International Journal of Engineering Materials and Manufacture (2023) 8(4) 106-123
https://doi.org/10.26776/ijemm.08.04.2023.03

Revolutionising Cancer Diagnosis and Treatment: A Review on Advancements in Nanomaterial-based Theranostics

Merjan Jabarkhil, Ayisha S. Azizi, Syeda Z. Imam, Abdul R. Alrabbat, Khawaja D. Hasan and Muhammad H. Hasan

Received: 09 September 2023
Accepted: 26 September 2023
Published: 20 October 2023
Publisher: Deer Hill Publications

ABSTRACT
The persistent struggle against cancer has given rise to the development of nanotheranostics, a domain that integrates therapeutic and diagnostic capabilities within nanoscale structures. This paper explores advancements in nanomaterials and nanoparticles for cancer nanotheranostics, focusing on their design, significance, and applications. The incorporation of biocompatible nanoparticles in cancer therapy offers personalised, targeted approaches while minimising side effects. The use of nanomaterials such as metals, polymers, and lipids enable precise drug delivery and imaging. Various imaging modalities, including ultrasound and fluorescence, complement therapeutic strategies for enhanced precision. Critical parameters for nanomaterial selection and design are discussed, emphasising biocompatibility, targeting efficiency, and drug delivery capacity. Biocompatibility ensures safe interactions within biological systems, requiring mitigation of toxicological concerns through strategies like anti-inflammatory peptides or ligand-functionalization. Targeting efficiency combines passive and active targeting to enhance specificity, reshaping cancer diagnostics and therapy. Drug delivery capacity is achieved through engineered core-shell structures with distinct properties, including liposomes, micelles, and dendrimers, each tailored for targeted therapy and imaging. This paper also discusses the advancements in the field of cancer treatment using nanotheranostics and its economic impact on the Canadian healthcare systems while following the ethical guidelines towards patients' consent, privacy, and the proper use of emerging technologies.
Keywords: Cancer nanotheranostics, biocompatibility, drug delivery capacity, bioethics, economic impacts.

1 INTRODUCTION
1.1 Background
Cancer remains one of the most significant global health challenges, with a mortality rate that increases every year (Siddique & Chow, 2022). The pursuit of finding an effective cancer treatment has led to the development of various modalities that aim to target and eliminate cancer cells while minimising the possibility of adverse effects. Current cancer treatment modalities include surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapies (Mun et al., 2018). However, despite substantial progress, challenges persist in achieving complete eradication of cancer cells and preventing disease recurrence due to tolerability and adherence (Mun et al., 2018). Nanotheranostics is an emerging field that combines therapeutic and diagnostic functionalities within a single nanoscale system (Siddique & Chow, 2022). These nanoscale platforms have the potential to revolutionise cancer diagnosis and treatment by offering targeted drug delivery and precise imaging capabilities (Siddique & Chow, 2022).

1.2 Significance of Nanomaterials in Cancer Nanotheranostics
By integrating diagnostic and therapeutic capabilities into biocompatible nanoparticles, nanotheranostics can provide a more personalised and targeted approach to cancer therapy (Ladju et al., 2022). Biocompatible nanoparticles can be designed to identify specific biomarkers of the target cancerous region and can also serve as therapeutic or imaging agents which allow for real-time tracking and imaging of the site during treatment (Ladju et al., 2022). By using nanoparticles, targeted drug delivery becomes more precise, reducing off-target effects and damage to healthy tissue, moreover, there is a significant increase in the effectiveness and control of biodistribution thus decreasing the toxicity of drugs (Siddique & Chow, 2022).

Merjan Jabarkhil ✉, Ayisha S. Azizi, Syeda Z. Imam, Abdul R. Alrabbat, Khawaja D. Hasan and Muhammad H. Hasan
[1]Department of Electrical, Computer and Biomedical Engineering
[2]Department of Mechanical and Industrial Engineering
Toronto Metropolitan University, 350 Victoria Street
Toronto, ON M5B 2K3, Canada.
E-mail: merjan.jabarkhil@torontomu.ca

Reference: Jabarkhil et al. (2023). Revolutionising Cancer Diagnosis and Treatment: A Review on Advancements in Nanomaterial-based Theranostics. *International Journal of Engineering Materials and Manufacture*, 8(4), 106-123.

In the last 10 years, the selection of theranostic therapies has significantly grown to incorporate a variety of imaging modalities like ultrasound imaging, photoacoustic (PA), near-infrared fluorescence etc, alongside therapeutic modalities including x-rays, hyperthermia, or chemotherapeutic agents (Ladju et al., 2022). Nanoparticles can be composed of several different materials each with unique characteristics, depending on the diagnostic and therapeutic modality being used. They can be composed of metals, polymers, carbon, and lipids and are a key component of nanotheranostic agents some of which include DNA nanostructure, gold and silver nanoparticle, quantum dots nanoparticle, liposomes, and plasmonic nanobubbles (Siddique & Chow, 2022). Several therapeutic characteristics of nanomaterials differentiate them from their bulk counterparts, the most crucial being their small size. Nanomaterials also have high affinity, high thermal stability, good solubility, and minimal off-target accumulation, and are able to very effectively penetrate dense tissues (Siddique & Chow, 2022).

The focus of this paper will be to highlight the advancements in nanomaterials and nanoparticles for their use in cancer nanotheranostics, discuss the parameters required for the material design and selection, including the biocompatibility of nanomaterials, as well as the in-depth composition of several types of nanomaterials, current limitations in this field, commercial viability, the advantages of using nanomaterials and nanoparticles over conventional cancer treatments, and finally the future development of cancer nanotheranostics

2 PARAMETERS TO CONSIDER IN MATERIALS DESIGN/SELECTION

2.1 Biocompatibility and Safety

The application of nanomaterials in medical contexts is contingent upon their biocompatibility and safety attributes. Biocompatibility refers to the ability of nanomaterials to coexist harmoniously with biological systems without inducing adverse reactions (Fraser et al., 2021). As these materials are intended to interact with living organisms for diagnostic and therapeutic purposes, ensuring their safety is of the utmost importance.

Nanomaterials are particularly well suited for applications in medicine due to their unique properties, including a high surface area-to-volume ratio and compact size. However, with these properties come the potential for more reactive and toxic effects in comparison to bulk materials (Abbasi et al., 2023). Prior to being incorporated into existing medical frameworks, these dual-edged properties demand a careful and thorough assessment of their biocompatibility and safety features.

The introduction of nanomaterials has led to a discussion of potential toxicological concerns and a demand for methods to improve their biocompatibility profile. It has been found that nanoparticles have the potential to cause unwanted immunological reactions, inflammation, or cytotoxicity when in contact with biological entities (Abbasi et al., 2023). The following are potential toxicological concerns and strategies for enhancing biocompatibility in the context of cancer Nanotheranostics.

1. Immunotoxicity and Inflammation: Nanomaterials can activate immune cells such as macrophages, dendritic cells, and neutrophils. This activation can be a double-edged sword, as it may be necessary for the therapeutic effect, such as in cancer immunotherapy, but it can also lead to excessive inflammation and tissue damage. Furthermore, when immune cells recognize nanomaterials as foreign or potentially harmful, they may release signalling molecules called cytokines. Excessive cytokine release can lead to an exaggerated inflammatory response. This heightened inflammation can be detrimental to patient well-being. Nanomaterials may also induce the recruitment of immune cells to the site of interaction. While this can be beneficial for immune-based therapies, it can contribute to localised inflammation and may lead to adverse effects if not tightly regulated (Aljabali et al., 2023).

Enhancement Strategy: The deployment of natural biomolecules, such as anti-inflammatory peptides or proteins, holds intrinsic promise in attenuating immune cell reactivity. For instance, the integration of anti-inflammatory cytokines, such as interleukin-10 (IL-10), onto nanomaterial surfaces has the capacity to dampen immune cell-mediated inflammation through modulation of signalling pathways (Iyer et al., 2012).

2. Non-Specific Uptake and Off-Target Effects: Nanomaterials may undergo non-specific uptake by healthy cells. Non-specific uptake refers to the unintended internalisation of nanoparticles by cells that are not the target of the therapy or imaging. For example, if the therapeutic or imaging agents were to interact with healthy tissues or organs, this could result in unintended side effects or damage to normal cells. This scenario can compromise the precision and efficacy of cancer nanotheranostics (Sousa de Almeida et al., 2021).

Enhancement Strategy: Ligand-functionalization involves grafting specific molecules onto nanomaterial surfaces, imparting them with the ability to recognize and bind to receptors overexpressed on cancer cells. This molecular targeting approach aims to enhance specificity, thereby reducing non-specific uptake by healthy cells (Wang et al., 2022). By equipping nanomaterials with ligands that can recognize and bind to cancer cell receptors, researchers aim to minimise non-specific uptake by healthy cells, enhance the specificity of the treatment or imaging, and ultimately improve patient outcomes in the fight against cancer.

3. Reactive Oxygen Species (ROS) Generation: Certain nanomaterials possess the propensity to generate ROS upon interaction with biological components. ROS can induce oxidative stress, DNA damage, and cellular dysfunction, potentially undermining therapeutic goals and compromising patient safety (Huynh et al., 2021).

Enhancement Strategy: Surface modification of nanomaterials with antioxidant molecules, such as catalase or superoxide dismutase mimetics, can counteract ROS generation and oxidative stress. This strategic augmentation aims to preserve cellular integrity and alleviate potential cytotoxic effects (Huynh et al., 2021).

4. Renal Clearance and Long-Term Accumulation: Nanomaterials may accumulate in vital organs, including the kidneys, upon systemic administration, potentially inducing renal toxicity and hindering long-term biocompatibility (Asmatulu et al., 2022).
Enhancement Strategy: Designing nanomaterials with optimal size and surface properties to facilitate efficient renal clearance can mitigate long-term accumulation. Additionally, the integration of biodegradable components into nanomaterial structures can enhance their degradation within the body, reducing the risk of persistent accumulation (Asmatulu et al., 2022).
5. Nanoparticle-Induced Genotoxicity: Nanomaterials, due to their unique properties, may interact with cellular DNA and induce genotoxic effects, raising concerns about potential mutagenicity and carcinogenicity. Nanoparticles can induce various forms of DNA damage, including single-strand breaks, double-strand breaks, DNA-protein crosslinks, and base modifications. These types of damage can compromise the integrity of the genetic material and, if not properly repaired, may lead to mutations and genomic instability (Shukla et al., 2021). Furthermore, DNA damage caused by nanoparticles can have several cellular consequences. It can trigger cell cycle arrest, apoptosis (programmed cell death), or uncontrolled cell division, potentially leading to the formation of tumours (Carriere et al., 2016).
Enhancement Strategy: Incorporating DNA repair enzymes or protective coatings onto nanomaterial surfaces can mitigate potential genotoxic effects. This strategic integration aims to safeguard genomic integrity and minimise nanoparticle-induced DNA damage (Shukla et al., 2021).
SiC particles (SiC_p) were exposed to surface oxidation and preheating pretreatment operations prior to composite

2.2 Targeting Efficiency

Optimising targeting effectiveness is a crucial predictor of therapeutic accuracy and efficiency in cancer nanotheranostics. The coordination of passive and active targeting strategies aims to navigate cancerous tissues while protecting healthy tissues. This pursuit of targeted specificity is a way to reshape the landscape of cancer diagnosis and therapy by utilising the inherent properties of nanomaterials. The steps of passive and active targeting are explained below, and Figure 1 demonstrates both mechanisms for nanomedicine-mediated tumour targeting.

Passive Targeting (Attia et al., 2019)

Step 1: Tumour tissues exhibit abnormal and leaky blood vessels due to rapid angiogenesis (the formation of new blood vessels). These vessels have irregular and enlarge gaps between their endothelial cells, which allows for increased permeability.
Step 2: The lymphatic drainage system in tumours is often compromised, leading to impaired clearance of interstitial fluid. This results in the accumulation of fluid and molecules within the tumour tissue.
Step 3: The enhanced permeability and retention (EPR) effect capitalises on the leaky vasculature and impaired lymphatic drainage in tumours. Nanoparticles, liposomes, or other drug carriers administered into the bloodstream can exploit these features by passively extravasating from blood vessels into the tumour interstitium and remaining there for an extended period.
Step 4: As the drug carriers extravasate into the tumour tissue, they become trapped due to the reduced ability of the tumour's compromised lymphatic system to clear them. This leads to the accumulation of drug carriers and their cargo within the tumour microenvironment.
Step 5: The accumulation of drug carriers within the tumour microenvironment allows for sustained exposure of cancer cells to the therapeutic payload. This prolonged presence enhances the effectiveness of the treatment.

Active Targeting (Attia et al., 2019)

Step 1: Drug carriers, often nanoscale particles, are coated or conjugated with ligands. Ligands can be antibodies, peptides, small molecules, or even aptamers—short single-stranded DNA or RNA molecules—that have a strong binding affinity for specific receptors or markers on target cells.
Step 2: Once administered to the body, the ligand-functionalized drug carriers circulate through the bloodstream. When they encounter cells with the corresponding receptors or markers, the ligands on the carriers bind specifically to these targets.
Step 3: The binding triggers cellular internalisation, usually through endocytosis, wherein the target cell engulfs the drug carrier along with its cargo. This process ensures the precise delivery of therapeutic agents directly to the target cells.
Step 4: After internalisation, the drug carrier releases its therapeutic payload inside the target cell, exerting its therapeutic effect. This could involve the release of chemotherapy drugs, genes for gene therapy, or imaging agents for diagnostics.

If passive targeting is used, leaky blood vessels and the EPR effect allow nanoparticle extravasation. Through active targeting, binding is induced to receptors that are overexpressed by cancer cells and endothelial cells by conjugating recognition motifs, such as antibodies, to the outer surface of the nano formulations (Arranja et al., 2017). Ultimately, both strategies aim to enhance the specificity and effectiveness of drug delivery while minimising side effects on healthy tissues using distinct mechanisms.

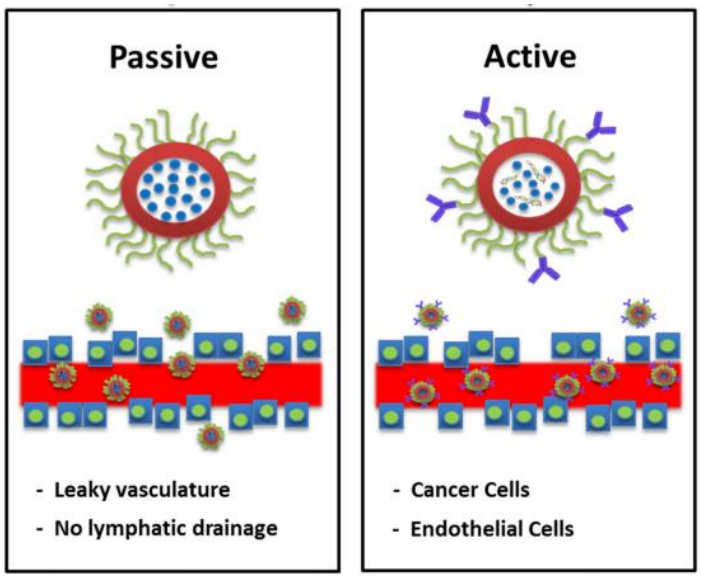

Figure 1: Round red spheres are used to represent nanomedicines; green for polymer-coated surfaces; and blue for therapeutic substances that have been entrapped (Arranja et al., 2017).

2.3 Drug Delivery Capacity

The remarkable capacity of nanoparticles to act as precise drug delivery systems is at the forefront of ground-breaking developments in cancer theranostics. These nanoscale carriers, which include polymeric nanoparticles and liposomes, provide a way to encapsulate and deliver therapeutic molecules with previously unheard-of precision and effectiveness. A fundamental shift in the field of cancer treatment is anticipated as a result of the essential role that engineering ideas play in drug delivery capacity.

Factors influencing drug loading, release kinetics, and controlled release in nanotheranostic systems are multifaceted and interconnected. These factors collectively determine the efficiency, timing, and precision of drug delivery. Some key factors that influence these processes include, nanomaterial composition and structure, hydrophilicity/hydrophobicity, carrier modification and surface functionalization, and physiological factors such as pH, temperature, and enzymatic activity (Parodi et al., 2020).

The composition and structure of nanocarriers wield substantial influence over drug encapsulation and release. Particle size, surface charge, and core-shell architecture delicately govern drug-carrier interactions, mediating the balance between encapsulation efficiency and release kinetics (Contri et al., 2021). Nanocarriers' compact nature also gives them a substantial surface area-to-volume ratio, which allows for the ideal loading of diverse therapeutic payloads. Nanomaterials provide an extensive substrate for encapsulation, protecting the contents from premature deterioration and reducing systemic exposure, whether it be chemotherapeutic drugs, nucleic acids, or proteins. This capacity increases the stability of delicate substances and offers protection from enzymatic breakdown while in transit (Abbasi et al., 2023).

The hydrophilic or hydrophobic nature of both the therapeutic agent and the carrier material influences drug loading capacity. Hydrophobic therapeutic agents, characterised by their aversion to water, find a natural affinity within the lipophilic domains of carrier materials. These hydrophobic pockets within the carrier structure provide a hospitable environment for the encapsulation of hydrophobic drugs, effectively shielding them from aqueous surroundings. This intercalation harnesses the hydrophobic interactions, promoting efficient loading and enhancing the stability of these agents during transport (Mitchell et al., 2020). Conversely, hydrophilic therapeutic molecules, which exhibit an affinity for water, are accommodated within aqueous compartments of the carrier. These aqueous domains serve as protective reservoirs, enclosing hydrophilic drugs and safeguarding them from potential degradation. By encapsulating hydrophilic agents in such a manner, the carrier ensures their preservation while enabling controlled release dynamics upon reaching the target site (Li et al., 2020). Reports show high loading of hydrophobic and hydrophilic agents via small immunostimulatory carriers for enhanced tumour penetration and combinational therapy. The carrier is composed of vinylbenzyl chloride, 4,4'-dithiodibutyric acid, oligo (ethylene glycol) methacrylate and 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (Sun et al., 2020).

Tailoring the surface of nanocarriers with ligands or stimuli-responsive moieties offers a gateway to engineer controlled release. Ligand-mediated release, triggered by specific cellular cues or environmental factors, enhances site-specific drug delivery and minimises off-target effects (Kaushik et al., 2022). For example, by harnessing environmental factors such as pH, temperature, or enzymatic activity, the nanocarrier can adapt its behaviour. This responsiveness not only fine-tunes the temporal profile of drug release but also ensures that therapeutic agents are liberated precisely where and when they are needed the most (Fang et al., 2021).

Finally, the microcosm of physiological conditions has a significant impact on the controlled release of drugs. For example, pH-sensitive nanocarriers skilfully take advantage of the acidic environment found in tumour tissues. These carriers customise drug release upon cellular internalisation under the guidance of this intrinsic diversity, overcoming therapeutic obstacles. Precision medicine gains a responsive component from temperature-sensitive structures that use thermal gradients to control medication release (Sim et al., 2017). Enzymatic activity also plays the role of a conductor as therapeutic payloads are released from nanocarriers in response to biomolecular cues, illustrating the seamless coexistence of biology and nanotechnology (Onzi et al., 2021).

2.4 Imaging Modalities

A new era of medical diagnostics that transcends traditional boundaries is introduced through the interaction between nanomaterials and imaging modalities. The three primary subjects are quantum dots, iron oxide nanoparticles, and fluorescent nanoparticles, each of which offers a unique perspective. These nanoscale objects seamlessly interact with a variety of imaging methods, such as computed tomography (CT) scans, MRIs, and fluorescence imaging. This interaction connects cellular accuracy with anatomical knowledge, resulting in a comprehensive understanding of disease progression (Siddique et al., 2020).

These nanomaterials' distinctive qualities are shown through a comparative examination in Table 1, highlighting their contributions to medical imaging. Ultimately, the selection of imaging modality depends on the specific objectives of cancer nanotheranostics. Quantum dots excel in high-resolution capabilities, iron oxide nanoparticles provide detailed anatomical insights through MRI, and fluorescent nanoparticles offer dynamic imaging of cellular and molecular processes. The selection should consider factors such as resolution, tissue penetration, biocompatibility, and toxicity concerns to tailor the approach to the specific diagnostic and therapeutic goals.

Table 1: Comparison of nanomaterials in the context of imaging modalities

Imaging Modality	Comparison
Quantum Dots: are small particles of semiconductor material, usually a few nanometres in size. They have optical and electronic properties that depend on their size and shape and can emit different colours of light when excited by ultraviolet radiation. They are used in various applications, such as bioimaging, solar cells, displays, and sensors (Bera et al., 2010)	• Offer exceptionally high resolution, enabling visualisation at the nanoscale and tracking of individual cellular processes. • Exhibit intense and stable fluorescence, providing strong signals for imaging. • Concerns about potential toxicity due to heavy metal components may limit their clinical translation (Zhang et al., 2022).
Iron Oxide Nanoparticles: have a diameter of between one and one hundred nanometres. They have magnetic properties and can be used for various applications such as biosensing, drug-delivery, magnetic data storage, etc (Geppert & Himly, 2021).	• Excel in providing detailed anatomical information and functional insights through MRI. • Many iron oxide formulations are biocompatible and have been approved for clinical use, reducing concerns about toxicity. • Unfortunately, signal intensity can be influenced by nanoparticle concentration and local magnetic field strength (Geppert & Himly, 2021).
Fluorescent Nanoparticles: are nanoparticles that emit light when excited by an external source. They can be made of different materials, such as polymers, silica, or quantum dots, and can be coated with many fluorophores (molecules that fluoresce) to enhance their brightness and stability. They have applications in optical data storage and fluorescent imaging of cells and tissues (Wolfbeis, 2015).	• Allow real-time dynamic imaging of cellular and molecular processes with high sensitivity. • Well-suited for cellular and molecular imaging, tracking drug delivery, and monitoring real-time changes. • However, fluorescent nanoparticles have limited tissue penetration compared to iron oxide nanoparticles, restricting their use in deep tissue imaging (Wolfbeis, 2015).

3 CATEGORIES AND TYPES OF NANOMATERIALS

3.1 Inorganic Nanoparticles

"Inorganic" is an umbrella term used to encompass both metallic and non-metallic nanoparticles, excluding those containing carbon. Notably, these nanoparticles primarily comprise of Gold [Au], Iron Oxide, and Silica (Silicon Dioxide). Nanoparticles represent a specific type of matter (from about 1 to 100 nm in size). They have unique physical and chemical properties and are transitional in size between bulk materials and atomic/molecular structures. These properties relate to a high surface area to volume ratio and have developed interest from professionals in

multiple fields such as engineers, physicists, chemists, and biologists (Sharma et al., 2015). The use of engineered nanoparticles has increased dramatically in recent years due to their substantial use in newer technologies.
From the theranostic point of view, Inorganic nanoparticles are non-toxic, hydrophilic, biocompatible, and highly stable in comparison to organic materials (Huang et al., 2020). These properties make inorganic nanoparticles, mainly semiconductors such as gold, widely explored for imaging and diagnosis (D'Souza & Shegokar, 2016). The unique electrical and magnetic properties of these materials allow them to be highly effective for medical imaging and diagnosis, since they can be seen by several imaging techniques including X-ray computed topography, MR imaging, luminescence imaging, etc. In theranostics for cancer therapy, the inorganic nanoparticles can occupy various locations within the bilayer of liposomes, which are organic nanoparticles (D'Souza & Shegokar, 2016). The inorganic nanoparticles could be present as embedded within the bilayer of liposomes, nanoparticles stabilised on the surface of liposomes via chemical conjugation or adsorption, or nanoparticles encapsulated within the liposome. The inorganic nanoparticles might exist in three forms within liposomes: embedded within the bilayer, stabilised on the liposome's surface through chemical conjugation or adsorption, or encapsulated within the liposome. Inorganic nanoparticles are also very effective for targeted drug delivery since they can be functionalized with specific targeting ligands (antibodies or peptides). These ligands can enable the nanoparticles to selectively bind to cancer cells. This delivery system allows for the precise delivery of anticancer drugs directly to sites of malignant tumours coupled with reduced systemic toxicity and enhanced efficiency of treatment.

3.2 Organic Nanoparticles

Organic nanoparticles are nanoscale particles composed primarily of carbon-based compounds. These nanoparticles typically range in size from 1 to 100 nanometres and can have a variety of shapes and structures. Organic nanoparticles are of interest in various fields, including medicine, materials science, and electronics, due to their unique properties and potential applications. Organic nanoparticles can be synthesised from a wide range of organic materials, including polymers, lipids, proteins, and small organic molecules. These materials can be modified and engineered to achieve specific high biocompatibility and improved drug loading capacity (Lombardo et al., 2019). The most prominent organic nanoparticles for drug delivery are liposomes, micelles, and dendrimers.

Liposomes are self-assembled lipid bilayer structures that mimic biological cell membranes. Comprising amphiphilic molecules, liposomes form closed vesicles with an aqueous core encapsulated by hydrophobic lipid layers (Akbarzadeh et al., 2013). This versatile structure allows liposomes to entrap a wide variety of substances, ranging from drugs to genetic material, within their core or lipid bilayers. This property has led to their application in drug delivery, where liposomes can enhance the solubility and bioavailability of therapeutic agents, enabling targeted and controlled release. Moreover, the biocompatibility of liposomes makes them ideal candidates for personalised medicine and diagnostic imaging, enabling multifunctional delivery systems tailored to individual patient needs.

Micelles, another class of organic nanomaterials, are spherical amphiphilic structures that have a hydrophobic core and hydrophilic shell (Aguilar, 2013). However, unlike liposomes, micelles adopt a more compact structure, with their hydrophobic tails gathering in the core while their hydrophilic heads face outward, interacting with the surrounding medium. This arrangement allows micelles to solubilize hydrophobic compounds that would otherwise be insoluble in aqueous environments (Ray & Mitra, 2017). Consequently, micelles have found applications in drug delivery, enhancing the delivery of poorly water-soluble drugs, as well as in environmental remediation, where they can encapsulate and remove pollutants from water systems. The tuneable nature of micelle properties, such as size, composition, and surface functionality, offers a platform for tailoring their behaviour to specific applications.

Dendrimers, on the other hand, are precisely defined, branched macromolecules that exhibit a tree-like structure. They consist of a central core with multiple layers of repeating units radiating outward, resulting in a hierarchical arrangement. This distinctive architecture grants dendrimers remarkable control over their size, shape, and surface properties (Abbasi et al., 2014). Dendrimers have found utility in drug delivery, imaging, and diagnostics due to their ability to encapsulate drugs within their core and be functionalized with targeting ligands or imaging agents on their surface. Additionally, their unique architecture allows them to encapsulate and solubilize guest molecules, potentially revolutionising catalysis, and sensing applications.

4 DETAIL COMPOSITION: PURPOSE OF EACH ELEMENT IN THE STRUCTURE

4.1 Core Material

Core materials in the context of drug delivery and imaging functionalities refer to the central components of nanoparticles or nanocarriers designed with a core-shell structure to encapsulate therapeutic agents for drug delivery or contrast agents for imaging purposes. The type of core material used distinguishes the physical, chemical, and biological properties of the nanoparticles which can influence the overall performance for the specified applications. The major applications include theranostics, targeted therapy and drug delivery, analytical and imaging tools, and tissue engineering regenerative medicine (Patra et al., 2018).

The core material is a critical component of nanoparticles utilised in drug delivery and imaging applications. Drug delivery is a concept that is defined by the transfer of a specific therapeutic drug dosage such as synthetic or natural drugs, genes, and proteins to the desired location in the body within a time limit with the assistance of technical devices or derived formulas (Albinali et al., 2019). Targeted drug delivery is an approach to delivering therapeutic agents to an intended organ or tissue to increase efficacy and reduce toxicity mostly with the assistance of nanocarriers

and nanotechnology. The nanoparticles expand on the possibilities and advancement in targeted therapy and accurate diagnostic imaging (Smith et al., 2019). Nano-particle-based methods have been developed which are a combination of treatment and imaging modalities of a cancer diagnosis. This technology is a significant component for the evolution of medicine formulations, targeting arena, and controlled release and delivery. Nanotechnology employs curing agents at a nanoscale of 1 to 100 nanometres to develop nanomedicines. For example, nanostructures aid in preventing drugs from being influenced by the external environment in the gastrointestinal region and delivering the water-soluble drugs to the target location. Nano drugs display higher oral bioavailability because they exhibit normal uptake mechanisms of absorptive endocytosis (Patra et al., 2018).

Core material also has an essential impact on imaging functionalities. Biomedical imaging is a necessary tool for early diagnosis of any disease. The current imaging technologies include X-ray radiography, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, positron emission tomography (PET), single photon emission computed tomography (SPECT), and fluorescence imaging (Han et al., 2019). Nanomaterials have improved biomedical detection and imaging because of their passive, active and physical targeting characteristics. Since they are small in dimension, they demonstrate enhanced permeability and retention effects (EPR) in tumours. Nanomaterials' size heavily impacts biodistribution, blood circulation half-life, cellular uptake, tumour penetration and targeting. This technology has enhanced fluorescence imaging by allowing an increase in the number of fluorescent dye molecules to be loaded into nanoparticles for more signals (Han et al., 2019).

Different types of core materials display certain properties and are beneficial for certain applications. These core materials include lipid-based, metal-based, polymer-based and silica nanoparticles. Lipid-based core materials such as lipids, liposomes, and lipid nanoparticles, are often used as core materials due to their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic drugs. They can mimic cell membranes and can be functionalized for targeted drug delivery. Lipid-based core materials are well-suited for applications requiring controlled drug release and effective delivery to specific cells or tissues (Albinali et al., 2019). On the other hand, metal-based core materials include nanoparticles made of metals like gold, silver, and iron oxide. These materials possess unique properties that make them suitable for imaging applications. For example, gold nanoparticles have strong absorption and scattering properties in the near-infrared region, making them useful for photoacoustic imaging and photothermal therapy. Iron oxide nanoparticles are magnetic and are employed as contrast agents for magnetic resonance imaging (MRI) (Albinali et al., 2019).

Polymer-based materials, both natural and synthetic, are versatile core materials that can be engineered to achieve specific drug release profiles and stability. Biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA) are often used to create nanoparticles with controlled release properties. They can enhance drug bioavailability, reduce side effects, and improve patient compliance. Most polymer-based core materials have applications in the field of biomedical including tissue engineering and healing (Albinali et al., 2019). In addition, polymer-based nano agents are the most used organic-based photothermal carriers for cancer therapy.

Silica nanoparticles have been explored as core materials due to their high surface area, tuneable porosity, and stability. They can be loaded with drugs or imaging agents and functionalized for targeted delivery. Silica-based nanoparticles have shown promise in drug delivery, cancer therapy, and diagnostic imaging applications (Albinali et al., 2019). However, carbon-based materials like carbon nanotubes and graphene can also serve as core materials. These materials possess unique electrical, thermal, and mechanical properties. They are being investigated for various applications, including drug delivery, imaging, and theranostics (combined therapy and diagnostics) (Albinali et al., 2019). Core materials have a huge influence not only on drug delivery but also on imaging functionalities. Nanotechnology is also part of other applications which depend on the type of core material used and its characteristics.

4.2 Surface Functionalization

A significant method in nanotechnology is surface functionalization, which involves adding particular ligands or functional groups to the surface of nanoparticles to give them the necessary physical, chemical, or biological properties and interactions (Sanità et al., 2020). According to the Springer Series in the Biomaterials Science and Engineering book series, surface functionalization is a process where nanomaterials go through surface modifications to improve the adsorption capacity of biomolecules on the functionalized surface (Park, 2014). This is done by adding ligands or functional groups to the surface of nanoparticles to give them the necessary properties and interactions. This process is important for various applications, including biomedical ones. This modification is usually made to solid materials, but there are rare cases of such modifications being performed to the surface of specific liquids (Sanità et al., 2020).

Surface functionalization is important for target specificity and improved biocompatibility. Target specificity and better biocompatibility are achieved using this method in the variety of applications mentioned in Section 4.1. In addition, in the case of nanoparticles, their physicochemical properties, including surface composition, superficial charge, size, and shape, are considered the main factors that affect the biocompatibility and uptake efficiency of the nanoplatforms (Sanità et al., 2020). Researchers can improve the ability of nanoparticles to bind to cells, tissues, or chemicals while limiting potential negative effects on healthy cells by customising the nanoparticle surface. The modifications can be accomplished by different methods to alter a wide range of characteristics of the surface, such as roughness, hydrophilicity, surface charge, surface energy, biocompatibility, and reactivity (Sanità et al., 2020).

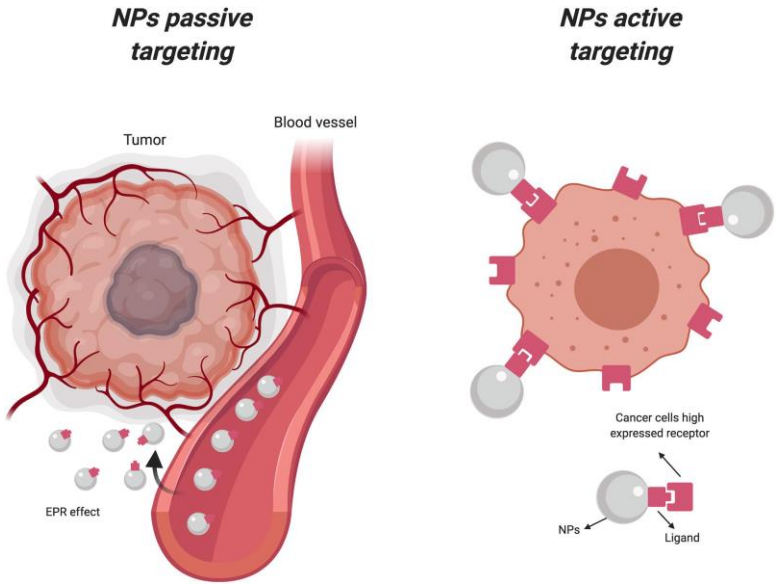

Figure 2: Active and passive uptake of nanoparticles display how enhanced permeability retention (EPR) is actively and passively targeted by nanoparticles. (Sanità et al., 2020).

In biological settings, the surface functionalization of polymers is intended to influence implant biocompatibility, thus reducing thrombogenicity and tuning the adhesion of proteins and cells. Surface engineering and modification become important strategies to allow medical device designers to retain desirable bulk properties while improving biocompatibility. The goal of these approaches is to modify the material surface properties known to influence biocompatibility, such as surface topography, water wettability (surface energy), surface chemistry, surface charge, surface chemical patterns, and roughness, to create a chemical and/or physical environment that offers a favourable response to hard or soft tissue while simultaneously minimising adverse responses such as pathogenic infections or thrombosis while contacting blood (Xu & Siedlecki, 2022).

Various ligands and functional groups can be used for surface modification. Polymers comprising one or more anchoring ligands, such as hydroxyl, amine, carboxylic acid, sulphonic acid, phosphonate, and phosphate groups, have received the most attention among surface modification techniques in regard to modifying the positively charged surface of upconverting nanoparticles (UCNPs) and other inorganic nanoparticles. In addition to polyethylene glycol (PEG), the surface modification of liposomes has been performed with suitable ligands like small molecules, vitamins, carbohydrates, polysaccharides, peptides, aptamers, antibodies, and enzymes based on their application (Khan et al., 2020). These ligands can be bonded to the liposome phospholipid bilayer directly or through polyethylene glycol (Khan et al., 2020).

Surface functionalization of MXenes has been the focus of research in diverse applications, including biomedicine, sensing, catalysis, energy storage and conversion, adsorption, and membrane-based separation. In recent years, many surface functionalization strategies have been cleverly developed to expand the potential of MXenes in different fields. The summary of various ligands and functional groups for surface modification is presented in Table 2.

4.3 Therapeutic Payload

Cancer nanotheranostics is an emerging field that combines the use of nanotechnology for both cancer diagnosis and therapy in the form of therapeutic payloads. A therapeutic payload refers to the active component of a drug that is responsible for its therapeutic effect. In the context of targeted drug delivery, the therapeutic payload is the drug or biologically active molecule that is delivered to a specific site in the body to achieve a desired therapeutic effect (Chehelgerdi et al., 2023). For example, in the case of antibody-drug conjugates (ADCs), the therapeutic payload is the cytotoxic drug that is linked to an antibody, which targets specific tumour cells. The approach using nanotheranostics aims to improve the accuracy, efficiency, and stability of cancer treatments, particularly in the delivery of therapeutic agents to specific tissues, resulting in cancer cells going into programmed death (Zhou et al., 2021). It enables targeted delivery of therapeutic agents while simultaneously providing real-time imaging and monitoring of treatment response.

A wide range of therapeutic agents are being employed in cancer nanotheranostics, including chemotherapy drugs, RNA-based therapies, and gene-based therapies (Zhou et al., 2021). An overview of therapeutic agents used in cancer nanotheranostics is summarised in Table 5 (Zhou et al., 2021). However, for a treatment to be effective and efficient, the appropriate therapeutic payload is essential, especially when it comes to targeted medication delivery. The active ingredient in the medicine that produces its therapeutic effect is referred to as the therapeutic payload. For instance, the therapeutic payload of antibody-drug conjugates (ADCs) is a lethal chemical attached to

an antibody that specifically targets tumour cells (Sutton, 2023). To ensure that the drug can successfully target and cure the disease while reducing unwanted effects, the therapeutic payload must be chosen carefully. As seen by the rise of preclinical and clinical-stage unconventional payload-conjugated ADCs, payload diversity is anticipated to play a significant role in future advances in the ADC sector. For treatment to be precise, the therapeutic payload must be matched to the disease or condition (Marei et al., 2022).

Table 2: Summarization of each ligand and functional group for surface modification

Ligands & Functional Groups	Surface Modification
Antibodies and Peptides	• Attached to the nanoparticle surface to specifically recognize and bind to target antigens or receptors on cells. • Enables precise targeting in cancer therapy and diagnostics. • For example, Herceptin-conjugated nanoparticles have been used for targeted delivery to (HER2-positive) breast cancer cells - breast cancer cells with higher-than-normal levels of human epidermal growth factor receptor
Polyethylene Glycol (PEG)	• To improve the biocompatibility of nanoparticles by creating a hydrophilic "stealth" layer that reduces protein adsorption and immune recognition. • PEGylation prolongs the circulation time of nanoparticles, enhancing their potential for passive accumulation in tumour tissues via the enhanced permeability and retention (EPR) effect.
Folic Acid and Ligands	• Folic acid-conjugated nanoparticles have been developed to target cells that overexpress folate receptors, commonly found in cancer cells. • Such ligands facilitate active targeting and internalisation of nanoparticles into cancer cells.
Small Molecules	• Attached to the nanoparticle surface to achieve specific interactions. • For instance, aptamers are single-stranded DNA or RNA molecules that can be selected to bind with high affinity and specificity to various targets, enabling targeted drug delivery and imaging.
pH Responsive Ligands	• Designed to detach from nanoparticles under specific conditions, such as the slightly acidic environment of tumour tissues. • Allows controlled drug release at the target site, enhancing therapeutic efficacy while reducing side effects.

Table 3: Roles of specific therapeutic agents in advancing nanotheranostics (Zhou et al., 2021)

Therapeutic Agents	Roles in Advancing Cancer Nanotheranostics
Chemotherapy Drugs	• Nanotechnology provides a way to choose and directly target chemotherapies to malignant cells and other neoplasms. • Guide in surgical resection of tumours • Enhance the therapeutic efficacy of radiation-based and other treatment modalities. • Limited by off target effects and systemic toxicity
RNA-Based Therapies	• Includes RNA molecules such as mRNA, small interfering RNA (siRNA), microRNA, and sgRNA regulate cancer-specific genes. • Suppress tumour progression and metastasis by selectively upregulating and silencing these genes
Gene-Based Therapies	• Involve the inhibition of expression of specific messenger RNA that signals for uncontrollable cell growth and proliferation, most notably with carcinoma cells. • Enhance body's natural defence against cancer. • Allow the release of the drug or medicinal component in response specific stimuli from the environment (ie; change in pH levels)

Compared to a generalist treatment, a medicine that targets the underlying biological pathways of disease would produce more effective effects. Greater tumour regression and fewer side effects, for instance, can be achieved in cancer therapy by using chemotherapeutic medicines or targeted biological therapies that directly interact with the molecular properties of tumour cells (Vanneman & Dranoff, 2012). Another factor to consider for effective treatment is each patient's different medical background, genetic makeup, and therapeutic response. As a result, the appropriate therapeutic payload considers unique patient characteristics, enabling individualised treatment plans. For instance, in the context of immunotherapy, picking the right immune checkpoint inhibitors based on a patient's immunological profile might strengthen the body's inbuilt defences against cancer cells and raise the possibility of a successful outcome. In addition, usage of right therapeutic payloads minimises the side effects, maximises drug delivery efficiency, and assists in adaptation to drug resistance (Conilh, 2023).

To conclude, the integration of therapeutic agents into cancer nanotheranostics offers a multifaceted approach to cancer treatment. Chemotherapy drugs encapsulated in nanoparticles enable targeted and controlled drug delivery, reducing systemic toxicity. RNA-based therapies benefit from enhanced intracellular delivery and protection, leading to effective gene silencing. Gene-based therapies, facilitated by nanoscale delivery systems, hold potential for correcting genetic abnormalities and modulating cancer-related pathways. The convergence of therapeutic agents and nanotechnology in cancer nanotheranostics showcases the potential to revolutionise cancer treatment by improving efficacy, reducing side effects, and enabling personalised medicine approaches. As well as, the selection of the right therapeutic payload enables precision, personalization, reduced side effects, improved drug delivery, and adaptability to changing disease dynamics.

5 ADVANTAGES & DISADVANTAGES OR LIMITATIONS

5.1 Advantages

Cancer evolution and related changes that occur at the nanoscale level, require early intervention, treatment, or diagnosis to prevent more severe implications (National Cancer Institute). Nanomaterials are an ideal tool for cancer therapy due to the various advantages they possess, including compact size, and precision. By employing nanoparticles, numerous applications and modalities have been created to improve and enhance the effectiveness of traditional procedures. For example, nanomaterials can be applied to imaging or therapeutic applications in order to enable real-time monitoring of treatment progress and optimise therapy adjustments (Siddique & Chow, 2022).

Nanomaterials can be produced in an assortment of sizes and forms and possess qualities that allow them to carry out functions that resist varying environmental conditions (National Cancer Institute). One of the key advantages of nanomaterials is their compact nature, which can vary from 1 to 100 nm and enables them to bypass several physical barriers in the body that are often impediments to medication treatments and imaging modalities (National Cancer Institute) (Cheng et al., 2021). Since they are 100–1000 times smaller than human cells, they can interact with proteins, receptors, and enzymes, as well as enter cells and bypass blood vessels. For instance, in pancreatic cancer, the fibrotic stromal tissue operates as a barrier that prevents effective imaging or treatment in that area in order to protect the tumours. Nanomaterials can get across this barrier to improve MRI imaging or even transport treatments straight to the tumours (National Cancer Institute). To effectively combat cancer, it is crucial that nanomaterials be able to cross barriers by utilising their size. This process allows for specificity and targeted cancer cell elimination. Furthermore, because of the high surface area to volume ratio of nanomaterials, they can interact with biomolecules to increase their selectivity, allowing healthy cells to have less exposure to toxicity as a result of treatments (Cheng et al., 2021).

Typically, treatments such as chemotherapy target a specific area of the body; however, the invention of nanomaterials has allowed for the selective targeting of individual cells, which can be done through passive or active targeting techniques. Passive targeting is a process that utilises the enhanced permeability and retention effect (EPR). According to the EPR concept, leaky blood vessels cause molecules of particular sizes to accumulate in cancer cells considerably more than they otherwise would in healthy tissues. In the case of cancer, tumours expand quickly, increasing the requirement for oxygen and nutrients. As a result, rapid networks of blood vessels are formed to fulfil these requirements. These vessels are poorly managed and have leakages in comparison to ordinary vessels, thus allowing nanomaterials to pass through and reach tumours. The absence of lymphatic tubes, responsible for cleaning such nanoparticles, makes it easy to have a high particle concentration around tumours. Active targeting involves nanomaterials seeking out and attaching to specific targets by connecting molecules that recognize cancer cells to the nanomaterial. The molecules are antibodies or peptides that attach specifically to cancer cells, increasing specificity and efficiency in targeting tumours for treatment and imaging. These molecules can interact with the cell surface receptors present on the target cell, causing the cell to engulf them through endocytosis. Reducing interstitial fluid pressure to normalise blood vessels within the tumour microenvironment (TME) is one of the tactics used to improve tumour penetration and the accumulation of nanomaterials around tumours. Due to an increase in cell density and abnormal arteries that raise interstitial fluid pressure within tumours, TME in some cases contains barriers that prohibit nanomaterials from reaching their target. This pressure reduces the permeability and the EPR effect and is averse to nanoparticle diffusion. Hyperthermia, radio frequencies, or high-intensity ultrasounds are employed to increase nanomaterial accumulation to overcome these obstacles (National Cancer Institute).

Furthermore, another advantage of using nanomaterials is their capacity to be biocompatible, which primarily depends on the components that were used in the nanomaterials creation as different materials offer various characteristics and uses. Nano-drugs, for example, have a biocompatible surface coating that allows them to stay in

the body for longer (National Cancer Institute) (Cheng et al., 2021). In the case that the nanomaterial is not made with highly biocompatible materials, it will still have the capacity to maintain its normal functions by being coated with biocompatible polymers. Dextran and polyethylene glycol are two examples of biocompatible polymers that are used as coatings (Siddique & Chow, 2022). Overall, although there is still more to be learned in this field, the majority of nanomaterials used are less harmful and offer more advantages than core materials (National Cancer Institute). It is also apparent that nanotechnology will provide a way to create personalised therapies based on the patient's needs to maximise the efficiency of treatments while mitigating side effects which are usually observed in conventional methods. This is due to its customizability which helps achieve various therapeutic tasks under different conditions. Customization options like the type of material or size could be specifically made to meet a patient's body condition or to access specific areas to deliver the therapy. On top of that, coatings and surface modifications can be done to enhance specificity and provide the particles the ability to target specific cells. All these features provide a wide range of ways to create a personalised treatment that is fitting to the patient. Further research is still in development as this is a vast field, which as a result may add more ways to customise the treatments on a case-to-case basis (Kim et al., 2013) (Mura et al., 2012).

Polymer-Based Nanomaterials:

Polymer-based nanomaterials are among the most widely implemented and have a variety of uses, including imaging and medical therapies. Nonbiodegradable polymers such as polymethyl methacrylate, polyacrylamide, polystyrene, and polyacrylates are commonly used to produce these nanomaterials as they do not remain in the body for a prolonged duration to avoid triggering inflammation or toxicity. Recently, biodegradable polymers such as polylactic acid, amino acids, chitosan, alginate, gelatine, and albumin are becoming more frequently employed to prevent toxicity or inflammation. Polymer nanoparticles can store different treatments or pharmaceuticals and release them at locations. These can range from anti-cancer medications to small interfering RNAs, radionuclides, and ultrasound-responsive nanoparticles. Some polymer-based nanoparticles can respond to ultrasound and be used to detect or even treat cancer. These nanoparticles become thermally affected by ultrasound, which causes them to split and release the compounds inside. Additionally, fluorescent polymeric nanoparticles are employed in a technique known as theranostic to examine and cure tumours. However, there are drawbacks, namely hazardous degradation, with polymer-based nanostructures (Cheng et al., 2021).

Metallic-Based Nanomaterials:

Another common class of nanomaterials is metallic-based nanomaterials. They are mainly used for imaging, such as MRI imaging, as well as in drug delivery due to their magnetic properties. As for drug delivery, metallic-based nanomaterials are usually guided by a magnetic field which is externally made to target specific areas, resulting in decreased toxicity for healthy cells and increased specificity. The reaction capabilities of metals allow them to be an effective method in treating cancer because of their ability to catalyse the making of free radicals (oxidative) that damage DNA or proteins, resulting in cell death. Iron-based nanostructures cause hydroxide (OH) radicals to form in the target cell which results in irreversible damage. An example of an iron-based nanostructure is a superparamagnetic iron oxide which is used due to its small size, high targeting specificity, controllable releasing speed, and immune evasion ability. Other metals that are also used are gold and copper. One concern about metal nanomaterials is their high toxicity (Cheng et al., 2021).

Carbon-Based Nanomaterials:

Due to their biocompatibility and distinctive mechanical, electrical, and thermal capabilities, carbon nanomaterials are also extensively used in the medical industry. They are effective at medication delivery because they can be loaded with chemical pharmaceuticals thanks to interactions with hydrophobic molecules (Cheng et al., 2021). Moreover, carbon dots are an example of a carbon nanomaterial, and research into their potential for cancer treatment and bioimaging is ongoing. An advantage of carbon dots is that they have the necessary electrical and mechanical properties to be highly stable while having low toxicity. Due to this, these materials are used in biological tracers or fluorescent probes (Jia et al., 2020).

Overview of Cancer Imaging and Therapy Advantages:

As was previously indicated, imaging and therapeutic applications of nanomaterials exist. The type of material, structure, and qualities all affect the functionalities of these medical imaging and therapy techniques. Nanomaterials can quickly identify cancer-causing chemicals and molecular alterations when used in imaging and detection. Due to their capacity to accumulate at tumours passively or actively, they can also be coupled with imaging modalities like MRI and CT to improve imaging and defining lesions. Additionally, the capacity of nanomaterials to carry different imaging contrast while focusing on specific cells makes them ideal for aiding in imaging deep layers due to their capacity to penetrate diverse biological obstacles and tissues. This helps administer drugs to specific cells located deep within tissues and organs while allowing for real-time monitoring of their effects (National Cancer Institute). Therefore, nanomaterials have the capacity to combine imaging and therapy simultaneously. Using MRI and nanomaterials is a good example of this. Multimodal imaging, which combines MRI with magnetic particles, photoacoustic imaging, and iron-based nanomaterials, produces extremely detailed images (Siddique & Chow, 2022).

With the aid of the images produced, MRI can also be used to regulate drug distribution. Moreover, MRI technology can be used to monitor a tumour's progress or to precisely define the area of the tumour to be removed during surgery, minimising the damage to good tissues (National Cancer Institute). Nanomaterials also aid in cancer immunotherapy treatments as they may become intertwined with the membrane of a cancer cell and draw the immune system to the tumour site (Siddique & Chow, 2022). These methods of imaging and therapy are all significantly less intrusive and highly specific and focused on the treatment site (National Cancer Institute).

5.2 Disadvantages/Limitations

Although nanomaterials exhibit various advantages, they also possess a few critical disadvantages and concerns that need to be addressed. Major issues that are in the process of being improved include increasing efficiency, reducing side effects, drug resistance prevention, and decreasing chances of toxicity (Cheng et al., 2021). Examples of these issues include carbon nanotubes having been associated with tissue damage in animals upon testing them (National Cancer Institute), the ability of these nanomaterials to bypass various organic barriers enabling them to intoxicate highly sensitive regions that could pose health hazards, and the unintended immunological reactions that could result in inflammation due to the nanomaterials used (Cheng et al., 2021).

The delivery methods employed, notably passive targeting, are another area of concern. Passive targeting mainly relies on the EPR effect, which could malfunction given how hostile the TME environment is. An unfavourable diffusion environment could be established which limits the permeability of nanomaterials and diffusion of nano-drugs. EPR also varies among tumours and patients which could lead to different outcomes. It also does not function within large tumours due to an extremely hypoxic environment. Hypoxia also leads to an anoxic metabolic pathway which generates lactic acid thus increasing the Ph level causing nanoparticles present to become unstable and unpredictable. More research is needed to develop materials that could withstand such harsh conditions, while also maintaining biocompatibility to avoid side effects. Also, a more effective and precise method to direct nanomaterials to desired targets is needed in case EPR is unsuccessful (National Cancer Institute).

6 COMMERCIAL VIABILITY

The commercialization of nanomaterials for cancer nanotheranostics is steadily advancing, with promising market potential (Fornaguera & García-Celma, 2017). However, despite their proven effectiveness, the adoption of cancer nanotheranostics in clinical settings faces substantial hurdles, including biological complexities, large-scale production, biocompatibility and safety concerns, government regulations, and cost-effectiveness compared to existing therapies and formulation technologies (Hua et al., 2018). Moreover, several setbacks exist in scaling up production for commercialization, such as the complex manufacturing process of nanotheranostic agents, batch-to-batch variability, and complexities surrounding patents and intellectual property (Fornaguera & García-Celma, 2017).

There have been numerous research studies carried out on nanomedicines and nanoparticles and although the pharmaceutical industry has recognized the multitude of benefits they offer, very few nanomedicines have become clinically commercialised, as seen in Figure 3 (Fornaguera & García-Celma, 2017). A list of some of the current cancer nanomedicines that are currently in pharmaceutical development or have already been in the market can be seen in Figure 4.

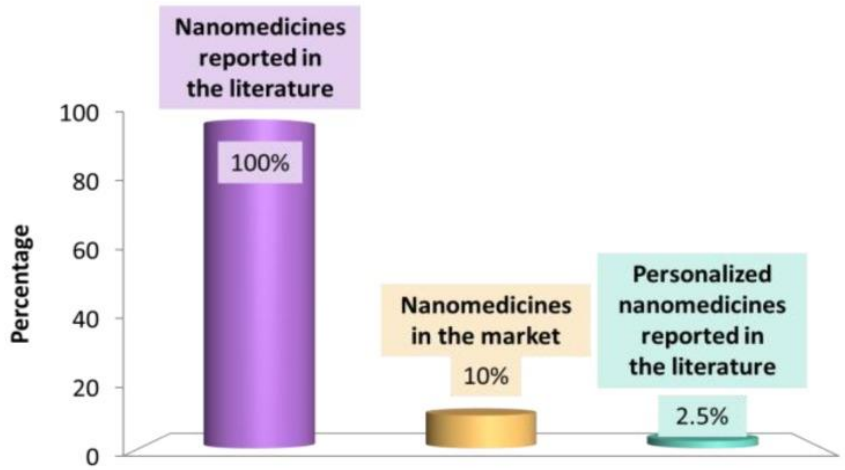

Figure 3: Plot representing the current nanomedicine world, where percentages correspond to literature available in 2017 (Fornaguera & García-Celma, 2017).

Drug Name (Trade Name/Active Principle)	Company	Type of Nanoformulation	Indication/Route of Administration	Status
Abraxane/Paclitaxel	Abraxis (Warminster, Penn State, USA) and Celgene (Summit, New Jersey, USA)	Albumin nanoparticles	Various cancers/IV	Marketed
Adcetris/Brentuximab	Seattle Genetics (Bothell, Washington, USA)	Antibody-drug conjugate	Non-Hodgkin lymphoma/IV	Marketed
ALN-TTR02 (Patisiran)/siRNA	Alnylam Pharmaceuticals (Cambridge, Massachusetts, USA)	Liposome	Transthyretin amyloidosis/IV	Phase II
Aurimune/---	Cytimmune sciences (Rockville, MD, USA)	Colloidal gold	Solid tumors/IV	Phase I/II
Auroshell/---	Nanospectra Biosciences (Houston, Texas, USA)	Gold-silica nanoshells	Lung cancer/IV	Phase I
BIND-014/Docetaxel	Bind Therapeutics (Cambridge, Massachusetts, USA)	Polymeric NPs	Solid tumours/IV	Phase II
Caelyx/Doxorubicin	Janssen (Beerse, Belgium)	PEGylated liposome	Solid tumours/IV	Marketed
DaunoXome/Daunorubicin	Galen Limited (Portadown, United Kingdom)	Liposome	Solid tumours/IV	Marketed
Doxil/Doxorubicin	Janssen (Beerse, Belgium)	PEGylated liposomes	Various cancers/IV	Marketed
Eligard/Leuprorelina	Tolmar (Fort Collins, Colorado, USA)	PEGylated polymeric NPs	Prostate cancer/IV	Marketed
Genexol-PM/Paclitaxel	Samyang Biopharm (Seongnam, South Korea)	PEG-PLA polymeric micelles	Various cancers/IV	Marketed

Figure 4: Examples of current non-personalized cancer nanomedicines on the market as of 2017 (Fornaguera & García-Celma, 2017).

7 REASONS FOR MATERIAL SELECTION: ADVANTAGE OVER CONVENTIONAL MATERIALS

Nanomaterials exhibit many advantages over conventional materials and therapies used in the medical field. Current therapies used to combat cancer, such as chemotherapy and radiotherapy lack specificity, have ineffective concentrated cell-killing abilities, and have adverse effects. Moreover, existing cancer therapies can result in the development of resistance to drugs used in chemotherapy or radiotherapy. While chemotherapy is effective in treating various types of cancer, it still lacks efficiency and carries significant disadvantages. The major ones being the harm to healthy tissue, and the impact on gastrointestinal tract cells as well as bone marrow. Moreover, unspecific distribution or accumulation of chemotherapy drugs can occur on cells, which causes low doses in some areas and higher doses in others. This has the potential to create drug resistance if the received dose is too low, making it non-lethal to the cancerous cell. Chemotherapy also has a short drug half-life due to immune cells and other components of the body that work to eliminate the drug. To overcome such disadvantages, the development of drug carriers using nanomaterials was developed to provide greater specificity, a longer half-life, and enhanced permeability through dense tissue (Cheng et al., 2021).

Targeted delivery is significant as nanoparticles carrying drugs can specifically target cancer cells and release a lethally controlled dose to eliminate them, which as a result reduces the chances of resistance and harm to healthy cells (Cheng et al., 2021). In terms of imaging, current modalities only detect cancer once visible changes occur, and by that time, the cancer would have already progressed. On top of that, biopsies are required to assess if tumours are malignant or benign, through the use of nanomaterials, specific cancer proteins or particles can be detected and targeted, which improves the diagnosis and prevention of cancers at an early stage. Nanomaterials can also increase the efficiency of surgeries that are performed to extract tumours due to their specificity in imaging. Often during such procedures, cancerous tissues as well as healthy tissue get extracted, which can lead to complications and further damage to healthy tissue. This is especially dangerous when dealing with tissue of vital organs (National Cancer Institute).

8 ETHICAL AND ECONOMIC ASPECTS OF NANOTHERANOSTICS IN CANCER TREATMENT

8.1 Ethical Considerations

The technological advancements in the use of nanotheranostics for cancer treatment raise ethical and bioethical concerns regarding patients' privacy and consent while questioning the proper use of emerging technologies. Nanotheranostics include both diagnostic and therapeutic aspects, thus requiring clinical testing, which involves the use of various devices and data collection, either medical or personal, on humans. It is important to understand that there are multiple therapies that are classified under theranostics used in cancer treatment, for which the ideology of bioethics may differ. Specifically discussing risk assessment, somatic-cell versus germline-cell therapy, the enhancement of human capabilities, risk management of engineered nanomaterials, research into human embryonic stem cells, and

the toxicity of nanoparticles and nanomedicine, there have been reported concerns regarding the uncontrolled function and self-assembly of nanoparticles (Canada, 2023). Moreover, this field also expresses ethical issues involving the lack of knowledge of potential toxic effects of nanomaterials on the human body and its environment, social inequality for nanomedicine availability, and accessibility of nanomaterials without medical indication.

One of the fundamentals of any medical intervention is informed consent, which is also considered for the use of nanotheranostics. It is essential that patients understand the potential risks and benefits associated with these treatments before they agree to undergo them. This includes understanding the possible side effects, the likelihood of success, and any alternatives that may be available. In addition to obtaining informed consent, it is also important to respect patient privacy. This includes ensuring that any personal information collected during treatment is kept confidential and used only for its intended purpose. (Canada, 2023) Expanding on the matter of patients' privacy during treatment is a vast segment of ethical practice. The therapies involve the collection of sensitive information, such as genetic information and health monitoring data, which cannot be accessed by unauthorised personnel and require strict access controls, either tangible or intangible.

Lastly, the responsible use of emerging technologies such as nanotheranostics is another important ethical consideration. This includes ensuring that these technologies are used in a way that is safe, effective, and fair. It also involves considering the potential long-term impacts of these technologies on society and the environment. (Canada, 2023) For example, there may be concerns about the potential for these technologies to exacerbate existing health disparities if they are not accessible to all patients. Therefore, while nanotheranostics hold great promise for improving cancer treatment, there are a range of ethical concerns for this field that need to be seriously inspected when considering either research or diagnosis.

8.2 Economic Impact on Healthcare Systems

As discussed, nanotheranostics is the application and further development of nanomedicine strategies for advanced theranostics involving the use of various nanocarriers such as polymer conjugations, dendrimers, micelles, liposomes, metal and inorganic nanoparticles, carbon nanotubes, and nanoparticles of biodegradable polymers for sustained, controlled, and targeted co-delivery of diagnostic and therapeutic agents. Such an approach can lead to better theranostic effects with fewer side effects (Muthu et al., 2014). However, the economic aspects of nanotheranostics are complex and have multiple aspects. The cost-effectiveness of nanotheranostics in healthcare is a critical factor in their widespread adoption. Cost-effectiveness analysis (CEA) provides a formal assessment of trade-offs involving benefits, harms, and costs inherent in alternative options. It has been increasingly used to inform public and private organisations' reimbursement decisions, benefit designs, and price negotiations worldwide. (Kim et al., 2021) With growing and ageing populations and a rapidly expanding range of healthcare interventions, decision-makers face growing pressure to effectively distribute resources. (Shields & Elvidge, 2020)

However, there are challenges in synthesising cost-effectiveness estimates. The costs associated with the development and production of nanotheranostics can be high due to the complexity of the technologies involved. Furthermore, the regulatory hurdles for approval can also add to the overall costs. Despite these challenges, the potential benefits of nanotheranostics in terms of improved patient outcomes could justify the costs. Therefore, careful economic evaluations are needed to assess whether these technologies can be made cost-effective for widespread adoption in healthcare systems.

9 SUMMARY AND CONCLUSIONS

1. The field of cancer nanotheranostics presents a promising avenue for revolutionising cancer diagnosis and treatment. The integration of nanotechnology into cancer therapy and imaging offers a multifaceted approach that capitalises on the unique properties of nanomaterials to overcome the limitations of conventional treatments. Through precise targeting, enhanced drug delivery, and real-time monitoring, nanomaterial-based theranostics have the potential to significantly improve patient outcomes.
2. Nanomaterials bring several advantages to the table, such as their compact size, ability to bypass physiological barriers, and capacity for targeted delivery. These attributes enable nanomaterials to interact with biomolecules, receptors, and cells in ways that traditional therapies cannot, resulting in increased efficacy and reduced side effects. Passive and active targeting techniques, coupled with the enhanced permeability and retention effect, contribute to the specificity and precision of nanotheranostics, enhancing their potential in cancer therapy and imaging.
3. The adoption of nanotheranostics in clinical settings faces challenges that necessitate further research and development. Issues such as toxicity, immunological reactions, and the need for improved manufacturing processes and regulatory guidelines must be addressed to ensure the safety and efficacy of nanomaterial-based treatments. The intricate interplay between nanomaterials and biomolecules, as well as the variability of responses within different tumour microenvironments, underscores the complexity of this field and the need for thorough investigation.
4. The commercial viability of nanomaterials in cancer nanotheranostics is steadily advancing. Market potential is evident, and ongoing efforts to bridge the gap between research and clinical application are paving the way for innovative treatments. The successful commercialization of select cancer nanomedicines demonstrates the tangible progress achieved and the potential for future breakthroughs.

5. Personalised medicine and combination therapy emerge as promising directions for further research. By tailoring treatments to individual patients and combining different therapeutic modalities within a single nanocarrier, researchers can maximise treatment efficacy and minimise resistance.
6. Advances in nanomaterial design, manufacturing, and clinical translation hold the key to unlocking the full potential of cancer nanotheranostics and transforming the landscape of cancer diagnosis and therapy.
7. The integration of nanomaterials into cancer nanotheranostics represents a remarkable convergence of science, technology, and medicine. As research continues to uncover the intricacies of nanomaterial behaviour, interactions, and applications, the prospect of precise, personalised, and effective cancer treatments becomes increasingly tangible. With sustained dedication to overcoming challenges and exploring innovative approaches, the realm of cancer nanotheranostics holds the promise of brighter and more hopeful futures for cancer patients worldwide.
8. The use of nanotheranostics in cancer treatment raises socio-ethical and bioethical concerns, particularly related to patient privacy, consent, and the responsible use of emerging technologies, including risks associated with nanoparticles' function and self-assembly. Informed consent is fundamental in nanotheranostics, ensuring patients understand the risks, benefits, side effects, and alternatives, while also emphasising the importance of patient privacy and the confidential handling of sensitive information.
9. Nanotheranostics involve enhanced nanomedicine technologies for various nanocarriers for targeted co-delivery of diagnostic and therapeutic agents, potentially leading to improved theranostic outcomes with fewer side effects. However, the economic aspects of nanotheranostics are intricate, involving cost-effectiveness analysis to evaluate benefits, harms, and costs in healthcare adoption, especially crucial as healthcare interventions expand amid growing and ageing populations. Even though with low economic benefit due to high cost, the growing field of nano theranostic technology promises cost effectiveness and efficiency in the medical department through the long run making them best suited to be adopted by healthcare systems in the near future.

9.1 Research Gap

The field of cancer diagnostics and treatment using nanomaterial-based theranostics has shown great potential, yet several critical research gaps and limitations exist. Further research is required in design and manufacturing, action and response for interaction between biomolecules and nanotheranostics, regulatory and safety aspects, and translation to clinical applications. To specify, the design and manufacturing of nanotheranostics is a complex process that requires careful consideration of various factors such as size, shape, surface chemistry, and biocompatibility (Mhaske et al., 2021). There are still challenges in developing nanotheranostics with optimal properties for specific applications. For example, at translation at the clinical and preclinical stage. The effectiveness of theranostic drugs is dependent upon heterogeneity at the cell-specified target and is not recommended for a broader range of patients due to its nature of personalised treatment (Ojha, 2021). In addition, nanoparticles can have toxic effects on the body which require thorough evaluation, and their distribution throughout the body can be difficult due to the autoimmune response (defence system) of the human body (Ojha, 2021).

Furthermore, the interaction of nanotheranostics with biomolecules such as proteins and nucleic acids can affect their performance due to factors such as surface properties and patterns. For example, the formation of a protein corona on the surface of nanoparticles can alter their biodistribution and targeting ability (Cheng et al., 2021). While the hydrophilicity of nanoparticles also affects their blood rotation, towel penetration, and protein nimbus adsorption, appreciatively and negatively charged nanoparticles parade distinct cell uptake effectiveness and towel distribution. The protein corona is a layer of proteins that forms on the surface of nanoparticles when they encounter biological fluids. According to Saptarshi (2013), this protein nimbus may have an impact on the cellular immersion, inflammation, accumulation, declination, and concurrence of the nanoparticles. Also, the nanoparticle face might beget conformational changes in protein motes that have been adsorbed, which may impact the nanoparticle's overall bio-reactivity (Saptarshi, 2013).

The last two challenges which require further investigation and understanding are the regulatory and safety aspects of nanotheranostics, and the lack of results from clinical studies regarding nanotheranostics (Zhang et al., 2019). Overall, while nanotechnology has shown great promise in the field of cancer diagnosis and treatment, there is still much work to be done to overcome these limitations and fully realise its potential.

9.2 Future Research Guidelines

While significant progress has been made in using nanomaterials for cancer nanotheranostics, there are still many unexplored regions and promising directions that call for more study. Combination therapy and personalised nanotheranostics are two examples of therapeutic approaches that may pave the way for more accurate, effective, and patient-centred cancer interventions (Wang et al., 2022).

Combination therapy is a type of therapy that combines two or more therapeutic substances. Because it targets important pathways in a manner that is typically synergistic or additive, the combination of anti-cancer medications improves efficacy compared to the mono-therapy strategy. This strategy may lessen medication resistance while also having therapeutic anti-cancer advantages, such as reducing tumour development and metastatic potential, stopping mitotically active cells, lowering cancer stem cell populations, and triggering apoptosis (Bayat et al., 2017). Future studies should focus on the combined advantages of mixing several treatment modalities inside of a single nanocarrier.

Initiating multidimensional assaults on cancer cells while reducing medication resistance is possible with the development of hybrid nano systems that seamlessly combine chemotherapy, immunotherapy, and gene therapy.

Furthermore, for personalised medicine, nanotheranostics—the combination of diagnostic and therapeutic functions in a single device employing the advantages of nanotechnology—is very alluring. Cancer therapy must be customised for each patient because there is no universal approach to treating cancer. That is what personalised, and precision medicine (PM) does. It identifies biomarkers to better understand the diagnosis and then treats the condition in accordance with the accurate diagnosis. Nanotheranostics can be used to noninvasively discover and target image biomarkers and subsequently provide treatment based on the biomarker distribution by primarily utilising the unique features of nanoparticles to achieve biomarker identification and drug administration (Kim et al., 2013). Ultimately, personalised nanotheranostics have the potential to improve treatment precision and effectiveness.

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