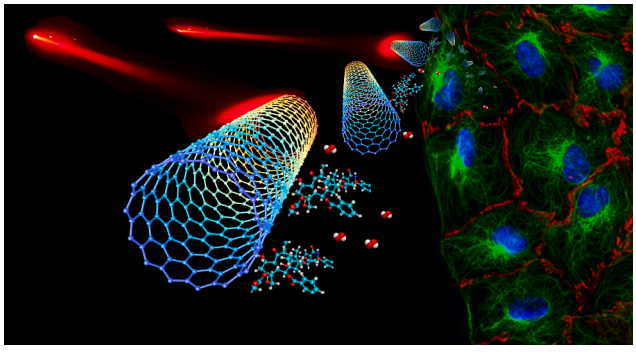
## GRAPHICAL ABSTRACT



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## ABSTRACT

In this review, we explore key innovations in photoactivated therapeutic programming of carbon-based nanomaterials (CBNs), focusing on their diverse nanostructural configurations and their exceptional photothermal, photochemical, and photoacoustic properties. These attributes position CBNs as remarkable phototherapeutic agents, capable of addressing critical challenges in targeted cancer therapy through their precision, multifunctionality, and adaptability to specific therapeutic modalities. We will explore their diverse derivatives, and the role of chemical augmentation and site-specific surface functionalisation, which are pivotal in optimising the targeting and efficacy of phototherapeutic interventions. The biological and physical relevance of this ever-growing library of nanomaterials in targeted phototherapy will be thoroughly explored. Dynamic photo-triggering of the underlying molecular mechanisms of action e.g., energy conversion modalities lie at the heart of these therapeutic innovations. We will further discuss the tunability and programming of these carriers and structure–function alterations at specific therapeutic wavelengths. The application space of phototherapies is thoroughly mapped exploring the three primary approaches of photothermal therapy, photodynamic therapy and photochemical internalisation as well as emerging techniques and promising multimodal approaches that

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combine two or more of these processes. The specificity of the target tissue site and the approach under study forms another critical focus area of this review, with an emphasis on three types of cancer—breast cancer, lung cancer, and gliomas—that have demonstrated some of the most promising outcomes from photomedicine. We also provide a perspective on *in vitro* and *in vivo* validation and preclinical testing of CBNs for phototherapeutic applications. Finally, we reflect on the potential of CBNs to revolutionise targeted cancer therapy through data-driven materials design and integration with computational tools for biophysical performance optimisation. The exciting integration of machine learning into nanoparticle research and phototherapy has potential to fundamentally transform the landscape of nanomedicine. These techniques ranging from supervised learning algorithms such as random forests and support vector machines to more advanced neural networks and deep learning, can enable unprecedented precision in predicting, optimising, and tailoring the properties of nanoparticles for targeted applications. The transformative impact of photoactivated CBNs in advancing cancer treatment, paves the way for their clinical application and widespread adoption in personalised photomedicine. We conclude with a section on the current challenges facing the reproducibility, manufacturing throughput, and biocompatibility of these nanostructured materials including their long-term effects in trials and degradation profiles in biological systems as evaluated *in vitro* and *in vivo*.

## 1. Introduction to this review

Cancer remains a major global health challenge, requiring a multidisciplinary approach to treatment. Traditional modalities such as surgery, chemotherapy, radiotherapy, and immunotherapy have played indispensable roles in managing the disease. Surgery offers direct tumour removal but in spite of advancements in image-guided surgical removal, it is limited by its invasiveness and inability to reach all affected areas [1,2]. Chemotherapy, a cornerstone of cancer treatment, often leads to severe side effects and suffers from issues such as drug resistance encountered by 90 % of patients with metastatic cancer [3,4,5], whereby cancer cells develop mechanisms to reduce the intracellular concentration of chemotherapeutic agents, significantly impacting the therapeutic efficacy [6,7]. Radiotherapy is effective for localised treatment but is limited by the resistance posed by hypoxic conditions within the tumour microenvironment, which can severely reduce its effectiveness. This is due to the critical role of oxygen in enhancing DNA damage through the generation of reactive oxygen species. Additionally, hypoxia activates pathways that promote tumour aggressiveness and therapy resistance [8,9,10]. Immunotherapy, while offering revolutionary potential by harnessing the body's immune system, is hindered by low response rates and risks of autoimmune reactions [11,12,13]. Amid these challenges, phototherapeutic alternatives such as photodynamic therapy (PDT) and photothermal therapy (PTT) have emerged as promising strategies due to their non-invasive nature, precise controllability, and selective targeting of cancer cells, minimising impact on healthy tissues. These techniques use photothermal, photochemical or photomechanical energy conversion enabled by the interactions of light with multifunctional molecular agents to target cancer cells and tissues. Notably, carbon-based nanostructured materials (CBNs) have garnered attention in phototherapy for their exceptional light absorption characteristics, high conversion efficiency, biocompatibility, and ease of design and functionalisation in contrast to that of key competitors such as catecholic agents (Table 1).

In this review, we delve into the expansive realm of photoactivated cancer therapies, focusing on the advances in carbon-based nanostructures for phototherapy and illustrating how these materials are enhancing the efficacy of cancer treatment while reducing adverse effects. Initially, we will explore the key modalities of photoactivated therapy, which include both monotherapies that often leverage a mode of energy conversion from the irradiated incident light into a secondary form of energy useful in the context of localised repair, and multimodal therapies. These combinational approaches integrate multiple monotherapeutic approaches, enhancing efficacy through synergistic effects. As we shall see, the utilisation of complex nanostructured materials is pivotal in achieving this seamless integration and coherence, allowing for targeted delivery and controlled release mechanisms, thereby maximising therapeutic outcomes while minimising adverse effects.

Following this foundational overview, our focus will shift towards CBNs, a particularly promising subset of nanostructures. While the applications of CBNs in cancer therapy have been explored since the early 2000 s, this review highlights the significant advancements made in recent years, examining the diverse morphologies of CBNs and their evolving implications for cancer phototherapy. Special attention will be paid to the evolving landscape of structure design and optimisation, which now increasingly employs advanced high-throughput experimental techniques alongside computational approaches. This latter segment of the review is dedicated to a detailed exploration of experimental and data-driven nanomaterials discovery, design and testing. We first explore the advancements in *in vitro* and *in vivo* testing and validation of CBN systems and then study new avenues of computational nanomaterials engineering. As we stand on the brink of a new era in materials science, driven by machine learning and data science, these technologies offer unprecedented opportunities for the discovery and development of carbon-based nanostructures. By harnessing these innovative tools, researchers are predicting material behaviours, optimising therapeutic properties, and accelerating the transition from lab research to clinical application. This review will encapsulate the state-of-the-art in CBNs for photoactivated cancer therapy, providing a critical examination of current technologies and offering a perspective on future directions. Integrating traditional scientific inquiry with modern

**Table 1**
Comparative properties of carbon-based nanomaterials and catecholic agents (e.g., polydopamine) in phototherapy.

| Property | Carbon-based nanomaterials | Catecholic agents (e.g., polydopamine) |
|---|---|---|
| Light absorption | Broad spectrum, strong NIR absorption | Broad spectrum, moderate NIR absorption |
| Photothermal conversion efficiency | High (>40 % in CNTs, graphene) | Moderate (20–30 %) |
| Photostability | Excellent, resistant to photobleaching | Good, though prone to degradation under prolonged exposure |
| Biocompatibility | High, dependent on functionalisation | Excellent, intrinsic biocompatibility |
| Ease of functionalisation | High (π-π stacking, covalent modifications) | High (abundant reactive sites for conjugation) |
| Drug loading capacity | High (large surface area, π-conjugation networks) | Moderate (depends on polymeric structure) |
| Reactive oxygen species (ROS) generation | Limited (enhanced when combined with photosensitisers) | Strong intrinsic ROS generation under light irradiation |
| Bio-adhesiveness | Low to moderate (requires modification) | High, strong adhesion to biological surfaces |
| Degradability | Variable (depends on structure; graphene less degradable) | Biodegradable under physiological conditions |
| Cost & scalability | Moderate to high (depending on synthesis method) | Low-cost, simple synthesis from dopamine precursors |

data analytics, we aim to highlight the transformative potential of these materials in the ongoing battle against cancer.

While numerous reviews have tackled individual aspects of phototherapeutic technologies and their applications, the present review stands out by providing a laser-focused overview and in-depth perspective on the advancements in phototherapeutic modalities, specifically targeting CBN systems. We endeavour not only to capture the state-of-the-art in CBN-enhanced phototherapy—including PTT, PDT, and other emerging techniques—but also delve into the mechanistic underpinnings, design strategies, and translational aspects of these technologies. By integrating insights from recent breakthroughs and seminal works in the field, this review seeks to articulate a nuanced understanding of how CBNs hold potential to revolutionise the landscape of cancer therapy and beyond. Special emphasis is placed on the unique properties of carbon nanotubes, graphene, and carbon nanodots which as we shall explore, offer unique advantages that make them ideal candidates for targeted phototherapeutic applications.

## 2. Photo-exposure and biological matter

### 2.1. Exposure wavelength regimes and specific implications

Understanding the interactions of light and biological tissues has been fundamental to the field of photomedicine, enabling both diagnostics and therapeutics. The key to its application is the selection of appropriate wavelength regimes, which in turn determines the depth of penetration, absorption, and biological effects. Clinically, several wavelength regimes are already widely utilised, each with specific properties that make them suitable for various medical applications, including targeted cancer therapy (Table 2). Each of these wavelength regimes offers distinct interactions with tissue, influenced by factors such as absorption coefficients, scattering properties, and permissible exposure levels. These interactions define the clinical utility of each wavelength range, from surface treatments using UV and visible light to deeper tissue interventions with near-IR (NIR) wavelengths.

As research continues, particularly in the NIR-II range, the boundaries of phototherapy and photodiagnosis are continually expanding, offering new possibilities for targeted, minimally invasive therapies for cancer and other diseases [14,15]. A promising early technology which will not be discussed in this review is NIR photoimmunotherapy (PIT) which is currently undergoing phase 3 clinical trials [16]. NIR-PIT differs from conventional cancer therapies operating on the basis of an antibody conjugate binding a target overexpressed cancer-associated antigen, with the aid of a NIR-excitable photoactivating agent. The light activation hence results in selective cell targeting [17]. Due to the deeper penetration depth, lower light absorption and scattering in tissues as well as higher maximum permissible exposure (MPE) intensity (1 W cm − 2 for 1064 nm, 0.72 W cm − 2 for 980 nm and 0.33 W cm − 2 for 808 nm), NIR-II (1000–1700 nm) photo-therapies appear to be more superior than NIR-I (700–1000 nm) photo-therapies, and has become a research hotspot in the recent years. The table below (Table 2) shows the distinct features of each source [18]. Please note that the values reported here are approximate averages, and actual penetration depths can vary depending on tissue composition, optical properties, and experimental conditions.

Precise tuning of light intensity is also instrumental considering the high optical absorbance of CBNs such as graphene and carbon nanotubes in the NIR region. Excessive irradiance can lead to overheating beyond what is required in hyperthermia [19,20], which might damage both cancerous and surrounding healthy tissues. On the other hand, insufficient incident irradiation dose may not achieve the desired therapeutic temperatures for effective tumour ablation in photothermal therapies. Modern laser systems allow for adjustable power outputs to tailor the laser output based on the depth of the target tissue, but also in real-time based on image-based temperature sensors incorporated externally near the treatment site [21,22]. The duration of exposure to NIR light must be

**Table 2**
Characteristics of various clinically used wavelength regimes, and their corresponding advantages, limitations, and applications in photomedicine.

| Light source | Wavelength range (nm) | Penetration depth (mm) | Description and main application |
|---|---|---|---|
| Ultraviolet | ***100—400*** | < 0.1 | Delivers high energy potentially inducing photodamage and photochemical reactions. Clinically, it is used primarily for ***surface treatments*** due to its shallow penetration depth, limited by strong absorption and scattering in tissue. Applications in skin disinfection and phototherapy for skin disorders |
| Visible | ***400—700*** | 0.5 – 2 | Used in various diagnostic imaging techniques and photodynamic therapy (PDT). In PDT, visible light interacts with photosensitizer to produce reactive oxygen species that can kill cancer cells. However, its penetration in tissue is limited to a few millimetres, restricting its use to ***near-surface*** treatments |
| Near-IR I | ***700—1000*** | 2 – 5 | Offers deeper tissue penetration than visible light, making it valuable for ***deep imaging*** and therapeutic applications. While it is used in photothermal therapy (PTT) where it induces localised thermal release, its penetration depth and therapeutic depth are still limited compared to NIR-II |
| Near-IR II | ***1000—1700*** | 5 – 15 | Achieves superior penetration depth, lower tissue absorption and scattering compared to NIR-I. With higher maximum permissible exposure intensities, NIR-II allows for more effective ***deep-tissue*** photothermal conversion with enhanced penetration and safety profile making it particularly interesting for targeting ***deep-seated tumours***. |
| Near-IR IIa | ***1000–1300*** | 5 – 8 | Deep-tissue penetration, relatively low to moderate scattering and absorption. Used in PTT, PDT, PA imaging, fluorescence imaging. |
| Near-IR IIb | ***1300–1500*** | 8 – 12 | Deeper penetration than NIR-IIa with enhanced contrast and lower scattering. Use in PAT, image-guided therapy, hyperthermia |
| Near-IR IIc | ***1500–1700*** | 12 – 15 | Maximum penetration of NIR-II and minimal autofluorescence and background. Used in deep-tissue imaging and real-time monitoring, controlled drug release, multimodal therapy |
| Mid-IR | ***3000—8000*** | < 0.5 | Is absorbed strongly by water molecules, limiting its penetration in tissue but making it useful for ***high-precision ablation of superficial tissues***. This is a key characteristic in certain surgical and dermatological applications. |

carefully balanced for heat propagation through the tumour while eliminating thermal damage to adjacent tissues. Time-gated laser systems can be synchronised with imaging techniques such as magnetic resonance imaging (MRI), photoacoustic imaging (PAI), fluorescence imaging (FLI), computed tomography (CT), and ultrasound (US) to enhance the precision of phototherapies. These imaging techniques facilitate real-time monitoring of nanomaterial accumulation, tumour response, and thermal distribution to optimise therapeutic efficacy while preventing overtreatment. To this end, superparamagnetic iron oxide nanoparticles and graphene-based nanocomposites have been utilised as MRI contrast agents to track nanoparticle accumulation in tumours before PTT activation. MRI provides high spatial resolution and deep tissue penetration, allowing precise pre-treatment planning and monitoring of tumour response during therapy. PAI leverages the photoacoustic effect, where light absorption generates ultrasound waves, enabling high-resolution imaging of blood oxygenation levels, vascular structure, and nanomaterial biodistribution. PAI is particularly useful in guiding PTT and PDT by visualising real-time changes in tissue perfusion and oxygenation. FLI uses fluorescently labelled carbon nanodots, quantum dots, and photosensitisers to enable high-sensitivity imaging of tumour margins, assisting in precise tumour localisation before PTT or PDT. Hybrid gold-carbon nanocomposites and nanoparticles have been explored for CT-guided phototherapies, where CT imaging provides anatomical details for accurate nanoparticle localisation and dose modulation. Pulsed lasers are preferable with CBNs in phototherapies to avoid continuous heat accumulation [23]. Pulsed NIR lasers can deliver high peak powers for short durations, allowing the nanomaterials to reach the necessary temperatures to induce cell death and then cool down between pulses, minimising the risk of heat diffusion to surrounding healthy tissues. High spatial coherence is essential for focusing light precisely on small target areas, typical in the use of carbon nanotubes and graphene in tumour targeting. Laser systems with adjustable beam profiles and coherence properties are now being used to enhance targeting precision. The interaction of coherent and incoherent light with cells is either endogenous where the energy is directly absorbed by the cell constituents or exogeneous where light energy is absorbed through agents such as photosensitizers. The latter which is the main focus of the present review often involves a low-power coherent laser and in many cases incoherent light emitting diodes as the primary source [24].

.2.2 Coupling energy delivery modes and conversion through nanostructured design

As we shall carefully study in this review paper, nanostructured materials provide a unique platform for the integration of various therapeutic modalities. CBNs especially highly tuneable nanotubes and nanodots have shown to be highly efficient absorbers of NIR generating substantial amounts of heat following NIR exposure. These materials can be readily engineered at the nanoscale to possess specific properties—such as size, shape, surface chemistry, and optical characteristics—that make them ideal for targeted cancer therapy. The

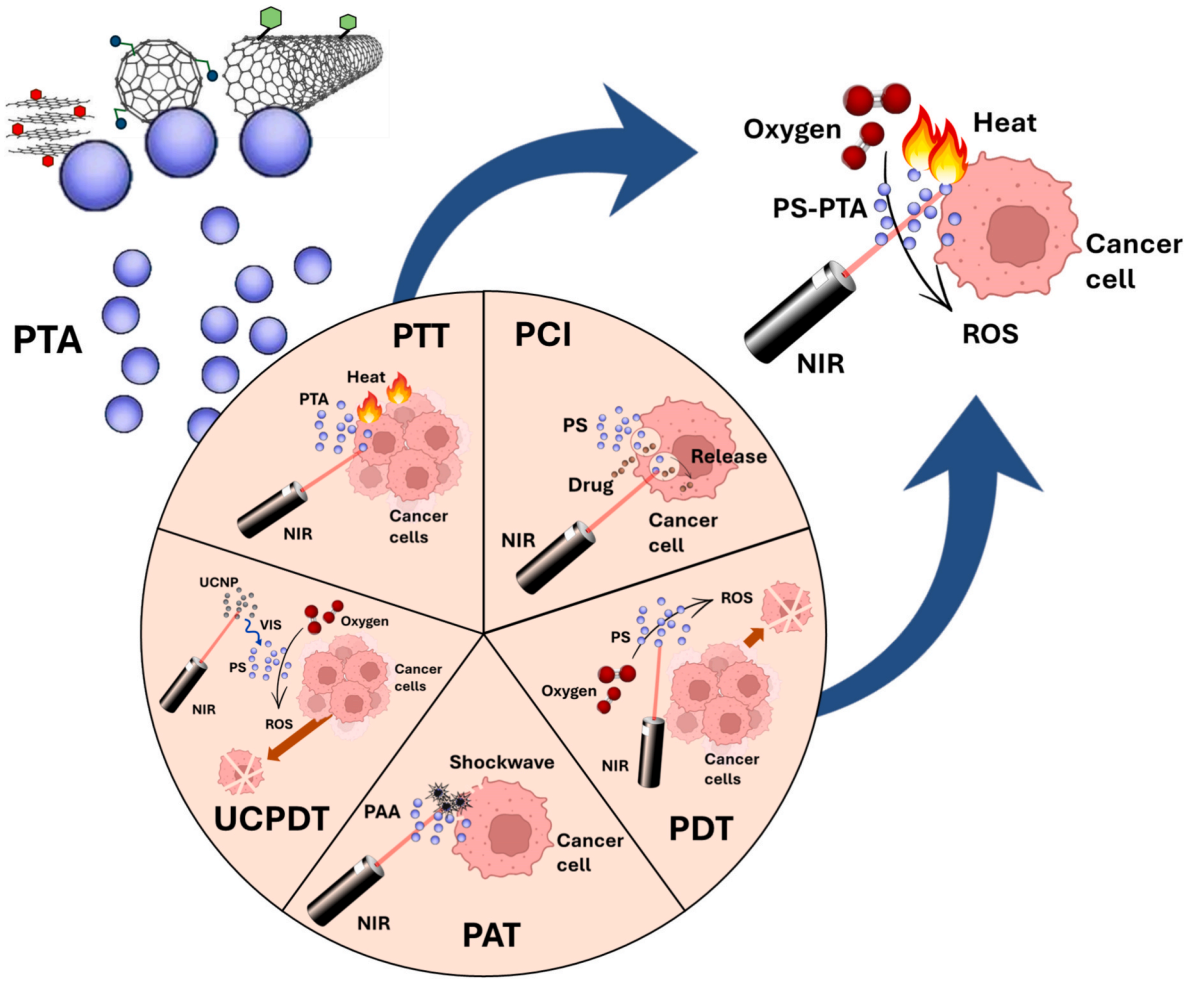


**Fig. 1.** Photoactivation strategies for selective tumour targeting. Various modalities can be combined to deliver optimal selectivity, yield, and microenvironment control. Energy transfer in some form is of essence in all technologies. NIR: near-infrared; VIS: visible; PS: photosensitizer; PTA: photothermal agent; ROS: reactive oxygen species; UCNP: upconversion nanoparticle; PTT: photothermal therapy; PCI: photochemical internalisation; PDT: photodynamic therapy; PAT: photoacoustic therapy; and UCPDT: upconversion photodynamic therapy.

multifunctionality of these nanomaterials allows for the simultaneous delivery of both therapeutic and imaging agents, and energy conversion, which can be activated in the tumour microenvironment. Nanostructures can convert and couple different forms of energy in unique and efficient ways. In the context of targeted cancer therapy, these conversions typically involve optical energy, thermal energy, acoustic energy, and chemical energy (Fig. 1). Secondary modes can occur when physical effects are confined within tens of nanometres with pulse durations timed shorter than the characteristic heat diffusion time of the nanoparticle. In such cases, energy can be effectively transformed into reactive cavitation bubbles that can damage the neighbouring tissue [25,26]. Alternatively with the dose set just below the ionisation threshold and the use of wavelengths that are similar to the resonance frequencies of the nanoparticles, plasmonic oscillations can be induced to trigger photoionisation in the proximity of the nanoparticle [27]. Nanostructures allow for the design freedom to optimise the conversion of these energy modes within the cellular or tissue environment to achieve therapeutic effects.

The early studies on photoactivated CBNs for targeted cancer therapy triggered massive interest for innovative multimodal approaches in oncology [28,29,30,31]. These pioneering efforts demonstrated the potential of single-walled carbon nanotubes (SWCNT), graphene oxide (GO) and carbon nanodots as multifunctional platforms capable of drug delivery, photothermal therapy (PTT), photoacoustic therapy (PAT), photodynamic therapy (PDT) and photoacoustic imaging. Photothermal therapy (PTT) has received increasing attention in the past decade, which utilises various photothermal agents (PTAs) to absorb near-infrared (NIR, 700–1700 nm) light and convert the light energy into hyperthermia for tumour ablation. In contrast to the conventional treatment techniques, photoactive therapies are non-invasive and spatiotemporally controllable with higher therapeutic efficacy and low healthy-tissue damage, these advantages make PTT, PAT and PDT attractive and promising candidates for use in anti-cancer therapy. In short, and before diving deeper into each process, PTAs exhibiting passive or active targeting capacities are capable of selectively accumulating in the tumour and then conducting accurate PTT with the help of localised NIR, since water, blood and other tissue components in body show insignificant NIR absorption.

### 2.1.1. Photothermal therapy

Photothermal therapy (PTT) uses photoactivated agents e.g., nanoparticles or other nanostructured materials that absorb NIR light and convert it into heat. Conventionally, nanoparticles such as gold nanoshells, nanorods, and copper sulphide were used to absorb NIR and convert it into heat through non-radiative relaxations. As we shall discuss, numerous competitive CBN systems have been proposed since. PTT uses NIR-I irradiation typically in the 800–980 nm range with diode-based lasers [32]. The local heat generation can be used to cause hyperthermia and ablate cancer cells or clusters directly or to enhance the permeability of drug carriers. This localised heat generation effectively kills cells without harming the surrounding healthy tissue. PTT selectively targets cancer cells due to their lower heat tolerance compared to healthy tissues. The mechanism relies on the differential thermal sensitivity between malignant and normal cells, influenced by factors such as metabolic activity, vascular structure, and the expression of heat shock proteins (HSPs). While healthy cells typically withstand temperatures up to ~ 43 °C due to efficient thermoregulation and HSP upregulation, cancer cells undergo irreversible apoptosis at **42–45 °C** and necrosis at **~ 50 °C**, as their chaotic vasculature hinders heat dissipation. Furthermore, tumour cells often exhibit deficiencies in HSP-mediated thermal adaptation, making them highly susceptible to hyperthermia-induced cell death. This selectivity is enhanced by NIR-absorbing CBNs, which accumulate preferentially in tumours through the enhanced permeability and retention (EPR) effect, allowing localised heat generation while sparing surrounding healthy tissues. Pulsed laser strategies and real-time thermal monitoring further improve selectivity by optimising nanoparticle-mediated heating and minimising off-target thermal damage. By leveraging these mechanisms, PTT provides an effective and highly selective approach to cancer treatment while preserving normal tissue integrity. The effectiveness of PTT is therefore highly dependent on the photothermal transducer's ability to absorb NIR light and convert it efficiently into thermal energy. Recent advancements focus on developing efficient photothermal agents, particularly CBNs due to their exceptionally well-coupled optical and thermal properties. A key example of breakthroughs in PTT were the development of carbon nanomaterials that are conjugated with gold nanoparticles which have been extensively researched due to their tuneable optical properties, allowing for optimal absorption of NIR light [33]. These new avenues of coating or functionalising CBNs with targeting molecules to increase their accumulation in tumour tissues have grown vastly in the recent years. The seminal work by Huang and colleagues demonstrated that gold nanorods targeted to tumour cells could effectively convert NIR light into heat, causing irreversible damage to the tumour while sparing healthy tissue [34]. This was a precursor to the development of nanorod-conjugated nanotubes for coupled phototherapy and imaging [35]. More recent studies have explored graphene oxide for its high surface area and excellent photothermal properties. Graphene oxide sheets can be loaded with anticancer drugs to provide a synergistic combination of chemotherapy and PTT. Also widely studied is the use of CNT mediated PTT (also termed as CNMTT) allowing for enhanced and localised heat generation within the tumour in addition to the advantage of internalisation by cells [36].

### 2.1.2. Photodynamic therapy

Certain nanostructures can facilitate photocatalytic reactions when exposed to light, converting light energy into chemical energy. This is particularly utilised in generating reactive oxygen species (ROS) which are cytotoxic and can induce cell death. Photodynamic therapy (PDT) involves three key components: a photosensitizer, light, and oxygen. For deeper tissue penetration, modifications with dopants or sensitizers that shift the absorption to the NIR region are explored. PDT uses light emitting diodes with much lower irradiance than PTT, and exposure wavelengths in the 630–730 nm range [32]. The photosensitizer is activated by light of a specific wavelength, leading to the generation of ROS that can oxidise cellular components and induce cell death. While PDT usually involves a mild hyperthermic effect (<42 °C), the ROS agents deliver the main impact [37]. PDT's selectivity comes from the localised light activation, allowing for targeted therapy with minimal impact on surrounding healthy tissues. Cancer cells are particularly vulnerable to ROS due to their inherently high oxidative stress levels and weakened antioxidant defence systems compared to healthy cells. While normal tissues rely on robust enzymatic scavenging systems (e.g., superoxide dismutase, catalase, glutathione peroxidase) to neutralise ROS, tumour cells often exhibit compromised redox homeostasis, making them more susceptible to oxidative damage. Additionally, PDT-induced ROS generation is spatially confined to areas of photosensitiser accumulation and light exposure, preventing systemic toxicity. However, effective PDT requires sufficient oxygen supply, which can be limited by tumour hypoxia. CBNs address this challenge by acting as oxygen carriers or by facilitating photochemical reactions that enhance localised ROS production. Furthermore, surface-engineered CBNs improve photosensitiser targeting efficiency, prolong retention in tumour tissues, and reduce off-target ROS diffusion, further refining PDT selectivity.

The development of chlorin-based photosensitisers, such as temoporfin and radachlorin, has been crucial. These molecules absorb light at longer wavelengths (650–800 nm), which penetrates deeper into tissues, making them effective against thicker tumours. Allison et al. highlighted their use in clinical settings, showing significant efficacy in treating head and neck cancers [38]. Carbon-based nanodots have been designed to be outstanding photosensitisers with an ability to generate ROS by functionalisation of an amino group. This has allowed for a strong photodynamic effect under two photon excitations in the NIR range.

Nanoparticles have also been further functionalised with dual targeting moieties, folic acid for targeting tumour cells and triphenyl phosphonium for mitochondria targeting, enhancing both selectivity and treatment efficacy. This dual-targeting approach not only significantly improves cellular uptake and mitochondrion targeting efficiency but also generates a high amount of reactive singlet oxygen $^1O_2$ crucial for photodynamic destruction of cancer cells [39]. These studies have observed that the treatments lead to significant tumour regression in a short period.

#### 2.1.3. Photochemical internalisation

Photochemical internalisation (PCI) is a novel technique that enhances the delivery of macromolecules into the cytosol of cancer cells. It uses photosensitizers that localise in endosomal membranes; upon light activation, these sensitise the production of ROS, disrupting the endosomal membranes and releasing their contents into the cell cytoplasm. This mechanism is particularly useful for delivering large molecules like proteins, peptides, and nucleic acids, which do not easily cross cell membranes. Berg et al. were pioneers in showing that PCI could effectively release macromolecules into the cytosol, enhancing the biological efficacy of drugs that are otherwise compartmentalised into endosomes [40].

#### 2.1.4. Photoacoustic therapy

While the photoacoustic effect has been primarily used for imaging, photoacoustic therapy (PAT) has also introduced a novel therapeutic modality that combines principles of optical and ultrasound imaging to provide a unique approach to cancer treatment [41,42]. CBNs, particularly those like carbon nanotubes, graphene, and carbon dots, are increasingly utilised in this field due to their strong optical absorption properties. When nanotubes absorb NIR light, they rapidly convert this energy into heat, leading to a thermoelastic expansion that generates acoustic waves detectable by ultrasound equipment. This property allows for dual functionality in both imaging and therapy, where the heat can be used therapeutically to damage tumour cells, while the acoustic signal provides real-time imaging feedback. The same effects can be seen in nanodots and nanosheets with prospects such as graphene's broad-spectrum absorbance and the nanodot confinement enabling tunability. Kang et al. have shown that folic acid functionalised single-walled carbon nanotubes exhibit a large photoacoustic effect in suspension under the irradiation of 1064-nm millisecond pulsed lasers. They were able to use the strong absorption to trigger a firecracker-like explosion at the nanoscale. With functionalised nanotubes binding selectively to overexpressed folate receptors on the surface of the cell membrane, the localisation and explosion impact can be maximised. The uptake pathways of folate-conjugated nanotubes also showed high selectivity [43].

### 2.2. Combinational therapeutic approaches

The integration of these modalities within a single nanostructure or a combination of nanostructures can lead to synergistic effects, enhancing therapeutic outcomes. For instance, a nanoparticle designed for both photothermal and photocatalytic activities can use the heat generated by NIR absorption not only to damage cells directly but also to enhance the photocatalytic generation of ROS by increasing the reaction kinetics. Combining different functionalities within a nanostructure requires: (i) materials that are compatible in terms of chemical and physical properties; (ii) precise control over the activation of each modality which is crucial to ensure targeted therapy and avoid off-target effects; (iii) optimal balancing of absorption characteristics to efficiently convert energy across different modalities.

#### 2.2.1. Integration of PCI and chemotherapy

The work of Selbo et al. combining PCI with chemotherapeutic agents demonstrated that PCI could significantly enhance the efficacy of chemotherapy drugs by facilitating their entry into cancer cells. They specifically showed improved outcomes in treating resistant cancer cells, paving the way for combinatorial approaches that could potentially overcome drug resistance in cancer therapy [44]. Another key study demonstrated the application of PCI in conjunction with chemotherapy using a new class of dual degradable nanoparticles loaded with a chemotherapeutic compound and a phototoxic drug (hematoporphyrin). The simultaneous photo- and chemo-degradations, allowed for light- and pH-controlled cellular insertion of therapeutics, allowing for photo–chemotherapeutic potency [45].

#### 2.2.2. Integration of PTT and PDT

One of the most promising approaches in nanostructured design is the integration of photothermal and photodynamic therapies. This is achieved by developing nanoparticles that can carry a photosensitizer for PDT and also exhibit strong absorption in the NIR region for PTT. A typical well-established non-carbon-based design involves coating gold nanoparticles with a layer of silica, which is then conjugated with a photosensitizer. The gold core strongly absorbs NIR light, facilitating effective photothermal conversion, while the photosensitizer embedded in the silica shell can generate ROS upon light activation. This dual functionality enables a synergistic therapeutic effect where the heat generated by PTT can enhance the effectiveness of PDT by increasing oxygen supply to the tumour and thus boosting ROS production. Chen et al. discuss the advantages of combining PDT and PTT using nanostructure design, underscoring the dual therapeutic benefits and enhanced efficacy while reducing side effects, a promising direction in overcoming limitations of traditional therapies [46].

#### 2.2.3. Integration of upconversion nanoparticles and PDT

UCNPs absorb NIR light and emit it at visible wavelengths, activating traditional photosensitizers for PDT in deep tissues. This unique property allows UCNPs to function as bridges between the deep tissue penetration capabilities of NIR light and the effective activation range of traditional photosensitizers, which typically absorb in the visible range [47]. Chen et al. demonstrated that UCNPs could be used to activate photosensitizers like Rose Bengal and methylene blue at depths previously unreachable with conventional PDT, expanding the potential of PDT to deeper tumours [48]. Conventionally, the core–shell design of UCNPs, where a lanthanide-doped core is encapsulated in a shell that has been functionalised with photosensitizers. These not only protect the core from quenching but also provide a site for chemical attachment of therapeutic agents or targeting ligands. This innovative design enhances the stability of the particles and optimises the energy transfer efficiency between the NIR excitation and the visible emission, effectively activating the photosensitizer in deep tissues. In another study by Liu et al., graphene oxide nanodots were paired with UCNPs to enhance the efficacy of PDT. When conjugated with UCNPs, these nanodots could be excited by NIR, enabling them to emit visible light that acts as a light transducer. This system allows for deep tissue penetration of NIR light and subsequent local conversion to visible light, which is effective for activating the photodynamic process [49].

#### 2.2.4. Integration of PTT and chemodynamic therapy

Recently Wu et al. developed a NIR-II photoactivatable hybrid nanomedicine, utilising copper sulphide nanoparticles, and achieving synergistic photothermal and chemodynamic therapy (CDT) in preclinical cancer models and marking a significant step in multifunctional therapeutic design [50]. This study reported the development of an enzyme-loaded photoactive nanomedicine containing a thermoresponsive liposome shell loaded with copper sulphide nanoparticles and glucose oxidase. Upon 1064 nm laser irradiation, the nanoparticles mediate local heat generation, leading to the destruction of the liposome shell and on-demand release of therapeutic agents. This approach enables synergistic NIR-II PTT and CDT, achieving complete tumour ablation in mouse models. For example, nanoparticles based on hollow

porous carbon coated metal sulphide cores allow for the catalysis of $H_2O_2$ to produce ·OH. The carboxy groups on the surface of the carbon shell can be functionalised with polyethyleneimine and integrated with charged graphene oxide via electrostatic interactions with the use of folic acid for cancer cell targeting. The carbon shell effectively converts the NIR light to heat for temperature enhancement, speeding up the Fenton reaction for a PTT-CDT combination. The graphene oxide then catalyses glucose, and the produced $H_2O_2$ could generate abundant highly toxic ·OH to destroy cancer cells. The hollow structure and metallic core further allow for ultrasonic and magnetic resonance imaging [51].

#### 2.2.5. Integration of PTT, PDT and CDT

While previous studies have been limited to a single approach or a combination of the two therapies, a few recent studies have looked at the combination of over two modalities. With the use of a sodium polyacrylate modification, the metal-nitrogen-carbon nanoparticles were able to initiate a metal-based Fenton-like reaction to generate ·OH and $O_2$ for CDT, while the porphyrin-like metal centre in the FeNC@PAA nanoparticles was used as a photosensitizer for PDT. In fact, the PDT effect was enhanced by $O_2$ generated in CDT. Furthermore, the FeNC@PAA nanoparticles were also found to be effective in PTT with a conversion efficiency of 29 %, owing to a high NIR absorbance [52].

## 3. Cbns offer key competitive advantages

### 3.1. Early pioneering examples of photoactivated CBN-based cancer therapies

One of these early examples was the work of Liu et al. showing for the first time that SWCNTs could efficiently deliver anticancer drugs like doxorubicin, leveraging the EPR effect for targeted release at tumour sites [5354]. This research which utilised a pH-sensitive linker allowing for drug release in the acidic tumour microenvironment (TME) was complemented by Yang et al., highlighting the biocompatibility and reduced immune response of PEGylated graphene, which exhibited stable biodistribution and minimal toxicity *in vivo*, opening the door for graphene's potential clinical use [55]. Robinson et al. advanced this study by exploring SWCNTs' unique NIR properties for simultaneous imaging and PTT, achieving precise tumour ablation with minimal collateral damage and setting a benchmark for NIR-based PTT [56], while Zhang et al. extended their application for high-resolution, non-invasive tumour imaging via photoacoustic modalities [57]. The promise of GO in combination therapies, was also demonstrated in this study developing GO as a matrix for enzyme immobilisation, enhancing its stability and therapeutic potential, particularly for antioxidant therapies targeting tumour oxidative stress. Another significant milestone was achieved by Juzenas et al., who introduced carbon nanodots capable of producing ROS under ultraviolet light for PDT, a precise approach to inducing cancer cell death via apoptosis without a systemic effect [58]. Together, these collective efforts provided critical mass and insights into safety, targeting capability, and multifunctional potential of CBNs. Although most of these examples as well as recent studies we will leaf through focus on mice models with clinical translation still ongoing, the large array of follow-up studies and the foundational findings of these studies underscore their profound influence on our understanding of the biological response characteristics of photoactivated carbon-based nanostructures. As we will see in the following section, recent advancements in in this area have brought exciting innovations, particularly in developing multifunctional, multimodal and responsive nanoplatforms for enhanced therapeutic efficacy. Sun et al. also provide a comprehensive review of carbon dots as effective photosensitizers in PDT, with robust ability to generate ROS, showing their promise for future clinical use against cancers and infections [59]. The review of Zhang et al. focuses on NIR-II hollow nanoplatforms, noting their enhanced biocompatibility and application in single and multimodal cancer therapies, an area with growing interest in clinical translation [60]. The review by Wang et al. provides insights into copper-incorporated nanomaterials including carbon-based nanoparticles, highlighting their unique physicochemical properties for applications in PTT and combination therapies, and emphasising their translational potential due to tuneable nanostructures and favourable biosafety profiles [61].

### 3.2. Morphological significance of CBNs

In the diverse realm of nanomaterials, carbon-based nanostructures stand out due to their unique morphological properties and their potential to host add-on features through functionalisation and coating (Fig. 2). In this section we delve into the distinct characteristics of carbon nanoparticles, illustrating how their specific forms contribute to their exceptional functionalities. Each type of nanostructure—whether the elongated, cylindrical carbon nanotubes, the quasi-spherical carbon nanodots, or the atomically thin graphene nanosheets—demonstrates tailored properties that are critically dependent on their shape. We will briefly explore how the inherent geometric uniqueness enables specialised applications in phototherapy.

#### 3.2.1. Carbon nanotubes

Carbon nanotubes (CNTs) consist of rolled graphitic sheets of $sp^2$ carbon in a single or multiwalled format and have proven effective in localised heat generation. In this regard, multiwalled CNTs (MWCNTs) have demonstrated improved effectiveness over single-walled CNTs (SWCNTs) [62]. Coating CNTs with light-absorbing polymers or conjugating them with NIR fluorescent dyes can significantly increase their NIR absorption capacity. Conventionally, CNTs have been functionalised with targeting ligands that specifically bind to cancer cell receptors, to enhance the delivery of chemotherapeutic agents directly to cancer cells, thereby increasing treatment efficacy. With multilayer functionalisation, CNTs are used in dual therapy modes, combining PTT with other treatments such as chemotherapy or immunotherapy. This approach uses the heat generated by CNTs during PTT to enhance the efficacy of the combined treatment methods. Shao et al. modified SWCNTs with insulin-like growth factor 1 receptor and HER2 to achieve selective attachment to breast cancer cells. Upon NIR exposure, these modified SWCNTs showed complete inhibition of cancer cells, demonstrating their potential for targeted PTT [63].

Doping can also dramatically alter the electrical and optical properties of CNTs further enhancing the NIR absorption by introducing impurity levels into the electronic structure of CNTs, thus broadening their light absorption spectrum. Nitrogen doping not only improves CNT photothermal conversion efficiency but also enhances the chemical reactivity and stability, while incorporating metals such as gold, silver, or platinum into CNTs can induce localised surface plasmon resonances (LSPRs), which are collective oscillations of conduction electrons at the metal-nanotube interface excited by light. These resonances can significantly increase the NIR light absorption, boosting the photothermal therapeutic efficacy.

CNTs are conveniently internalised by cells [69] rendering them brilliant delivery vehicles to incorporate multiple diagnostic and therapeutic functions through sequential coatings into a single structure allowing for enhanced function in applications such as image guided therapy [70,71,72]. The superior surface area to volume ratio in tandem with the high aspect ratio of CNTs allow for ease of crossing through membranes and the use of a high density of therapeutic and imaging agents which can improve the effectiveness of delivery and sensitivity for multimodal imaging. Panchapakesan et al. employed SWCNTs for both PTT and photoacoustic imaging, exploiting the intrinsic fluorescence of SWCNTs in the NIR-II region for real-time monitoring of therapy delivery and efficacy in cancer phototherapies [73].

The cytocompatibility of CNTs remains under question. While the role of CNT doping with nitrogen and other dopants [74] and

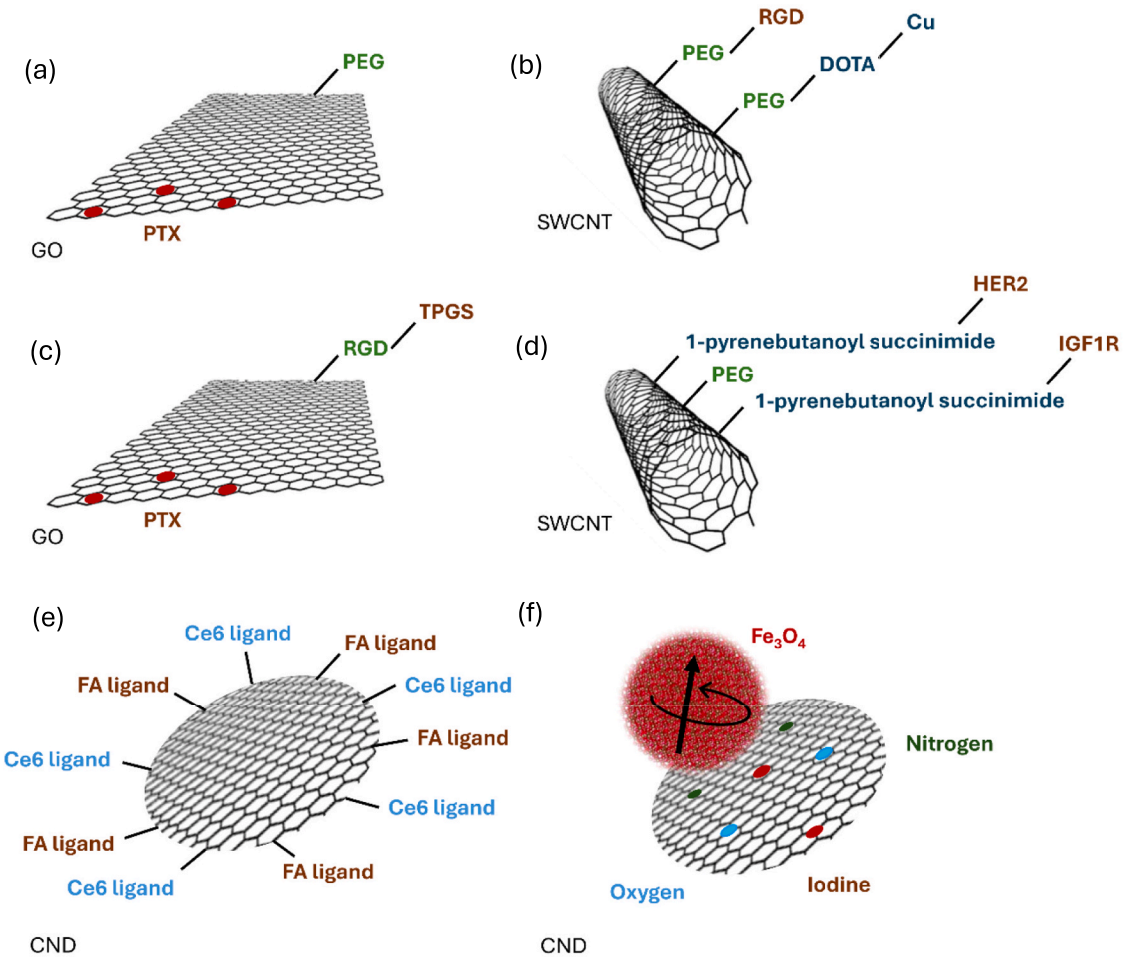


**Fig. 2.** Examples of multifunctional CBNs developed for phototherapeutic applications: (a) Xu et al. covalently introduced PEG onto the GO surface and conjugated the GO-PEG with PTX to deliver a stable and biocompatible product that could quickly enter human lung cancer A549 and human breast cancer MCF-7 cells [64]; (b) Early developments by Liu et al. using functionalised SWCNT to improve biodistribution and targeting of the nanotubes [53]; (c) Mo et al. demonstrated that the RGD-TPGS-nGO-PTX multifunctional GO targeted drug delivery system could improve PTX delivery and reverse MDR increasing the efficacy of breast cancer treatment [65]; (d) Work by Shao et al. showing that SWCNT functionalised with HER2 and IGF1R specific antibodies exhibit selective attachment to breast cancer cells [66]; (e) Ji et al. introduced a double covalent functionalisation of CNDs allowing for a high loading of poorly soluble Ce6 on CNDs. This significantly improved the drug solubility in physiological conditions while maintaining NIR PS properties [67]; (f) Li et al. introduced I@CNDs-Fe3O4 nanoparticles exhibiting wavelength-tuneable fluorescent imaging in tandem with X-ray attenuation for CT image enhancement, and T2-Weighted MR imaging for real-time phototheranostics [68]. GO: graphene oxide; CND: carbon nanodot; SWCNT: single-walled carbon nanotube; PEG: polyethylene glycol; PTX: paclitaxel; RGD: arginylglycylaspartic acid; DOTA: tetraxetan; and TPGS: tocopherol polyethylene glycol succinate.

composition with inorganic polymers such as polylactic acid [75,76] on viability has been widely emphasised, the nanostructure design seems to have a dominant influence on toxicity [77,78]. The majority of these studies introduce CNTs as cellular scaffold elements, investigating cell adhesion and migration processes. The micropore size, morphology, and the surface roughness have an optimal value at the proximity of the cellular dimensions [79]. The stability and aggregation avoidance are also key with smaller and hydrophilic CNTs, and colloidal dispersions that maintain stability at physiologic pH levels more desirable *in vivo* [80].

### 3.2.2. *Carbon nanodots*

Carbon nanodots (CNDs) are nano-sized particles with quantum confinement and edge effects that influence their electronic properties. Hence, they are also referred to as carbon quantum dots (CQDs). Xu initially discovered these nanostructures et al. in 2004 during the preparative electrophoresis process used for purifying single-walled carbon nanotubes. CNDs are characterised by their remarkable optical and physicochemical properties including biocompatibility, excellent water solubility, size-dependent photoluminescence, tuneable fluorescence, and high photo stability. Their small size (sub 10 nm) and spherical shape affect how they interact with light and convert it into energy, making them suitable for PDT and PTT [81,82]. While majority of CNDs absorb light in the UV region, recent publications showed broadened absorption and emission spectrum into the NIR range enhances the potential of CNDs as effective agents for NIR phototherapies [83,84].

While this nanostructural configuration is primarily known for its fluorescent properties, CNDs can also convert NIR irradiance into heat. The conversion efficiency depends on the surface functional groups and core structure, which can be engineered to enhance light absorption and heat generation for effective PTT. The ultra-small size of CNDs facilitates deeper tissue penetration and better bio-distribution, potentially allowing for more effective targeting of dispersed or hard-to-reach tumours. Kim et al. have successfully developed bio-sulphur-doped carbon dots exhibiting significant NIR absorption properties. The administration of a low concentration of sulphur-doped CNDs (45 μg/mL) via intra-tumoral injection, in conjunction with moderate laser irradiation at 808 nm resulted in a high photothermal conversion efficiency of 55.4

%. This method achieved complete tumour destruction while sparing adjacent healthy tissues, illustrating a safe and effective strategy for cancer treatment [85].

CNDs can also be engineered to have dual functionality, serving both as imaging agents and as therapeutic agents. Their strong luminescence allows for precise imaging of tumours, while their photoactive properties are utilised to initiate therapeutic actions such as ROS generation for PDT. Surface modifications of CNDs have allowed for the targeted delivery of these nanoparticles to specific types of cancer cells. Ji et al. demonstrated a multifunctional CND as a NIR laser-triggered nano agent constructed by covalent functionalisation with folic acid and a hydrophobic PS, chlorin e6 (Ce6). The resulting CND showed high colloidal stability in different physiological environments, an enhanced NIR PS effect, and a highly improved photothermal activity [67]. Functional groups can also be added to the surface of CNDs to improve their biocompatibility and enhance their ability to generate reactive oxygen species under light irradiation. Hybrid systems that combine CNDs with other types of nanoparticles, such as magnetic nanoparticles, to utilise the properties of both materials. These hybrids can be used for multimodal treatment approaches, enhancing the overall therapeutic outcomes [68].

The ultra-small size of CNDs may also lead to uncontrolled migration through tissue, raising concerns about off-target accumulation and systemic toxicity. Delocalisation of CNDs could reduce therapeutic efficacy by preventing adequate retention at the tumour site and increasing clearance through the renal or hepatic pathways. Furthermore, excessive off-target accumulation, particularly in organs such as the liver, spleen, or brain, may induce unintended toxicological effects. To address these challenges, functionalisation strategies such as conjugation with tumour-targeting ligands (e.g., folic acid, peptides, or antibodies) to enhance tumour retention and reduce systemic diffusion have been implemented. Additionally, hybrid nanoplatforms incorporating hydrophilic coatings, such as PEG, improve circulation time while limiting nonspecific uptake by healthy tissues. Controlled aggregation of CNDs within tumours, triggered by pH-sensitive or enzyme-responsive coatings, further prevents widespread diffusion. These design considerations are critical for ensuring that ultra-small CNDs maintain their therapeutic efficiency while minimising safety concerns associated with uncontrolled migration *in vivo*.

#### 3.2.3. Carbon nanosheets

Graphene's two-dimensional planar structure provides a high surface area that interacts extensively with light. The sp2 hybridisation of carbon atoms in graphene allows for dense electron cloud formations, which are beneficial for light absorption and heat generation. Graphene absorbs across a wide range of the electromagnetic spectrum, including the NIR region, for deep tissue penetration in PTT applications. The heat is generated over the plane of the graphene sheet, providing a uniform thermal effect. The atomic thickness of graphene facilitates extremely fast heat distribution, which is advantageous for quickly reaching the thermal threshold needed to damage tumour cells without overheating, thus preserving surrounding healthy tissue. Graphene oxide (GO) is an oxidised form of graphene, with a similar two-dimensional structure. The vast interest in GO can be attributed to the exceptionally low toxicity [64], dispersity in water and high stability [86]. This is partly due to the hydrophilic surface groups that can be further functionalised. Similar to graphene, GO has high efficiency for photothermal conversion.

Graphene's extensive surface area allows it to function as a platform for the conjugation of multiple therapeutic agents. This has led to the development of graphene-based systems that can deliver drugs, produce heat, and generate ROS, providing a comprehensive treatment approach within a single system. Similar to CNTs and CNDs, the functionalisation of GO with chemotactic peptides enhances its ability to selectively deliver drugs to cancer cells. In a prior study, cervical carcinoma cells expressing the formyl peptide receptor were targeted with *N*-formyl-methionyl-leucyl-phenylalanine. Another significant advancement of this platform is its enhanced biodegradability. Neutrophils contain many types of granules which are the primary storage site of the most toxic mediators including elastase and defensin [87]. During degranulation, they dock and fuse with the membrane to release their contents. Studies as such with functionalised GO have demonstrated that this hybrid chemistry undergoes degradation post neutrophil degranulation, which is crucial for reducing long-term toxicity [88,89]. The same has been shown with the degradation of functionalised CNTs with released toxic mediators such as myeloperoxidase [90].

Advances in graphene technology have optimised its photothermal conversion efficiency, making it a more effective agent for PTT. Numerous GO-based multifunctional systems have been proposed for high-performance imaging as well as stimuli-responsive activation. A prominent example is metal oxides loaded onto exfoliated GO nanosheets. The resultant nanocomposites function as efficient MRI contrast agents due to the superparamagnetic metal oxides, while they are also used for coupled photo-induced and magnetic hyperthermia [91]. Modifications in the layering, doping, or compositing of graphene with other agents have enhanced its NIR light absorption and heat generation. One of the overexpressed membrane surface proteins in breast cancer cells is P-glycoprotein. As an efflux pump, it removes drugs from cancer cells exhibiting a multi-drug resistant (MDR) characteristic. Agents that can inhibit this transport system, can be used in conjunction with drugs such as Paclitaxel, used in breast and ovarian cancer. An interesting example is the hybrid system developed by Mo et al., which combines GO with Paclitaxel and an anti-MDR agent (in this case TPGS) to allow for a multifunctional delivery unit [65].

### 3.3. Delivery strategies for CBNs in phototherapy

The administration of CBNs plays a crucial role in optimising their therapeutic efficacy, stability, and biodistribution. The choice of delivery system significantly impacts their photothermal and photodynamic effects, as well as their ability to localise within tumours while minimising systemic toxicity. Various delivery platforms, including solution-based suspensions, hydrogels, lipid-based carriers, polymeric matrices, and implantable systems, have been used to enhance the therapeutic potential of CBNs in cancer treatment.

#### 3.3.1. Solution-based delivery

Solution-based administration remains the simplest and most widely used method for delivering CBNs, especially for injections. In this form, nanomaterials are often functionalised for stability and biocompatibility (e.g., PEGylation or antibody conjugation). They are administered intravenously relying on circulation and passive targeting through the EPR effect or active targeting via ligands or intratumorally relying on deposition within or around a tumour or lesion. Delivering CBNs in solution offers the advantage of potentially reaching both primary and metastatic sites through circulation. However, CBN suspensions are prone to rapid clearance by the reticuloendothelial system (RES), leading to reduced circulation times and potential off-target accumulation in organs such as the liver and spleen. Surface functionalisation strategies, including PEGylation and ligand conjugation, have been employed to improve colloidal stability and reduce immune recognition.

A recent example is the work of Lee et al. with functionalised MWCNTs with an antibody against the thyroid stimulating hormone receptor (TSHR) to target papillary thyroid cancer tumours [92]. The treated mice tumours showed significantly reduced recurrence over 5 weeks, demonstrating that solution-delivered, antibody-guided CBNs can achieve potent photothermal effects with controlled heat distribution. Similar solution-based approaches have been explored with other CBNs. Graphene oxide, for example, and PEGylated nano-GO and its reduced form (rGO) showed efficient tumour accumulation and heating [93]. By tailoring surface chemistry (PEG, antibodies, folate, etc.), CBN concentrations can be selectively maximised in the tumour.

#### 3.3.2. Hydrogel-based delivery

Hydrogels are water-rich, crosslinked polymer networks used widely as delivery matrices for CBNs in phototherapy. Hydrogels can be injected as liquids that solidify *in situ* or applied as pre-formed gels, acting as a local depot that holds nanomaterials at the target site. This confinement offers several benefits including localised concentration within the gel at the therapy site which minimises systemic dispersion and toxicity, controlled uniform distribution within the gel which may lead to more uniform heating of the target tissue, and additional modulation/control over heat dissipation via hydrogel properties (water content, thermal conductivity) to buffer heat flow due to its insulating polymer network, helping retain heat in the target area. Essentially, a hydrogel can localise the heat source (CBNs) and thereby confine the photothermal effect to its placement area. Numerous recent studies highlight the efficacy of hydrogel-based CBN delivery. Thermosensitive hydrogels are particularly convenient: these remain liquid at room temperature for easy injection and rapidly gelate at body temperature, conforming to the shape of the target site. Tan et al. developed an injectable chitosan-based hydrogel loaded with clinically used carbon nanoparticle suspension for tumour PTT [94]. Within this matrix, the carbon nanoparticles demonstrated a strong photothermal effect upon 808 nm laser irradiation, achieving effective ablation of 4 T1 breast tumour models. Notably, the localised treatment not only ablated tumours but also induced immunogenic effects – dendritic cell maturation and an antitumor immune response – leading to reduced lung metastases. This nanocarbon hydrogel provides an outstanding local delivery platform for PTT with minimal systemic spillover, exemplifying how a hydrogel can improve therapeutic outcomes by restraining the nanomaterial and heat to the tumour vicinity.

Hydrogels can also be engineered to synergise with CBNs for multimodal therapy. CNDs have been integrated into hydrogels to achieve combined PTT/PDT. Yue et al. reported a hyaluronic acid based hydrogel crosslinked by carbon dots for synergistic cancer therapy [95]. Uniquely, the carbon dots themselves acted as both the photothermal/PDT agent and the cross-linker for the gel network via Schiff-base bonding with aldehyde-modified HA. The resulting injectable CND-HA-based hydrogel generated localised hyperthermia (PTT) under a single 660 nm laser source and also produced singlet oxygen (PDT) to kill cancer cells in both *in vitro* and *in vivo* tests. This approach shows how the delivery matrix can simplify combination therapies through co-delivering and confining of multiple therapeutic modes in one scaffold Importantly, the hydrogel's retention of the CNDs at the tumour site means that both heat and reactive oxygen are generated precisely where needed, improving therapeutic selectivity. Another advantage of hydrogel delivery is the ability to incorporate different types of CBNs and compare or combine their effects [96]. In summary, hydrogel-based delivery of CBNs in phototherapy offers localised sustained treatment with enhanced control over nanoparticle distribution and heat delivery. By adjusting the gel composition, one can tune properties like gelation, degradation, and interactions with the CBN, further optimising therapy. These features make hydrogels a powerful strategy for administering photothermal agents in a safe and targeted manner.

#### 3.3.3. Other matrix-based delivery techniques

Beyond hydrogels, a variety of solid or semi-solid matrices have been explored to deliver CBNs for phototherapy. These include polymer scaffolds, films, microneedle patches, and surgical dressings that incorporate CBNs. Such matrices are particularly useful for topical or implantable phototherapy applications – for instance, treating a tumour resection site to eliminate residual cancer cells, or treating infected wounds with photothermal antimicrobial therapy. The matrix material can provide structural support, control release of the nanomaterial, and even add therapeutic benefits of its own such as tissue regeneration. Moreover, these solid matrices keep the CBNs fixed at the target location, offering highly localised heat generation upon irradiation. A compelling example is the use of a surgical dressing loaded with graphene-based nanomaterials for post-surgical cancer treatment. Wu et al. developed a protein-based graphene oxide surgical dressing for postoperative photothermal therapy of melanoma [97]. In this approach, silk fibroin was combined with GO, and a special low-temperature chemical reduction was employed to partially reduce GO within the dressing. The result was a tuneable photothermal material in the form of a bandage that could generate heat under NIR light while remaining biocompatible and bioactive. The rGO provided efficient photoexcitation, and by controlling the reduction extent, the researchers could adjust the photothermal intensity of the dressing. *In vivo* tests in a melanoma surgical model showed that placing this CBN-infused dressing over the tumour resection site and illuminating it prevented tumour recurrence and also promoted wound healing. Other innovative matrices include polymeric implants and microneedle arrays that carry CBNs. For instance, 3D-printed biodegradable scaffolds with embedded CNTs have been proposed for treating bone tumours. These scaffolds can support bone tissue while CNT-mediated PTT eliminates cancerous cells. Similarly, microneedles coated with graphene or carbon dots can be applied to skin tumours or infections; they pierce the tissue superficially and deliver intense localised heating upon laser exposure. In all these cases, the matrix determines how the nanomaterials are distributed in the target area and can influence the spatial profile of heat. A uniform distribution of CBNs in a solid matrix yields uniform heating of that matrix's volume, whereas a surface-coated matrix (e.g., microneedles) concentrates heat at the interface. Importantly, the matrix material can affect thermal conductivity and heat confinement. A matrix with low thermal conductivity may act as a thermal insulator, keeping heat within the nanoparticle-rich regions longer, whereas a higher conductivity matrix could spread the heat more quickly to surrounding tissue. This property can be leveraged depending on the application – for example, insulating matrices to confine heat for tumour ablation, or more conductive matrices if a slight spread of heat is desired for broader treatment of a tissue region.

## 4. Impact of immune responses on CBN-mediated PTT/PDT efficacy

Immune responses to CBNs significantly influence the effectiveness of photothermal therapy (PTT) and photodynamic therapy (PDT) in cancer treatment. This section completely reviews this influence is driven by several key mechanisms. This section provides a comprehensive review of the key mechanisms through which immune responses to CBNs impact the effectiveness of these therapeutic approaches. Understanding these complex interactions is essential for optimising the design and application of CBN-based cancer therapies, as they can both enhance treatment efficacy and introduce potential limitations.

### 4.1. Enhanced immunogenic cell death

CBN-mediated PTT and PDT have been shown to promote immunogenic cell death (ICD), a process that enhances the immunogenicity of dying cancer cells. During ICD, cancer cells release damage-associated molecular patterns (DAMPs) such as calreticulin, ATP, and HMGB1. These DAMPs act as danger signals, activating dendritic cells and other antigen-presenting cells, which in turn stimulate T-cell responses against tumour antigens [98]. For instance, Wang et al. (2019) reported that graphene oxide-mediated PTT increased the calreticulin expression on the surface of treated tumour cells, enhancing their immunogenicity [98]. This enhanced ICD resulting from CBN-based therapies may contribute to a more robust and sustained anti-tumour immune response, potentially improving long-term therapeutic outcomes [99].

### 4.2. Immune cell recruitment and activation

CBNs can influence the recruitment and activation of immune cells within the tumour microenvironment, which is crucial for effective anti-

tumour responses. One of the key mechanisms involves cytokine modulation, where CBNs influence chemokine expression, thereby promoting T-cell infiltration into tumours [100]. Additionally, some CBNs can directly activate dendritic cells, improving their antigen-presenting capabilities and strengthening T cell-mediated immune responses [100]. Another crucial aspect is the impact of PTT-induced hyperthermia, which enhances vascular permeability, facilitating the recruitment of immune cells into tumours [101]. These immunomodulatory effects work synergistically with the direct tumour-killing mechanisms of PTT and PDT, ultimately creating a more favourable immune environment that enhances tumour elimination.

### 4.3. Inflammation management

While inflammation is crucial for initiating anti-tumour immune responses, excessive or chronic inflammation can be detrimental to therapeutic efficacy [102]. CBNs play a complex role in this balance. Some CBNs, particularly multi-walled carbon nanotubes, have been shown to induce pro-inflammatory cytokine production (e.g., IL-6, TNF-α) which could potentially enhance anti-tumour immunity [103,104]. Conversely, certain CBNs like graphene oxide exhibit anti-inflammatory properties that may help manage excessive inflammation induced by PTT/PDT. For instance, small, thin graphene oxide sheets have been found to dose-dependently inhibit the release of pro-inflammatory cytokines while activating anti-inflammatory pathways [105]. The net effect on inflammation depends on factors such as CBN type, dose, and administration route. Careful titration of these parameters is essential to achieve optimal therapeutic outcomes [106]. Recent research has focused on developing functionalised CBNs and nanocomposites that can balance pro- and anti-inflammatory effects, aiming to leverage their unique properties for more effective cancer treatments[103,107]. These advancements highlight the potential of CBNs in fine-tuning the inflammatory response to enhance the efficacy of PTT and PDT while minimising adverse effects.

### 4.4. Immune clearance considerations

While immune activation can enhance therapeutic efficacy, rapid clearance of CBNs by the immune system may reduce their accumulation in tumour tissues, potentially limiting PTT/PDT effectiveness. Strategies to mitigate immune clearance while maintaining beneficial immune responses are an active area of research in optimising CBN-based PTT/PDT [99].

In conclusion, immune responses to CBNs significantly impact PTT/PDT performance through multiple mechanisms. While enhanced ICD and immune cell recruitment can improve therapeutic outcomes, careful management of inflammation and immune clearance is crucial. Ongoing research aims to leverage these immune interactions to maximise the efficacy of CBN-mediated cancer therapies.

## 5. The application of CBNs in various cancer tissue targets

### 5.1. Cbns in breast cancer

Breast cancer is one of the most common cancers globally, with over two million cases reported in 2020 and rising annual incidence rates expected to continue in the coming years [108,109]. Molecular classification of breast cancer is determined by the increased presence of specific biomarkers: human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR). Based on these markers, breast cancer is divided into four subtypes: HER2+, ER+, PR+, and triple-negative breast cancer (TNBC), which lacks expression of all these receptors [110].

Shao et al. developed a SWNTs conjugated with IGF1R monoclonal antibodies (anti-IGF1R) and HER2 monoclonal antibodies (anti-HER2) for targeted breast cancer therapy. This dual-targeting approach leveraged the overexpression of IGF1R and HER2 in tumour cells to enable precise delivery of the SWNTs via antibody-antigen interactions. *In vitro* studies demonstrated efficient internalisation of the antibody-functionalised SWNTs into cancer cells, significantly enhancing therapeutic specificity. Furthermore, this study showed that combining PTT with the described monoclonal antibody-based therapy demonstrated a substantial ability to eliminate breast cancer cells *in vitro*, suggesting that antibody-functionalised SWNTs, leveraging their inherent optical properties, offer a highly effective strategy for anticancer treatment [66].

Gao et al. introduced a novel nanoplatform using single-walled carbon nanohorns (SWNHs) functionalised with indocyanine green (ICG), aiming to achieve a synergistic anti-tumour effect through the integration of PTT and PDT. SWNHs enhance the photostability of ICG and conversely, ICG improves the dispersibility of SWNHs in aqueous environments. SWNH-ICG nanohybrids effectively inhibit 4 T1 triple-negative breast cancer growth through synergistic PTT and PDT under 808 nm NIR laser irradiation (0.3 W/cm$^2$). The nanohybrids generate hyperthermia and ROS, causing significant tumour cell apoptosis. *In vivo*, treated tumours exhibited marked growth suppression, demonstrating superior efficacy compared to free ICG or single-modality therapies [111]. In 2018, researchers developed a graphene oxide-methylene blue (GO-MB) nanocomposite as a PS for PDT targeting human breast cancer. By functionalising GO with MB, the nanocomposite improved MB's solubility, photostability, and ROS generation under red or NIR light, while GO's photothermal effect amplified therapeutic efficacy. Hosseinzadeh et al. demonstrated its potency on a human breast cancer cell line (MDA-MB-231), showing a 60 % cell viability reduction in dark conditions at 20 μg/mL and up to 80 % under 630 nm red LED illumination for 30 min [112].

Vinothini et al. developed a reduced graphene oxide (rGO)-based composite functionalised with magnetic nanoparticles ($Fe_3O_4$), camptothecin, 4-hydroxycoumarin, and allylamine for chemo-photodynamic cancer therapy. The rGO provided a high surface area with photothermal and photodynamic properties, while $Fe_3O_4$ enabled magnetic targeting. Camptothecin and 4-hydroxycoumarin served as chemotherapeutic agents, synergising with the photodynamic effect. Allylamine enhanced biocompatibility and dispersion, improving therapeutic selectivity. Upon laser irradiation at 365 nm, the composite generated significant ROS achieving substantial inhibition of MCF-7 human cancer cells [113].

### 5.2. Cbns in lung cancer

The most recent Global Cancer Epidemiology Report identifies lung cancer as the most common type of cancer globally. The most recent Global Cancer Epidemiology Report identifies lung cancer as the most common type of cancer globally [114]. Leveraging advancements in nanomaterials, innovative phototherapy approaches have shown promising potential in targeting lung cancer with enhanced therapeutic efficacy and precision [115].

A study by Wong et al. investigated the antitumor effects of a series of water-soluble fullerene derivatives (F1–F10) against non-small cell lung cancer (NSCLC) cells, with a focus on apoptosis and autophagy pathways. These derivatives were synthesised to incorporate functional groups based on amino acids (F1–F7) and thioacids (F8–F10). F4 and F10 effectively suppressed the growth of lung cancer cells. F4 induced autophagic cell death through disruption of mitochondrial bioenergetics, resulting in significant reductions in oxygen consumption and ATP production. In contrast, F10 facilitated apoptosis by elevating intracellular ROS levels, thereby impairing mitochondrial functionality. This analysis revealed that the chemical nature of the functional groups on the fullerene cage critically determines the pathway of tumour cell elimination. Furthermore, the derivatives demonstrated low systemic toxicity in mice [116].

In 2017 Zhang et al. treated A549 lung cancer cells using a dual-

modal approach with two different light sources: 808 nm for PTT and 450 nm for PDT. They employed nanohybrid rGO-Ru-PEG composed of rGO sheet functionalised with a phosphorescent PEG-modified ruthenium (II) complex. Ru-PEG served as both a photosensitizer and imaging agent. This combination demonstrated superior cytotoxicity compared to individual therapies, with *in vivo* tests showing a marked reduction in tumour volume. The PTT–PDT treatment inhibited tumour growth effectively, achieving a relative tumour volume value (V/Vo) close to zero, compared to increases of ~ 1.5 and ~ 2.5 observed with PTT or PDT alone [117,118].

In 2024 researchers developed a mesoporous reduced graphene oxide (rGO)-based nanocomposite loaded with Osimertinib (AZD), a photosensitizer (protoporphyrin IX, PPIX), and a targeted agent (hyaluronic acid, HA), denoted as rPPH@AZD for combined chemo-phototherapy against non-small cell lung cancer (NSCLC) through combined chemo/phototherapy. Under 808 nm NIR irradiation, the rPPH@AZD exhibited a photothermal conversion efficiency of 48 %, capable of raising the local temperature by 22 °C in tumour environments. pH- and hyaluronidase-sensitive drug release profiles were confirmed, with over 75 % of the drug released in acidic environments (pH ~ 5.5) within 24 h, compared to 20 % at physiological pH (~7.4), indicating strong tumour selectivity. Therapeutic effect of rPPH@AZD on A549 cells, evaluated via MTT assays, demonstrated significant cytotoxicity. At a concentration of 50 μg/mL rPPH, cell viability of A549 cells in the PTT group reduced to 59.3 %, and in the PDT group to 55.9 %. However, A549 cells viability in the combined chemotherapy/PTT/PDT group reduced dramatically to just 19 %. Tumour-bearing mice demonstrated significant reduction in tumour volume after 14 days of rPPH@AZD with 808 and 660 nm irradiation treatment [119].

### 5.3. Cbns in glioma

Gliomas, which are the most common malignant tumour of the nervous system in adults, typically originate from neuroglial stem or progenitor cells and primarily develop within the glial tissues of the brain. They can manifest anywhere throughout the central nervous system and are histologically classified into astrocytic, oligodendroglial or ependymal categories. Additionally, they are assigned WHO grades I to IV, which reflect their varying degrees of malignancy [120]. Among these several types, glioblastoma multiforme (GBM) represents the most aggressive form of astrocytic tumours, characterised by poorly differentiated neoplastic astrocytes [121].

CBNs have shown particular relevance in glioma research. Markovic et al. demonstrated that CDs, when photoexcited with blue light (470 nm), generate ROS, including singlet oxygen (1O2), which induce oxidative stress and lead to programmed cell death in U251 glioblastoma cells. Treatment with CDs or blue light alone did not significantly affect cell viability, but their combination effectively caused cytotoxicity. This effect involves dual pathways: apoptosis, evidenced by phosphatidylserine externalisation, caspase activation, and DNA fragmentation, and autophagy, indicated by LC3-I/LC3-II conversion and p62 degradation [122].

Qi et al. developed a controllable surface hydroxyl concentration for the PS CN11, addressing its limitations in hydrophilicity and dispersion. This modification significantly increased the availability of reaction sites and enhanced the occurrence of n-to-π* electron transitions, thereby improving the material's photodynamic properties. In comparison with graphitic carbon nitride (g-$C_3N_4$), CN11 exhibited a 4.6-fold increase in hydrogen peroxide production and a 2.43-fold improvement in PDT efficacy against murine glioblastoma GL261 cells under visible light irradiation. *In vitro* studies demonstrated that CN11 generated a broad spectrum of ROS (H2O2, ·OH, ·O2−, 1O2), resulting in significant tumour cell death while maintaining high biosafety [123].

In GBM, CD133 + cells exhibit cancer stem cell-like properties, including the ability to self-renew and initiate tumour formation. These cells are thought to drive tumour progression, therapy resistance, and recurrence. Wang et al. used SWNTs conjugated to an anti-CD133 monoclonal antibody to investigate the phototherapy against CD133. CD133 + cells, known for their tumorigenic potential and resistance to conventional therapies, were selectively targeted using this approach. Upon NIR laser irradiation, SWNTs induced localised hyperthermia, effectively eliminating CD133 + cells without affecting CD133 − or normal cells. This selective cytotoxicity was confirmed through *in vitro* assays, where GBM-CD133 + cells exhibited significant reductions in self-renewal, migration, and spheroid formation. Furthermore, *in vivo* experiments demonstrated that CD133 + cells treated with SWNTs and irradiated by NIR lasers lost tumorigenic capability in xenografted mouse models [124,125].

### 5.4. Toxicological considerations of CBNs in cancer therapy

While CBNs show great promise in cancer therapy, understanding their toxicological profile is crucial for safe and effective clinical translation. This section discusses the key toxicity mechanisms, factors influencing toxicity, recent advances in mitigation strategies, and the impact on biological processes.

CBNs have shown significant potential in various applications, but their toxicological effects remain a crucial concern. The toxicity of CBNs is influenced by multiple factors such as their physicochemical properties, surface functionalisation, dose, exposure duration, and the specific cell types or tissues involved [11]. For instance, graphene nanoparticles (GNPs) have been found to exhibit stronger toxicity than MWCNTs at lower concentrations, though this effect may reverse at higher concentrations [126]. CBNs can induce toxicity through multiple mechanisms, impacting cellular health and immune responses. One primary pathway is oxidative stress, where CBNs generate reactive oxygen species (ROSs), leading to cellular damage. For example, MWCNTs have been shown to increase ROS production in human lung epithelial cells, contributing to oxidative injury [127,128]. Additionally, CBNs can trigger inflammatory responses by stimulating the release of pro-inflammatory cytokines. A study demonstrated that exposure to carbon-based nanomaterials led to the secretion of pro-inflammatory cytokines IL-6 and TNF-α in macrophages after 24 and 48 h of exposure [129].

Additionally, research has shown that carbon nanotubes can induce the release of the pro-inflammatory cytokine IL-1β through activation of the NLRP3 inflammasome [129]. These findings suggest that CBNs can potentially exacerbate inflammation through cytokine production. Moreover, some CBNs impair phagocytic function in immune cells, which may lead to granuloma formation and hinder immune clearance. Another major concern is genotoxicity, as certain CBNs have been associated with DNA damage and chromosomal aberrations. Patlolla et al. reported that MWCNTs can induce such genetic alterations, raising concerns about their long-term biological effects [130]. Understanding these toxicological mechanisms is crucial for developing safer CBN-based applications in biomedical settings.

Recent research has focused on developing strategies to mitigate CBN toxicity, including surface modifications to improve biocompatibility and the development of biodegradable CBNs. For example, a study demonstrated that PEGylation of graphene oxide reduced its cytotoxicity and improved biocompatibility [131]. Additionally, research has explored the development of degradable carbon nanomaterials, such as oxidised carbon nanotubes that can be broken down by peroxidases [132]. However, the long-term effects of CBNs on biological processes such as metabolism, degradation, and potential impacts on reproduction and development require further investigation. A study on maternal airway exposure to carbon black during gestation showed testicular toxicity and altered postnatal behaviour, renal development, and immune and genotoxic effects in offspring, highlighting the need for more research in this area [133].

## 6. *In vitro* and *in vivo* validation and testing of CBNs for phototherapy

This section explores the *in vitro* and *in vivo* validation and testing of various CBNs for PDT and PTT applications. Briefly, we will discuss biological interactions, biocompatibility and the different approaches to validate and investigate CBNs in preclinical studies *in vitro* and *in vivo*.

### 6.1. Biological interactions between CBNs and the tumour microenvironment

CBNs exhibit complex interactions with the tumour microenvironment, which can significantly impact their therapeutic efficacy in cancer treatment. One of the key aspects of these interactions is the modulation of immune responses within the TME. CBNs have been shown to influence immune cell behaviour, particularly macrophages, which play a crucial role in tumour progression and response to therapy. For instance, graphene oxide nanoparticles can modulate macrophage polarisation, potentially enhancing anti-tumour immunity by promoting the shift from tumour-promoting M2-like macrophages to tumour-suppressing M1-like phenotypes [106,134].

The hypoxic nature of the TME is another critical factor that affects CBN performance. Some CBNs have been specifically designed to respond to hypoxic conditions, enhancing their therapeutic efficacy in these oxygen-deprived environments. This adaptability allows for more targeted and effective treatment strategies within the complex tumour landscape [135]. Additionally, CBNs interact with various proteins in the TME, forming protein coronas that can significantly influence their biological identity and function. These protein-CBN interactions play a crucial role in determining the nanomaterials' fate and efficacy within the tumour environment [131].

CBNs also interact with endothelial cells in the TME, potentially impacting tumour angiogenesis and vascular permeability. These interactions can have significant implications for drug delivery and overall treatment efficacy [135]. Furthermore, the acidic nature of the TME can influence CBN behaviour, and some CBNs have been engineered to respond to low pH, enabling targeted drug release in these specific conditions [136]. Lastly, CBNs may affect vascular structure and function within the TME, which can impact drug delivery and treatment efficacy. Understanding and leveraging these complex interactions between CBNs and the TME is crucial for developing more effective cancer therapies and overcoming the challenges posed by the tumour microenvironment [135,137].

### 6.2. Biocompatibility and safety considerations

Improving the biocompatibility and safety of CBNs is a critical step towards their successful clinical translation in cancer therapy. Recent advances have focused on enhancing the safety profiles of CBNs through various surface modification strategies. For instance, functionalisation with biocompatible polymers or biomolecules has been shown to reduce toxicity and improve the overall biocompatibility of CBNs [138]. These modifications not only enhance the dispersibility of CBNs in biological media but also can provide additional functionalities, such as targeted drug delivery or improved cellular uptake.

The development of biodegradable CBNs represents another promising approach to address long-term safety concerns. Researchers have explored methods to design CBNs that can be broken down by biological systems, potentially reducing the risk of accumulation and associated toxicity [139]. For example, oxidised carbon nanotubes are degradable by peroxidases, offering a pathway for their eventual elimination from the body.

However, despite these advancements, there remains a crucial need for comprehensive long-term studies to fully understand the effects of CBNs on biological processes. The potential impacts on metabolism, degradation pathways, and reproductive or developmental processes are areas that require further investigation [131,138]. These studies are essential to ensure the safety of CBNs for clinical use, as the long-term consequences of exposure to these materials are not yet fully understood.

The complex interactions between CBNs and the tumour microenvironment (TME) play a significant role in determining their therapeutic efficacy and potential side effects. Understanding these interactions is crucial for optimising the use of CBNs in cancer treatment. For instance, the ability of CBNs to modulate immune responses within the TME could be leveraged to enhance anti-tumour immunity [138]. Additionally, the unique properties of CBNs, such as their response to hypoxic conditions or their interactions with tumour vasculature, offer opportunities for developing more targeted and effective cancer therapies.

Future research in this field should focus on elucidating the intricate relationships between CBNs and various components of the TME. This includes studying their interactions with immune cells, tumour cells, and the extracellular matrix. By gaining a deeper understanding of these processes, researchers can develop strategies to maximise the therapeutic potential of CBNs while minimising their adverse effects [140]. This may involve designing CBNs with specific surface properties to enhance their accumulation in tumours or developing combination therapies that leverage the unique capabilities of CBNs to improve overall treatment outcomes. In conclusion, while CBNs hold significant potential for cancer therapy, their clinical success depends on overcoming challenges related to biocompatibility and safety. Ongoing research into surface modifications, biodegradability, and long-term biological effects will be crucial in realising the full potential of these materials in cancer treatment [141,142].

### 6.3. In vitro investigation of CBNs for phototherapy

*In vitro* studies of CBNs for phototherapy applications typically begin with a thorough assessment of their cellular uptake and localisation [143]. This critical step provides valuable insights into how these nanomaterials interact with cells and their potential effectiveness as therapeutic agents. Researchers employ various techniques to [144,145,102], and flow cytometry [146]. These methods allow for precisely tracking nanomaterials entering cells and localising in specific subcellular compartments [147,148]. An example of such research is the work of Huang and colleagues, who investigated the cellular uptake of functionalised GO in human hepatocellular carcinoma cells (HepG-2) [149]. Their study demonstrated that GO functionalised with $Fe_1O_4$ significantly enhanced the penetration of a photosensitizer into the nucleus of HepG-2 cells. This finding is particularly important because it highlights the potential of CBNs to function as delivery vehicles for photosensitizers, improving their intracellular distribution and, consequently, the efficacy of photodynamic therapy. The ability of functionalised GO to facilitate nuclear localisation of the photosensitizer suggests that it can overcome cellular barriers that typically limit the effectiveness of phototherapy agents.

The enhanced cellular uptake and improved intracellular localisation observed in such studies are crucial for advancing the field of phototherapy. By optimising the delivery of photosensitizers to specific subcellular targets, researchers can potentially increase the therapeutic efficacy of photodynamic and photothermal treatments while minimising off-target effects. Furthermore, understanding the mechanisms of cellular uptake and intracellular trafficking of CBNs allows for the rational design of more effective nanocarriers, tailored to specific cancer types or cellular targets. This knowledge can lead to the development of more potent and selective phototherapy strategies, improving outcomes for cancer patients [150,151,152].

#### 6.3.1. Molecular interactions, cellular interactions

As discussed, CBNs have emerged as promising agents for phototherapy due to their unique structural and physicochemical properties. At the molecular level, CBNs interact with various biomolecules through

mechanisms such as π-π stacking, hydrophobic interactions, and electrostatic forces. For instance, graphene oxide (GO) can efficiently load photosensitizers like mTHPC through π-π stacking, enhancing their delivery to cancer cells8. The surface functionalisation of CBNs plays a crucial role in these interactions, with modifications like PEGylation altering their opsonisation and subsequent cellular interactions [153]. At the cellular level, the uptake and localisation of CBNs are critical factors determining their efficacy in phototherapy [154]. The internalisation of CBNs is influenced by their size, shape, and surface properties. For example, Arnida et al. demonstrated that PEGylated gold nanorods accumulated less in murine macrophages than nanospheres, affecting their circulation time *in vivo* [155]. CBN uptake mechanism of CBNs can vary, with some materials internalised via clathrin-mediated endocytosis (CME) and others through caveolae-mediated pathways. Surface charge has been shown to have a dominant effect on both the uptake mechanism and intracellular fate of nanoparticles [146].

### 6.4. *In vivo testing*

*In vivo* studies of CBNs for phototherapy applications typically begin with a comprehensive assessment of their biodistribution and pharmacokinetics. These evaluations are crucial for understanding how CBNs interact with biological systems and accumulate in target tissues. Researchers employ various imaging techniques to track the movement and accumulation of CBNs in tumours and other organs over time. For instance, fluorescence imaging has been used to detect Ce6-conjugated carbon dots *in vivo*, demonstrating enhanced fluorescence detection compared to Ce6 alone [149]. Similarly, radiolabelling techniques have been utilised to track the biodistribution of PEGylated hydrophilic carbon clusters, showing primary accumulation in the liver and spleen [156].

The pharmacokinetic profile of CBNs is another critical aspect of *in vivo* evaluation. Studies have shown that the blood circulation time and organ distribution of CBNs can vary significantly depending on their size, shape, and surface functionalisation. For example, PEGylated gold nanorods have demonstrated longer circulation times compared to nanospheres, affecting their accumulation in target tissues [153]. The clearance of CBNs from the bloodstream is often rapid, with studies showing that more than 95 % of injected doses can be eliminated from circulation within one hour [157]. This rapid clearance highlights the importance of optimising CBN design to enhance their therapeutic efficacy and minimise off-target effects.

The biodistribution of CBNs is heavily influenced by the reticuloendothelial system, with significant accumulation often observed in the liver and spleen. For instance, studies have shown that up to 50 % of injected doses of certain CBNs can accumulate in the liver within two weeks of administration16. However, the biodistribution can be modulated through surface modifications and targeting strategies. Active targeting approaches, such as functionalising CBNs with folate for cancer-specific delivery, have shown promise in enhancing tumour accumulation and reducing off-target effects5. Additionally, the formation of protein coronas on CBN surfaces in biological environments can significantly impact their biodistribution, pharmacokinetics, and cellular uptake, emphasising the need for careful consideration of these factors in CBN design for *in vivo* applications [155,131].

Besides, the ability of CBNs to selectively accumulate in tumours is crucial for effective phototherapy. Studies have demonstrated that CBNs can leverage both passive and active targeting strategies to enhance their accumulation in tumour tissues. Passive targeting primarily relies on the EPR effect, a phenomenon unique to solid tumours characterised by leaky vasculature and impaired lymphatic drainage [153,155]. This effect allows nanoparticles to accumulate preferentially in tumour tissues compared to normal tissues. For instance, PEGylated hydrophilic carbon clusters (PEG-HCCs) have shown effective tumour accumulation and drug delivery capabilities in an orthotopic murine model of oral squamous cell carcinoma [145].

Active targeting strategies involve functionalising CBNs with specific ligands that can recognise and bind to overexpressed receptors or other biomolecules on cancer cells. This approach aims to enhance the specificity and cellular uptake of CBNs in tumour tissues. Various targeting moieties have been explored, including antibodies, peptides, aptamers, and small molecules [158,159]. For example, graphene oxide functionalised with folic acid has demonstrated enhanced uptake in folate receptor-positive cancer cells [149]. Similarly, carbon dots conjugated with hyaluronic acid have shown improved targeting and accumulation in CD44-overexpressing tumours [160]. The combination of passive and active targeting strategies can significantly improve the therapeutic efficacy of CBN-based phototherapy. By optimising the size, shape, and surface properties of CBNs, researchers can enhance their circulation time and tumour accumulation via the EPR effect [156]. Simultaneously, the incorporation of targeting ligands can facilitate cellular internalisation and retention within the tumour microenvironment [161]. This dual-targeting approach has shown promise in various preclinical studies, demonstrating enhanced phototherapeutic effects, and reduced off-target toxicity. As research in this field progresses, developing more sophisticated targeting strategies for CBNs is expected to improve the efficacy and safety of cancer phototherapy.

### 6.5. *In vivo holistic evaluation of multimodal efficacy*

While the phototherapeutic efficacy of monotherapies has been studied more thoroughly, there are also examples of comprehensive studies that have reported NIR-responsive CBNs facilitating multiple phototherapeutic modes such as local hyperthermia (PTT) and singlet oxygen generation (PDT) in tandem. Each *in vivo* study in this section underscores the potential of CBNs to advance multimodal phototherapy with compact, readily functionalised nanostructures.

Graphene-family nanomaterials such as GO have been widely explored as platforms to integrate PTT and PDT. In *in vivo* cancer models, these materials enable simultaneous tumour heating and ROS generation, leading to enhanced efficacy over single-modality treatments. For example, a folate-targeted GO-PEG-FA was used for bimodal PTT/PDT against melanoma, yielding synergistic tumour ablation and significantly extended survival in mice (average $>$ 30 days, $\sim$1.8 $\times$ longer than chemotherapy alone) [162]. Another study demonstrated a GO carrying indocyanine green (ICG) as the NIR photosensitizer and a fluorescent tag allowing for tumour imaging and combined phototherapy; this theranostic GO achieved effective tumour growth suppression with concurrent PTT and PDT under 808 nm laser irradiation [163]. Covalent loading of traditional photosensitizers such as chlorin e6 or methylene blue onto GO sheets, has also yielded enhanced tumour regression when PTT and PDT were applied together, compared to either therapy alone [164]..

CNDs have been implemented in various *in vivo* studies serving as single-platform PDT/PTT agents. Ma et al. developed nucleolus-targeting carbon dots conjugated with ICG and folic acid (CNDs-ICG-FA) that exhibit strong NIR absorption (photothermal conversion efficiency $\sim$ 34 %) and efficient ROS generation [165]. In breast cancer models, this CND nanocomplex accumulated in tumours and upon 808 nm laser exposure, produced a pronounced synergistic PTT/PDT effect, concurrently heating the tumour and inducing oxidative damage which significantly inhibited tumour growth in mice. CNTs – both SWCNTs and MWCNTs – have been utilised as hybrid phototherapeutic agents due to their strong NIR absorption (for PTT) and large surface area for photosensitizer attachment. In one representative *in vivo* study, SWCNTs were modified with a porphyrin derivative photosensitizer, enabling combined treatment in a tumour model. Wang et al. reported that such SWCNT–photosensitizer complexes achieved enhanced therapeutic outcomes in mice, attributing this to the dual mechanism and improved targeting of the nanotubes [166]. Similarly, MWCNTs loaded with the clinically used photosensitizer mTHPC (Foscan®) have been tested for dual phototherapy: under two wavelengths (650 nm to excite Foscan for

PDT, and 880 nm for CNT-mediated PTT), the nanocomposite induced efficient tumour cell death *in vivo* [167]. This multi-wavelength approach confirmed that CNT-based platforms can leverage both thermal and photochemical tumour damage. Beyond PTT/PDT alone, CNT systems are being combined with drug delivery for PCI effects. For instance, photothermal heating by CNTs can trigger release of co-loaded chemotherapeutics or disrupt endosomal membranes, while simultaneous PDT adds oxidative stress – a tandem that dramatically improves cancer cell kill rates [168].

Collectively, *in vivo* evidence across GO variants, CNDs, and CNTs consistently shows that multimodal approaches indeed yield synergistic therapeutic effects. Combination phototherapy addresses the shortcomings of each individual modality, and the result is often more complete tumour destruction and improved survival outcomes compared to single-mode treatment. Many of the cited studies report significantly enhanced tumour regression, higher apoptosis rates, or extended animal survival when using dual-mode CBNs, underscoring the therapeutic synergy.

### 6.6. Clinical translation of CBNs in phototherapy

The use of CBNs for phototherapeutic cancer treatment remains largely in preclinical stages, with only a few pioneering clinical investigations. To date, there are no completed human trials specifically using CNTs or graphene-based CBNs for photothermal or photodynamic therapy – a clear translational gap noted in the literature [93]. Nonetheless, some early clinical efforts provide optimism. For example, a carbon nanoparticle suspension injection (CNSI) approved for lymph-node mapping in cancer surgery (NCT06048367) has been proposed for off-label photothermal ablation. In preclinical models of thyroid carcinoma, CNSI (trade name 'Canarine') showed efficient NIR absorption and completely halted tumour growth when laser-activated, with treated tumours eradicated without recurrence over three months [169]. The use of CNTs in cancer treatment has been investigated in pioneering trials such as NCT02328352, demonstrating that even at early phases, there is clinical interest in exploring the safety and efficacy of nanotube-based therapies. Additionally, the trial NCT02698163 further underscores the ongoing efforts that will aid the evaluation of biodistribution, toxicity, and therapeutic outcomes of CBN-based interventions in oncology. These studies, although preliminary, indicate that the integration of CBNs into clinical protocols is not only feasible but also aligns with the broader trend of nanotechnology-based approaches that have successfully reached later-stage clinical trials, such as gold nanoshell photothermal therapy. These results suggest that clinically-used CBN formulations could be repurposed as photothermal agents. Apart from such off-label explorations, most ongoing clinical phototherapy trials have utilised other nanomaterials, with CBNs expected to enter trials once safety concerns are addressed.

Encouragingly, the road to clinical adoption of nanophototherapy has been paved by other nanomaterials, suggesting that CBNs could be the next logical step. Gold nanoparticles in particular have achieved significant clinical progress in phototherapy. A prime example is AuroShell® silica–gold nanoshell technology which are PEG-coated gold nanoshells that convert NIR light to heat. This platform has undergone multiple clinical trials for photothermal ablation of tumours [170]. In Phase I studies on solid tumours (refractory head and neck cancers and lung metastases), systemically administered gold nanoshells followed by fibre-optic laser irradiation were able to produce targeted tumour heating. Although early trials saw some side effects in heavily pretreated patients, refinements in particle design and delivery led to improved outcomes in prostate cancer. A recent pilot in men with low-risk prostate tumours demonstrated successful focal laser ablation using gold nanoshells, with 94 % of treated tumours ablated and no significant adverse events or organ damage observed [170]. Notably, at 1-year follow-up, patients showed no device-related toxicities, underscoring the *feasibility and safety* of nanoparticle-mediated phototherapy in humans [171]. Other inorganic nanoplatforms have entered trials. Silica-based nanoparticles as cores or matrices for photothermal agents have been used in clinical imaging and drug delivery. For example, ultrasmall silica 'C-dots' were safely used in a Phase I trial as tumour imaging agents, hinting at their potential for phototherapy (NCT03465618). Similarly, iron oxide nanoparticles (though employed in magnetic hyperthermia rather than optical therapy) are approved in Europe for thermoablation of brain tumours, validating the concept of nanoparticle heat induction in oncology. Even traditional photodynamic therapy has benefited from nanoparticle carriers – liposomal photosensitizers like Visudyne® are FDA-approved, and antibody–dye conjugates such as IRDye-700DX linked to cetuximab have reached Phase III trials in head & neck cancer. These successes illustrate that nanotechnology-enhanced phototherapy is nearing mainstream clinical adoption. Within this context, carbon-based nanomaterials stand out as the next wave.

## 7. Machine learning for nanoparticles: Advancing materials discovery research and applications

As has been briefly demonstrated in this review, nanotechnology has transformed biomedicine in many ways, where nanoparticles are extensively used for drug delivery, diagnostics, and therapy. The emergence of nanotechnologies and nanoplatforms reviewed here has occurred in tandem with major developments in cancer phototherapy, but also in computational biology and data-driven materials science (Fig. 3). As we have discussed, CBNs possess unique physicochemical properties such as tuneable size, shape, surface charge, and chemical composition, which make them suitable for applications ranging from molecular imaging to targeted therapeutics. Despite these advancements, the complex interplay between nanoparticle properties and biological systems presents challenges in their design and application. Machine learning (ML), a data-driven computational tool, has emerged as a powerful approach to address these challenges, enabling efficient modelling, optimisation, and prediction of nanoparticle behaviour. In this section we will study a few examples of ML utilisation in CBNs and more broadly nanomaterials design, characterisation and functional evaluation.

### 7.1. The role of ML in nanoparticle design

Nanoparticle design often involves synthesising particles with specific properties such as size, surface functionalisation, and drug encapsulation efficiency. This process is highly iterative and resource-intensive, typically guided by trial-and-error experimentation. ML algorithms streamline this process by identifying patterns in large datasets, allowing researchers to predict outcomes and optimise experimental parameters. For instance, ML methods like neural networks and random forests are frequently applied to predict the size and polydispersity index (PDI) of nanoparticles based on variables such as temperature, sonication time, and composition [172]. These models provide actionable insights into optimal conditions, significantly reducing experimental efforts. In addition, ML-guided synthesis enables precise control over nanoparticle morphology, essential for tailoring their functionality. Recent studies have demonstrated the use of supervised learning algorithms to optimise reaction conditions, such as reagent concentration and reaction time, achieving desired particle sizes and surface characteristics [173]. For instance, ML methods have accelerated the fabrication and biological application of CNDs, making these nanomaterials more accessible for biomedical uses [174].

#### 7.1.1. Accelerating nanoparticle synthesis

One of the most resource-intensive aspects of nanoparticle research is identifying the synthesis parameters associated with specific particle characteristics and properties. Traditional synthesis methods often involve numerous iterations to identify optimal processing conditions. ML has revolutionised this process by modelling the relationships

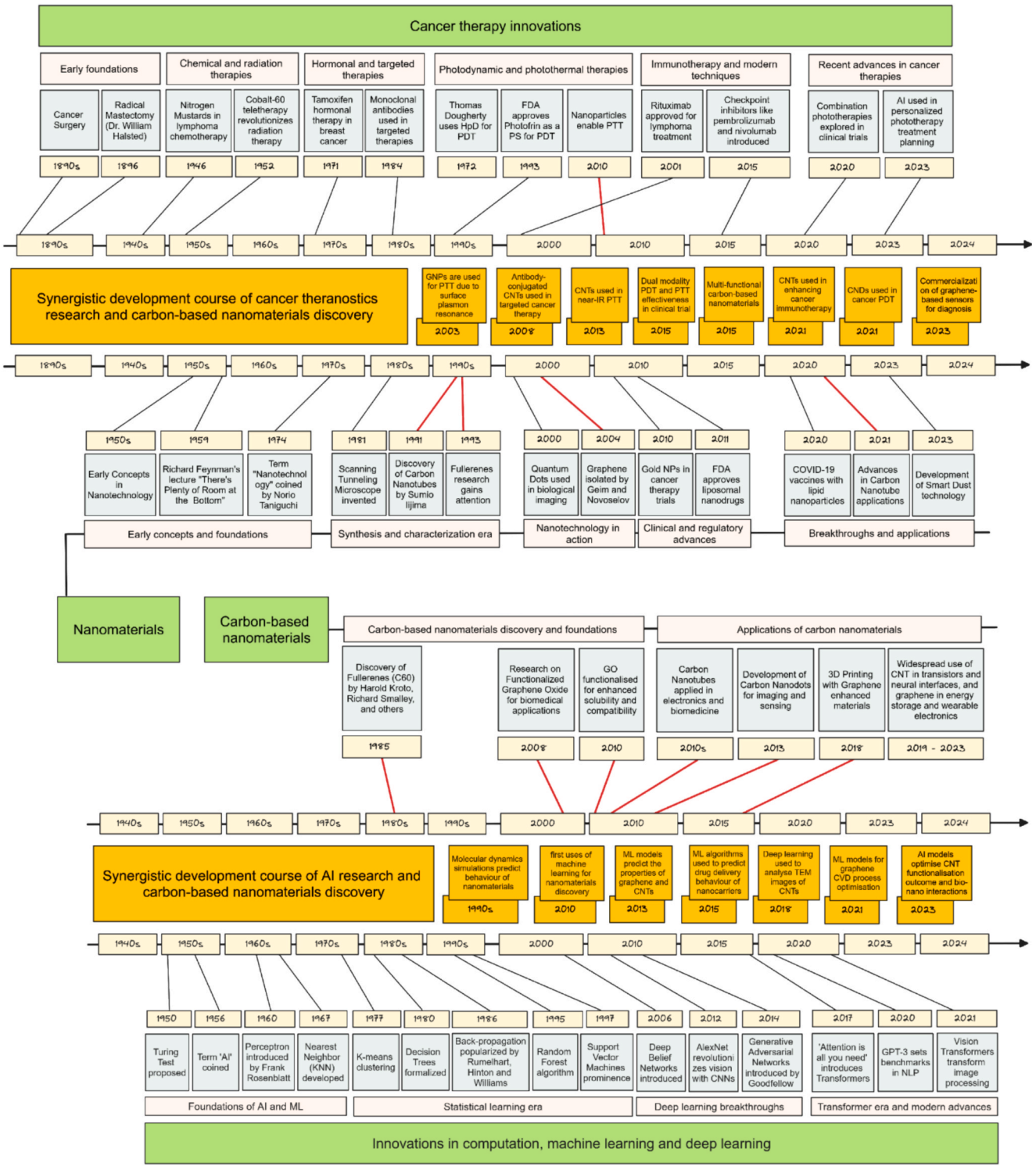


**Fig. 3.** The co-development of technologies, platforms and innovations in cancer therapy, nanomaterials, and machine learning. Orange blocks represent the key technologies enabled by the fusion of these technologies with a CBM focus.

between input parameters (e.g., reagent type and reaction conditions) and output properties (e.g., particle size and shape) [173]. Supervised learning algorithms, such as support vector machines and gradient boosting, have been employed to predict synthesis outcomes, enabling researchers to focus on the most promising experimental conditions. The role of ML in optimising carbon dot fabrication underscores its potential to enhance accessibility and reduce production complexity [174]. In addition to predicting outcomes, ML algorithms are used to guide experimental planning. Active learning techniques prioritise data collection efforts by identifying the most informative experiments, further reducing resource consumption while maximising knowledge gain [173].

### 7.2. Predicting biomedical and therapeutic efficacy

#### 7.2.1. Cellular uptake and internalisation

The efficacy of nanoparticles in biomedical applications largely depends on their ability to interact with and penetrate target cells. Cellular uptake is influenced by factors such as surface charge, hydrophobicity, and the presence of targeting ligands. ML models, particularly regression algorithms and neural networks, are widely used to predict cellular internalisation rates based on these features. For instance, hydrophobically modified polyethyleneimine (PEI) nanoparticles designed for RNA delivery demonstrated enhanced uptake when optimised using ML [175]. Such predictions enable researchers to fine-tune nanoparticle properties to improve therapeutic efficacy and minimise off-target effects. Furthermore, ML models can classify cancer cell types based on their interactions with nanoparticles, facilitating precision medicine approaches. By leveraging datasets of cellular responses, ML algorithms have achieved high accuracy in distinguishing TNBC cells from other subtypes, providing critical insights into nanoparticle-based diagnostic platforms [176].

#### 7.2.2. Drug delivery performance

Nanoparticles are integral to modern drug delivery systems, offering targeted delivery and controlled release of therapeutic agents. ML-based models play a crucial role in optimising the parameters governing drug delivery, such as nanoparticle size, surface charge, and drug encapsulation efficiency. For example, ensemble learning approaches have been used to model the effects of independent factors like extrusion temperature and sonication time on liposomal nanoparticle formulations [172]. These models enable precise control over particle size and PDI, critical determinants of nanoparticle stability and bioavailability. Additionally, integrating ML with nanotechnology enhances cancer detection and therapeutic precision. Gold nanoparticles (GNPs) as well as CNTs, owing to their optical properties, are widely used in imaging and PTT. ML algorithms, including artificial neural networks, have improved nanoparticle design for optimised tumour targeting and detection, enabling personalised therapies based on patient-specific data [177]. For instance, ML tools can analyse biological datasets to design nanoparticles tailored for drug delivery in complex tumour environments, thus enhancing treatment efficacy and minimising side effects.

### 7.3. Advancing cancer nanomedicine

Cancer remains one of the most challenging diseases to treat, with conventional therapies often limited by toxicity and lack of specificity. Nanoparticle-based drug delivery offers a promising alternative, and ML has become indispensable in its optimisation. Predictive models have been developed to evaluate the efficiency of nanoparticle delivery to tumours, considering factors such as the EPR effect and specific targeting strategies [178,179]. For example, ML models have identified zeta potential and core material as critical features influencing delivery efficiency, enabling the design of nanoparticles with improved targeting capabilities [179]. Moreover, ML facilitates the integration of physiologically based pharmacokinetic (PBPK) modelling with nanoparticle design, providing insights into drug biodistribution and clearance. By combining experimental data with computational simulations, ML-based frameworks have successfully predicted nanoparticle behaviour *in vivo*, paving the way for personalised cancer therapies [178].

#### 7.3.1. Precision diagnostics using nanoparticles

Nanoparticles are also valuable in diagnostics, particularly for diseases with high heterogeneity like cancer. ML techniques, such as pattern recognition algorithms, have been applied to classify patient samples based on their interaction with diagnostic nanoparticles. For instance, ML models analysing carbon nanoparticle interactions with breast cancer cells achieved diagnostic accuracies exceeding 98 %, demonstrating their potential for clinical applications [176]. Additionally, ML-driven insights into nanoparticle interactions with biological systems contribute to the development of biosensors and imaging agents. By correlating nanoparticle properties with diagnostic performance, these models enable the design of more effective diagnostic tools.

#### 7.3.2. Nanotechnology and ML in phototherapy

As we have seen, PDT employs photosensitizers activated by specific wavelengths of light to generate ROS, leading to cancer cell death. Magnetic nanoparticles, owing to their excellent magnetic and optical properties, are used in PTT and PDT to enhance therapeutic outcomes. ML algorithms optimise parameters such as laser intensity, photosensitizer concentration, and nanoparticle configuration for tailored treatments [180,181]. Magnetic nanoparticles are also integrated into central nervous system (CNS) therapeutics, leveraging their ability to cross the blood–brain barrier. ML models predict optimal nanoparticle features for brain-targeted delivery, including particle size, coating type, and magnetic responsiveness. This approach is particularly beneficial for diseases like Alzheimer's and Parkinson's, where targeted treatment remains a challenge.

The integration of machine learning into nanoparticle research has significantly advanced the field by enabling predictive modelling, optimisation, and efficient experimental design. From enhancing drug delivery systems to advancing cancer diagnostics, ML continues to play a transformative role in the development of nanoparticle-based technologies (Table 3). As datasets grow and algorithms improve, the potential for ML to address complex challenges in nanotechnology will only expand, driving innovation and accelerating progress in biomedicine. The studies outlined here represent the niche space of CBNs which is growing in size and popularity. Further inspiration is driven from other nanomaterial systems studied so fat as outlined in Table 3 below.

## 8. Conclusions and future perspectives

Carbon-based nanomaterials have emerged as one of the most versatile platforms for advancing cancer therapies, particularly in the realm of phototherapeutics. This review highlighted the unprecedented opportunities provided by CBNs in enhancing PTT, PDT, PAT, and other synergistic multimodal approaches as evidenced by a large array of preclinical *in vitro* and *in vivo* studies and early clinical trials. The unique structural, optical, and physicochemical properties of CBNs—ranging from carbon nanotubes and graphene oxide to carbon dots and nanosheets—offer unmatched precision in light absorption, energy conversion, and tumour-specific targeting. These materials have demonstrated significant promise in preclinical studies for their ability to deliver localised therapeutic effects with minimal off-target impacts. This section critically examines the clinical gap and proposes steps to bridge them.

### 8.1. Long-term effects, bio-accumulation and retrieval of CBNs

Despite the impressive developments made to date in CBN research, significant challenges remain. Biocompatibility and long-term biosafety are critical concerns that need rigorous exploration, particularly as these materials transition from animal testing to clinical trials. The use of *in vitro* chip-based and 3D printed models to explore the performance of these platforms in the proximity of human cancer cell lines, has been surprisingly extremely limited. These geometrically, and chemically complex environments can provide unparalleled insights towards the temporal evolution of events. Reproducibility in the synthesis of nanostructures and scalability for manufacturing are equally pressing, as they directly impact the efficacy, cost, and accessibility of CBN-based phototherapies. The degradation and clearance profiles of these nanostructures *in vivo* has been studied very briefly, also requires rigorous characterisation to ensure their safety and efficacy over extended durations. Regulators are especially wary of how and if the body can

**Table 3**
Examples of recent computational biological studies focusing on various nanostructures, chemical compositions, and interactions of interest.

| Structure | Chemistry | Therapy | Interaction studied | Data-Driven Approach | Biological Experiment | Reference |
|---|---|---|---|---|---|---|
| Nano ribbon | Gold, Silica | PTT | Structural optimisation for enhanced PTT conversion efficiency | Supervised ML models (e.g., RF, SVM) | *In vivo* testing on mice: efficacy in ablation | ML predicting optimal preparation of silica-coated gold nanorods for photothermal ablation. [182] |
| Nanosheet | rGO and Metal ions (Co, Fe, Cu, Ce) | NA | Interactions of various gases (acetone, isoprene, ammonia) | IBM SPSS for stat. analyses, PCA and LDA pattern recognition ANN classification | EB analysis from volunteers for lung cancer diagnosis using a sensor array to detect specific biomarkers | Constructing an E-Nose Using Metal-Ion-Induced Assembly of Graphene Oxide for Diagnosis of Lung Cancer via Exhaled Breath. [183] |
| Nanodot | CND | NA | Interactions of CNDs with metal ions (Co2 + and Fe3 + ) | Active Adaptive Method with machine learning | Used in dental diagnosis, treatment, early caries detection, remineralisation therapies. | Expediting CND synthesis by the active adaptive method with ML and applications in dental diagnosis and treatment. [184] |
| Nanodot | CND functionalised with boron and nitrogen | NA | Optimisation of synthesis parameters for enhanced fluorescence intensity | ML models (e.g., polynomial regression, random forest) | *In vivo* validation using Wistar rats to monitor fluorescence behaviour after intravenous injection | Graphene Quantum Dots with Improved Fluorescence Activity via ML: Implications for Fluorescence Monitoring. [185] |
| Nanotube | CNT; Aryl groups; Diazonium chemistry | NA | Interaction of OCC-DNA nano-sensors with serum biomarkers | ML (e.g., SVM) | Serum analysis for ovarian cancer detection | Detection of ovarian cancer via spectral fingerprinting of quantum-defect-modified CNTs in serum by ML. [186] |
| Nanotube | SWCNTs functionalised with ssDNA | NA | Protein adsorption dynamics influenced by surface properties of SWCNTs | Supervised learning (Random Forest Classifier) | Validation of adsorption predictions using (LC-MS/MS) and corona exchange | Supervised learning model predicts protein adsorption to carbon nanotubes. [187] |
| Nano particle mixture | Various NPs (metallic, polymeric, liposomal) | NA | Protein corona formation on nanoparticles and subsequent cellular interactions. | ML (e.g., RF) | Validation through proteomics and cellular uptake studies | ML predicts the composition of the protein corona and cellular recognition of nanoparticles. [188] |
| Nanotube | MWCNTs with systematically reduced oxygen functional groups | NA | Interaction of MWNTs with embryonic zebrafish (surface charge-related mortality) | Statistical modelling (e.g., Logistic regression model) | Toxicity testing on zebrafish embryos to determine the lethal and sub-lethal impacts of MWNTs | Toward safer MWCNT design: establishing a statistical model that relates surface charge and embryonic zebrafish mortality. [189] |
| Nanodot | CND | NA | Prediction and control of optical properties such as FL colour and excitation dependence for enhanced bioimaging | Supervised learning (e.g., RF, Gradient Boosting) | Deep Convolutional Neural Network (DCNN) | Exploiting deep learning for predictable carbon dot design. [190] |
| Nanodot | CD | NA | Integration of CND with biological systems for imaging and therapy. Optimisation of biocompatibility, and binding specificity | ML models (e.g., XGBoost, logistic regression, PCA) | *In vivo* studies on bioimaging, pH monitoring, FL-based bacterial tracking in Gram-positive or negative systems | Utilising ML to expedite the fabrication and biological application of CNDs. [174] |
| Light-Driven Nanorobot | CHL integrated with GCS-PPy nanoparticles | PT, PS, PTH | Interaction of CHL-GCS-PPy nanorobots with the TME | AI algorithms for navigation and therapy optimisation | *In vitro* and *in vivo* testing for bladder cancer treatment efficacy | Light-Driven, Green-Fabricated AI-Enabled Nanorobots for Multimodal Phototherapeutic Management of Bladder Cancer. [191] |
| Nano particle mixture | Gold, Meta- mTHPC | PTT + PDT | Prediction of optimal phototherapy parameters e.g., laser power, wavelength, exposure time | ML (regression, interpolation, analytical function fitting) | *In vitro* neuroblastoma SH-SY5Y cell treatment using AuNP-mTHPC with PDT and PTT | A predictive model for personalisation of nanotechnology-based phototherapy in cancer treatment. [192] |
| Nanotube | MWCNT | NA | MWCNTs interactions with biological systems that could lead to DNA damage or other toxic effects | ML modelling (e.g., Random Forest, Logistic Regression) | *In vivo* (DNA strand breaks via Comet assay) *in vitro* (gene mutation assessment via micronucleus test) | Machine learning methods for MWCNT genotoxicity prediction. [193] |
| Nano particle (other) | Gold chloride and TDTAA | PDT | Dynamic effects of PDT on cancer cells e.g., morphological changes, circularity, and curvature | Deep learning (Cell pose algorithm for segmentation) | PDT treatment on HepG2 hepatocellular carcinoma cells | Deep Learning Insights into the Dynamic Effects of Photodynamic Therapy on Cancer Cells. [194] |
| Nanotube | Oxidised CNT (–OH and –COOH) | NA | Effect of pristine and oxidised CNTs on mitochondrial respiration, oxygen consumption, proton gradient disruption, and ATP synthesis | Nano-QSPR modelling using Raman spectroscopy, ML algorithms | *In vitro* assays using isolated rat liver mitochondria | Experimental–computational study of CNT effects on mitochondrial respiration: *In silico* nano-QSPR ML models based on new Raman spectra [195] |
| Nanotube | MWCNT Pristine, –OH, –COOH and $–NH_2$ | NA | Genotoxicity assessment focusing on DNA damage and mutagenicity by physicochemical properties of MWCNTs | Ensemble super learning (RF, Gradient Boosting, SVM) | *In vitro* (e.g., Comet assay, micronucleus test), *in vivo* toxicity profiling studies | Ensemble super learner-based genotoxicity prediction of MWCNT. [196] |
| Nanotube | MWCNT functionalised with mTHPC | PTT + PDT | Mechanistic constructive collaboration between PDT and PTT effects causing mitochondrial damage, ROS generation, and oxidative stress leading to apoptosis | Genomic and proteomic analysis of oxidative stress pathways and apoptosis-related proteins | *In vitro* studies using SKOV3 ovarian cancer cells (cell viability assays, flow cytometry, microscopy, and molecular analyses) | Synergic mechanisms of photothermal and photodynamic therapies mediated by photosensitizer/carbon nanotube complexes. [197] |

(*continued on next page*)

**Table 3** (*continued*)

| Structure | Chemistry | Therapy | Interaction studied | Data-Driven Approach | Biological Experiment | Reference |
|---|---|---|---|---|---|---|
| Nanotube | Carbon, Boron-Nitride, Silicon-Carbide nanotubes functionalised with azacitidine | NA | Azacitidine Encapsulation efficiency and binding mechanisms in nanotube cavities through adsorption energies and charge transfer | Density Functional Theory (DFT), Molecular Dynamics (MD) simulations | *In silico* study, no experimental validation included | Comparative study of the efficiency of silicon carbide, boron nitride and carbon nanotube to deliver cancerous drug, azacitidine: A DFT study. [198] |
| Nanotube | CNT | NA | Interaction of fluorouracil anticancer drug with CNTs | Computational modelling (Ab initio methods, Monte Carlo simulations) | *In silico* study, no experimental validation included | Studies of ab initio and Monte Carlo simulation on interaction of fluorouracil anticancer drug with CNT. [199] |
| Nanotube | SWCNT with functional groups, Pristine | NA | Physisorption of penicillamine drug on nanotubes; functionalisation effect on adsorption energy, solubility, and intermolecular interactions | Computational modelling (DFT and MD Simulation) | *In silico* study, no experimental validation included | Modelling the interaction between anti-cancer drug penicillamine and pristine and functionalised CNT for medical app.: DFT and MD. [200] |

eliminate CBNs. Unlike small-molecule drugs, many CBNs are not biodegradable or easily metabolised. Studies have shown that ultra-stable nanoparticles like gold or graphene can only be cleared via slow metabolic excretion, if at all [201]. Large CBNs such as micron-length CNTs or multilayer graphene often accumulate in the liver, spleen or lungs and resist breakdown [202]. Regulatory agencies thus demand evidence of either safe degradation pathways or complete long-term clearance. The volume of such data is increasing as observed broadly in this review. Enzymatic processes such as peroxidases can partially degrade graphene oxide, but it's unclear if this suffices for full clearance *in vivo*. As a result, CBN-based phototherapy agents have yet to earn FDA approval for clinical use[203].

Hence, in addition to optimising the therapeutic efficacy of CBNs in phototherapy, there is a growing research interest in developing retrievable systems to mitigate long-term toxicity. One promising avenue is the incorporation of magnetic nanoparticles into CBN-based composites. By functionalising CBNs with magnetic components, it is possible to direct and subsequently retrieve these materials using external magnetic fields to reduce the risk of chronic toxicity [204]. Another strategy involves engineering CBNs with biodegradable coatings or stimuli-responsive functional groups that promote controlled degradation *in vivo* [205]. Such design modifications are critical to addressing the persistent issue of nanoparticle accumulation, which can lead to long-term adverse effects. Future research in this direction could enable multi-phase treatment protocols, where nanoparticles first deliver the therapeutic payload to the tumour site and are subsequently removed or degraded, paving the way for more sustainable and clinically viable phototherapy platforms.

### 8.2. *Commercialisation and clinical use challenges*

Clinical implementation of CBNs in cancer phototherapy are advancing, though still relatively nascent due to regulatory challenges and the rigorous safety requirements for nanomaterials. Despite encouraging *in vitro* results, the clinical translation of CBN-based phototherapeutics faces significant hurdles. Key challenges span regulatory approval difficulties, reproducibility in synthesis, conflicting data in the literature, inadequate testing models, and complexities in combining therapies. CBN-based phototherapies are still far from regulatory approval, largely due to safety uncertainties. Nanomaterials such as GO and CNTs tend to persist in the body, raising concerns about chronic toxicity and long-term clearance [202]. Graphene derivatives in particular have shown long-term retention in organs, prompting fears of cumulative damage over time. Regulatory agencies require comprehensive toxicological profiles, yet demonstrating *complete* biocompatibility and clearance of CBNs remains difficult. Even when acute toxicity is low, any indigestible nanoparticle is scrutinised for potential latent effects. These factors contribute to a slow and cautious approval pathway.

Carbon-based platforms, such as PEGylated graphene and GO, and SWCNTs, have shown immense promise in preclinical settings for targeted drug delivery, PTT, and imaging. However, only a few products have reached the stage of clinical testing. For example, *NanotubeX* by Biocompatibles (now BTG International) explored SWCNTs for drug delivery, although regulatory constraints have slowed its progress. *AuroLase Therapy* by Nanospectra Biosciences represents one of the closest commercial examples; it uses gold-coated silica particles, paving the way for carbon-based PTT, for localised hyperthermia in solid tumours and has progressed to human trials. Furthermore, GO derivatives, licensed to companies like *Graphenea*, are marketed for research and preclinical applications, facilitating wider study of graphene-based solutions.

On the diagnostic front, CBNs are being assessed for applications in photoacoustic imaging and NIR fluorescence imaging, where their optical properties can help visualise tumours non-invasively. Companies such as *CytImmune Sciences* have pursued gold nanoparticle-based

platforms for drug delivery, with clinical trials for solid tumours, and continue to influence the potential pathways for carbon-based materials in diagnostics and treatment. Regulatory hurdles remain high for these materials, particularly concerning long-term toxicity and biodistribution. As a result, clinical translation has so far been more common in diagnostic than in therapeutic applications. The initial commercialisation and research-use-only products set a crucial precedent, paving the way for future developments in clinical applications of carbon-based nanostructures in cancer therapy.

### 8.3. Lack of standardised evaluation

There is a lack of consensus on how to evaluate CBN phototherapeutics preclinically, which complicates regulatory review. Different studies use disparate methods to measure photothermal conversion efficiency, dose, and safety, making it hard for regulators to compare results. Biological models and tracking methods vary widely, leading to inconsistent data across studies. In practice, one lab's definition of 'photothermal efficiency' or 'toxicity' may differ from another's. Without standardised metrics and reporting formats, regulators face complications assessing CBN safety and efficacy. This gap has led experts to call for common characterisation and biological testing protocols [206]. Establishing such standards is essential to accelerate clinical translation. For example, adopting a standardised data reporting format for CBN experiments would enable better comparisons of structure–property relationships and even aid predictive modelling. In summary, regulatory approval is hindered not only by toxicity concerns but also by inconsistent preclinical evidence. Addressing this requires more rigorous long-term studies and industry-wide standards for evaluating CBN-based therapeutics.

In preclinical animal studies, frameworks also vary. Tumour models can differ (subcutaneous vs. orthotopic tumours, immunocompetent vs. nude mice), and evaluation endpoints range from tumour regression to survival to systemic toxicity. Establishing standard preclinical models such as a set of common tumour types in mouse models and measurement of efficacy and biodistribution in each case would greatly aid in benchmarking CBN therapeutics. Another often overlooked issue is that *in vitro* experiments sometimes use laser powers or durations that would be unsafe *in vivo*. For instance, many *in vitro* PTT studies irradiate cells at high power densities (>5 W/cm^2) which cannot be applied to tissues in a living organism without causing burns to healthy tissue. In fact, safety standards limit clinical laser exposure to about 0.33–1 W/cm^2 (depending on wavelength) [203]. This discrepancy means some *in vitro* results are achieved under conditions that aren't clinically relevant.

### 8.4. Reproducibility and scalability

Producing CBNs with consistent properties is notoriously difficult. Small changes in synthesis parameters (temperature, precursor, reaction time) can yield batches with different sizes, surface chemistries, or impurities. This leads to batch-to-batch variability that undermines reproducibility. Two batches may differ in composition enough to affect their phototherapeutic performance. For example, planar CBNs such as GO produced in different settings can vary in layer number, lateral size, and oxidation level, which dramatically alters their behaviour in biological experiments. One cause of irreproducibility is inadequate reporting of nanomaterial characteristics. Studies sometimes lack detailed information on CBN size distribution, surface functionalisation, purity, or aggregation state. To improve reproducibility, comprehensive characterisation data (dynamic light scattering, transmission electron microscopy, Raman, XPS for graphene, TGA for purity of CNTs etc.) should be reported and ideally standardised.

Even if a CBN formulation works in the lab, scaling up production for clinical use is challenging. Methods that produce small quantities with fine control may not translate to mass production. For instance, liquid-phase exfoliation can generate GO at relatively high yield, but cannot obtain size and shape uniformity at scale. While certain routes yield high quantities of graphene, the morphology of the obtained graphene are not very uniform, synthesizing CNTs in bulk can introduce variability in length and residual catalyst content, and scaling up CND production can lead to particle aggregation or batch heterogeneity that isn't observed at small scale. These manufacturing issues hinder clinical translation because pharmaceutical production demands strict batch consistency and quality control. Continuous-flow or microreactor systems may offer better control for producing CBNs in larger volumes with uniform properties. Similarly, purification and fractionation steps can improve batch uniformity, though they add complexity. Another approach is bottom-up synthesis of carbon nanostructures in a controlled way. Additionally, adhering to Good Manufacturing Practice (GMP) standards for nanomaterials, including rigorous characterisation of each batch, will be vital. The field is gradually recognising that a successful clinical product needs not just good performance in the lab, but also a manufacturable, consistent material.

### 8.5. The future of CBNs

Looking ahead, the field is well-positioned to benefit from rapid advancements in high-throughput experimental techniques and machine learning-driven materials design. Data-driven approaches are transforming the discovery, optimisation, and testing of CBNs, enabling researchers to predict material behaviours with high precision and streamline the development of new nanoplatforms. Integrating these computational tools with experimental workflows can address challenges in synthesis variability, enhance the specificity of tumour targeting, and optimise the energy conversion modalities critical for phototherapy. Furthermore, the combination of CBNs with other therapeutic modalities, such as immunotherapy and CDT, is an exciting avenue for current and future research. Multifunctional nanoplatforms capable of delivering synergistic effects across multiple therapeutic mechanisms could redefine treatment paradigms for cancers that are resistant to conventional therapies. Innovations in photoactivation strategies, such as deeper tissue penetration via NIR-II and multi-step processes and dual-function systems for simultaneous imaging and therapy, are also expected to drive considerable progress.

Triple-negative breast cancer as a key example mentioned in this review, remains one of the most aggressive and difficult-to-treat subtypes of breast cancer due to its lack of ER, PR, and HER2 expression and its immunosuppressive tumour microenvironment. This absence of molecular targets limits the efficacy of conventional hormone and targeted therapies, leaving chemotherapy, radiotherapy, and emerging phototherapies as the primary treatment strategies. However, TNBC is characterised by high heterogeneity, metastatic potential, drug resistance, and immune evasion, necessitating innovative approaches for effective treatment. Such subtypes often exhibit MDR due to overexpression of efflux pumps, reducing intracellular drug retention. As described here, CBNs, such as GO and CNTs, enable π-π stacking and electrostatic interactions with hydrophobic chemotherapeutics (e.g., doxorubicin, paclitaxel), facilitating high drug loading capacity. Functionalised GO has been utilised as a pH-responsive drug carrier, enabling selective drug release in the acidic tumour microenvironment, thereby enhancing therapeutic efficacy while reducing systemic toxicity.

Functionalised CNTs and graphene-based nanostructures can also assist with effective penetration into tumour tissue due to their high aspect ratio and passive targeting via EPR. Also mentioned are active targeting strategies including conjugation with folic acid and hyaluronic acid for CD44-overexpressing TNBC cells, and monoclonal antibodies (e.g., anti-EGFR, anti-CD133) for selective delivery. The high glycolytic activity and mitochondrial dysfunction of such cancer cells, make them highly sensitive to hyperthermic conditions induced by PTT, which in turn enhances chemotherapy by increasing membrane permeability and drug penetration. CBNs functionalised with immune adjuvants (e.g., CpG oligonucleotides, R848, anti-CD40 antibodies) can promote

dendritic cell activation, T-cell recruitment, and macrophage repolarisation, helping to restore anti-tumour immunity. As an example, GO conjugated with immune-modulating agents has demonstrated the ability to enhance antigen presentation and reverse tumour-induced immunosuppression, offering potential for CBN-based immuno-phototherapies in TNBC.

Future research should focus on optimising CBN multifunctionality and multimodal performance through surface modifications, enhancing biocompatibility, and more thorough validation of these nanostructures in preclinical and clinical settings to further advance targeted phototherapies. The actionable steps from standardising studies to designing safer nanomaterials are clear. CBNs represent a revolutionary class of materials in the fight against cancer, with their applications extending beyond traditional boundaries of treatment. As the field evolves, interdisciplinary collaboration between material scientists, oncologists, and computational researchers will be critical to overcoming limitations and realising the full clinical potential of CBN-based phototherapeutics. By leveraging the unique capabilities of these nanostructures, we stand at the cusp of transforming cancer treatment into a more precise, effective, and patient-tailored discipline.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Data availability

No data was used for the research described in the article.

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