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Nanotechnology-based strategies in cancer medicine: A comprehensive review

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I. Resum

El càncer continua sent una de les principals causes de mort a tot el món i suposa un gran desafiament en la investigació, requerint innovació constant per aconseguir avenços significatius. En els darrers anys, la nanotecnologia s'ha convertit en una tecnologia prometedora amb el potencial de revolucionar la medicina del càncer. Aquesta revisió bibliogràfica proporciona una descripció detallada de la literatura disponible sobre l'ús de la nanotecnologia en la investigació del càncer.

Les propietats idònies i la diversitat dels nanomaterials els converteixen en candidats ideals per atacar cèl·lules canceroses i administrar fàrmacs terapèutics. S'analitzen detalladament diversos tipus de nanopartícules, com liposomes, polímers i quantum dots, juntament amb les seves aplicacions en la detecció, el diagnòstic i el tractament del càncer. El seu alt rendiment i la facilitat per modificar i funcionalitzar-les amb lligands per a objectius específics converteixen les nanopartícules en eines útils a la teràpia contra el càncer. Tot i que l'ús de la nanotecnologia en el tractament del càncer és bastant nou, el nombre d'assaigs clínics i nanopartícules aprovades està en constant augment.

Aquesta revisió explora les estratègies basades en la nanotecnologia en diverses àrees de la teràpia del càncer, com ara la teràpia gènica, la immunoteràpia i la teràpia fototèrmica i fotodinàmica. També destaca alguns dels desafiaments actuals, incloent-hi l'optimització del disseny de nanopartícules, la superació de barreres biològiques i la minimització de la possible toxicitat i els efectes secundaris per millorar l'administració dirigida de medicaments. Estudis recents també s'han centrat a millorar l'estabilitat, la biocompatibilitat i l'alliberament controlat de nanopartícules terapèutiques. A més, la nanotecnologia també pot tenir un paper important en la detecció precoç del càncer mitjançant la seva aplicació en tècniques de diagnòstic per imatge de tumors, augmentant la resolució i sensibilitat.

Finalment, aquesta revisió també analitza alguns dels potencials passos futurs, com la combinació de diferents teràpies basades en nanotecnologia. La contínua investigació i la col·laboració entre científics són molt importants per superar els desafiaments actuals i maximitzar el potencial terapèutic de la nanotecnologia en la medicina del càncer.

II. Resumen

El cáncer sigue siendo una de las principales causas de muerte en todo el mundo y supone un gran desafío en investigación, requiriendo innovación constante para lograr avances significativos. En los últimos años, la nanotecnología se ha convertido en una tecnología prometedora con el potencial de revolucionar la medicina del cáncer. Esta revisión bibliográfica proporciona una descripción detallada de la literatura disponible sobre el uso de la nanotecnología en la investigación del cáncer.

Las propiedades idóneas y la diversidad de los nanomateriales los convierten en candidatos ideales para atacar a células cancerosas y administrar fármacos terapéuticos. Se analizan en detalle varios tipos de nanopartículas, como liposomas, polímeros y quantum dots, junto con sus aplicaciones en la detección, el diagnóstico y el tratamiento del cáncer. Su alto rendimiento y la facilidad para modificar y funcionalizarlas con ligandos para objetivos específicos convierten a las nanopartículas en herramientas útiles en la terapia contra el cáncer. Aunque el uso de la nanotecnología en el tratamiento del cáncer es bastante nuevo, el número de ensayos clínicos y nanopartículas aprobadas está en aumento constante.

Esta revisión explora las estrategias basadas en la nanotecnología en diversas áreas de la terapia del cáncer, como la terapia génica, la inmunoterapia y la terapia fototérmica y fotodinámica. También destaca algunos de los desafíos actuales, incluyendo la optimización del diseño de nanopartículas, la superación de barreras biológicas y la minimización de la posible toxicidad y los efectos secundarios para mejorar la administración dirigida de medicamentos. Estudios recientes también se han centrado en mejorar la estabilidad, la biocompatibilidad y la liberación controlada de nanopartículas terapéuticas. Además, la nanotecnologia también puede jugar un papel importante en la detección temprana del cáncer mediante su aplicación en técnicas de diagnóstico por imagen de tumores, incrementando la resolución y sensibilidad.

Por último, esta revisión también analiza algunos de los potenciales futuros pasos, como la combinación de diferentes terapias basadas en nanotecnología. La continua investigación y la colaboración entre científicos son de suma importancia para superar los desafíos actuales y maximizar el potencial terapéutico de la nanotecnología en la medicina del cáncer.

III. Abstract

Cancer remains one of the leading causes of death worldwide and poses a major challenge in health research, requiring constant innovation in order to make significant progress. In recent years, nanotechnology has emerged as a promising technology with the potential to revolutionize cancer medicine. This bibliographic review provides a comprehensive overview of the available literature on the use of nanotechnology in cancer research.

The superior properties and diversity of nanomaterials make them ideal candidates for targeting cancer cells and delivering therapeutic drugs. Several types of nanoparticles, such as liposomes, polymers or quantum dots, along with their applications in cancer detection, diagnosis and treatment are discussed in detail. The high specific yield and the facility to modify and functionalize them with ligands for specific targets make nanoparticles useful tools in cancer therapy. Although the use of nanotechnology in cancer treatment is quite new, the number of clinical trials and approved nanoparticles is constantly increasing.

This review further explores nanotechnology-based strategies in various areas of cancer therapy such as gene therapy, immunotherapy and photothermal and photodynamic therapy. It also highlights some of the current challenges, including nanoparticle design optimization, overcoming biological barriers and minimizing possible toxicity and side effects to improve drug delivery and targeting. Recent studies have also focused on improving the stability, biocompatibility and controlled release of therapeutic nanoparticles. Furthermore, nanotechnology can also play a significant role in the early detection of cancer through its application in tumor imaging diagnostic techniques, increasing resolution and sensitivity.

Lastly, this review also discusses some potential future steps, such as the combination of different nanotechnology-based therapies. Continuous research and collaboration among scientists are of utmost importance to overcome current challenges and maximize the therapeutic potential of nanotechnology in cancer medicine.

IV. Reflexions

Ethical considerations in cancer research

The competitive nature of cancer research raises the following important ethical considerations about the **interests of the investigators and funders** that cannot be overlooked. Firstly, it can lead to a **conflict of** interest among authors, as investigators are often required to publish positive results in a short period of time, which could lead to hiding **negative results and data falsification**. Additionally, private companies tend to finance those diseases with more financial benefits, as a result, the least common types of cancers are underfunded [1]. I think achieving a balance between public and private financing is crucial. Government figures should take an active role in public funding and scientists should adhere to rigorous scientific practices and ethical guidelines no matter their circumstances.

Sustainability in cancer and nanotechnology:

Although anticancer drugs are prescribed in lower concentrations than others, their mutagenicity could be hazardous, especially for aquatic environments, so there is a current effort to **prevent and control such toxic residues** [2]. Nanotechnology increases cancer treatment efficacy while reducing drug toxicity for the patient and for the environment. It can also be less costly, which would benefit healthcare systems in developing countries, the third goal in the **sustainable development agenda** [3]. Despite this, there is still a need for protocols for sustainable residue disposal and large production methods that most studies do not address yet. In my opinion, nanotechnology approaches have the potential to be sustainable tools in cancer research, but studies should also focus on safety and environmental concerns before applying their technology.

Gender perspective in cancer research:

It is necessary to evaluate gender inequalities in cancer research, such as the underrepresentation of women in leadership roles in oncology. Women often work in lower **employment categories** than men, this is clearly represented in the **authorship** of papers from five major oncology journals in recent years, which indicated that although the number of women who conduct and write research has increased, there is not the same tendency for leading roles and men tend to have more citations [4]. I consider that, although great advances have been made in recent years, women are still unrepresented in the field and gender discrimination is still a major concern.

1. Introduction

1.1 Introduction to cancer.

1.1.1 History of cancer.

Cancer research has been present in society for centuries if not millenniums, as its first denomination was given by the Greek physician Hippocrates who used the terms *carcinos* and *carcinoma* alluding to tumors: tissues of the body with abnormal growth, benign or malign. The word cancer takes its inspiration from its meaning in Greek, "crab", as its projections have a shape that is similar to that of a crab. Eventually, later in history, it would be called *oncos*; another Greek word referring to tumors, which means "swelling". Although its existence was known quite early in the cradle of medicine, it was not until the scientific method was established and autopsies were performed that oncology was shaped, and society developed greater knowledge of the disease. The first proper surgeries to remove tumors were possible only after major advances in anesthesia. Then, the first radical mastectomy was performed in 1894, removing the patient's breast, muscle, and lymph nodes. In the nineteenth century, the scientist Rudolph Virchow paved the way for the modern pathologic study of cancer, which later allowed improvement in surgeries and the development of treatments and techniques such as radiation and MRI scans [5].

Undoubtedly, society has gained great knowledge of cancer throughout history, which takes us to its current definition: according to the WHO, it is "a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs" [6].
By virtue of the aforementioned, cancer is a malignant growth due to the uncontrolled cell division that can invade the surrounding tissues (also called malignant tumor), which then spreads to other parts of the body through a process called metastasis, as illustrated in *Figure 1*. Therefore, cancer can be considered a type of tumor or neoplasm and, although the condition is not hereditary, the predisposition to have it can be inherited. The abnormal cell growth occurs after certain genes key to proliferation or apoptosis suffer from genetic mutations or epigenetic changes. These can be tumor-suppressor genes or the so-called proto-oncogenes, or oncogenes once the mutation has occurred [7].

Nowadays, scientists all around the world are cooperating to study cancer comprehensively, and yet, this condition remains one of the greatest challenges in health research. Cancer impacts the lives of millions daily, directly or indirectly. As stated by the World Cancer Research Fund International, there were an estimated 18.1 million cancer cases in 2020, thus becoming the second leading cause of death by disease in the world. The number of cases is expected to increase to 27 million by 2040, as a result of demographic ageing, population growth, and exposure to risk factors [8].

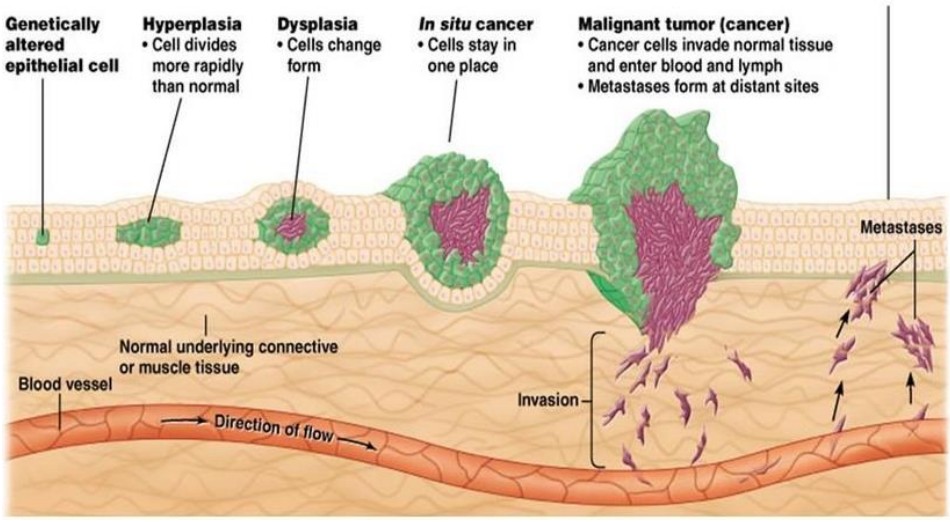

Figure 1. Stages of tumor development and metastasis. Extracted from Kanwal et al., 2013 [9].

Cancer comprises more than 100 different diseases, with different causes and genetic backgrounds. It has been confirmed that many of them can be instigated by carcinogens or harmful lifestyles such as alcohol, tobacco smoke or UV radiation, among others. Logically, the older the person, the higher the probability of contracting it due to natural causes, since the cells have undergone multiple years of proliferation and are more susceptible to the deterioration of the DNA repair mechanisms. According to the WHO Australia is the leading country in cancer rate, with Spain in the 28th position of the same classification [6].

1.1.2 Overview of cancer incidence, diagnosis, prognosis, and therapy.

According to the NIH, cancer types can be classified either depending on the primary site; the part of the body where it is first developed; or according to the type of tissue where it originates, which is called the histological type [10]. The histological type comprises six different categories: carcinomas, sarcomas, myelomas, leukemias, lymphomas and mixed types [10]. According to the primary site. the most common types of cancer worldwide in 2020, were breast, lung, colon and rectum, prostate and skin cancer, in that order [11].
The prognosis of cancer varies greatly according to the type of cancer, its stage or when it is detected, among other factors. One of the crucial aspects when carrying out a cancer prognosis is the stage in which it is detected. Some types of cancer are detected earlier due to their nature or position in the body, while others can develop for years without individual awareness.

Regarding prostate cancer, which will be addressed more specifically along this work, it is not a type of cancer with high mortality rates, but its incidence has risen in recent years, and it remains one of the most common in men. Prostate cancer originates in the epithelial cells of the prostate gland, which produces the seminal fluid that transports and nourishes sperm in healthy individuals. In most cases, prostate cancers are

adenocarcinomas, grow slowly, and are detected early; hence count with an approximate 98% survival rate when detected in early stages. even after 10 years of their diagnosis [12] [13]. The serum prostate-specific antigen (PSA) levels detection test, which is used for its diagnosis, is usually carried out together with digital rectal examination, before performing a biopsy. Previous studies have concluded that although the PSA test is highly sensitive, it is not as specific since high levels of PSA are indicative of prostate disease including cancer and other benign diseases such as benign prostate hyperplasia (BPH). In addition, its accuracy may vary depending on the race, age, and prostate size of the patient, among other factors [14].

There are different methods to diagnose different types of cancer and determine its stage, such as physical exams, laboratory tests, imaging tests, (which comprise magnetic resonance imaging (MRI), computerized tomography, positron emission tomography (PET), ultrasound, X-ray and bone scans) and lastly, biopsies, which often are the only method to certainly diagnose cancer [15].

The type of cancer and its stage will be key to determining which type of treatment, or combination of them, the patient should undergo. The most conventional treatments are chemotherapy, radiotherapy, and surgery. When surgery is viable, the tumor and tissues surrounding are removed, although in some specific cases, it is not recommended as it may be invasive and mean a difficult recovery. On the other hand, chemotherapy and radiotherapy imply a lack of specificity, cytotoxicity, and therefore unwanted side effects and reduced efficacy. Similarly, although not as widely used, immunotherapy treatments strengthen the patient's immune system with drugs, vaccines, or artificially selected T-cells, making it react against the tumor. It is not selective either, so patients can also suffer side effects. Immunotherapy in cancer is currently under considerable research since one of the main challenges of cancer treatment consists of the immune evasion from the tumor cells. Other challenges in cancer treatment include poor solubility and the short life of current cancer drugs, induction of multi-drug resistance or stem-like cell growth [16].
Many other promising biological treatments such as hormone therapy, photodynamic therapy or targeted therapy arose to partially overcome traditional treatments' obstacles and side effects; [17].

Biological studies carried out during the last decades have allowed the scientific community to obtain a great deal of knowledge of cancer progress at a molecular level, discovering many new cellular pathways which are promising to target for cancer treatment. It has been described that cancer cells must undergo a series of changes at the molecular level in order to become malignant, for example, to sustain proliferative signalling, evade growth suppressors, resist cell death, achieve replicative immortality, induce angiogenesis, and promote invasion and metastasis [18]. In this regard, cellular metabolic pathways are crucial for tumor growth, as abnormal growth and cell survival require a high nutrient intake. Cancer cells alter metabolic pathways to produce the energy and precursors needed, in addition to maintaining REDOX balance. There are three remarkable metabolic pathways currently under research, which are involved in lipid, amino acid, and glucose metabolism. Targeting molecules from these pathways

could negatively impact biomass production in cancer cells and thus be key to potential treatments [19].

The high uptake of precursor molecules is related to the tumor microenvironment, which includes surrounding blood vessels, fibroblasts, immune cells, signaling molecules and their interaction with the tumor. Compared to healthy tissues, there is an accumulation of macromolecules in these microenvironments, caused by the formation of new leaky blood vessels because of the stimulation of a process called angiogenesis. New vessels count with increased permeability and a higher retention effect, which play an important role in the spread of tumor cells through the bloodstream. These features, typical of tumors, are currently under research to further develop novel treatments against cancer [20].

Despite the great advances so far, there are still many limitations that cannot be solved by conventional methods. Cancer research must be constantly reinventing and innovating itself to keep advancing and implementing knowledge from different fields, such as physics or engineering. Here nanotechnology will play an important role in cancer research.

1.2 Introduction to nanotechnology.

Nanotechnology could be defined as the technology devoted to design, produce and manipulate devices, structures or systems at an atomic or molecular level, specifically, at the nanoscale, which ranges from 1nm to 100nm. By combining biology and nanotechnology, bionanotechnology refers to the implementation of biological materials in such technology. Since the electronic microscopy development, nanotechnology has gained remarkable attention. At the nanoscale, it is possible to find structures like DNA, liposomes, metallic particles, polymer chains or viruses, as shown in *Figure 2* [21] [22].

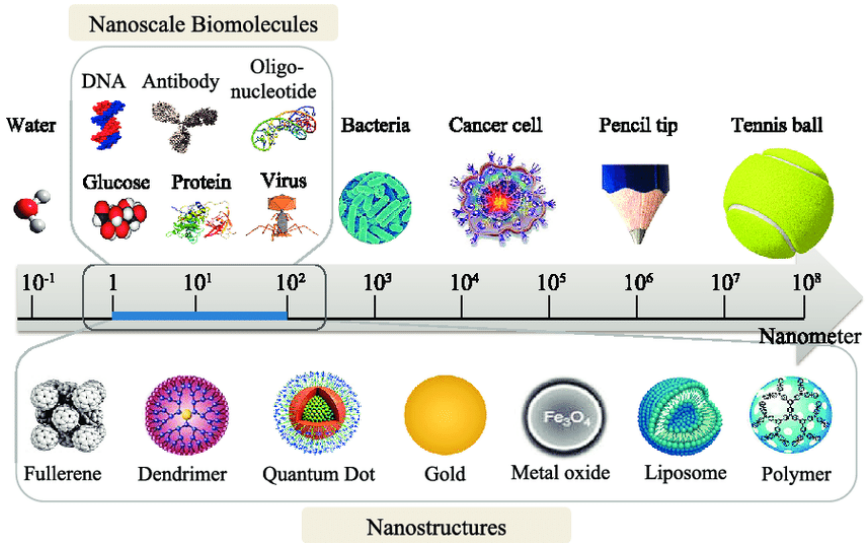

Figure 2. Representation of biomolecules and nanostructures found at the nanoscale compared to objects of different sizes. Extracted from Saallah et al., 2018 [23].

At the nanoscale, materials acquire new physical and chemical properties, which opens a wide range of novelties in diverse applications. In the study of cancer, we could highlight the use of bionanotechnology for the rapid detection of molecules related to the disease, using systems that have already been proven to have great sensitivity. The term “nanoparticle” (NP) refers to those particles in the nanoscale which exhibit different properties due to their small size and high surface-to-volume ratio [24]. NP-based drug delivery systems are also key for the future role of nanotechnology in cancer treatments. These systems have greater stability, permeability, retention and also a precise targeting, with the possibility of a triggered release. These characteristics allow new therapies to overcome cytotoxicity and low specificity common in traditional therapies [25]. In addition, nanocarriers can penetrate the endothelium of tumors, including the brain-blood barrier, and accumulate for drug delivery, detection or eradication [26]. Furthermore, radiation therapy is affected by the implementation of nanoparticles, which can be used as radiosensitizers to increase specificity [27] [28]. On the other hand, immunotherapy treatments are also being benefited by the introduction of nanotechnology approaches, which mainly have inhibitory effects on tumors [29]. Cancer diagnosis can be improved with the application of this technology as well. For example, by enhancing imaging in PET, CT and MRI scans using magnetic nanoparticles.

Despite the rapid expansion and great innovation of this technology, only a few nanodrugs have been approved for clinical use. There are still many challenges that hindered their release to the market, including government regulations, intellectual property, large-scale manufacturing, biocompatibility, safety and overall cost-effectiveness compared to current therapies [30].
Overall, nanotechnology can be considered a promising tool in cancer research, so it is necessary to further study and develop this technology. This review focuses on current advances in bionanotechnology-based strategies applied to cancer treatment and diagnosis and how to overcome previous limitations.

2. Objectives

The following objectives have been defined in order to provide a complete review of the current research status of nanotechnology-based strategies in cancer medicine and to highlight their potential applications. This review covers all types of cancer; however, prostate cancer is emphasized:

2.1 To provide an extensive review of the current state of research on the application of nanotechnology in cancer treatment and diagnosis.

2.1.1 To describe the different types of nanoparticles and nanomaterials that have been investigated for cancer medicine.

2.1.2 To describe the main studies and applications in therapy and diagnosis, including a review of the currently approved nanoparticles in cancer therapy.

2.1.3 To assess the challenges and limitations associated with the translation of nanotechnology-based cancer strategies from preclinical studies to clinical applications.

2.2 To highlight the future research directions in the field of nanotechnology for cancer treatment and diagnosis.

3. Materials and methods

Several parameters were considered to ensure a high-quality review of recent studies about the application of nanotechnology in cancer medicine.

3.1 Literature search:

Firstly, reputable databases and peer-reviewed journals were used for a comprehensive search of relevant articles. For example, some of the used databases included PubMed, Scopus, Web of Science or Google Scholar.
Some of the key terms used for the search in this review included “nanotechnology/cancer/ treatment/diagnosis”, “nanotechnology: current status and perspectives in cancer treatment”, “Nanotechnology in photothermal/photodynamic therapy/immunotherapy/gene therapy”, “types of nanomaterials: advantages and limitations” …

3.2 Selection of relevant sources:

High-quality articles from reputable journals were exclusively selected to uphold the rigor and credibility of the bibliographic review. Notable examples of these journals include the Journal of Nanobiotechnology, Journal of Nanomedicine, ACS Nano, Biomaterials, Nature, Journal of Immunology and Journal of Controlled Release.
In order to evaluate their relevance for this review, the reputation of these journals was assessed based on their impact factor. Articles with an impact factor below 3 were excluded, while preference was given to those publications with higher ratings at the time of their publication. Other methods to evaluate their quality included checking the authors’ credentials, the number of citations and the coherence of the text. To ensure that the bibliographic review was updated, recent articles were primarily selected, except in cases where older articles were necessary for providing context and background information.

3.3 Structuration and reference management:

Articles were organized according to a previously designed structure using the reference management software Zotero.

3.3 Analysis of selected sources, integration of information and critical evaluation:

The articles were read to highlight relevant information that could contribute to the review. The information was integrated, providing a coherent narrative and lastly, they were subject to a critical evaluation, assessing the strengths and limitations of each study.

3.4 Review:

After the text was written it was revised for clarity coherence and overall quality.

4. Results and discussion

4.1 Nanomaterials, nanoparticles and their properties.

Nanoparticles (NPs) are made up of materials with nanoscale dimensions, called nanomaterials (NMs). Therefore, the absorption and dispersion of NPs inside the tumor microenvironment are strongly influenced by NMs' physical and chemical properties.
NMs can be classified into three broad categories: inorganic, organic and hybrid, which will determine the nature of NPs, as shown in *Figure 3*:

-Inorganic NMs: Due to their larger surface area to volume ratio, these materials offer many benefits, including versatility in surface conjugation chemistry and their simple adaptability. However, they present some limitations such as poor biodegradability and biocompatibility. For instance, the NMs of AuNPs, included in metallic nanomaterials, are one of the most studied and promising candidates in drug delivery systems, used in immunotherapy, photothermal therapy and gene therapy, among others. After its surface modification, it reduces drug resistance and enhances accumulation in tumors [26,31–33]. Carbon nanotubes (CNTs), on the other hand, have also demonstrated potential in the delivery of anticancer drugs, such as doxorubicin (Dox). The material of these NPs produces heat when exposed to near-infrared radiation, facilitating thermal ablation in photothermal therapy [34,35]. On the other hand, silica NPs are superior drug delivery vehicles due to their large pore size, which facilitates drug capture, encapsulation and release. They offer higher stability and pharmacokinetics. Specifically, porous silicon NPs have already demonstrated great promise in immunotherapy [25,36–39]. Lastly, quantum dots (QDs) are artificially made nanostructures, crystals capable of transporting electrons and therefore emitting light after receiving UV radiation. By doing modifications, QDs offer many optical and chemical advantages that could be applied to targeted gene delivery, bioimaging or photodynamic therapy among other treatments [40].

-Organic NMs: They are renowned for being versatile and biocompatible, which makes them promising candidates in sensing approaches and drug delivery. Future technologies may incorporate biodegradable designs thanks to their organic nature, which could contribute to reducing toxicity. However, they generally present less stability than inorganic NMs and offer very different properties. Polymeric NMs, micelles, dendrimers, liposomes, niosomes, exosomes, nanocrystals, and nanoemulsions are examples of organic NMs [41,42].

-Organic-inorganic NMs: Hybrid NPs have emerged as a promising method for the creation of sophisticated treatments to deliver multiple elements in cancer therapy. However, for the best in vivo efficacy, more research and developments are required, such as surface and formulation optimization. There are benefits to using a single delivery vehicle for several medicines, including lower costs and better monitoring [43].

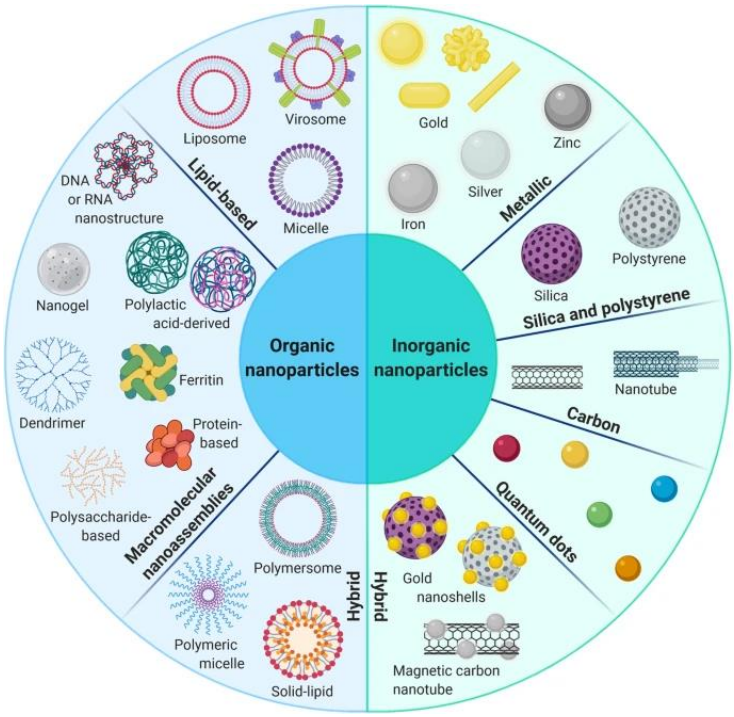

Figure 3. Promising NPs made of organic, inorganic and hybrid nanomaterials for cancer treatment. Extracted from Briolay et al., 2021 [44].

NPs size distribution and shape are also important for effective targeting and delivery. Particularly, NPs need to be smaller than 12 nm to pass through the capillaries of healthy tissues, however, the size of NPs required for passing through tumor vessels ranges from 40 to 200 nm. Furthermore, diverse nanoparticle shapes, including spherical, rod-shaped, and filamentous morphologies, have exhibited substantial improvements in tumor accumulation and overall effectivity [41]. In addition to size and shape, surface charge plays an important role in NP-cell interactions. For instance, positively charged NPs show faster absorption than negative and neutral ones due to the negative charge of cell membranes. Furthermore, positive charge alters cell membrane potential, causing calcium ions to cross the membrane and be released from intracellular stores, inhibiting cell development, as shown in *Figure 4* [45].

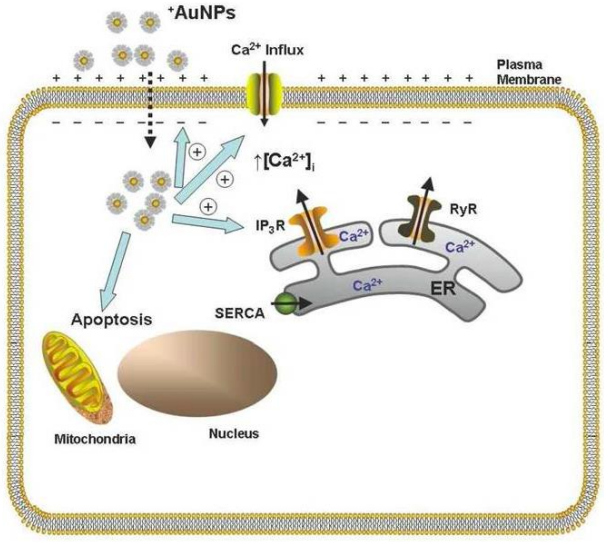

Figure 4. Membrane depolarization is caused by the entrance of gold NPs in the cell, inducing [Ca2+] influx and release of intracellular [Ca2+] storage. Extracted from Arvizo et al., 2010 [45].

Because of their distinctive characteristics and adaptability, NPs have become useful carriers for cancer therapy and diagnosis. NPs' versatility and unique properties lead to enhanced therapeutic effectiveness, decreased off-target effects, and better tumor targeting and accumulation. They can be combined with different therapy methods to offer precise targeting of tumor cells, depicted in *Figure 5*. The potential of different NP types is being thoroughly studied; these are some of the most used NPs:

-Lipid-Based NPs (LNPs): Solid lipid NPs (SLNs) and liposomes are two examples of lipid-based NPs (LNPs). Liposomes are versatile in terms of size, surface charge, and composition, which allows modifications to improve stability, targeting specificity, and controlled release of the drug [46].

-Polymeric NPs: Polymeric NPs, such as polylactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), and chitosan NPs, can encapsulate nucleic acids and shield them from degradation whilst offering controlled release kinetics. To improve specificity and cellular uptake, surface modifications can be added [47].

-Inorganic NPs, such as gold NPs (AuNPs), magnetic NPs (MNPs), silica NPs and carbon-derived NPs, have recently garnered attention. Silica NPs provide advantages such as a high surface area and can be modified to present a positive charge for functionalization with nucleic acids. Initial research demonstrated effective DNA transfection in cell models and successful drug delivery [48]. Recent investigations, however, have raised questions regarding toxicity and inflammation, which limit their potential as genetic material carriers [49]. Lastly, carbon nanotubes (CNTs) and graphene NPs are two examples of NPs derived from carbon. CNTs can transport biomolecules across biological membranes, however, their toxicity restricts where they can be used [50]. Graphene NPs, on the other hand, can be combined with photothermal therapy to improve delivery [51].

-Biological NPs: Exosomes, for example, are derived from the endosomal system and can be engineered to deliver therapeutic agents to target cells with reduced immune response [46].

- Hybrid NPs: Most researchers nowadays are working on hybrid NPs, including different elements such as carbon nanotubes, gold nanoshells or polymeric micelles, as depicted in *Figure 3*. They combine the advantages of each component, including increased stability, controlled release, and higher cellular uptake, which increases the efficacy of the treatment [46].

The type of NP used in each study is determined by several parameters, For example, the aims of each specific treatment, the type of target cells, the kinetics, and the potential toxicity.

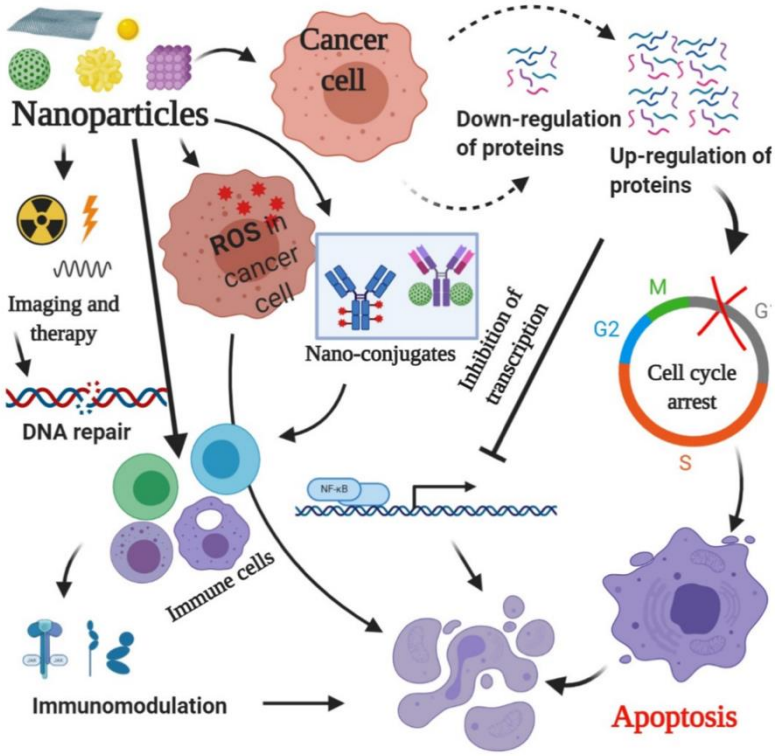

Figure 5. Combination of NPs with different types of cancer therapies that lead to tumor cell death, Extracted from Mundekkad et al., 2022 [52].

The nanotechnology-based cancer drug therapies approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), shown in *Table 1*, indicate that organic NPs have played an important role in the origins of this field. However, strategies are getting more and more creative and diverse every year, as scientists gather evidence about NMs' properties and how to exploit them in mechanisms against different types of cancer.

It is worth noting that there are two approved NPs for prostate cancer therapy, iron oxide and polylactic-co-glycolic acid (PLGA) NPs. Additionally, the National Cancer Institute publishes current therapies in clinical trials in the US. From a total of 135 current studies, six are for prostate cancer, including trials for targeted delivery, imaging, detection and photothermal therapy [53].

Nanotechnology-based treatments are relatively new, and many techniques are in the early stages of development, which can explain these low numbers of current clinical trials. NMs go through a complex process of design, synthesis, characterization and validation, which takes time and effort from the scientific community. Additionally, the potential risks of applying this new technology to human beings make it necessary to previously study its effects in vitro and in animal models with regulatory scrutiny before implementing it in clinical trials. Undoubtedly, these numbers will increase shortly, as nanotechnology application in cancer medicine is gaining more interest.

Table 1. Approved nanotechnology-based cancer drug therapies. Based on data provided by the National Cancer Institute, 2017 [54], Biopharma PEG, 2021 [55], and Rodriguez et al., 2022 [56].

Approval year	Product	Nanoparticle material	Drug	Indication	Mechanism of action	Effect
2019 (EMA)	Hensify (NBTXR3)	Hafnium oxide	-	Locally advanced soft tissue sarcoma (STS)	·Amplifies ionizing radiation effect	Cytotoxic activity
2019 (EMA)	Pazenir	Albumin bound nanoparticle	Paclitaxel	Breast cancer	·Binds to tubulin and stabilizes the microtubule polymerization ·apoptotic death inductor	Antimitotic and cytotoxic activity
2019 (FDA)	Kadcyla	Anti-HER2 antibody-drug conjugate	Emtansine	Breast cancer	·Tubulin polymerization inhibitor ·Antimitotic activity ·Apoptotic death inductor	Cytotoxic activity
2018 (FDA) 2010 (EMA)	NanoTherm	Iron oxide	-	Glioblastoma, prostate cancer	Magnetic hyperthermia	Cytotoxic activity
2017 (FDA) 2018 (EMA)	Vyxeos	Liposome	Cytarabine/ Daunorubicin	Acute myeloid leukemia	Cytarabine: ·Antimetabolite ·Inhibition of DNA synthesis ·Apoptotic death inductor Daunorubicin - see DaunoXome	Cytotoxic activity
2016 (FDA) 2011 (EMA)	Ameluz	Liposome	5-aminolevulinic acid	Basal cell carcinoma	Oxygen-free radicals production	Cytotoxic activity
2015 (FDA)	Onivyde	Liposome	Irinotecan	Metastatic pancreatic cancer	·Intercalation into DNA duplex ·Inhibition of topoisomerase I activity ·Replication arrest and DNA double-stranded breaks ·Apoptotic inductor	Cytotoxic activity
2012 (FDA)	Marqibo	Liposome	Vincristine	Acute lymphoid leukemia	·Binds to tubulin ·Interfere with AMPc, glutathione metabolism, aa, $CMCa^{2+}$ transport ATPase activity ·Cellular respiration ·Nucleic acid and lipid biosynthesis ·Antimitotic activity	Cytotoxic activity
2009 (EMA)	Mepact	Liposome	Mifamurtide MTP-PE	Osteosarcoma	·Ligand for TRL4 and NOD2 in monocytes and macrophages ·Immunostimulatory activity	Innate immunity activation
2007 (South Korea)	Genexol-PM	PEG-PLA polymeric micelle	Paclitaxel	Breast cancer, lung cancer, ovarian cancer	·Binds to tubulin and stabilizes the microtubule polymerization ·apoptotic death inductor	Cytotoxic activity

Approval Year	Product	Nanoparticle material	Drug	Indication	Mechanism of action	Effect
2006 (FDA) 2016 (EMA)	Oncaspar	Polymer protein conjugate	L-asparaginase	Leukemia	·Conversion of asparagine to aspartic acid and ammonia ·Depletion of plasma asparagine	Cytotoxic activity
2005 (FDA) 2008 (EMA)	Abraxane	Albumin bound nanoparticle	Paclitaxel	Breast cancer, pancreatic cancer, non-small-cell lung cancer	·Binds to tubulin and stabilizes the microtubule polymerization ·Blocking mitosis progression ·apoptotic death inductor	Cytotoxic activity
2004	Eligard	PLGA	Leuprolide acetate	Advanced prostate cancer	·GhRHR agonist ·Suppresses gonadotrope secretion of LH and FSH ·Blocking gonadal production of sex steroid	Antitumor activity
2000 (EMA)	Myocet	Liposome	Doxorubicin	Breast Cancer	·Intercalation into DNA duplex and tRNA ·Inhibition of topoisomerase II activity ·Replication arrest and DNA double-stranded breaks	Cytotoxic activity
1999	Ontak	Immuno toxin fusion protein	Denileukin Diftitox	Cutaneous T-cell lymphoma	·Binds to IL2R ·Protein synthesis inhibitor	Cytotoxic activity
1999	DepoCyt	Liposome	Cytarabine	Neoplastic meningitis	·DNA polymerase inhibition ·DNA/RNA intercalation	Cytotoxic activity
1996	DaunoXome	Liposome	Daunorubicin	Kaposi's sarcoma	·Intercalation into DNA duplex and tRNA ·Inhibition of topoisomerase II activity ·Replication arrest and DNA double-stranded breaks	Cytotoxic activity
1995 (FDA) 1996 (EMA)	Doxil	Liposome	Doxorubicin	Kaposi's sarcoma, Ovarian cancer, Breast cancer, Multiple myeloma	·Intercalation into DNA duplex and tRNA ·Inhibition of topoisomerase II activity ·Replication arrest and DNA double-stranded breaks	Cytotoxic activity

4.2 NPs-based drug delivery systems

Traditional drug delivery methods, such as oral administration or subcutaneous injections, can imply several limitations, for instance, poor bioavailability, toxicity and lack of specificity. The wide range of NMs and unique physical and chemical properties of NPs, on the other hand, translates into targeted drug delivery, enhanced bioavailability and controlled release. Therefore, NP-based drug delivery systems are a promising tool to overcome these limitations in cancer treatment [57].

Two main targeting strategies—passive and active—can be used in nano-based drug delivery, shown in *Figure 6*. Passive targeting concentrates NPs on the tumor by taking advantage of the inherent features of the tumor site, such as the Enhanced Permeability and Retention (EPR) effect and Tumor Microenvironment (TME) properties. Tumor cells promote the formation of new blood vessels, resulting in a leaky vasculature with pores that allow NPs to enter and concentrate within the tumor. However, the tumor microenvironment's interstitial fluid pressure may limit the uniform distribution of NPs. Diffusion is a key process in passive targeting, which is also affected by several variables such as size, shape, and surface characteristics. For example, some studies have concluded that particle size should be between 40 and 400 nm and have a rigid and spherical shape with a size between 50 and 200 nm for improved bioavailability and reduced renal clearance [58]. Normally, NPs could be removed from tissues via the mononuclear phagocyte system or glomerular filtration in the kidney, so it is necessary to avoid renal clearance in the target areas. Even though the EPR effect improves drug accumulation in tumor cells, certain obstacles such as abnormal tumor vasculature, solid stress, and interstitial fluid pressure can impede nanoparticle delivery [59].

Active targeting, on the other hand, employs particular chemicals or ligands hybridized with NPs to specifically target cell surface receptors expressed by cancer cells, like EGFR or folate receptors. This method allows for more accurate targeting, but it requires prior knowledge about specific receptors and ligands, and therefore it is also known as ligand-mediated targeting. Nanocarriers may also exploit TME features such as acidic pH, increased redox potential, and production of lytic enzymes to ensure homogeneous drug distribution throughout the tumor. Each targeting strategy has advantages and limitations, and their efficacy may vary depending on the type and location of the tumor [57,60].

By modifying NPs' surface, it is possible to target specific tissues or cells, which increases the efficiency of the treatment and minimizes the possible side effects by avoiding healthy tissues. Not only it is possible to target a specific area, but also to release the drug in a controlled manner over time, allowing sustained therapeutic effects. This is possible by incorporating the drug into the NP matrix or using stimuli-responsive NMs, sensitive to changes in the environment such as pH, enzyme activity or temperature. One of the most used targeting methods is the drug delivery system that responds to pH variations, depicted in *Figure 7*. Tumor cells produce a great deal of lactic acid as a result of the Warburg effect, which allows them to thrive in acidic and low-oxygen settings. As a result, developing pH-responsive NPs that are stable at physiological pH but break down particularly in the acidic pH of the tumor microenvironment is an effective technique to target tumor cells [61].

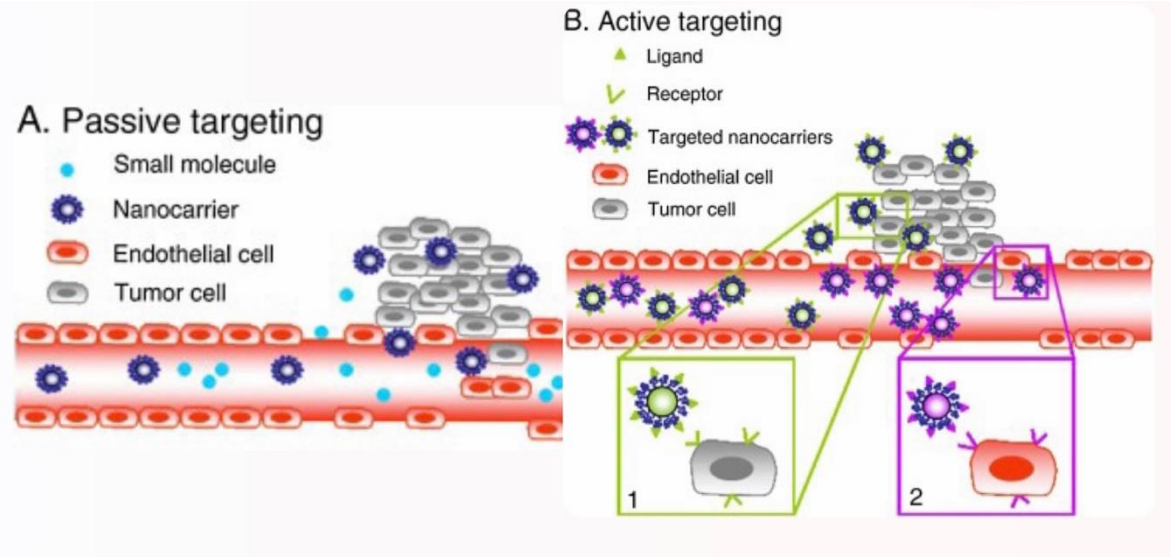

Figure 6. A) Mechanism of passive targeting, nanocarriers take advantage of the tumor microenvironment to target the tumor cell. B) Mechanism of active targeting, nanocarriers have surface modifications to target the receptor of tumor cells or surrounding ones. Extracted from Danhier et al., 2010 [62].

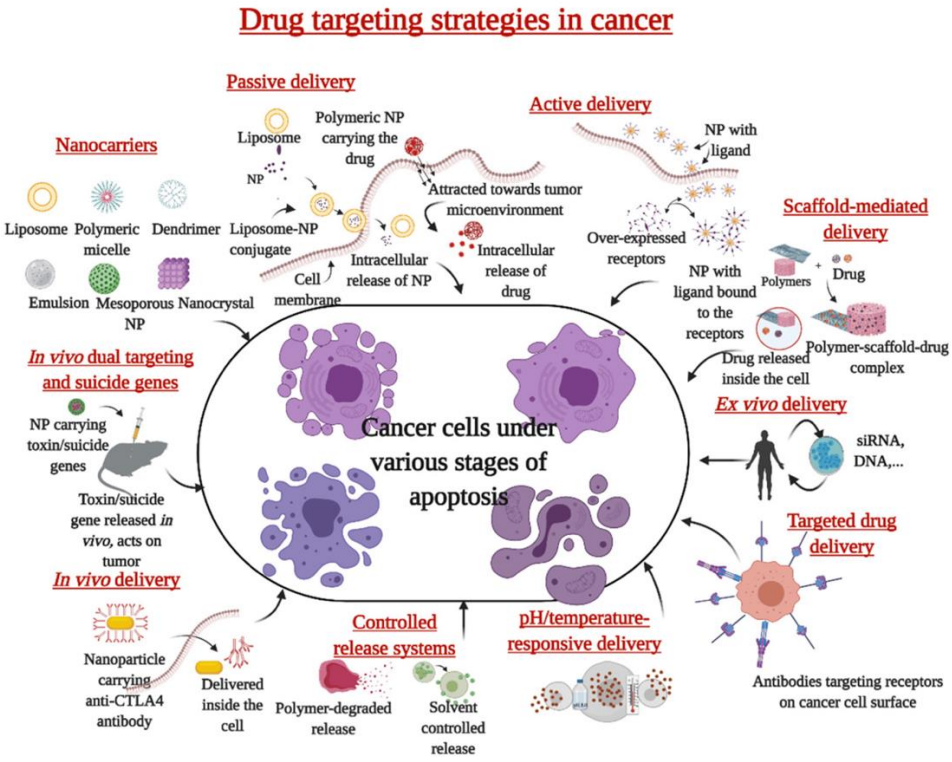

Figure 7. Drug delivery systems used to deliver therapeutic drugs and specifically target tumor cells. Extracted from Mundekkad et al., 2022 [52].

Recently, a new NP made of gelatin and nanochitosan was cleverly designed to deliver Dox targeting tumor cells (GNDNPs), which has shown promising results in treating cancer in animal models. Doxorubicin (Dox) is a common chemotherapy drug used to treat several types of cancer, it works by generating free radicals and intercalating into the DNA of cancer cells, thus preventing division and growth. The whole system of the study works thanks to an enzyme called matrixmetalloproteinase-2 (MMP-2), which is often overexpressed in tumor cells and promotes metastasis. GNDNPs have hydrophilicity and stability properties for protection, which allows the drug to have a long circulation time in blood. When it reaches

the tumor site, the enzyme MMP-2 degrades the gelatin from the 178 nm NP, releasing 4 nm nanochitosan/Dox NPs able to penetrate the tumor cells by endocytosis. The intracellular low pH and MMP-2 further trigger the release of Dox, resulting in a greater inhibitory capacity against cancer cells in a mouse liver tumor-bearing model [63].

Other previous research has demonstrated overcoming the limitations of conventional methods by using different types of nanocarriers to deliver anticancer drugs and exploiting their properties. Several types of these nanocarriers are shown in *Figure 7*. For instance, norcantharidin (NCTD) is an anticancer drug that has been used in several studies with NPs, as it promotes apoptosis and inhibits proliferation in tumor cells by targeting different pathways, such as Wnt/β-catenin, EGFR, c-Met and PP5. It also inhibits metastasis and angiogenesis and regulates the macrophage-mediated immune response. Nevertheless, it can also lead to organ toxicity, poor solubility, short half-life and weak tumor-targeting ability in its free form. Several delivery systems have been tested to reduce its toxicity and improve its efficacy, such as liposome-based delivery or micelle-based delivery systems [64].
As another example of these NP-based drug delivery systems, different polymers such as PLA-PEG (Polylactic acid-polyethylene glycol) are used as carriers for targeted drug delivery and controlled drug release. NCTD-PLA-PEG NPs showed better efficacy in mice models, apart from no side effects at LD50, the median lethal dose in which 50% of the population die under exposure to the drug, in contrast with NCTD alone [65]. Similarly, deacetylated chitin is another polymer that could be used as a coating material for NPs, as in some studies it has improved the stability, biocompatibility and targeting capacity of NCTD [66].

Another promising type of NPs is the nanostructured lipid carrier (NLC), a mix of liquid and solid lipids that can be loaded with NCTD. Its properties allow encapsulating hydrophilic, hydrophobic and amphiphilic drug molecules, enhancing drug solubility, release rate and bioavailability. NCTD-NLCs showed an enhanced tumor inhibition and release rate compared to free NCTD [67] [68].
Lastly, a new study concluded that zinc-based coordination polymers are a promising delivery system as they can release drugs in a targeted manner in slightly acidic tumor environments, enhancing their therapeutic effect on tumors by forming a strong bond with adenosine triphosphate (ATP), which is highly required in cancer cells [69]. Other studies have used this type of NP for a pH-responsive drug release of NCTD. resulting in a suppression of tumor growth with few side effects in a pH of 5,5 and using a HepG2 and Hep3B cell line; in contrast with the results in neutral environments and using healthy cells, which confirms that these NPs have pH-responsive drug release properties and specificity [70].

Overall, it can be concluded that NPs show great potential in targeted drug delivery thanks to their many applications. Moreover, one of the main challenges in cancer therapy using conventional treatments is palliating their side effects, therefore, combining them with this technology would significantly reduce undesired cell damage, as there is evidence that proves their potential to discriminate healthy cells.
Stimuli-responsive NPs with controlled drug release are also a key finding in current research. This allows for numerous combinations to achieve the ideal NP in targeted drug delivery, which would have high bioavailability, specificity and no side effects. However, these combinations are usually complex and this field of study is very new.
Some NMs could have negative effects on the body that are still unknown due to a lack of practical evidence, thus, the assessment of NPs' toxicity will most likely remain one of the

most significant challenges until this technology is more established. This complexity also leads to a higher cost and need for expertise and specialized equipment. Although these studies offer many different new strategies that have proved to improve current cancer therapies, they cannot be implemented until research is more advanced to ensure these limitations are surpassed.

4.3 NPs-based gene therapy

Gene therapy is one compelling strategy that has attracted loads of attention in recent years. When therapeutic genes are delivered to target cells, they modify their function or correct genetic defects associated with diseases like cancer. In the context of bionanotechnology-based methods for cancer diagnosis and treatment, this section seeks to give an overview of gene therapy.

In order to alter the patterns of gene expression in cells, nucleic acids such as DNA or RNA molecules, are delivered during gene therapy, through ex vivo or in vivo approaches. Gene therapy aims to fix genetic defects or improve the cellular machinery's capacity to combat cancer diseases by adding external genetic material [71]. Recent studies aim to enhance the effectiveness and safety of gene therapy methods through new strategies for the efficient and targeted delivery of therapeutic genes into cancer cells.
Microinjection or electroporation are physical techniques that exhibit excellent efficiency in vitro but fall short for in vivo applications. On the other hand, although commonly used, viral vectors have important limitations such as immunogenic responses, limited packaging capacity, off-target effects, and expensive production costs. Consequently, interest in non-viral vectors based on nanotechnology and material science has increased [72]. Until now, bionanotechnology-based vectors, including NPs, liposomes, and viral vectors modified with nanoscale features, have shown superior qualities, such as high stability, biocompatibility, and the capacity to get past biological barriers, while minimizing off-target effects. Multiple biological obstacles, such as the extracellular matrix, immune system reactions, and intracellular trafficking, prevent the effective delivery of therapeutic genes to cancer cells. In order to effectively deliver genes, nanocarriers can be designed to penetrate the extracellular matrix, avoid immune tracking and many other biological barriers shown in *Figure 8* [73].

Bionanotechnology-based strategies in gene therapy can also be combined with other techniques, such as chemotherapy, immunotherapy, or photothermal therapy. The combination of these tools provides personalized treatment strategies by enabling real-time monitoring of the effects of therapy. Gene therapy can take advantage of the huge diversity of NPs in order to deliver genetic material.

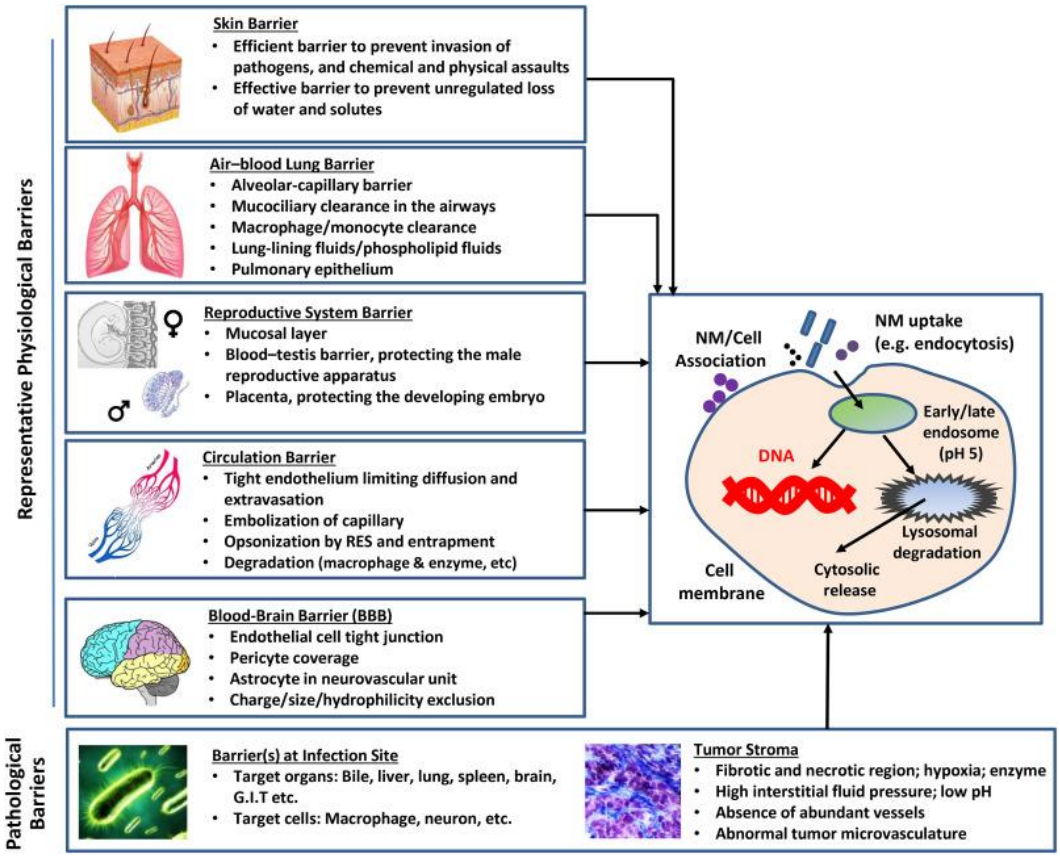

Figure 8. Illustration of the numerous biological barriers drugs need to overcome in different tissues. Extracted from Meng et al., 2018 [74].

For instance, there are NPs made up of lipid bilayers that can encapsulate and protect nucleic acids, making it easier to deliver such substances to targeted cells [75]. Polymeric NPs are also quite beneficial for gene delivery, as they are biocompatible and can deliver cargos of different natures, such as hydrophilic and hydrophobic molecules or with different molecular weights [76].

For gene delivery and controlled release, AuNPs exhibit a promising property known as localized surface plasmon resonance (LSPR). By illuminating gold NPs with the light of a specific wavelength, the absorbed energy generates local heat, triggering the release of therapeutic genes. AuNPs also demonstrated excellent stability and are easily modifiable. As a result, they are frequently functionalized with short hairpin RNA (shRNA) for gene silencing. On the other hand, magnetic NPs, such as superparamagnetic iron oxide NPs (SPION), offer the ability for targeted delivery using external magnetic fields in gene therapy, owing to their iron core [77]. As an example of SPION, Nanotherm NPs have already been approved for hyperthermia treatment, included in *Table 1*.

Other types of biological NPs are also used broadly in gene therapy, for example, exosomes have been used in a recent study by Gong et al., 2019 [78], who modified an exosome to deliver Dox and cholesterol-modified miRNA 159 (Cho-miR159) to a breast cancer cell line. The hydrophobic cholesterol modification enhances the stability and promotes the internalization of the miRNA that targets the gene TCF-7, a transcription factor associated with the Wnt signaling pathway. The modified exosome enhanced the targeting, stability and biocompatibility of the system, which in the end effectively silenced the target gene and improved anticancer effects.

Although this technology has improved over the years, there are still several limitations that need to be addressed, such as reduced transfection efficiency when compared to viral vectors or blood clearance before reaching the target site [79]. Novel NP formulations and techniques are being investigated as research in this sector continues to grow to solve existing constraints and improve the effectiveness of gene therapy for cancer treatment [46,71].

The incorporation of CRISPR-Cas9 technology in gene therapy has also been a promising innovation. Gene editing technology has opened up many opportunities for precise and targeted modifications in the genome of cancer patients. The CRISPR-Cas9 system can be successfully targeted to cancer cells when combined with nanocarriers, presenting an effective strategy for fighting genetic defects that promote carcinogenesis. This combination of bionanotechnology with CRISPR-Cas9 could be a key step in creating individualized gene therapies for cancer treatment. Currently, CRISPR/Cas9 has the potential to be applied in many areas of cancer research, such as tumor-associated genes modification, tumor immunotherapy, tumor modeling and anticancer drug resistance [72].
CRISPR/Cas9 can knock out oncogenes for tumor growth inhibition and can repair tumor suppressor genes [80]. Target genes that are involved include, among others, EGFR, p53, FAK, BRCA ALK, KRAS and PTEN. The results of multiple studies on cancer therapy using CRISPR/Cas9 are promising for the future of cancer research, for instance, by focusing on oncogenic KRAS mutant alleles, CRISPR/Cas9 has been used to induce tumor regression significantly [81].

In another study, Zhang et al., 2022 [80] developed multiplexed dendrimer lipid NPs to overcome biological barriers and target ovarian tumor tissues in mouse models. Co-delivering Cas9 mRNA, sgRNA and focal adhesion kinase (FAK) siRNA led to effective delivery and improved gene editing performance, in which FAK refers to a protein kinase involved in cell adhesion. These NPs proved a 10-fold increase in gene editing due to the inhibition of FAK, which led to a disruption of the extracellular matrix and an increase of the uptake and tumor penetration, as shown in *Figure 9.* Furthermore, CRISPR/Cas9 gene editing successfully altered programmed death-ligand 1 (PDL-1) expression, a protein that evades the immune response in cancer and which plays an important role in cancer immunotherapy.

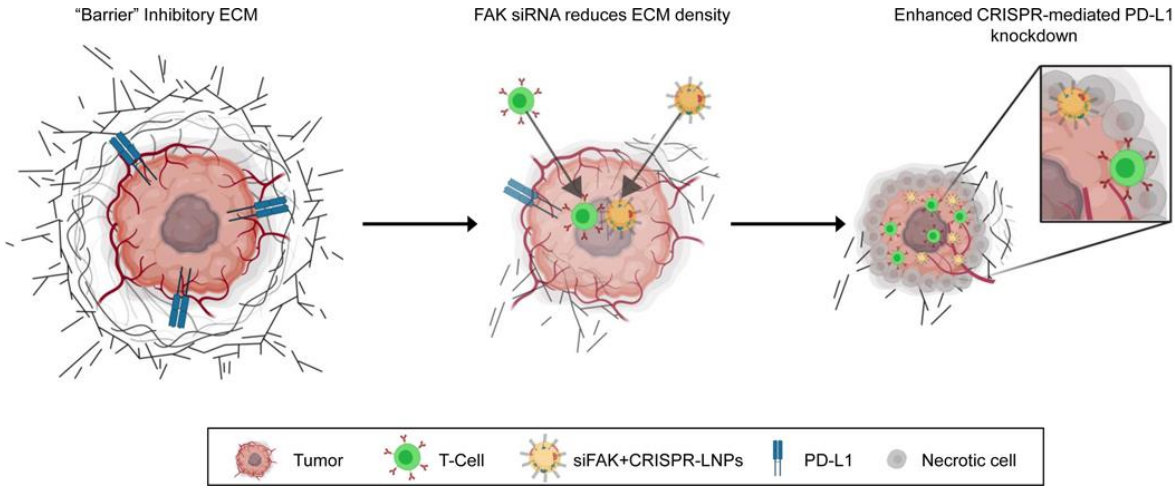

Figure 9. Disruption of the extracellular matrix (ECM) of tumor cells by lipid NPs containing FAK siRNA, Cas9 mRNA and sgRNA to ultimately knockdown PD-L1 expression. Extracted from Zhang et al., 2022 [80].

As an example of prostate cancer treatment, Poddar et al., 2020 [82] assessed the application of ZIF-C to gene therapy in human prostate cancer cells, using RNA interference (RNAi) silencing at the cytoplasmic level and CRISPR/Cas9 at the genomic level. ZIF-C is a type of zeolitic imidazolate structure or framework and a subtype of metal-organic framework (MOF), which are a type of porous material made of metal ions or clusters coupled to organic ligands. They fall under the category of nanomaterials due to their nanoscale size range and unique properties. The LAM67R protein, a product of the RPSA gene and associated with cancer metastasis and angiogenesis, is specifically targeted since downregulation of LAM67R has been shown to reduce cancer cell viability and increase apoptosis. Another essential element for the study is the phytochemical EGCG, extracted from green tea, which coated ZIF-C to enhance cellular delivery. As shown in *Figure 10,* the CRISPR/Cas9 system and RNAi strategy were tested separately for RPSA knockdown at different levels of gene expression.

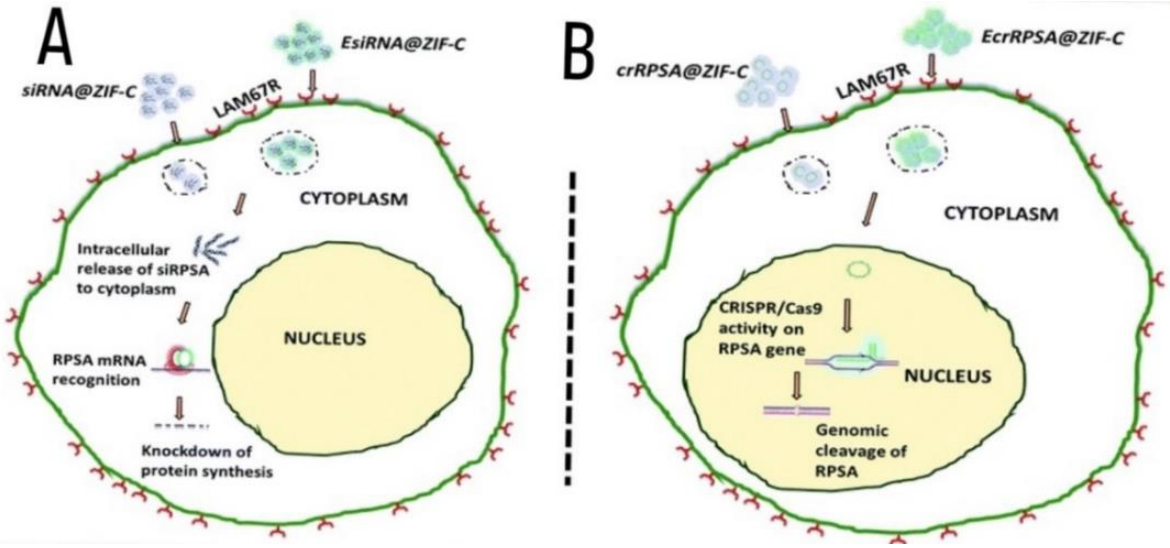

Figure 10. A) RPSA knockdown at cytoplasmic level by RNAi using ZIF-C, coated and not coated with EGCG. B) RPSA knockdown at chromosomal level by CRISPR/Cas9 using ZIF-C, coated and not coated with EGCG. Extracted from Poddar et al., 2020 [82].

Overall, the study concluded that ZIF-C in combination with siRNAs and CRISPR/Cas9 successfully decreased RPSA gene expression at both the cytoplasmic and genomic levels. EGCG coating, in particular, increased cellular uptake and enhanced the knockdown up to 40% whereas NPs without EGCG had only a 22%. According to the article, siRNA drastically decreased gene expression when compared to CRISPR/Cas9, leading to the hypothesis that targeting pathways downstream of the chromosomal genetic level can lead to more disruptions in protein expression [82].

4.4 NPs-based Photothermal and photodynamic therapy

NPs-based photothermal therapy (PTT) and photodynamic therapy (PDT) have drawn a lot of attention because of their capacity to specifically kill cancer cells with minimal damage to healthy tissues.

PTT uses materials with strong light-absorbing properties, typically in the near-infrared region. It produces localized hyperthermia as a result of converting light energy into heat when exposed to laser irradiation. The heat produces protein denaturation, cell membrane damage, and thermal ablation. Furthermore, when combined with this technology other methods like chemotherapy or immunotherapy can have amplified effects.

On the other hand, PDT uses photosensitizing particles that, when activated by particular light wavelengths, can produce ROS to damage and kill cancer cells. NPs enhance the targeting and function as drug carriers with controlled release. They can also extend the half-life of the photosensitizer, increase ROS generation efficiency, and solve previous limitations such as poor solubility and bad bioavailability.

The application of NPs aims to solve the limitations associated with conventional PTT and PDT, which include their limited selectivity, possible collateral damage on surrounding tissues, poor penetration of light through biological tissues, reduced efficacy in hypoxic tumors, and post-treatment toxicity [83].

4.4.1 Photothermal therapy

Despite significant advancements in PTT, the conventional method with laser device only has been limited due to its low photothermal conversion rate, biosafety concerns, minimal tumor accumulation, and heat resistance of particular types of cancer. NPs with photothermal characteristics are called nanosized photothermal agents and, using the EPR effect and active targeting approaches, they are designed in order to accumulate in tumors. There are several benefits over small molecule photothermal agents, such as higher tumor accumulation and photothermal conversion efficiency. CNTs and AuNPs are a few examples of nanosized photothermal agents [84].

-AuNPs can be designed in a variety of sizes and shapes, allowing for distinct "vibrations", known as plasmonic resonances, to align with light wavelengths in the near-infrared (NIR) region. AuNPs can be beneficial as a non-invasive tumor treatment because biological tissues do not absorb much light in this region, allowing for deeper penetration while causing less damage to healthy tissues. Additionally, targeting ligands or antibodies added to the surface of AuNPs make them accumulate specifically in tumors, increasing the effectiveness of the treatment.
For example, Sun et al., 2016 [85] designed a pioneering drug delivery system that uses Dox and Au nanocages coated with cancer cell membrane vesicles (CMVs) to target metastatic breast cancer. Nanocages are a type of NPs that possess a special hollow structure capable of enclosing significant quantities of drugs and CMVs facilitate the selective targeting of cancer cells and hyperthermia-triggered drug release, thereby increasing efficacy.
Additionally, in a recent clinical trial about localized prostate cancer treatment, researchers utilized gold-silica nanoshells (GSNs) in conjunction with magnetic resonance-ultrasound fusion imaging. GSNs were employed for tumor ablation within the prostate and to overcome the limitations that traditional laser ablation techniques can involve, such as inaccuracies in temperature monitoring as well as the potential risk of overheating. The research involved the recruitment of 16 prostate cancer patients and resulted in a success rate of 94% in focal laser ablation using GSNs, with no significant side effects. The findings of this pilot device study provide evidence that utilizing GSN-directed laser excitation and ablation is a safe and technically viable method for selectively eliminating prostate tumors [86].

-Given their remarkable light absorption in the near-infrared region, CNTs have also proven potential in PTT. Due to their superior thermal conductivity and large surface area relative to their volume, CNTs efficiently generate heat when exposed to laser light. These qualities facilitate effective tumor ablation. Surface functionalization of CNTs with biocompatible

coatings or targeting molecules makes them more specific and facilitates their cell uptake [87].

Furthermore, PTT can be used along with other types of treatments. A combination of PTT and chemotherapy is used by Nam et al., 2018 [88] as a novel strategy to induce powerful anti-tumor immune responses against cancer and metastasis. This work is based on previous studies that state that hyperthermia promotes the immune response in dying tumor cells by releasing antigens or pro-inflammatory cytokines [89]. In this approach, polydopamine-coated spiky gold NPs are merged for increased efficiency and stability and then combined with the chemotherapeutic drug Dox. This combination demonstrated a significant elimination of locally treated tumors and untreated distant tumors, leading to a significant survival rate, surpassing 85% in a colon cancer mice model. The animals subjected to treatment demonstrated resistance to tumor relapse over an extended period, suggesting the acquisition of immunological memory to fight recurrent tumor growth. The reason is that this treatment stimulates proteins involved in the immune response, namely heat shock protein 70 (HSP70) and murine UL16-binding protein-like transcript 1 (MULT1). HSP70 is a stress response protein involved in protein folding and it is frequently overexpressed in cancer cells, whereas MULT1, triggers immunological responses against malignant cells. These proteins promote immune activation and antigen presentation, involving CD8+ T cells and NK cells. CD8+ T cells play a crucial role in suppressing the proliferation of tumor cells and stopping their recurrence.

4.4.2 Photodynamic therapy

PDT, on the other hand, uses photosensitizers (PS) to absorb photons and then transfer that energy to other molecules, causing ROS damage. Some examples of PS include polyacetylenes, curcumins, porphyrin, chlorin, phthalocyanine derivatives, methylene blue, or alkaloids. PDT research currently faces several limitations, such as light delivery to target tissues, reduced efficacy in hypoxic tumors, the different inherent properties of photosensitizers, the incomplete comprehension of the mechanisms of action, the lack of consistent clinical results and a limited selectivity and target specificity [90,91].
Many recent studies offer innovative strategies to overcome one of the major hurdles in PDT: the lack of oxygen supply in hypoxic tumor microenvironments. The crucial role of oxygen in PDT is facilitating the generation of ROS, key for tumor growth suppression [92–96].

Luo et al., 2018 [97] introduced the design of artificial red blood cells (ARCs) that were loaded with a combination of hemoglobin (Hb) and indocyanine green (ICG), which acted as the PS. Researchers encapsulated Hb, a natural oxygen carrier, within the ARCs. The ICG and Hb-loaded ARCs preferentially aggregate in tumor tissues via passive targeting. This nanocomplex led to higher retention and efficacy of both chemicals during PDT, as well as increased cytotoxicity in the targeted cancer tissues due to the oxidation of Hb into ferryl-Hb.

Despite all of the benefits that nanotechnology implementation carries, some challenges remain, such as nanoparticle scalability, long-term safety profiles, and individualized therapy optimization. The effective translation of nanoparticle-based PTT and PDT into routine clinical practice requires the establishment of standardized protocols, robust manufacturing procedures, and detailed assessment of treatment responses.

4.5 NPs-based immunotherapy

It is no doubt cancer immunotherapy has revolutionized cancer treatment, harnessing the body's immune system to recognize and eliminate cancer cells. Nonetheless, many types of cancer do not respond effectively, approximately just 15% of 27 different types of cancer respond, which include melanoma or mismatch repair-deficient colorectal cancer [98], thereby requiring new strategies that increase the efficacy and safety of immunotherapy. The latest advances in the field of nanotechnology may help increase the accuracy and efficacy of immunotherapeutic treatments, reduce side effects and overcome other limitations. These developments have the potential to significantly improve patient outcomes and modernize cancer treatment [99].
Although immune activation in cancer immunotherapy can produce potent anticancer effects, it can also trigger autoimmune reactions, known as immune-related adverse events. Researchers can target the activity of immunostimulatory therapy on specific cells or tissues using drug delivery methods, reducing dispersion in the body and undesired side effects [100]. They can also slowly release therapeutic doses, resulting in persistent target engagement rather than instantaneous saturation and dispersion of the therapeutic agent, which could lead to toxicity. This strategy has the potential to significantly improve cancer immunotherapy's safety and efficacy.

Another challenge in immunotherapy is based on the immunosuppressive nature of the tumor microenvironment. Some of the strategies to solve it include:

-Adoptive cell therapy: Artificially modifying T-cells could make them more effective against cancer cells. Some researchers have opted to attach “backpacks” with different anticancer drugs or molecules to T-cells to enhance their function [99]. For example, it is possible to attach cytokines like IL-21, which induce the activation and proliferation of T-cells, or artificially modified patients’ T-cells with new receptors to recognize cancer cells [101]. The backpacks may also include chemotherapy drugs or immune checkpoint inhibitors to modify the tumor microenvironment, resulting in major T-cell infiltration and alleviated immunosuppression. Immune checkpoints are molecules present on T-cells to regulate the immune response, avoiding excessive or autoimmune reactions in healthy tissues, but sometimes exploited by cancer cells to evade the immune attack [102]. Immune cells can become “exhausted” after long exposure to these molecules in tumor tissues, no longer triggering the immune response. As shown in *Figure 11*, T-cells can be “rejuvenated” when these checkpoints are blocked or inhibited. Backpacks can also release their cargo in a controlled manner through stimuli-responsive substances or enzymatic degradation [103]. Until recently this approach has been quite limited due to a lack of immunoengineering techniques [104].

-Endogenous immune response enhancement: To enhance the endogenous immune response, Chimeric antigen receptors (CARs) can be generated in situ by delivering DNA in NP to encode these receptors in the cell [105]. Reprogramming macrophage polarization is another strategy used to promote the endogenous immune response. While M1 macrophages prevent tumor growth, M2 macrophages promote tumor growth and immune suppression. Certain NPs can alter this polarization in order to reprogram tumor macrophages, for example, iron oxide NPs [106]. As seen in Table 1, iron oxide NPs have already been approved for magnetic hyperthermia treatment in prostate cancer and glioblastomas, and they are also widely used to treat anemia [107]. It is not entirely clear how

iron oxide NPs polarize macrophages, but it is thought that their interaction promotes physiological changes and starts signaling pathways that lead to polarization. The NPs' production of cytokines and ROS, or the NPs' properties, such as their size, charge and surface functionalization, may also play an important role [108]. For instance, Zanganeh et al., 2016 [109] tested iron oxide NPs in mouse models bearing a type of mammary carcinoma. These NPs successfully inhibited tumor growth by inducing pro-inflammatory macrophage polarization. This is an interesting novel approach and a potential candidate for future approval.

-Nucleic acids delivery: Using NPs, nucleic acids can be delivered to target cells more effectively [99]. For instance, the cytosolic delivery of nucleic acids via NPs could lead to the activation of pattern recognition receptors and the synthesis of immune system proteins. Incorporating pH-responsive blocks in NPs is one example of an immunoengineering strategy that promotes endosomal escape and receptor activation [110].

-Vaccination: Nanotechnology has the potential to significantly enhance cancer therapy vaccines in a variety of ways. Firstly, it facilitates the co-delivery of antigens and adjuvants, which improves their recognition and ensures a simultaneous delivery to immune cells. Additionally, NPs can specifically target lymph nodes through active targeting using lipophilic albumin-binding tails [111]. Lymph nodes are key in the initiation of the immune response, so NPs' application improves the efficacy and also limits the side effects [99]. Immunoengineering approaches like glycoengineering, on the other hand, are used to replicate natural immunological responses, enhancing immune activation [112]. Personalized vaccines, depicted in *Figure 11,* are also garnering growing attention due to their remarkable adaptability to the unique circumstances of each patient. Nanotechnology plays an important role in the efficacy of mRNA-based vaccinations by protecting the mRNA and facilitating an effective delivery. Further study is still required to fully discover and exploit the potential of nanotechnology in the creation of cancer vaccines.

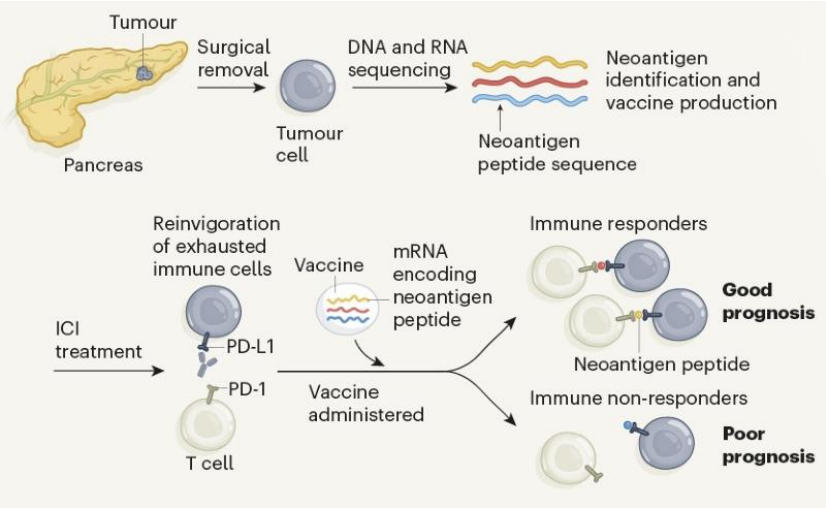

Figure 11. Personalized neoantigen vaccine for pancreas cancer cells. Neoantigens are generated from DNA and RNA of surgically removed tumor cells. The immune checkpoint inhibitor (ICI) treatment blocks immune checkpoints, such as PD-1 or PD-L1, to restore exhausted T-cells that were no longer normally functioning due to prolonged exposure to the signals from these checkpoints. The vaccine is then administered, and if those neoantigens are recognized by T-cells there will be a better prognosis. Extracted from Huff et al., 2023 [113].

In a very recent article that has drawn the public's attention Rojas et al., 2023 [114] published the results of phase I clinical trial in which the efficacy of a customized neoantigen vaccine

called "autogene cevumeran" was tested. To treat 16 individuals with pancreatic ductal adenocarcinoma (PDAC), one of the types of cancer with the least response to immunotherapy [98], this neoantigen was contained in a lipoplex NP together with atezolizumab, an immune checkpoint inhibitor that targets PD-L1, and mFOLFIRINOX, a chemotherapy treatment. Each patient's autogene cevumeran was unique since it was created from surgically removed PDAC tumors.
In 50% of the patients, this technique led to neoantigen-specific T-cell responses. The percentage of T cells generated accounted for up to 10% of all blood T cells and included long-lived polyfunctional effector CD8+ T-cells. The correlation between vaccine-expanded T-cells and prolonged relapse-free survival after 18 months suggests a delay in PDAC relapse. These findings prove the potential of customized neoantigen vaccines coupled with immunotherapy and chemotherapy for PDAC treatment, advocating for more research in larger studies with diverse patient populations, in PDAC and other types of cancer, along with more research of biomarkers able to predict the vaccine responses.

4.3 NPs-based imaging techniques

Early cancer detection and identification are crucial for effective therapy. Traditional imaging approaches for cancer diagnosis include X-rays, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound and positron emission tomography (PET). Each of these techniques has strengths and limitations that must be considered while determining the best imaging method.
Firstly, X-rays are often used to image dense tissues, whereas their applicability for soft tissue imaging is limited. These tests have low sensitivity for early-stage cancer detection and are inadequate for detecting small metastases [115].
CT scans, on the other hand, provide cross-sectional images of the body by using a sequence of X-rays. CT scans offer high sensitivity when detecting malignancies and can produce detailed images of the body's internal architecture. Nevertheless, they involve ionizing radiation, which can be potentially hazardous for individuals who require repeated imaging [115,116].
MRI creates detailed images of soft tissues in the body by using a strong magnetic field and radio waves. Compared to CT scans, it is safer because it offers a good resolution and does not expose users to ionizing radiation. Nonetheless, MRI is costly and time-consuming [115,117].
Ultrasound works through the application of high-frequency sound waves. It is especially effective for visualizing the abdominal and pelvic organs and for guiding biopsies. However, ultrasound has poor contrast, is not suitable for air-containing cells and has a depth limit [115,118].
Lastly, PET scans provide visuals of metabolic activity by using radioactive tracers. They are especially helpful to identify metastases. Yet, their resolution could still be improved [115,118].

Imaging approaches based on nanotechnology use NMs with unique optical, magnetic and electronic properties. As shown in *Figure 12*, different NPs can be combined with conventional approaches in order to improve them. Novel imaging techniques can offer detailed images of cancer cells and tissues with outstanding sensitivity and specificity taking advantage of those properties.

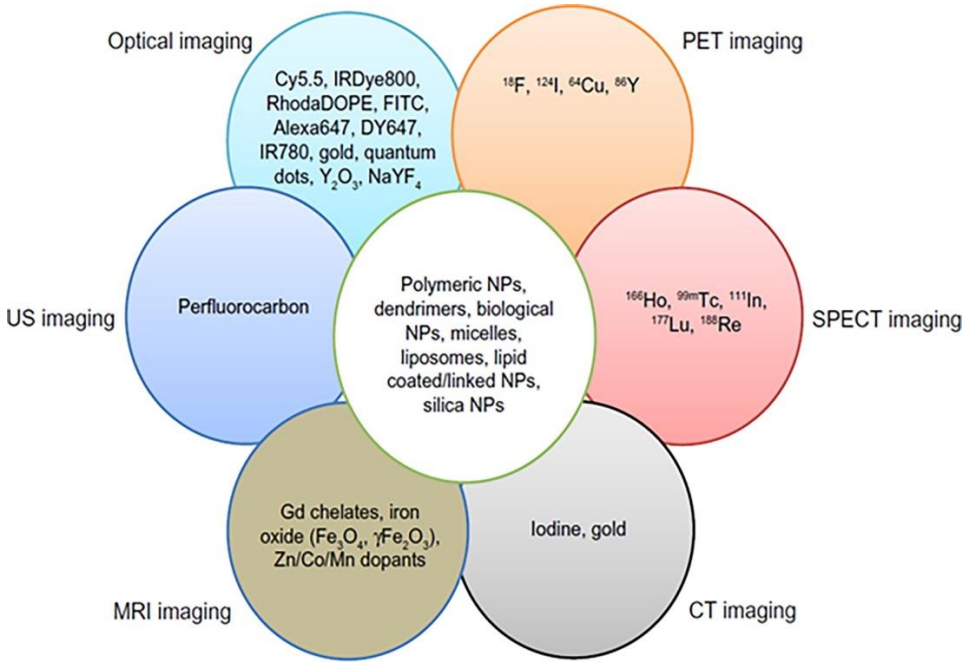

Figure 12. Comprehensive list of NPs applied to the different conventional approaches of cancer imaging. Extracted from Ma et al., 2017 [119].

As shown in *Figure 12,* fluorescent NPs, such as QDs, are used to enhance optical imaging. After being injected into the body, they accumulate in malignant tissues through passive or active targeting thanks to the tumor microenvironment properties previously shown in *Figure 6*, and then emit fluorescent signals that can be detected by irradiating light of a different wavelength, the result is highly sensitive and selective imaging techniques.
The application of magnetic NPs for cancer imaging is another bionanotechnology-based imaging approach that could be combined with MRI, to be used as contrast agents. When magnetic NPs are delivered into the body, they aggregate in malignant tissues and modify the magnetic field, leading to higher sensitivity and specificity in cancer detection. Since this technique is non-invasive and lacks ionizing radiation, it is safer for the patient.
NPs have also been employed as probes in cancer imaging, these probes are combined with targeting molecules that allow them to specifically bind and be delivered to cancer cells or tissues. Therefore, this method is highly sensitive and specific, but also useful to detect small tumors and metastases, otherwise difficult to see using conventional imaging techniques [120].

Meng et al., 2023 [121] carried out an experiment to test a pH-sensitive, charge-conversional and ultrasound-responsive nanodroplet-based drug delivery system for cancer imaging and therapy. This design was already tested successfully in previous studies but had some limitations such as NP toxicity, elevated cost and operational complexity [122,123]. This study focused on further improving this strategy and evaluating its ultrasound imaging ability, biocompatibility, tumor accumulation and antitumor efficiency in a model of prostate tumor-bearing mice.
The nanodroplets were Dox-loaded O-carboxymethyl chitosan/perfluorohexane nanodroplets. Chitosan stabilizes nanodroplets in aqueous solutions while also providing a surface for subsequent modification with targeted ligands. It also leads to the release of the drug in a pH-dependent manner, which enhances the specific targeting of tumor cells thanks to their acidic microenvironment. Perfluorohexane (PFH), depicted in *Figure 12*, is a type of fluorocarbon that is vaporized when exposed to ultrasound waves due to the acoustic

droplet vaporization effect, which results in the release of Dox [124]. The combination of pH sensitivity and PHF vaporization provides a more controlled and targeted drug release.
The results confirmed the nanodroplets' pH-sensitive drug release capacity, with a slow release at pH 7.4 and a faster release in acidic environments, this leads to a significant preferential accumulation in tumor cells compared to healthy ones. Additionally, due to the acoustic droplet vaporization, ultrasound exposure caused a rapid burst release of Dox. The nanodroplets also verified an enhanced contrast in ultrasound imaging capability, with higher brightness of ultrasound signals in a dose-dependent manner. Using an ultrasound scanner system, the In vivo ultrasound imaging revealed the nanodroplets' fast accumulation and phase change near tumor locations, highlighting their potential for ultrasound-induced tumor-targeting imaging and treatment. Biocompatibility and biosafety tests confirmed their low cytotoxicity and, when compared to free Dox, nanodroplets demonstrated longer stability, effective transport, and sustained accumulation in tumor locations. Furthermore, the nanodroplets demonstrated enhanced anticancer efficacy under ultrasound stimulation in vivo, inducing tumor cell apoptosis.
Based on these findings, the scientists concluded that these nanodroplets have a promising future as a smart and multi-responsive system for cancer diagnosis and treatment [121,125].

A new study published in the journal Cancer Nanotechnology demonstrates how the biocompatible polymer-coated QDs (PQDs) coupled with folic acid (FA-PQDs) can be used for targeted tumor imaging in living severe combined immunodeficiency (SCID) mice. The study assesses the in vitro and in vivo efficacy of FA-PQDs for targeted imaging of prostate cancer and verifies their feasibility as cancer nanoprobes.
Human prostate cancer cells LNCaP were injected subcutaneously in the flank of the mice to test in vitro targeted imaging with FA-PQDs. Folic acid targets folate receptors, proteins that then trigger endocytosis, which results in folate/folic acid uptake. These receptors are expressed in a variety of solid tumors, including the lung, brain, ovarian, prostate, breast, gastric, and colorectal, as it is involved in DNA synthesis, repair, and methylation. Nevertheless, their expression is insignificant in healthy cells, making them suitable for cancer imaging [126]. As a result of the folate receptor-mediated mechanism, FA-PQDs were internalized in greater numbers than PQDs during the first part of the experiment, suggesting their capacity to target cancer cells in vitro. ImageJ software was used to confirm that FA-PQDs had higher particle absorption than PQDs.
The distribution of PQDs was also assessed in vivo using SCID mice and whole-body fluorescence imaging along with CT scanning. The authors discovered that PQDs undergo renal clearance after a short period of time circulating in healthy organs and finally accumulating in the urinary bladder.
Lastly, prostate cancer-induced mice were used to assess in vivo imaging with FA-PQDs (Targeted group), PQDs (Non-targeted) and without QDs (control group). The solutions were injected in the tail vein.
As shown in *Figure 13*, the targeted group had higher fluorescence intensity at the tumor site, between the ribcage and hind leg, than the non-targeted and control groups, confirming that FA-PQDs were more specifically delivered to the tumor.

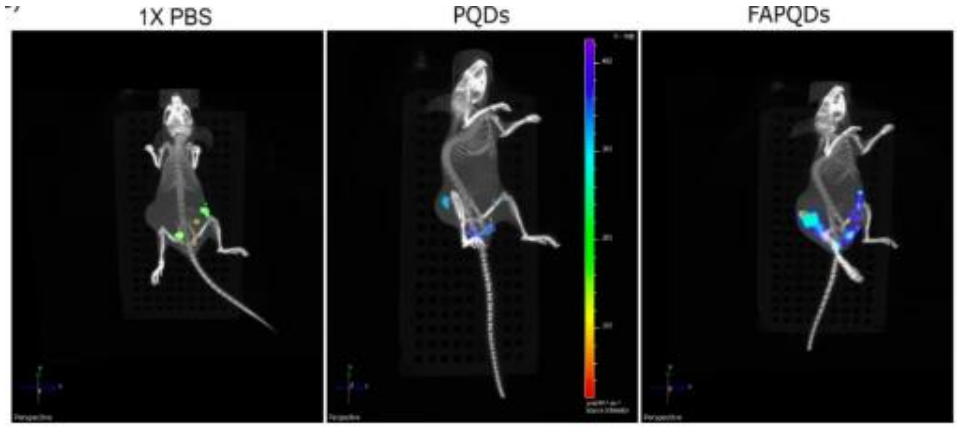

Figure 13. Computed tomography scan of control (1X PBS), non-targeted (PQDs) and targeted groups (FAPQDs), 60 min post-injection. The control group was administered Phosphate-Buffered Saline (PBS) and showed low autofluorescence in a small number of organs, depicted in green and yellow. The non-targeted group showed more fluorescence compared to the control; however, it was still very distributed. The targeted group showed the highest fluorescence in the tumor site. Extracted from Pandey et al., 2023 [127].

In view of the aforementioned, the authors concluded that FA-PQDs were effective at targeting prostate cancer cells in mice. Moreover, the use of FA-PQDs for cancer-targeted imaging resulted in successful PQD accumulation at the tumor location. Thus, QDs could be employed for tumor imaging in living mice, which makes them an appealing alternative to traditional fluorescent dyes for cancer diagnosis. Likewise, PQDs can be conjugated to different cancer-specific biomarkers for in vivo cancer imaging as well as cancer-specific drugs for other targeted cancer treatments [127].

In a recent study, Kuo et al., 2019 [128] presented the results of combining multi-photon microscopy and antibody-conjugated QDs to detect and image circulating tumor cells (CTCs) and cancer stem cells (CSCs) in living mice. They used cancer cells that expressed fluorescent proteins, then they generated tumors on the mouse earlobes to later detect CTCs and observe their behavior. The researchers then applied antibody-conjugated QDs in real-time imaging to successfully visualize and monitor the different subpopulations of CTCs at different stages of tumor growth. However, there are certain limitations as well, such as the necessity to improve in vivo labeling efficiency in order to detect rare cell-cell interactions and its restricted application to tumors that can be reached by laser light.
CTC detection is essential in cancer diagnosis and management, while identifying subpopulations with high metastatic potential, such as CSCs, is particularly important. According to recent studies, CTCs have emerged as key biomarkers for cancer diagnosis and prognosis, although many uncertainties about their origin and subpopulations remain. It is difficult to tell the difference between CTCs that can spread in the body and those that cannot, considering different types of CTCs can have substantial genomic, proteomic, and functional differences. Understanding CTCs' spatiotemporal behavior and identifying particular subpopulations is essential for taking advantage of them as a prognostic biomarker. Researchers can gain vital insights regarding cancer progression and therapy response by monitoring the behavior of CTCs in the bloodstream. There is a dire need to develop and validate detection techniques with high sensitivity and specificity, therefore nanotechnology is the most active area of research among them [129].
There is currently just one FDA-approved CTC detection platform, the CellSearch® system, which detects and quantifies circulating tumor cells (CTCs) of epithelial origin. It is recommended as an aid for monitoring patients with metastatic breast, colorectal, or

prostate cancer. It separates CTCs from other blood cells using epithelial cell adhesion molecule (EpCAM) antibody-modified magnetic NPs to target EpCAM+ or CD45- CTCs. The specificity of these isolation approaches, however, is dependent on surface indicators and the results can be misleading if CTCs do not display these markers [130].

As shown above, nanotechnology has shown promising results in cancer imaging and diagnosis in recent studies, which is essential to treat any type of cancer. Recent studies have proven increased specificity and selectivity The main challenges in current studies are achieving longer stability, effective transport and specific tumor accumulation of NPs [121,127]. It would be interesting to combine recently developed nanotechnology techniques with previous methodologies, as next-generation cancer biomarkers would provide more information, specificity and sensitivity in combination with currently used biomarkers.

4.4 Noteworthy considerations and future outlook

In this review, multiple nanobiotechnology-based strategies have been reviewed for different fields of cancer medicine. Although there is a wide diversity of NPs and each of them has unique properties to offer, certain key supporting arguments consistently emerge across the different studies. These arguments highlight the significant impact that NPs can have on advancing cancer treatment and their potential to revolutionize current practices:

1. They allow targeted drug delivery, enhancing the treatment efficacy while reducing toxicity and damage to healthy cells, avoiding side effects in the patient as well.
2. They can improve the solubility and stability of anticancer drugs which normally would have poor results in these areas if not encapsulated in NPs
3. It is possible to combine multiple therapies, delivering multiple anticancer drugs or using different treatment modalities, simultaneously or sequentially, leading to synergistic effects and better outcomes.
4. They hold the potential for personalized therapy approaches. NPs can be customized according to the genetic profile and disease of each patient.
5. Using diverse NMs, NPs could overcome drug resistance by evading common resistance mechanisms in cancer cells, which would maximize drug concentration at the targeted site.
6. NPs can be designed to release drugs in a controlled manner. Overall, they offer more control and monitoring at every step of the treatment.
7. NPs can intervene with the tumor microenvironment, sensitizing tumor cells or promoting immune recognition.
8. NPs can serve as contrast agents, so not only they could enhance cancer therapy but also cancer diagnosis, which is essential for the patient's survival.

While nanotechnology holds a huge potential, it is important to acknowledge the current limitations that have shown up in the aforementioned studies and this field is currently facing:

1. The safety concerns of NMs are a very controversial matter in every study, as they may exhibit unexpected toxicity or long-term effects. Due to their novelty and therefore lack of evidence, the potential risks are still unknown.
2. The manufacturing and scale-up of nanosystems is a demanding process that requires the right equipment and expertise. It is necessary to develop robust

3. manufacturing processes able to reproduce NPs with consistent quality, as homogeneity is essential in their performance.
4. Expanding on the previous point, the cost of design, synthesis and scale-up can be quite elevated, limiting their use and contributing to the lack of research.
5. Due to their uniqueness and novelty, nowadays the process for regulatory approval and standardization can be complex and take a lot of time, in order to assure their safety.
6. The variability in NPs' effects within different tumor types and individuals makes this standardization difficult.
7. NPs could potentially trigger unwanted immune reactions, causing inflammation or possibly long-term conditions in the patient.
8. As NPs are relatively new in the field of oncology, the public could raise concerns about their safety and efficacy, reducing the investments in this technology and the number of volunteers in clinical trials, and therefore increasing the time or stopping its implementation.

For the future implementation of NPs in the field of oncology it is essential to address all these limitations. Until recently, studies were mainly focused on exploring what nanotechnology could offer, discovering where the limits are and discerning its compatibility with cancer medicine. Now that scientists have gathered more knowledge and evidence there has been a substantial change. It is time to start addressing not only the more practical challenges but also the social ones, as more and more studies are starting clinical trials every year and need investments and regulatory frameworks to continue. Scientific divulgation may play an important role in this matter, as public acceptance will contribute to this process or slow it down.

On the other hand, this does not mean research should decline, as there are still many safety risks and potential applications to discover. Future research directions should focus on developing novel targeted drug delivery systems, refining nanotechnology imaging techniques, integrating nanotechnology with other cutting-edge technologies, and ensuring the safety of NMs in the human body. The continuous advancements in various fields offer exciting opportunities to implement novel ideas and techniques in nanotechnology-based strategies for cancer treatment and diagnosis. For example, thanks to advances in genetics, the promise of patient-specific nanomedicine becomes a reality, where treatment decisions are guided by molecular profiling. This personalized approach ensures more effective and tailored approaches. Advancements in these areas will pave the way for more effective and personalized cancer therapies, early detection, and accurate diagnosis. Continued collaborations, funding support and the effort of the scientific community will be crucial in driving this research forward and transforming cancer medicine.

It is reasonable to suggest that there are still many applications to discover in this field, for example, many authors have started suggesting the implementation of biodegradable NPs to reduce long-term toxicity. Future ideas like this one and many more innovative strategies that have already been implemented are what make nanotechnology such a promising tool for cancer therapies and diagnosis.

5. Conclusions

In conclusion, nanotechnology holds great potential for advancing cancer research through multiple innovative strategies. This review provided an overview of the current state of research of nanotechnology in cancer medicine:

1. One of the key advantages of its application lies in the diverse range of nanomaterials available, enabling the development of a wide variety of NPs that can overcome limitations associated with conventional approaches. While organic nanomaterials have been prominent thus far, recent studies suggest that inorganic nanomaterials may play a crucial role in the future, which is reflected in the different types of approved NPs over time.

2. The versatility of NPs is a significant advantage, allowing for strategies tailored to specific treatments through changes in the internal structure, composition and surface modification. These include liposomes, polymeric NPs, metallic NPs and many others. Nanotechnology offers many several benefits for cancer therapy, including targeted delivery, improved solubility, biocompatibility, non-invasiveness, and controlled drug release. NPs can revolutionize several areas such as gene therapy, immunotherapy, photothermal therapy, and photodynamic therapy,

3. NPs have also potential applications in tumor imaging and cancer diagnosis, providing valuable insights into disease progression and essential molecules involved in tumor cells.

4. However, despite nanotechnology's immense potential, there are challenges that need to be addressed. It is imperative to thoroughly assess the potential risks and safety concerns associated with NPs before their introduction into the market, as long-term effects may not have been fully observed yet. Moreover, the scale-up process for nanotechnology remains largely uncharted territory, necessitating further research to make it safer and more cost-effective. Standardized protocols for manufacturing and handling NPs need to be developed to ensure consistency and reliability across different applications.

Finally, this review highlighted future research directions in the field of nanotechnology for cancer. It emphasized the need for multidisciplinary collaborations and continued innovation to overcome existing challenges and limitations. Promising areas for future investigation include the development of novel nanomaterials, advanced imaging techniques, personalized therapies, and the integration of nanotechnology with immunotherapies or other treatment modalities.

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