PROGRESS IN DRUG DISCOVERY & BIOMEDICAL SCIENCE

HH PUBLISHER

Review Article

Nanomedicine in Oncology: A Critical Review on Epidemiology, Health Impacts, Challenges, and Future Outlook

Article History

Received: 24th March 2024;

Received in Revised Form: 24th April 2024;

Accepted: 29th April 2024;

Available Online: 4th May 2024

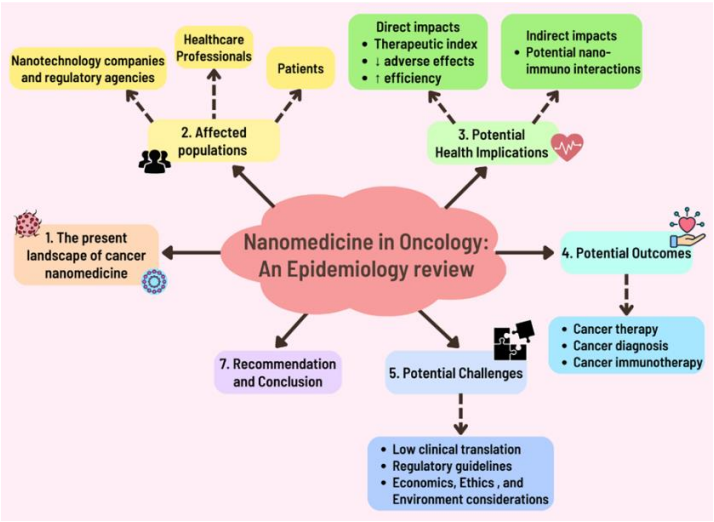
Teh Coey

Department of Biological science, Sunway University, Bandar Sunway, 47500 Petaling Jaya, Selangor, Malaysia; 22022479@imail.sunway.edu.my

Abstract: Cancer remains a leading public health issue globally due to its increasing morbidity rate, with cancer cases predicted to double over the next 20 years. While current conventional treatments are the primary go-to in treating cancers, they still present ineffective due to adverse side effects, poor targeting, and drug resistance. In recent years, nanomedicines have emerged as a better alternative for cancer treatment in maximizing drug delivery, bioavailability, and therapeutic efficacy through passive and active mechanisms. Despite having high potential, the poor clinical translations and recent fund retractions have led to limited progress in cancer nanomedicine. Thus, this review aims to review and identify the role of nanomedicine in oncology by analyzing the involved epidemiological populations, potential health impacts, possible outcomes, and current challenges in terms of economic, environmental, and ethical aspects. Further outlooks in improving nanomedicine therapeutic efficacy are also discussed, including switching approaches to nanomedicine development, modifying current regulatory guidelines, and providing training programs.

Keywords: Cancer, nanomedicine, oncology, therapeutics, diagnostic

Graphical Abstract:



1. Introduction

Cancer is one of the most significant public health problems and leading fatal diseases worldwide, with lung cancer and breast cancer being the most prevalent cancers in males and females, respectively[1,2]. Around 112 of 183 countries reported cancer as the first two causes of death before the age of 70, while the disease accounts for at least 18.1 million cases and 10 million deaths in 2020[2–4]. Typically, the hallmarks of cancer involve abnormal cell proliferation, cell differentiation, and altered signaling and metabolism regulation[5,6]. As a result, the transformed cells, or tumor cells, can spread to various parts of the body and present distinct clinical features[6]. Several risk factors contribute to the rise of the disease, including environmental pollution, genetic predisposition, and the individual's socioeconomic development[1]. At the same time, multiple studies have forecast the global healthcare burden to increase exponentially in the following decades due to demographic changes and population growth[1,2,7]. Notably, the National Cancer Institute[8] estimates a surge in the amount of cancer patients and cancer-related deaths by 2040, with a cancer case number of 29.5 million. While conventional cancer treatments, such as chemotherapy, surgery, and anticancer agents, are successful in improving the patient's survival, they still have limited efficacy in treating metastatic cancer[1,5]. Additionally, recent discoveries show tumor cell-resistance to anticancer agents and poor delivery to the target neoplastic tissue, which continues to be a challenge in the medical and research field[7]. Therefore, researchers are exploring the application of nanotechnology as an effective treatment for cancer to curb the prevalence and morbidity of cancer[5,7].

Over recent decades, the study of nanotechnology has continued to grow due to its potential and efficacy in treating various diseases. It is later termed the bridge between biological and physical sciences by applying natural, incidental, or manufactured miniature-structured particles within the nanometre range (1–100nm) or nanomaterials[9–11]. Concurrently, the breakthrough in nanotechnology has revolutionized the field of medicine, which led to the creation of a new discipline of nanomedicine in 1999[5,11]. Generally, nanomedicine addresses the current limitations of medical treatments by implementing techniques and knowledge of nanoscience for disease control and prevention, monitoring, and intervention for diagnosis, treatment, remediation, and regeneration[11,12] While nanomaterials come in various shapes, sizes, and surface chemical compositions based on specific physiochemical properties, the small-sized, three external nanospheres, or nanoparticles, are more popular due to higher surface area, reactivity, and better biomolecule adsorption, making them a crucial component for drug delivery[9,10,13,14]. These properties allow nanoparticles to assist in maximizing bioavailability, drug delivery, and target while minimizing dose and toxicity effects and improving drugs' transport across biological

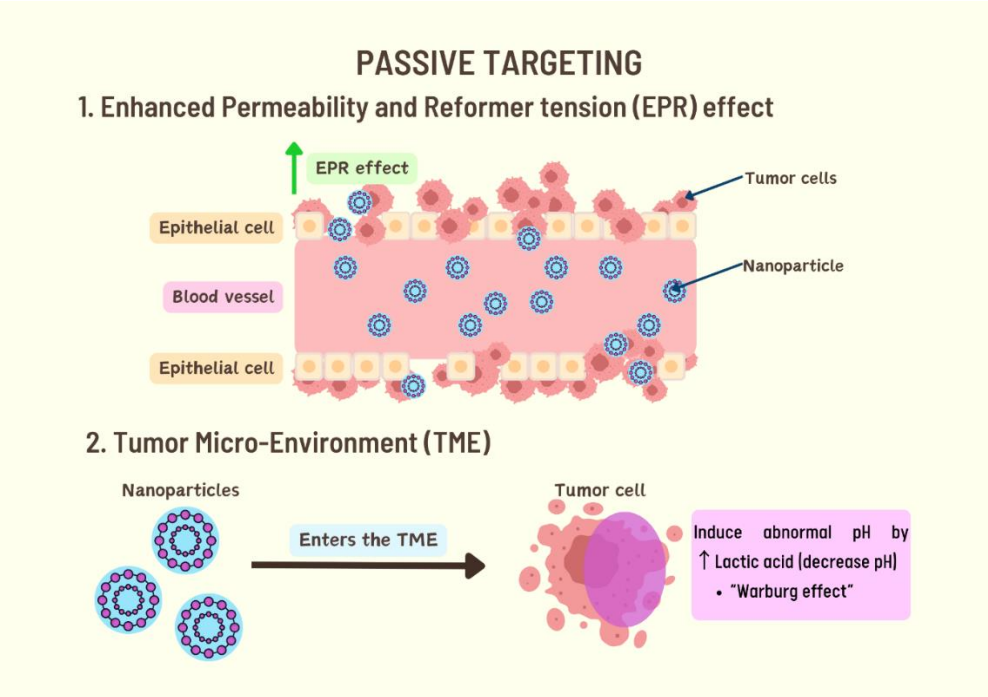
barriers like the blood-brain barrier (BBB)[1,5,13]. Hence, nanomedicine has become an attractive field for cancer in biomedical research and the pharmaceutical industry because of its improved drug delivery performance, such as pharmacokinetics, bioavailability, and low toxicity.

Presently, at least 15 cancer nanomedicines receive regulatory approval globally, with over 200 clinical trials evaluating at least 80 novel cancer nanomedicines[1]. Cancer nanomedicine primarily manipulate specific nanoparticles in target nano-therapy in delivering anticancer medications directly to the tumor tissue[10]. Hence, many anticipated nanomedicines to tackle the primary obstacles in cancer treatment by enhancing the permeability and plasma half-life of the drug while reducing multi-drug resistance and undesirable side effects[5,15]. For example, combining nanotechnology and the immune checkpoint blockades (ICBs) reduces cytotoxicity and provides promising results[16]. Notably, scientists have designed various therapeutic nanoparticle platforms, such as lipid-based, polymeric, and inorganic nanoparticles, each with their specific properties and efficacy, for the delivery of therapeutic nucleic acids, immunotherapeutic and chemotherapeutic agents in curing cancer[1,16,17]. Recent advances also led to the production of a series of nanocarriers, which researchers deemed a superior alternative to minimize off-target toxicity via tumor tissue-, cell-, and organelle-specific targeting[1].

There are two main mechanisms of action in nano-based drug delivery, which are the passive and active targeting methods[5,7,16]. The passive method is also known as the first-generation nanomedicine that relies primarily on regulating physiochemical properties by manipulating the pharmacokinetics and biodistribution of the drug to the tumor site. Within the passive methods, the effects can further be subdivided into the Enhanced Permeability and Reformer tension (EPR) and Tumor Micro-Environment (TME) properties[5]. Theoretically, tumor cells induce neovascularisation and large pores in the vascular walls, which favor passive targeting by permitting the particles to reach the tumor site [5, 16]. As the lymphatic system cannot drain the tumoral fluids, the particles can accumulate at the target site through the EPR effect[7,16]. Thus, EPR has become the centra dogma of cancer nanomedicine[18]. Also, nanocarriers may utilize TME properties like acidic pH, higher potential and redox, and differential secretion of lytic enzymes for uniform drug delivery[5]. On the other hand, active targeting therapy predominantly depends on the selective binding of ligands with the cell surface markers expressed by cancer cells, including antibodies, aptamers, carbohydrates, and peptide molecules[7,16]. The method provides better results in anticancer treatment due to its high specificity, resulting in lower cytotoxicity effects[16]. Following nanomedicine internalization, it transports the therapeutic agents to the nuclear

endosome, resulting in the degradation of the nanocarrier for subsequent processing and drug release[15].

[A]



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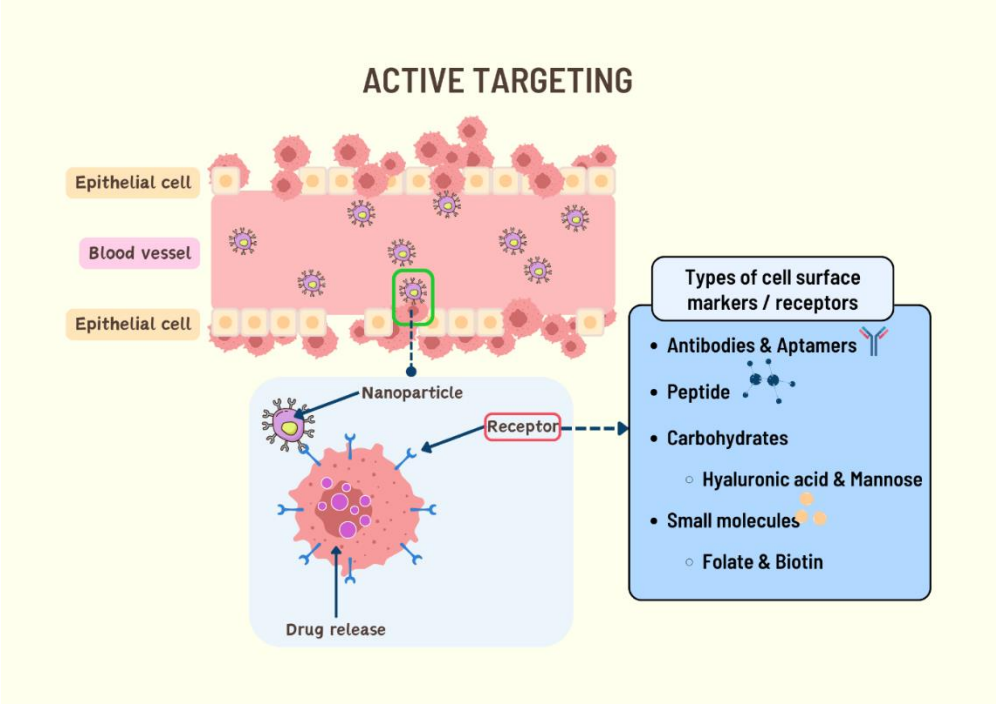

Figure 1. The passive (A) and active (B) targeting mechanisms in nano-based drug delivery.

Although current clinical settings have employed nanomedicine in cancer therapy, there remains several controversies in its application to cancer. Recently, the nanomedicine field have faced several big blows. The BIND Therapeutics and Cerulean Pharma, a prominent nanomedicine company had filed for bankruptcy after poor clinical trial performances. Also, current meta-analysis showed only 0.7% of the intravenously injected nanoparticles accumulates in tumor, which is lesser than the claimed therapeutic rate. At the same time, the US National Cancer Institute had discontinued funding for the Centers of Cancer Nanotechnology Excellence (CCNEs) since 2020, which lead to the public quoting these phenomenon as "the beginning of the end of the nanomedicine hype"[19]. However, some may argue that nanomedicine is still relevant for oncology uses. Thus, the report aimed to evaluate the use of nanomedicine in oncology from an epidemiology perspective.

2. Methods

A literature search was performed on PubMed, Springer Link, Nature, and Scopus (Elsevier) databases using the following keywords: cancer, nanomedicine, oncology, treatment, diagnostic, and nanotechnology. Specifically, the search strings used in the PubMed database were (cancer) AND (nanomedicine) and (oncology) AND (nanomedicine). The author further screened the titles and abstracts to select suitable papers. The author also included related materials from credible websites. Additional relevant references from the reviewers' reference lists were retrieved for the literature. The final literature search was conducted on the 8th of December 2023.

3. Affected Populations

3.1 Patients and Higher Risk Populations

Patients of varying cancers are the principal recipients of cancer nanomedicine in seeking better treatments, especially ovarian, breast, and pancreatic cancer patients[20]. While there are no exact statistics regarding its application to cancer patients, the increasing nanomedicine development for cancer treatment suggests a higher demand for said treatment in the market. Generally, patients receive nanomedicines in various anticancer modalities, including chemotherapy, radiotherapy, gene therapy, immunotherapy, photothermal therapy, and combination therapy[21]. Notably, the current medicinal field has integrated nano-based drugs, or nano-formulation, in cancer therapy, all of which is based on the EPR effects. For instance, Doxil® for ovarian cancer and Abraxane® for pancreatic and metastasized breast cancer are the most popular nano-based drugs that receive approval from the U.S. Food and Drug Administration (FDA) in clinical settings for cancer therapy[20,22]. Also, cancer patients who have received traditional radiotherapy and chemotherapy as part of their treatment

regimens previously may receive nanomedicine-based approaches to provide more optimal delivery and lesser side effects.

Some populations have a higher chance of becoming cancer patients. The most predominant non-modifiable risk factor is age, with approximately 60% of cancers occurring in elderly above the age of 65 due to a slower cell development rate[23]. Following age, other non-modifiable risk factors include sex, genetic factors, and family history of cancer[24–26]. Meanwhile, those with frequent tobacco use and alcohol abuse, excess exposure to occupational chemicals and sun radiation, unsafe sex practices, and obesity issues have a higher likelihood of developing cancer[25–27]. Additionally, patients who have cancer require regular follow-up visits to detect the reoccurrence of the tumor cells. As such, these issues highlight the need for accurate imaging modalities, as it is the first step in cancer diagnosis in understanding the tumor stage. Progress in nanomedicine helps to reduce the limitations of current diagnosis practices, which include a lack of sensitivity in small lesions detection, radiation exposure, and specificity. Hence, individuals with a higher probability of developing cancer may receive nanoparticle-based imaging approaches for diagnosis purposes, including positron emission tomography (PET) imaging agents, magnetic resonance imaging (MRI), and ultrasound contrast agents[17,28].

3.2 Healthcare Professionals

Among healthcare professionals, an oncologist is pivotal in integrating and administering nanomedicine into cancer care. An oncologist is a licensed doctor who specializes in diagnosing and treating cancer. They are the primary healthcare practitioners coordinating and overseeing cancer treatment with other health professionals, namely oncology nurses, dietitians, and pathologists[29]. Currently, most oncologists use the nano-based delivery of chemotherapy drugs in treating patients, including doxorubicin hydrochloride liposomal injection and paclitaxel protein-bound particles[30]. Additionally, oncologists have employed nanoparticles for tumor cell detection and imaging by targeting specific cancer genes and proteins for early diagnosis. Consequently, accurate diagnosis of the cancer can assist oncologists in creating a tailored treatment plan. For instance, current hospital settings are now using metallic, magnetic, liposomes, and dendrimer nanoparticles for monitoring and diagnosing breast, colon, and cervical cancer[17]. Nevertheless, with the various nanomedicine diagnoses and therapies developed, they are responsible for understanding the principles behind different nanomedicine products for prescribing personalized treatments to the specific needs of their patients and improving their quality of life.

While oncologist is at the forefront, researchers, nano-scientists, and nanotechnologists are the backbone of cancer nanomedicine, especially during the discovery and early developmental stages. To date, there are more than half of the nanomedicine in clinical trials are for cancer treatments, with breast cancer the most studied in the nanomedicine research community[21]. Researchers assist in nano-product development, doing in-depth physiochemical characterization, quality control, scale-up, and reproducibility testing in laboratory settings, while nano-scientists experiment with employing nano-sized particles, apparatus, or even robots in curing cancer[31,32]. Meanwhile, nanotechnologists design and manipulate new nanomaterials and nanoparticles, collect samples, and prepare information for assessments. Hence, the three roles often intertwine in accelerating the research and developmental (R&D) field of nanomedicine. At the same time, they have to undergo multiple clinical trials and modifications based on clinical data to ensure the safety and quality of the clinical and commercial drug, thus working closely with oncologists in deviating a suitable therapeutic candidate. Thus, they have a pivotal role in novel nanomedicine product development, especially in the oncology field while also revolutionizing its potential in cancer prevention, diagnosis and treatment[5].

3.3 Nanotechnology Companies and Regulatory Agencies

Nanotechnology companies play a vital role in transferring nanotechnology from research centres to the market. Notably, most major nanotech companies are based in the United States of America (USA), followed by Japan and Switzerland, with Asian companies showing the highest levels of funding, staffing, and sponsorship for nanotech development[33]. Under nanotech companies, large organizations work with current resources to investigate longer-term technologies to improve margins and increase market shares. On the other hand, start-ups create innovative tools to capture market interest[33]. Generally, nanotech companies mainly prioritize the design and budget management of the research aspects, and the end goal is designing patient-centric targets that address the current limits of conventional treatment[31]. Also, these companies usually work together with the financial sector to secure sizeable investments for the development of nano-products and the processes for implementing successful nanomedicine candidates for clinical uses, as these processes take on average 15 years and require at least 800 million to 3 billion USD in funds during the clinical trials. As estimates on the market size for cancer nanomedicine suggest in reaching USD 445.67 billion by 2030, nanotechnology companies are the key players in acquiring the necessary resources to assist the development and clinical translation of cancer nanomedicine candidates[34].

Beyond research and development, regulatory agencies play a crucial role in creating guidelines and policies for evaluating, regulating, and approving the safety and efficiency of nanomedicines and nanomaterials for cancer treatments[31]. They also oversee the translation process of preclinical studies into clinical therapeutics while reducing the risk of unanticipated adverse effects[35]. Correspondingly, some pharmaceutical companies have revised their R&D strategy for translational medicine based on the 5R framework, focusing on the right target, tissue, safety, patient, and commercial product[31]. Presently, global regulatory agencies, such as the European Medicines Agency (EMA) in Europe, the FDA from the USA, the Medicines and Healthcare Products Regulatory Authority (MHRA) in the United Kingdom (UK), the Pharmaceuticals and Medical Devices Agency in Japan, have created their legislation and guidelines on evaluating and handling nanotechnology-based products[36]. On the other hand, the Department of Occupational Safety and Health (DOSH) in Malaysia has also implemented guidelines on the control and safe handling of nanomaterials in the workplace[37]. Hence, regulatory bodies are vital in ensuring the maintenance and regulatory concerns for the development of nanomaterials and nanomedicine, as well as maintaining the confidence and trust of the public.

4. Potential Health Implications

4.1 Direct Health Impacts

Nanomedicine offers several advantages over the conventional cancer treatments. One aspect is the therapeutic index. While chemotherapy remains one of the primary treatment approaches for cancer, administration of the chemotherapeutics agents suffers from poor solubility and fast elimination, which influences the bioavailability and delivery of the drugs to the target site[38]. Nanoparticle-based drug delivery can help overcome the issue by utilizing hydrophilic-based nanoparticles or nanoparticles-coated polyethylene glycol (PEG) as a protective shield to improve drug release and drug pharmacokinetics through enhancing its stability and solubility, thus resulting in better efficacy[7,39]. For example, a novel nanoparticle-drug conjugate of camptothecin with cyclodextrin and PEG, CRLX101, presents a better therapeutic response for advanced rectal cancer patients in a phase Ib/II clinical trial[17,40]. Notably, the hydrophilic nature of PEGylated or lipid-based nanoparticles can also prolong the anticancer drugs' half-life in the systemic circulation, which assists in the controlled release of the drug to the tissue of interest by avoiding clearance by the immune system[21,39,41]. The nano-formulation for Doxil® uses the same principle by formulating PEG in conferring protection from clearance from the mononuclear phagocyte system[42]. Hence, nanoparticle-based drug delivery can improve the pharmacokinetics and pharmacodynamic profiles of the anticancer compounds.

The targeted delivery of nanoparticles also helps minimize the adverse effects and drug resistance mechanisms caused by the nonselective characteristics of anticancer drugs. The non-specific activity of conventional chemotherapy not only damages normal cells but also causes systemic toxicities[38,43]. Therefore, it may affect the patient's immune system and result in several adverse effects like hair loss or alopecia, blood-related side effects, loss of appetite, and pain[38,42]. On the other hand, the passive and active targeting mechanisms allow nanoparticles to reach the tumor tissue effectively without promoting cytotoxicity effects on the surrounding normal cells[1,44]. Another issue that halts the cancer treatment process is drug resistance. Almost 90% of cancer-related deaths result from tumor cell drug resistance[45]. Current data estimates that 55% of non-small cell lung cancer patients (NSCLC) suffer from relapse and die from the disease, while 70% of ovarian adenocarcinomas reoccur within a year post-surgery[45]. Fortunately, nano-formulated drugs can curb this issue by precisely delivering suitable doses of anticancer compounds to the intracellular tumor site through active targeting and stimuli-responsive targeting features. The nanocarriers then contain targeting ligands, such as antibodies and antibody fragments, lipids, proteins, carbohydrates, and aptamers, to facilitate the binding with tumor-specific receptors at the cell surface[1,42]. In turn, nanocarriers assist in elevating tumor tissue retention and accumulation while potentially reversing the current multidrug resistance challenges of tumor cells[1]. For instance, coupling tyrosine kinase inhibitors with recombinant monoclonal antibodies significantly improves their specificity with tumor-associated antigens in NSCLC patients while lowering the cytotoxicity profile and the maximal inhibitory concentration[46]. Similarly, folate-functionalized PLGA-PEG nanoparticles elevate the anticancer properties of Metformin on human breast cancer cells[47,48]. As a result, the functional targeting of nanocarriers proves to be an effective tool in improving the patient's quality of life by minimizing unwanted adverse effects and drug resistance.

At the same time, nanomedicine can enhance radiotherapy efficiency while decreasing its side effects. In current clinical treatment practices, approximately 50% of cancer patients receive radiotherapy or radiotherapy-based combination therapy[49,50]. In general, the treatment involves using high doses of ionizing radiation, particularly X-ray, to kill cancerous cells by damaging their genetic materials[49]. However, similar to chemotherapy, radiotherapy does not discriminate between tumor cells and healthy cells, and radiation exposure to normal tissue can cause severe damage to adjacent normal tissue or even body organs[51–53]. Also, due to the insufficient oxygen supply or hypoxia, the tumor cells may confer resistance to radiotherapy, leading to elevated radiation required for better therapeutic response[50,52]. Hence, although highly effective, radiotherapy is often a double-edged sword. With the development of nanomedicine, several organic and inorganic

nanoparticles have emerged to enhance the radiation response of the tumor cells. Among them, metal nanoparticles, including gold, platinum, and gadolinium, provide a better sensitizing effect due to the Compton scattering effects, generating free radicals and secondary electrons to promote DNA damage to tumor cells[50,53]. Ongoing clinical trials for AGulX, a nano-radiosensitizer based on gadolinium, show promising results in patients with brain metastatic tumors due to its ability to accumulate in brain tumor cells through the passive targeting mechanism[53]. Thus, nano-radiosensitizers can enhance radiotherapy efficacy and tumor selectivity without aggravating resistance against radiation, increasing its potential in treating cancer.

4.2 Indirect Health Impacts

While nanomedicine may increase the success rate of cancer treatments, there is still a lack of research on the potential side effects of nano-bio interactions. The complexity of nanoparticles, including size, charge, components, and surface properties, can affect the general behavior of nanoparticles[54]. However, we have a limited understanding of the nano-bio interactions, especially nano-immuno interactions, and the possible harmful health implications of nanoparticles' exposure to humans remains an unknown territory[54,55]. Experimental studies have shown that inhaling nanoparticles causes lung inflammation, which may translocate to extrapulmonary sites like blood, heart, liver, and brain[55,56]. Other than inhalation, nanoparticles can enter the human body via ingestion and skin contact and further exert toxic effects on the reproductive, endocrine, and immune systems, with the liver and spleen the primary site for nanoparticle accumulation[56,57]. Notably, most studies report metal-based nanoparticles, including gold and iron oxide, as the leading subject in promoting cytotoxicity and carcinogenicity due to their chemical properties[56]. Metal nanoparticles can generate reactive oxygen species (ROS) in developing oxidative stress, activating signaling pathways, DNA damage, and ultimately, apoptosis, leading to various cytotoxicity effects and development of diseases, including respiratory, cardiovascular, and neurological[58]. Cancer patients who use cationic nanoparticles for gene therapy treatment may also suffer from strong immunological responses, resulting in plasma membrane destabilization, tissue damage, and organ dysfunction[57]. With nanoparticles emerging as an essential field in cancer diagnosis and therapeutics, it is vital to conduct further research to comprehend the underlying nano-bio interactions to mitigate the adverse effects of nanoparticles.

5. Potential Outcomes and Challenges

5.1 Positive Outcomes of Nanomedicine in Cancer Therapy

Nano-formulations of the existing cancer therapy have demonstrated better specificity, accurate localized drug efficacy, and lower systemic toxicity[41]. Notably, several approved nano-therapeutics have provided safer administration in treating cancer patients while enhancing their therapeutic effect in real-time clinical practices (Table 1). For instance,

the albumin-bound nanoparticle of paclitaxel, Abraxane®, significantly enhances paclitaxel efficacy in delaying tumor growth, decreasing breast cancer stem cells, and increasing intracellular uptake of aldehyde dehydrogenase 1, making it superior for metastasized breast cancer treatment than Taxel[59]. At the same time, the success rate of nano-enabled drugs is higher compared to conventional oncology drugs, with an approval rate of 6% over 3.4%[60]. Nano-formulations enhance the permeability and half-life of the drugs while countering resistance mechanisms by promoting combinatorial drug use with dual-drug loading and utilizing physical modalities in eradicating cancerous cells[43,61]. A recent study by Zhang and colleagues[62] on the drug delivery modalities for advanced hepatocellular carcinoma (HCC) presents promising anti-tumor properties and greater bioavailability with lesser drug resistance by delivering doxorubicin (DOX) and sorafenib (SOR) using hybrid lipid-polymer nanoparticles containing a tumor-targeting peptide, iRGD. As such, it can help SOR achieve its therapeutic efficacy while reducing its side effects, showing great possibilities in treating HCC[61,62]. Another study by Han and colleagues[63] proposed PEG-PLA nanoparticles as a potential alternative to the oral administration of tyrosine kinase inhibitors, namely gefitinib, as the encapsulation allows better drug localization and stability for NSCLC. As the research on nano-therapeutics grows, it may not be long for personalized medicine to become a reality for cancer patients.

Table 1. Approved cancer nano-therapeutics using drug delivery mechanisms[22,42,44]

Year Approved	Product	Material	Advantages on MOA	Indication
1995 (FDA)	**Doxil/Caelyx**	PEGylated liposomal doxorubicin	↑ blood circulation time ↑ tumor uptake (EPR) ↓ cardiotoxicity	Myeloma, Kaposi's sarcoma, breast, and ovarian cancer
1996 (FDA)	**DaunoXome**	liposomal daunorubicin	↓ protein binding ↑ blood circulation time ↑ tumor uptake (EPR) ↓ cardiotoxicity	Kaposi's sarcoma
2000 (EMA)	**Myocet**	liposomal doxorubicin	↑ blood circulation time ↑ tumor uptake (EPR) ↓ cardiotoxicity	Breast cancer
2005 (FDA)	**Abraxane**	albumin-bound paclitaxel	↑ Solubility ↑ blood circulation time ↑ tumor uptake (EPR) ↓ severe toxicity	Breast, non-small-cell lung, and pancreatic cancer
2006 (China)	**Lipusu**	liposomal paclitaxel	-	Breast and non-small-cell lung cancer

Year Approved	Product	Material	Advantages on MOA	Indication
2006 (FDA)	**Oncaspar**	L-asparaginase conjugate	↑ blood circulation time ↑ tumor uptake (EPR)	Acute lymphoblastic leukemia
2007 (Korea)	**Genexol-PM**	paclitaxel micellar	-	Breast, non-small-cell lung, ovarian, and gastric cancer
2009 (EMA)	**Mepact**	liposomal mifamurtide	↑ blood circulation time ↑ tumor uptake (EPR) ↓ toxicity	Osteogenic sarcoma
2011 (EMA)	**NanoTherm**	Iron oxide nanoparticles	↑ blood circulation time ↑ tumor uptake (EPR) -heat production under stimulation with EMF -teranostic properties	Brain tumors
2012 (FDA)	**Marqibo**	Liposomal vincristine sulfate	↑ blood circulation time ↑ tumor uptake (EPR) ↓ toxicity	Acute lymphoblastic leukemia
2015 (FDA)	**ONIVYDE**	liposomal irinotecan	↑ blood circulation time ↑ tumor uptake (EPR) ↓ toxicity	Advanced pancreatic cancer
2017 (FDA)	**Vyxeos**	liposomal daunorubicin and cytarabine	↑ blood circulation time, ↑ accumulation in bone marrow	High-risk acute myeloid leukemia

5.2 Positive Outcomes of Nanomedicine in Cancer Diagnosis

Aside from therapeutic purposes, nanomedicine has significantly revamped cancer diagnostic and imaging field. To date, at least 50% of cancers cases are detected only at advanced stages, with pancreatic, esophageal, and ovarian cancers having extremely poor prognosis[64]. However, nanoparticles have made it possible to detect cancer in its early stages to enable timely treatment and increasing survival odds, especially inorganic nanoparticles, such as gold, iron oxide, and quantum dots, are commonly used for diagnostic imaging[42,65]. These nanoparticles can attach to specific biomarkers to enhance imaging modalities like MRI and PET scans in providing sensitive, accurate, and specific results[21,66]. As such, researchers termed the integration of novel therapeutic with modern diagnostic tools as nanotheranostic[17,67]. For instance, Resovist is an MRI imaging agent consisting of carboxydextran-coated superparamagnetic iron oxide nanoparticles for liver contrast-

enhanced MRI [21]. The immune superparamagnetic iron oxide nanoparticles (SPIONs) are another potential tool in detecting lung cancer[65]. Notably, quantum dots are suitable for colorectal, liver, and pancreatic cancer imaging as they emit fluorescence in the near-infrared spectrum[65]. Consequently, the rising trend of theranostics makes them the most promising candidates in providing highly accurate diagnostic test for effective detection in its early stages, which lowers patient cost and extend their survival.

5.3 Positive Outcomes of Nanomedicine in Cancer Immunotherapy

Recently, cancer immunotherapy has rapidly arisen as the next generation of nanomedicines. Instead of directing toward cancer cells, cancer immunotherapy focuses on the cells within the immune system, including immune checkpoint inhibitors, tumor-specific antigens (TSA), and regulatory T cells, in activating the body's anti-tumor immune response in recognizing and killing tumor cells[21,35]. Consequently, tumor immunotherapy has opened the door for cancer vaccine development. Typically, the immunogenic components of the cancer vaccine rely on the tumor-associated antigens (TAA) and TSA of the tumor cells, which help enhance the antigen stability and prevent antigen degradation[35,43]. They can further be categorized as cell-based, viral vector-based, or molecular-based vaccines (Table 2). Most cell-based tumor vaccine is dendritic cells (DC) vaccine. Among them, APCEDEN® is an autologous DC immunotherapy containing tumor antigen *ex vivo* to elicit tumor-specific T-cell-mediated tumor cell toxicity, and it is the only approved immunotherapy by the Central Drugs Standard Control Organization (CDSCO) in India to treat prostate cancer, colorectal cancer, ovarian cancer, and NSCLC[68,69]. One case study of a 63-year-old Asian male diagnosed with prostate adenocarcinoma showed significant tumor remission post APCEDEN® immunotherapy in combination with mitoxantrone treatment[69]. At the same time, an efficacy profile of APCEDEN® vaccine therapy also exhibits a survival benefit of at least 100 days, thus proving the vaccine to be a pivotal asset in potentially removing solid tumors[70]. Meanwhile, a viral-based tumor vaccine utilizing the oncolytic adenoviral virus, NG0348, possesses a similar mechanism as the CART-T therapies in modifying the patient's T cells to identify and eliminate the tumor cells effectively and is now approved for human clinical trials[21,35]. Therefore, cancer immunotherapy has substantially extended the therapeutic window in tumor clearance.

Table 2. Cell-based, virus-based, and molecular based, such as recombinant protein, peptide, DNA and RNA, cancer vaccine and their status (launched or in clinical trial)[21]

Cancer Vaccine types	Name of product	Carrier types	Indication	Status
OMV-based vaccine **(cell-base)**	GM3/VSSP	Proteoliposome (N-acetyl GM3 ganglioside in complex with Neisseria meningitides-derived	Breast cancer	Phase II

Cancer Vaccine types	Name of product	Carrier types	Indication	Status
		outer membrane vesicle)		
Autologous cellular vaccine **(cell-based)**	Oncoquest-CLL	Liposome loading Autologous tumor chronic lymphocytic leukaemia (CLL) and IL-2	Chronic leukaemia	Phase I
Oncolytic virus **(virus-based)**	Teserpaturev; Delytact	Replicating ICP34.5 and ICP47 gene-deleted oncolytic Herpes simplex virus (HSV)	Metastatic breast cancer	2021
Virus-like particle vaccine **(virus-based)**	9-Valent human papillomavirus vaccine	HPV L1 proteins derived from various HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58)	Cervical cancer	2015
Recombinant protein vaccine **(molecular based)**	OncoVax-CL	Liposome loaded with Recombinant epithelial cell adhesion molecule (Ep-CAM/KSA/GA733)	Lung and colorectal cancer	Phase II
Peptide vaccine **(molecular based)**	PVAC	Amphiphilles nanoparticle containing patient-specific neoantigens or cancer testis antigens (PVAC)	HCC, gastrointestinal cancer	Phase I
mRNA vaccine **(molecular based)**	mRNA-2416	Liposome loaded with mRNA encoding OX40L protein in miR-122 binding sites	Primary peritoneal carcinoma (ovarian); Lymphoma	Phase II

6. Addressing the Challenges in Cancer Nanomedicine

6.1 Challenges in Efficacy

Despite the successful therapeutic effects of nanomedicine interventions in the preliminary stages, less than 10% of the candidates have advanced to clinical applications[1,21,71]. A recent survey revealed the failure rate in phase II and phase III trials

was 52% and 86%, respectively, as these nanoparticles do not reach the expected therapeutic efficacy despite being a safer alternative[1]. One example is BIND-014, a PSMA-targeting polymeric nanoparticle that contains docetaxel for cervical cancer treatment, which failed the phase II clinical trial due to little therapeutic efficacy[21]. One of the main factors contributing to the disappointing efficacy is the inadequate understanding of the nano-bio interactions between different nanoparticles and the target focal area[44,54]. The protective features of biological barriers, such as the reticuloendothelial system (RES), the renal system, and the BBB, may restrict drug delivery to the tumor cells[39,66,72]. Although manipulating the nanoparticles' properties, including size, structure, and surface charges, can improve the permeability of the nanoparticles and decrease their clearance in said biological barriers, it may potentially lead to the accumulation of the drugs at the target organs and non-target organs due to systemic circulations, can cause short-term and long-term cytotoxicity[17,72]. For instance, the accumulation of metal-containing nanoparticles like silver and copper may degrade the BBB and lead to neurotoxicity. Additionally, while nanoparticles in cancer diagnosis provide a more accurate detection in current clinical practice, their potential toxicity and harmful effects remain a mystery. Hence, the limited understanding on the toxic profiles of different nanomedicines remains an obstacle in designing suitable cancer nanomedicine for clinical uses.

At the same time, researchers tend to overlook the pathophysiological features of the cancer cells while designing the nano-formulation, leading to a lack of reproducibility. The current research paradigm for cancer nanomedicine uses a more "formulation-driven" approach instead of a "disease-driven" approach[5,21]. One of the prominent examples is the variability of the EPR effects in tumor cells. Most nano-based drug delivery system uses the passive targeting mechanism as the main design to achieve drug retention in the tumor cells, making it the central dogma for nano-therapeutics development[39,73]. Still, researchers fail to consider the complexity and heterogeneity of the tumor microenvironment, which can hamper the therapeutic effects of EPR-based nanomedicine[43,74]. Several common factors influencing the EPR effect in efficiently distributing the nanoparticles to the tumor are the tumor blood flow and hydrostatic pressure[75]. However, most tumor models in the preliminary research stages use tumors with a diameter of approximately 5–7mm, and the highly vascular and genetically homogeneous properties of these tumors provide easily observed positive outcomes. Meanwhile, cancer cells in clinical settings highly differ between patients due to genetic mutations and epigenetic patterns, resulting in limited responses to the EPR-based nanomedicine and allowing for drug resistance[75]. Hence, these issues emphasize the need for a proper model system to understand its efficacy in cancer treatment.

6.2 Challenges in the Regulatory Aspect

The enormous scientific and regulatory gap is another obstacle that impedes the development of nanomedicine and its potential future uses[76]. Currently, most regulatory bodies, including the FDA and EMA, use the traditional benefit-to-risk framework in evaluating the new nano-formulations for therapeutic uses, which is not suitable for the complex nature of nanoparticles[72]. Despite originating from the same material, nanoparticles can interact differently with the cells and tissues due to varying physiological environments, leading to their multifunctional nature[76]. For instance, the safety and efficacy of polymeric-based nanoparticles depend on their molecular size and structure and conjugation chemistry[76]. However, most regulatory agencies fail to consider the diverse pharmacodynamic and pharmacokinetic activities based on the current regulatory framework[36]. Also, there is a severe lack of standardization for the definition and classification of nanomedicine, resulting in the geographically differed safety and efficacy standards for nanomedicine[36,77]. For example, EMA categorizes nanomedicine into biological and nonbiological medicine, while the FDA grouped it under complex products with multiple components[72]. The regulatory differences can also be found in the cancer vaccine, APCEDEN®. While the India FDA, CDSCO, has approved the use of APCEDEN® for pancreatic cancer treatment, its approval by the US FDA remains unknown[78]. As a result, the different safety and efficacy regulations have caused hundreds of nanomedicines to fail in phases of clinical trials while increasing the cost required to achieve regulatory approval[77]. Aside from the lack of regulation in the R&D field, only a few manufacturing organizations meet the requirements of Good Manufacturing Practices (GMP), which leads to a lack of standardization in producing nanomedicine products[76]. At the same time, there is still a need for a detailed critical quality attribute (CQA) for evaluating and understanding nanomedicine properties in the manufacturing process, which are typically inaccessible to researchers at the early development stages[36]. Therefore, the lack of specificity in existing regulatory frameworks make it challenging to the innovation of cancer nanomedicine.

6.3 Economic Considerations

As mentioned previously, the cost of developing a successful nanomedicine candidate in the clinical phase may require billions of dollars, which places a drastic financial burden on nanotechnology and pharmaceutical companies, especially if they do not meet the requirements to pass the clinical trials[43]. If the companies continue to fail to produce a feasible nano-product, investors might reduce the research funding. In an unfavourable situation, the lack of funding could lead to the withdrawal of the product or the company from the market. Additionally, the high cost of the raw materials and the production process,

including the advanced instruments, bioassays, and storage, influences the production yield of the nano-therapeutics[42,76]. The average treatment cost can go up to 130,000 USD, and these prices may fluctuate depending on the types and stages of the cancer and the direct and indirect costs for cancer care, diagnosis, and treatment[79,80]. Ironically, the rarity of nanomedicine does not help in alleviating the patient's financial burden, defeating its purpose of being a better alternative to conventional cancer medicine. For instance, the production cost for Doxil® and Abraxane® is far more expensive than their free-drug counterparts, namely doxorubicin and paclitaxel, resulting in the higher selling price for cancer nano-therapeutics[42]. Other cancer nano-therapeutics, such as CAR-T therapy, have a highly complex and time-consuming manufacturing process, thus requiring hundreds of thousands of dollars per treatment[81]. Hence, researchers have proposed to characterize nanomedicine products on a batch-to-batch basis in hopes of improving the cost-effectiveness of cancer nanomedicine and making the treatment accessible to all cancer patients.

6.4 Ethical Considerations

The traditional use of animal models in understanding the toxicology of the designed nanomedicines has raised some ethical concerns. Using specific animal models is crucial in determining the biodistribution and cytotoxicity effects of the nanoparticles[7]. However, as a large scale of test animal models, including monkeys, pigs, sheep, rabbits, and mice, are required in the preliminary and clinical stages to evaluate the toxicological and pharmacological aspects of nanomedicine, multiple studies have deemed these methods to be unethical, costly, and impractical[7,36]. Therefore, *in vitro* toxicity methods, like the 2-dimensional assays, are currently the main prioritization to assess the nanoparticles. Yet, these assays do not accurately present the biological and metabolic processes of the human body, and their interactions with the nanoparticles may interfere with the final results by providing false positives[36]. Consent issues due to a lack of context are another issue in employing nanomedicine in clinical trials. It may be due to the medical professionals' lack of understanding of the product and its behavior in the human body or the participant underestimating the potential risk of nano-formulations or nano-based diagnostic tools[82]. At the same time, with nanomedicine tools advancing to a more artificial intelligence (AI) stage, an AI system may store patient health data without their consent, potentially putting them at risk[82]. Hence, informed consent, privacy concerns, and animal testing require further addressing in the ethical aspects of cancer nanomedicine.

6.5 Environmental Considerations

Another issue to contemplate is the possible impact of environmental pollution. While the relationship between the nanoparticles in cancer therapy and diagnosis and environmental

pollution is still unclear, the development, use, and disposal of nanomedicine may pose significant environmental issues, with the possibility of inducing nano-pollution[36]. Nano-pollution is defined as invisible pollution, as its emission to the environment is usually unidentifiable, especially particulate air emission[83]. For instance, inhaling cylinder-shaped carbon nanotubes can easily penetrate the pulmonary epithelium and confer toxicity, while gold nanoparticles may bind to the cell membrane to induce oxidative stress[84]. Inappropriate disposal of nanoparticle-containing waste products into soils and water can also severely affect our aquatic and land ecosystems, with plants being the primary source of accumulation[84,85]. Subsequently, the accumulated nanoparticles can travel through the food chain, and prolonged exposure can result in critical illness and diseases in humans[84]. As such, further research is needed to investigate the potential environmental threats of these nanoparticles, and their impact on human health is crucial.

7. Recommendation

The rising number of cancer cases demands a significant improvement in the clinical translation of the nano-formulations. Notably, switching from traditional formulation-driven research to a more simplified, patient-centered paradigm may aid in improving the response rates while solving the issue of patient and disease heterogeneity[21]. One successful case in employing the patient-centered approach is Opaxio, formerly known as Xyotax™. It is a passively targeted poly [L-glutamic acid] paclitaxel that has shown substantial survival benefits in NSCLC women with pre-menopausal oestradiol levels, making it assigned by the FDA as a treatment for women with advanced NSCLC[21]. Therefore, its success highlights the importance of patient stratification by selecting a suitable patient group and a thorough understanding of the pathological characteristics of the disease[21,54]. Also, a better understanding of the tumor microenvironment regulation and delivery mechanism of nanomedicines to solid tumors may help to design drug carriers with maximum efficacy[5]. A recent study by Pandit *et al.*[86] suggests active transcytosis of endothelial cells to be a more effective mechanism in delivering nanoparticles to tumor cells, potentially replacing the current passive targeting approach of cancer nanomedicine development. Still, further understanding of the nano-bio interactions and employing suitable *in vitro* and *in vivo* study models may help to overcome issues on biological barriers, immune clearance, adverse reactions and bioaccumulation, and the lack of tumor penetration activity to provide sufficient therapeutic efficacy[5,21]. Besides changes in the research field, the nanomedicine research community should also balance their focus on nanomedicine development instead of only focusing on breast and lung cancer nano-therapies[87]. By addressing these issues, the accessibility of cancer nanomedicine for clinical uses could become a reality in the near future.

Overcoming the current regulatory challenges is also crucial in progressing cancer nanomedicine. The first step is to establish a widely acceptable international standard in defining the different terms in nanomedicine while also classifying it as an independent field rather than generalizing them with other compounds[21,60]. In addition, an appropriate regulatory framework on the CAQs, manufacturing process, and better refinement in clinical trials dedicated to nanomedicine development may also help to reduce the failure rates of clinical translation and their cost burdens[36,76]. Notably, in 2022, the FDA drafted a series of five "Final Guidances" on their current regulatory guidelines on nanotechnology product development in different industry sectors[42,88]. The EU-US Community of Research has also emerged as a collaborative effort between the National Institute of Standards and Technology (NIST) and the European Technology Platform on nanomedicine (ETPN) to address the gaps in nanomedicine standardization and regulatory framework [60]. Nevertheless, there is a need to develop a concise regulation in the innovation of nanomedicine products to balance their safety and quality in creating cost-effective treatments and significantly improving the patient's quality of life.

Lastly, changes in the education field may curb the current limitations in clinical translation. Current estimates on the nanomedicine industry projection suggest a 16% growth rate in the next ten years, indicating the expanding workforce in the field[31]. At the same time, more and more education organizations recognize the importance of educating researchers on the necessary knowledge and skills in applying nanotechnology for cancer research and diagnosis, especially at the academic level, to improve the success rate in clinical translation. Notably, the Mayo Clinic has developed a training program named the Translational Nanomedicine Program to provide the necessary skill set while exposing trainees to the various tools and principal concepts in advancing nanotechnologies for treating human diseases[89]. Northwestern University has also opened a well-rounded training program for master's and Ph.D. researchers to acquire the skills and knowledge for cancer translation research, including designing cancer nanomaterials, determining the biological properties, and understanding their safety and efficacy profiles[90]. Similarly, Stanford Medical School has provided a 3-year Cancer-Translational Nanotechnology Training (Cancer-TNT) program for teaching the new generation of cancer researchers to advance cancer research and clinical translation with the same aim and goals[91]. Hence, broad engagement across different fields of science and sectors may accelerate the delivery of nanomedicines to cancer patients.

8. Conclusion

In conclusion, nanomedicines have demonstrated promising potential in providing safe and accurate targeted drug delivery to tumor cells in the focal area compared to conventional cancer treatments due to their unique properties. Despite the challenges and obstacles, current evidence of the R&D field in nanomedicines and their application in clinical practices has held promise in changing the current landscape of cancer diagnosis and treatment. Still, several challenges can impede its progression, such as a lack of a patient-centred approach, limited toxicological data and assessment, and unsuitable regulatory approaches. Nevertheless, collaborative efforts between different parties to address and resolve these problems could enhance clinical translation and unleash the full potential of nanotechnology for personalized treatments, diagnosis, and, eventually, cancer prevention.

Author Contribution:

Acknowledgments: The author wishes to thank Prof. Long Chiau Ming (Sunway University) for his guidance and support on the work. The author also thanks the editor and peer-reviewers involved in the publication process of this paper.

Conflicts of Interest: The authors declare no conflict of interest in this work.

References

1. Fan D, Cao Y, Cao M, *et al*. Nanomedicine in cancer therapy. Signal Transduction Targeted Ther. 2023 Aug 7; 8(1).
2. Sung H, Ferlay J, Siegel RL, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. Ca Cancer J Clin 2021 Feb 4; 71(3): 209–49.
3. World Cancer Research Fund International. Worldwide cancer data | World Cancer Research Fund International [Internet]. WCRF International. World Cancer Research Fund International; 2022 [cited 2024 Mar 19]. Available from: https://www.wcrf.org/cancer-trends/worldwide-cancer-data/
4. World Health Organization. Cancer [Internet]. World Health Organization. 2022 [cited 2024 Mar 19]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer
5. Nirmala MJ, Kizhuveetil U, Johnson A, G B, *et al*. Cancer nanomedicine: A review of nano-therapeutics and challenges ahead. RSC Adv 2023; 13(13): 8606–29.
6. Upadhyay A. Cancer: An unknown territory; rethinking before going ahead. Genes Dis 2020 Sep; 8(5).
7. Rasool M, Malik A, Waquar S, *et al*. New challenges in the use of nanomedicine in cancer therapy. Bioengineered 2021 Dec 2; 759–73.
8. National Cancer Institute. Cancer Statistics [Internet]. National Cancer Institute. Cancer.gov; 2020 [cited 2024 Mar 19]. Available from: https://www.cancer.gov/about-cancer/understanding/statistics
9. Jeevanandam J, Barhoum A, Chan YS, *et al*. Review on Nanoparticles and Nanostructured materials: history, sources, Toxicity and Regulations. Beilstein J Nanotechnol 2018 Apr 3; 9(1): 1050–74.
10. Patra JK, Das G, Fraceto LF, *et al*. Nano based drug delivery systems: Recent developments and future prospects. J Nanobiotechnol 2018 Sep 19; 16(1).

11. Soares S, Sousa J, Pais A, *et al*. Nanomedicine: Principles, properties, and regulatory issues. Front Chem 2018 Aug 20; 6(360).

12. Liz-Marzán LM, Nel AE, Brinker CJ, *et al*. What do we mean when we say nanomedicine? ACS Nano 2022 Sep 27; 16(9): 13257–9.

13. Glisic S, Veljkovic V. Design of targeting peptides for nanodrugs for treatment of infectious diseases and cancer. Drug Targeting Stimuli Sensitive Drug Delivery Syst 2018; 343–81.

14. Zhu W, Wei Z, Han C, *et al*. Nanomaterials as promising theranostic tools in nanomedicine and their applications in clinical disease diagnosis and treatment. Nanomater 2021 Dec 10; 11(12): 3346.

15. Xu M, Han X, Xiong H, *et al*. Cancer nanomedicine: Emerging strategies and therapeutic potentials. Mol 2023 Jun 30; 28(13): 5145–5145.

16. Al-Zoubi MS, Al-Zoubi RM. Nanomedicine tactics in cancer treatment: Challenge and hope. Crit Rev Oncol/Hematol 2022 Jun; 174: 103677.

17. Alrushaid N, Khan FA, Al-Suhaimi EA, *et al*. Nanotechnology in cancer diagnosis and treatment. Pharm. 2023 Mar 1;15(3):1025.

18. Sindhwani S, Chan WCW. Nanotechnology for modern medicine: next step towards clinical translation. J Intern Med 2021 Jan 22;

19. Lammers T, Ferrari M. The success of nanomedicine. Nano Today. 2020 Apr 1; 31: 100853.

20. Jia Y, Jiang Y, He Y, *et al*. Approved nanomedicine against diseases. Pharm 2023 Feb 26; 15(3): 774.

21. Shan X, Gong X, Li J, *et al*. Current approaches of nanomedicines in the market and various stage of clinical translation. Acta Pharm Sin B 2022 Mar; 12(7).

22. National Cancer Institute. Current Nanotechnology Treatments [Internet]. National Cancer Institute. Cancer.gov; 2017 [cited 2024 Mar 19]. Available from: https://www.cancer.gov/nano/cancer-nanotechnology/current-treatments

23. Estapé T. Cancer in the elderly: Challenges and barriers. Asia-Pac J Oncol Nurs 2018; 5(1): 40–42.

24. Nindrea RD, Aryandono T, Lazuardi L. Breast cancer risk from modifiable and non-modifiable risk factors among women in Southeast Asia: A meta-analysis. Asian Pac J Cancer Prev 2017 Dec 1; 18(12): 3201–3206.

25. Olakowski M, Bułdak Ł. Modifiable and non-modifiable risk factors for the development of non-hereditary pancreatic cancer. Med 2022 Jul 22; 58(8): 978.

26. Ottavia C, Serena S, Chiara M, *et al*. Epidemiology of gastric cancer and risk factors. Acta Bio Med: Atenei Parmensis 2018; 89(Suppl 8): 82–87.

27. Stein CJ, Colditz GA. Modifiable risk factors for cancer. Br J Cancer. 2004 Jan 26;90(2):299–303.

28. Liu CH, Grodzinski P. Nanotechnology for cancer imaging: Advances, challenges, and clinical opportunities. Radiol: Imaging Cancer 2021 May 1; 3(3): e200052.

29. Eske J. What is an oncologist? Everything you need to know [Internet]. www.medicalnewstoday.com. 2020 [cited 2024 Mar 19]. Available from: https://www.medicalnewstoday.com/articles/what-is-an-oncologist

30. Byrne J. Nanomedicine in oncology: Tiny particles, huge potential [Internet]. www.healio.com. 2022 [cited 2024 Mar 19]. Available from: https://www.healio.com/news/hematology-oncology/20220603/nanomedicine-in-oncology-tiny-particles-huge-potential

31. Nance E. Careers in nanomedicine and drug delivery. Adv Drug Delivery Rev. 2019 Apr; 144: 180–189.

32. Brown A. Nanoscientist: Education and skills needed for the job [Internet]. Nanotechnology News. 2021. Available from: https://www.nanotechetc.com/nanoscientist-education-and-skills-needed-for-the-job/

33. Organisation for economic co-operation and development. opportunities and risks of nanotechnologies report in co-operation with the OECD International futures programme contents [Internet]. [cited 2024 Mar 19]. Available from: https://www.oecd.org/science/nanosafety/44108334.pdf?fbclid=IwAR18kg7MmH7KPzP-2A3iA9KMMLaXS27bCLYGvwRCv5qGu6t2NOm-T_gB10E

34. Data Bridge Market Research. Cancer Nanomedicine Market Size Expected to Reach USD 445.67 Billion with Growing CAGR of 12% by 203 [Internet]. PharmiWeb.com. 2023 [cited 2024 Mar 19]. Available from: https://www.pharmiweb.com/press-release/2023-10-04/cancer-nanomedicine-market-size-expected-to-reach-usd-44567-billion-with-growing-cagr-of-12-by-203

35. Hou S, Hasnat M, Chen Z, *et al*. Application perspectives of nanomedicine in cancer treatment. Front Pharmacol 2022 Jul 1; 13.

36. Foulkes R, Man E, Thind J, *et al*. The regulation of nanomaterials and nanomedicines for clinical application: current and future perspectives. Biomaterials Science [Internet]. 2020;8(17):4653–64. Available from: https://pubs.rsc.org/en/content/articlehtml/2020/bm/d0bm00558d

37. Ismail S, Budin S, Md. Ali SA. The nanotechnology application and workforce health and safety - a study of the Malaysia laws, statutory regulations and guidelines on nanotechnology. J Phys: Conf Ser 2019 Nov; 1349: 012031.

38. Shukla A, Maiti P. Nanomedicine and versatile therapies for cancer treatment. MedComm. 2022 Aug 18; 3(3).

39. Tran S, DeGiovanni PJ, Piel B, *et al*. Cancer nanomedicine: a review of recent success in drug delivery. Clin Transl Med 2017 Dec; 6(1).

40. Tian X, Nguyen M, Foote HP, *et al*. CRLX101, a nanoparticle–drug conjugate containing camptothecin, improves rectal cancer chemoradiotherapy by inhibiting DNA repair and HIF1α. Cancer Res 2016 Oct 26; 77(1): 112–122.

41. Yao Y, Zhou Y, Liu L, *et al*. Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. Front Mol Biosci 2020 Aug 20; 7(193).

42. Rodríguez F, Caruana P, De la Fuente N, *et al*. Nano-based approved pharmaceuticals for cancer treatment: Present and future challenges. Biomol 2022 Jun 4; 12(6): 784.

43. Kemp JA, Kwon YJ. Cancer nanotechnology: Current status and perspectives. Nano Convergence 2021 Nov 2; 8(1).

44. Salvioni L, Rizzuto MA, Bertolini JA, *et al*. Thirty years of cancer nanomedicine: Success, frustration, and hope. Cancers 2019 Nov 25; 11(12): 1855.

45. Wang X, Zhang H, Chen X. Drug resistance and combating drug resistance in cancer. Cancer Drug Resist. 2019; 2(2).

46. García-Fernández C, Fornaguera C, Borrós S. Nanomedicine in non-small cell lung cancer: From conventional treatments to immunotherapy. Cancers 2020 Jun 18; 12(6): 1609.

47. Choudhury H, Pandey M, Wen LP, *et al*. Folic acid conjugated nanocarriers for efficient targetability and promising anticancer efficacy for treatment of breast cancer: A review of recent updates. Curr Pharm Des 2020 Dec 12; 26(42): 5365–5379.

48. Jafari-Gharabaghlou D, Dadashpour M, khanghah OJ, *et al*. Potentiation of folate-functionalized PLGA-PEG nanoparticles loaded with metformin for the treatment of breast cancer: Possible clinical application. Mol Biol Rep 2023 Jan 20; 50: 3023–3033.

49. Arif M, Nawaz AF, Ullah khan S, *et al*. Nanotechnology-based radiation therapy to cure cancer and the challenges in its clinical applications. Heliyon [Internet]. 2023 Jun 1; 9(6): e17252. Available from: https://www.sciencedirect.com/science/article/pii/S2405844023044602#coi0010

50. Liu W, Chen B, Zheng H, , *et al*. Advances of nanomedicine in radiotherapy. Pharm 2021 Nov 1; 13(11): 1757.

51. DuRoss AN, Neufeld MJ, Rana S, *et al*. Integrating nanomedicine into clinical radiotherapy regimens. Adv Drug Delivery Rev 2019 Apr; 144: 35–56.

52. Haque M, Shakil S, Mahmud KM. The promise of nanoparticles-based radiotherapy in cancer treatment. Cancers 2023 Mar 22; 15(6): 1892–2.

53. Song X, Sun Z, Li L, *et al*. Application of nanomedicine in radiotherapy sensitization. Front Oncol 2023 Feb 15; 13.

54. Bhatia SN, Chen X, Dobrovolskaia MA, *et al*. Cancer nanomedicine. Nature Rev Cancer. 2022; 22(10): 550–556.

55. Gwinn MR, Vallyathan V. Nanoparticles: Health effects—pros and cons. Environ Health Perspect 2006 Dec; 114(12): 181818–25.

56. Lihui X, Zhao J, Skonieczna M, *et al*. Nanoparticles-induced potential toxicity on human health: Applications, toxicity mechanisms, and evaluation models. MedComm 2023 Jul 14; 4(4).

57. Missaoui WN, Arnold RD, Cummings BS. Toxicological status of nanoparticles: What we know and what we don't know. Chemico-Biological Interactions [Internet]. 2018 Nov 1; 295: 1–12. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0009279718309463

58. Damasco JA, Ravi S, Perez JD, *et al*. Understanding nanoparticle toxicity to direct a safe-by-design approach in cancer nanomedicine. Nanomater 2020 Nov 2; 10(11): 2186.

59. Yuan H, Guo H, Luan X, *et al*. Albumin nanoparticle of Paclitaxel (Abraxane) decreases while taxol increases breast cancer stem cells in treatment of triple negative breast cancer. Mol Pharm 2020 Jun 2; 17(7): 2275–2286.

60. Germain M, Caputo F, Metcalfe S, *et al*. Delivering the power of nanomedicine to patients today. J Controlled Release 2020 Oct 10; 326: 164–171.

61. Zhao Q, Cheng N, Sun X, *et al*. The application of nanomedicine in clinical settings. Front Bioeng Biotechnol 2023 Jun 27; 11: 1219054.

62. Zhang J, Hu J, Chan HF, *et al*. iRGD decorated lipid-polymer hybrid nanoparticles for targeted co-delivery of doxorubicin and sorafenib to enhance anti-hepatocellular carcinoma efficacy. Nanomed: Nanotechnol Biol Med 2016 Jul; 12(5): 1303–1311.

63. Han W, Shi L, Ren L, *et al*. A nanomedicine approach enables co-delivery of cyclosporin A and gefitinib to potentiate the therapeutic efficacy in drug-resistant lung cancer. Signal Transduction Targeted Ther 2018 Jun 22; 3(1).

64. Crosby D, Bhatia S, Brindle KM, *et al*. Early detection of cancer. Sci 2022 Mar 18; 375(6586).

65. Jin C, Wang K, Oppong-Gyebi A, *et al*. Application of nanotechnology in cancer diagnosis and therapy — A mini-review. Int J Med Sci 2020 Oct 18; 17(18): 2964–2973.

66. Malik S, Muhammad K, Waheed Y. Emerging applications of nanotechnology in healthcare and medicine. Mol 2023 Sep 14; 28(18): 6624–6624.

67. Ladju RB, Ulhaq ZS, Soraya GV. Nanotheranostics: A powerful next-generation solution to tackle hepatocellular carcinoma. W J Gastroenterol 2022 Jan 14; 28(2): 176.

68. Immun-Onkologisches Zentrum Köln. Dendritic Cells Inform the Immune System [Internet]. IOZK. [cited 2024 Mar 19]. Available from: https://www.iozk.de/en/portfolio-item/dendritic-cells-inform-the-immune-system/

69. Kumar C, Bagga J, Chiliveru S, *et al*. Substantial remission of prostate adenocarcinoma with dendritic cell therapy APCEDEN® in combination with chemotherapy. Future Sci OA 2019 Dec 1; 5(10).

70. Mastelic-Gavillet B, Balint K, Boudousquie C, *et al*. Personalized dendritic cell vaccines—Recent breakthroughs and encouraging clinical results. Front Immunol 2019 Apr 11; 10.

71. Zhang Y, Li M, Gao X, *et al*. Nanotechnology in cancer diagnosis: progress, challenges and opportunities. J Hematol Oncol 2019 Dec 17; 12(1).

72. Halwani AA. Development of pharmaceutical nanomedicines: From the bench to the market. Pharm 2022 Jan 3; 14(1): 106.

73. Wu J. The enhanced permeability and retention (EPR) effect: The significance of the concept and methods to enhance its application. J Pers Med 2021 Aug 6; 11(8): 771.

74. Maniam G, Mai CW, Zulkefeli M, *et al*. Challenges and opportunities of nanotechnology as delivery platform for tocotrienols in cancer therapy. Front Pharmacol 2018 Nov 26; 9.

75. Islam W, Niidome T, Sawa T. Enhanced permeability and retention effect as a ubiquitous and epoch-making phenomenon for the selective drug targeting of solid tumors. J Pers Med 2022 Dec 1; 12(12): 1964.

76. Hua S, de Matos MBC, Metselaar JM, *et al*. Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: Pathways for translational development and commercialization. Front Pharmacol 2018 Jul 17; 9.

77. Ros SA, Nurhidayah W, Perumal K, *et al*. Cancer nanomedicine and immune system—Interactions and challenges. Front Nanotechnol 2021 Jul 9; 3.

78. Sharan B, Chiliveru S, Bagga J, *et al*. Substantial tumor regression in prostate cancer patient with extensive skeletal metastases upon immunotherapy (APCEDEN). Med 2020 Feb 1; 99(8): e18889–9.

79. Blumen H, Fitch K, Polkus V. Comparison of treatment costs for breast cancer, by tumor stage and type of service. Am Health Drug Benefits 2016; 9(1): 23–32.

80. Bosetti R, Jones SL. Cost–effectiveness of nanomedicine: Estimating the real size of nano-costs. Nanomed 2019 Jun; 14(11): 1367–1370.

81. Lagae L. AI and nanotechnology could make cancer cell therapy affordable for all [Internet]. World Economic Forum. 2021 [cited 2024 Mar 19]. Available from: https://www.weforum.org/agenda/2021/05/ai-nanotechnology-cancer-cell-therapy-affordable/

82. Wasti ST, Lee IH, Kim S, *et al*. Ethical and legal challenges in nanomedical innovations: A scoping review. ELSI in Sci Genet 2023 Jan 1; 14: 1163392–2.

83. Jan N, Majeed N, Ahmad M, *et al*. Nano-pollution: Why it should worry us. Chemosphere 2022 Sep; 302: 134746.

84. Martínez G, Merinero M, Pérez-Aranda M, *et al*. Environmental impact of nanoparticles' application as an emerging technology: A review. Mater 2020 Dec 31; 14(1): 166.

85. Bundschuh M, Filser J, Lüderwald S, *et al*. Nanoparticles in the environment: Where do we come from, where do we go to? Environ Sci Eur 2018; 30(1).

86. Pandit S, Dutta D, Nie S. Active transcytosis and new opportunities for cancer nanomedicine. Nature Mater 2020 Apr 24; 19(5): 478–480.

87. Salvador-Morales C, Grodzinski P. Current landscape of treating different cancers using nanomedicines: Trends and perspectives. WIREs Nanomed Nanobiotechnol 2023 Sep 14; 16(1).

88. U.S. Food and Drug Administration. Nanotechnology Guidance Documents [Internet]. FDA. 2020 Feb [cited 2024 Mar 19]. Available from: https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-guidance-documents

89. Mayo Clinic. Translational Nanomedicine Program - Overview [Internet]. Mayo Clinic. [cited 2024 Mar 19]. Available from: https://www.mayo.edu/research/centers-programs/translational-nanomedicine-program/overview

90. Woloschak G. Cancer Nanotechnology Training Program - NCI [Internet]. www.cancer.gov. 2017 [cited 2024 Mar 19]. Available from: https://www.cancer.gov/nano/research/alliance/cntc/northwestern

91. Stanford Medicine. Cancer-Translational Nanotechnology Training [Internet]. Cancer-Translational Nanotechnology Training (Cancer-TNT) Program. [cited 2024 Mar 19]. Available from: https://med.stanford.edu/ctnt.html