The Application of Nanotechnology in Enhancing Immunotherapy for Cancer Treatment: Future Aspects

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Abstract

Nanotechnology is the investigation of matter at the molecular and atomic levels. It identifies and discovers the beneficial features at the nanoscale level. There are numerous applications of nanotechnology in modern science. Medicinal field has great impact of modern nanoscience. Nano disks, high density lipoprotein nanostructures, and gold nanoparticles are different example of nanotechnology applied in drug delivery system. The growing discipline of this nanotechnology fulfilled the demand for innovative methods in the detection and treatment of cancer. With the help of this advanced technology several functional molecules can be conjugated simultaneously such as tumor-specific ligands, antibodies, anticancer drugs, and imaging probes etc. Nanoparticles are biocompatible and biodegradable in nature. They act as a carrier, which target particular sites of cancer cell. Since, nanoparticles are 100-1000 times smaller than cancer cells, they can readily pass through leaky blood vessels. They can easily interact with tumor-specific proteins both on the outside and inside of cancer cells. This advance nanotechnology has brought a new hope for developing treatment of cancer therapy. In this article, we highlighted a review on the recent applications of nanoscience in enhancing immunotherapy and the treatment of cancerous cells.

Keywords: Cancer nanotechnology, Carbon nanotubes, Nanocarriers, Nano shells, Quantum dots.

1. Introduction

Cancer is the second most major cause of human mortality. Almost 7.6 million people die every year, which represents 13% of total population. The situation will be worse in near future. The rate of infection increases day by day. Cancer is defined by uncontrolled growth of cells and the absence of cell death, which causes an abnormal cell mass, or tumor [1]. Only in case of hematological cancer, this type of symptoms is not found [1]. A general term known as “malignancy” is used to describe a wide range of conditions characterized by uncontrolled division of cells. Initially, cancer diagonised as localized disease, but it is probably to spread to distant sites within the body, which makes incurable [2]. Cancer treatments have been performed on the basis of clinical and pathological staging that is determined using morphological diagnostic tools, such as radiological and different histopathological examinations. The

most common cancer treatments are limited to chemotherapy, radiation and surgery [3]. Despite of many advance treatments cancer therapy is still far from perfection due to some drawbacks. Currently available cancer therapies frequently face difficulties like nonspecific systemic distribution of antitumor agents, insufficient drug concentrations reaching the tumor site, intolerable cytotoxicity, restricted ability to monitor therapeutic responses [4-6]. Current diagnoses are insufficient to make predictions for successful treatment and patient outcome [7]. Therefore, there is an urgent requirement to develop new and unique technologies that might help to identify tumor margins, detecting micrometastates and recurrent tumor cells. It could help to figure out whether a tumor has been completely eliminated or not. Nanotechnology, a part of nanomedicine includes the use of nanotechnology has extended its application in various parts of biomedical science, depicted in FIG.1.

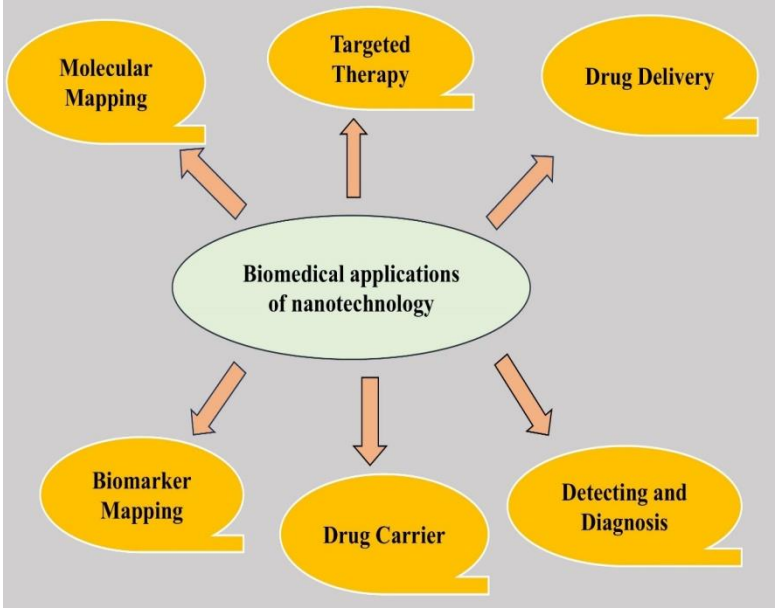

FIG.1. Therapeutic applications of nanotechnology in different biomedical applications

With the help of different nanoscale substances like gold nanoparticles, quantum dots, and other nanomaterials doctors can get transparent signals of cancer in human cells. This advance technology enables the histological diagnosis of cancer. The detection of cancer has been improved by this nanoparticle such as nano biosensor can particularly sensitive to detect several protein biomarkers in a very short time [8]. Nanomaterials has been used as an instrument of delivery system that can easily passes through many biological barriers. Nanomedicine is a part of medicine that combines with nanobiotechnology and nano pharmaceuticals for medical treatment. In a nutshell, nanomedicines are defined as the application of nanobiotechnology in medicine, which depends on the use of nanoscale materials. This device can improve drug administration process. Anti-cancer medications have been delivered via micelles, liposomes, dendrimers, nanoemluosion etc. As a result, these nanomaterials are being used to actively and passively target tumor cells due to their exceptional specificity. Despite the fact, there are numerous drugs are available that can be used to treat cancer but the challenge is in

precisely targeting cancer cells while minimizing collateral harm to healthy cells [8]. Through the application of nanomedicine, it is possible to improve the distribution and target uptake of therapeutic drugs. Different approaches to nanomedicine involving polymeric or nonpolymeric nanoparticles, dendrimers, carbon nanotubes, lipid and micelle-based nanoparticles are being investigated extensively [9]. The fabrication of a biocompatible nano system is necessary for the delivery of nanomaterial-conjugated medicine to a targeted tumor site. Specific examples of such systems include nanocrystals, strong lipid nanoparticles, nanostructured lipid carriers, lipid drug conjugates, nanoliposomes, dendrimers, nano shells, nanotubes etc (FIG.2).

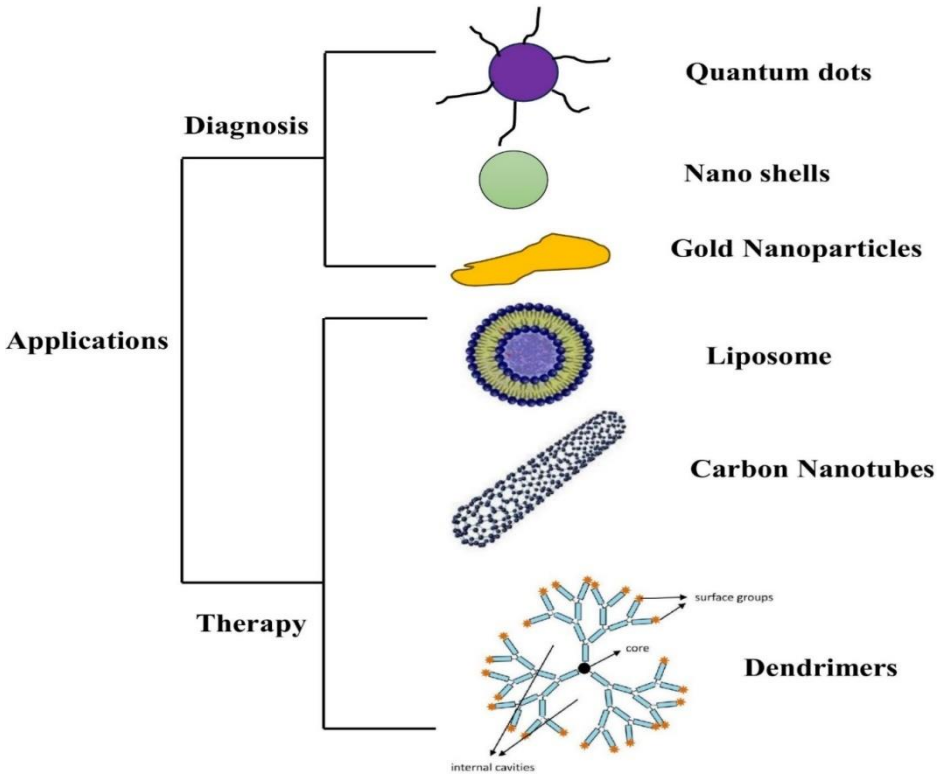

FIG.2. The implementation of nanomaterials in the detection and treatment of cancer

Nanomaterial and nanomedicine involve passive and active targeting strategies which can be make use of nano-drug delivery system. In advance research, more advanced nanoparticles are used for detection and treatment of cancer [11]. There are some nanoparticles are available, which act as a vehicle for conjugated drug delivery called nanovechiles. For cancer treatment, nanovechiles based drug delivery system specifically targets the tumor cells and the supportive cancer cell [12]. According to cancer cell imaging, one of the commonly used nanomaterials is quantum dot. This kind of nanoparticle has exceptional photophysical and photochemical properties. They are much brighter than standard fluorophores and possess very narrow emission spectra due to their very small size. These features might increase biological detection and imaging sensitivity by at least 10-100-fold [13]. Another nanoparticle carbon nanotubes (CNT) and dendrimers have different diagnostic properties which exploit in cancer therapy. They can deliver the nanodrugs directly to the cancer cells. Recent advancement of nanoscience has promoted the improvement in nanoparticle-based bio affinity tests for atomic and cell imaging [14]. The

present review article highlighted on the how different advance application of nanoscience enhance the immunotherapy for cancer treatment.

2. Uses of Nanotechnology in Cancer Screening

Genetic variations may impact whether some macromolecules are synthesised, which may lead to uncontrolled growth of cells and eventually malignant tissues. There are two types of cancer are happened; benign and malignant, respectively. Malignant tumor rapidly shed cells that penetrate nearby tissues as well as distant organs, while benign tumor are restricted to the area of cancer [15]. Cancer screening and therapy are required early detection and inhibition of cancerous cell growth and their spread [15]. There are different methods to detect cancer at very early stage. Such as positron emission tomography (PET), magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound etc [16]. Although the lack of good clinical information on various cancer kinds and stages limits the use of these imaging technologies. Therefore, it may be difficult to acquire a thorough evaluation of the illness state on the basis of which an optimal therapy can be provided [17,18].

3. Different Nanoscience Tools Helps to Diagnosis Cancer

According to ongoing research, cancer cells imaging at the tissue, cell, and molecular levels can be evaluated by nanotechnology [19]. For instance, tumor-associated fibroblasts cell membranes can be used to detect fibroblast activated protein a using pH response to fluorescent nanoprobes [20]. We can discuss some nanoscience-based technique that can help to track living cells and monitor cellular activity in tumors.

3.1 Quantum Dots

The use of visible spectrum imaging is restricted by its inability to penetrate things. This problem has been solved by developing quantum dots that emit fluorescence in the near infrared range(700-1000nm). This application is making more effective for imaging liver cancer, pancreatic cancer, and colorectal cancer [21-23]. Apart from that, it has been indicated that, the manufacture of Ag_2Te quantum dots (QD), which is made by silver and having a sulphur(S) source could help the representation of pictures with high resolution over a broad infrared range [24].

3.2 Nano shells

Nano shells are a frequently used application of nanotechnology. Nano shells are dielectric cores between 10 to 300 manometers in diameter, typically made of silicon, and coated with a thin metal shell, made by gold [25,26]. Such nano shells work by transforming electrical plasma energy into light energy. These nano shells are easily adjustable and absorbed/emitted UV-infrared arrays. Nano shells are being sought for their imaging property [27]. Nano shells used in cancer treatment depicted in FIG.3.

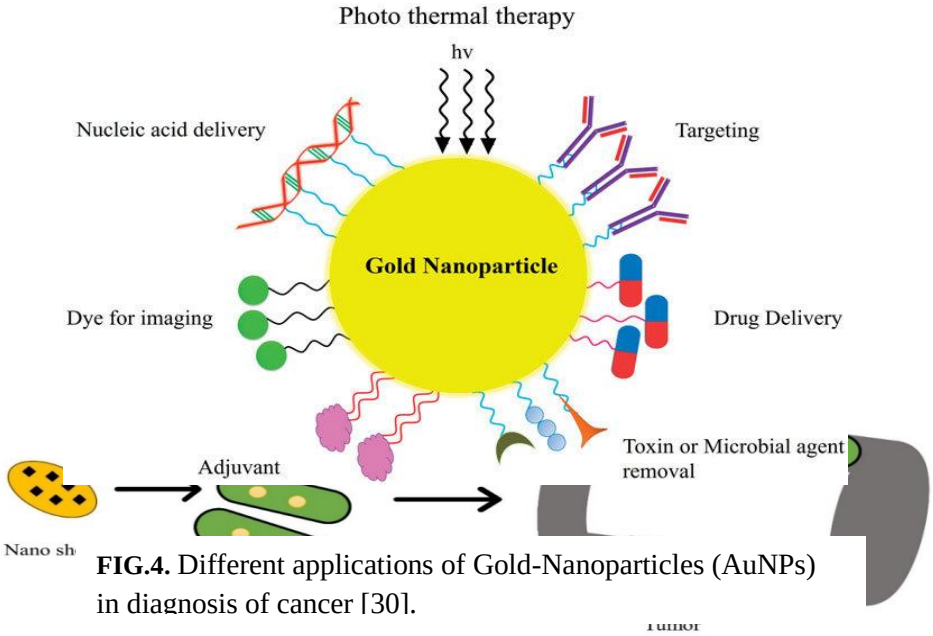

FIG.4. Different applications of Gold-Nanoparticles (AuNPs) in diagnosis of cancer [30].

FIG.3. Nano shells used in cancer

3.3 Gold Nanoparticle

Gold nanoparticles (AuNPs) is an excellent contrast agent due to their small size, good biocompatibility and high atomic number. According to ongoing research, AuNPs target cells in both active and passive ways. The permeability tension effect (EPR) in tumor tissues controls the concept of passive targeting, which is carried out by assembling gold nanoparticles (AuNPs). These particles are also helps to improve imaging [28]. On the other hand, active targeting is also carried out by coupling AuNPs with medicines that are specifically targeted against tumors, like EGFR monoclonal antibodies. The mass attenuation rate of gold is larger than that of substitute elements like iodine when the energy approaches 80 Kev, indicating a greater potential for gold nanoparticles [29]. These gold nanoparticles (AuNPs) act as contrast agents by scattering visible light, known as in vitro samples. For biopsies and the detection of pancreatic and cervical malignancies. In this way, gold nanoparticles function as a priority-based detection tool for various tumors [31]. Different applications of gold nanoparticle is depicted in FIG.4.

3.4 Dendrimers

Dendrimers are macromolecular molecules with an inner core surrounded by a set of branches whose size and shape may be customised, resulting in a desirable approach for transport of drugs [32-35].DNA assembled polyamidoamine dendrimer clusters were created for cancer-cell-specific targeting [36]. Dendrimer-5FU has been prepared via acetylation, releasing free radicals after hydrolysis. Dendrimer design permits multivalent attachment of targeting molecules and imaging probes. It can also use as a very effective diagnostic methods for analysing cancer. Dendrimer's distinctive structure allows for multivalent attachment of imaging probes and targeting moieties, allowing it possible to use them as an extremely efficient diagnostic tool for cancer imaging [37].

3.5 Carbon Nanotubes

Another type of nanodevice for cancer detection is the carbon nanotubes [38]. These are the carbon cylinders made of benzene rings that have been applied to biology as diagnostic instruments. These have been also used as sensors for detecting DNA and protein [39]. The study of attractive structural, mechanical, electrical, and optical properties of single-walled carbon nanotubes (SWNTs) for biological applications such as biosensors, molecular transporters for drug administration, and potential novel treatments is a developing area of nanotechnology [40]. New advances in biomedical imaging have focused on surface functionalization and the SWNTs near infrared fluorescence features. NIR spectrum remain between the biologically transparent zone (700-1300nm) where tissue and blood are scattered by minimum amount of autofluorescence, absorption. Multi walled carbon nanotubes with surface modification have been used successfully for bioimaging applications [41-43].In an in vitro experiment, it was found that medicines bound to carbon nanotubes were more effectively absorbed by cells than loosely bound pharmaceuticals.

4. Drug Targeting Methodologies for Cancer Treatment

4.1 Active Targeting

The most effective targeting approach for successfully delivering a nanoparticle into a malignant cell without resulting in any toxicity is active targeting of the medicine. This specific type of targeting usually depends on ligand-receptor interaction, in which nanoparticles have ligands that particularly bind to the receptors found on the surface of tumor cells. This targeting method reduces nonspecific interactions by providing the strong ligand-receptor binding to deliver the drug in peripheral tissue [44]. To be able to enhance some tumor-selective delivery of nanoparticles to tumor tissues, the polymeric nanoparticles have mostly failed to include the targeting moiety. However, these binary structure conjugate drug delivery systems must have inherent limitations. Active targeting is one suggested method of getting around these restrictions. To deliver a medicine to infected locations biological barriers based on molecular recognition processes, it involves the attachment of a homing moiety, such monoclonal antibody or ligand [45-47]. To build more effective delivery systems, several factors must be taken into account while creating ternary- structured nanoparticles (which consists of medicine and targeting moiety). Only tumor cells should express the antigen or receptor without being expressed on healthy cells. They must be expressed uniformly on all tumors cells that were selected. Apart from that, cell surface is

not suggested to release antigens and receptors into the bloodstream after interacting with the target, targeted conjugates internalize cells is a crucial factor in choosing the right targeting ligands. The most prevalent form of internalization is receptor-mediated endocytosis [1]. Target organelles get newly generated endosomes. If the drug has the necessary physico-chemical qualities to penetrate the endosomal membrane, it is released from the conjugate and enters the cytoplasm as the pH value in the interior of the endosome becomes acidic and lysozymes are activated. However, some ligands, like folate from food, have naturally high amounts in the human body and may compete with the ligand that has been conjugated to a nanoparticle for binding to a receptor. This would reduce the intracellular concentration of the medicine that has been delivered [2].

4.2 Passive Targeting

The accumulation of a drug delivery system at a specified position as a result of physico-chemical or pharmacological parameters is known as passive targeting. This method may effectively improve the efficacy and bioavailability of drugs. By this process the structural and functional variations between delivering the medicine to a particular spot via the normal and tumor vasculature Tumor blood flow is extremely might involve local delivery. Tumor blood flow is extremely distinct from healthy tissue. Tumor with angiogenic blood vessels, unlike typical tissues, include gaps that are as wide as 600-800nm between adjacent endothelial cells. Elevated quantities of vascular mediators including nitric oxide, bradykinnis, and others may be the cause of the leaky and incorrect architecture of tumor vasculature. The distinct pathophysiologic features of tumor vasculature in addition to inadequate lymphatic drainage, creates the EPR effect. These permit macromolecules, such as nanoparticles can extravasate into extravascular spaces through these gaps into voids and accumulate with tumor tissues [48]. The unique microenvironment that surrounding tumor cells, which is different from that of normal cells, is another factor is passive targeting. Fast-growing, hyperproliferative cancer cells have a high metabolic rate, which is typically not supported by the availability of oxygen and nutrients. In order to gain additional energy, tumor cells therefore use glycolysis, which creates an acidic environment. The pH -sensitive liposomes are made to be stable at a physiologic pH of 7.4, but they disintegrate to release active drugs in target tissues where the pH is lower than physiologic values, like the acidic environment of tumor cells. Additionally, the motion and survival methods of cancer cells are thought to be mediated by the expression and release of certain enzymes, such as matrix metalloproteinases. In an in invitro study, matrix metalloproteinases were found to effectively and specifically cleave an albumin-bound form of doxorubicin that had an octapeptide sequence specific to matrix metalloproteinase-2 between the drug and the carrier [49]. The entire active and passive targeting method depicted in FIG.5.

5. **Novel Cancer Therapies with Nanotechnology**

Targeted treatment, which destroys solely cancer cells while preserving healthy ones, has gained popularity in the fight against cancer. The development of nanotechnology has given rise to new resources and opportunities and entry points for the targeted chemotherapy for cancer. Different artificial characteristics of nanoparticles are providing various new ways for non-invasive cancer treatment methods, that were not previously feasible, including advanced cancer therapeutic methods. These new approaches are based on nanotechnology, such as photodynamic radiation (PDT), radiofrequency therapy and protons beam theragnostic etc (FIG.6).

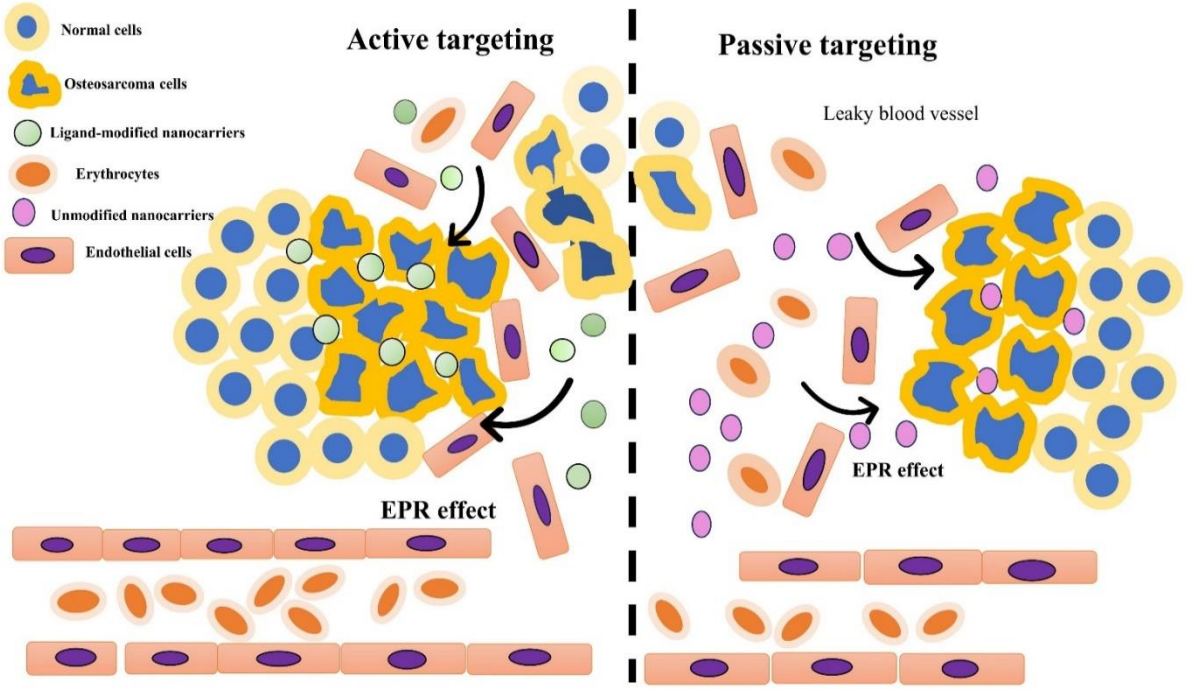

FIG.5. An example of a schematic illustrating active targeting and passive targeting of a nano-delivery system for cancer treatment. Enhanced permeability and retention (EPR) effects enable passive targeting. Through the leaky tumor vasculature, nanocarriers extravasate, circulate in the bloodstream, and accumulate in tumor tissue. Highly expressed receptors on the tumor cell can be bound by targeting ligand-modified nanocarriers, resulting in local drug delivery or internalization through receptor-mediated endocytosis.

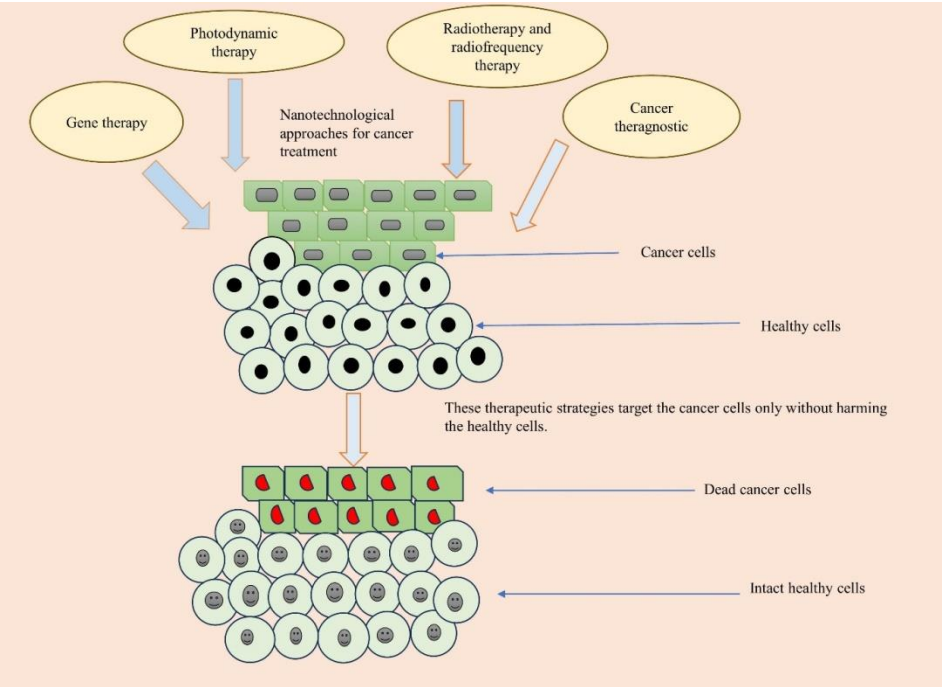

FIG.6. Different medications techniques of nanotechnology in cancer treatment.

5.1 Gene Therapy using Advanced Nanotechnology

The principal of gene therapy is that a few exogenous genes can be incorporated into the genome of tumor cells to have a tumoricidal effect. It refers to one of the areas of preclinical and clinical cancer research which is currently progressing rapidly. The toxicities, immunological and inflammatory reactions, gene control and targeting difficulties that come with viral vectors are problematic. There is also a risk that the virus will reactivate and spread disease. To reduce this risk factor, non-viral mediated gene transfer methods have received a lot of attention as a means of solving this. These non-viral vectors are harmless, they can be administered frequently for a very cheap cost and generate fewer immunological reactions [50]. Cationic polymers and nanoparticles delivered by liposomes are the most often employed nonviral vectors. The physical properties of nanoparticles, such as their shape, size, charge density and colloidal stability are essential factors in determining how effective they are as possible nonviral gene delivery systems [51].

5.2 Photodynamic Therapy using Advanced Nanotechnology

Photodynamic therapy (PDT) is a less damaging substitute to current adjuvant therapy that does not allow for the development of resistance and has negligible local or systemic treatment-related morbidity. PDT works by activating a photosensitizer, which activated by a certain wavelength of light. It causes the

generation of reactive oxygen species, which can directly destroy tumor cells and the vasculature around them, triggering tumor infraction. This problem may be solved by using polymeric nanoparticles to deliver a large number of photosensitizers to tumor cells via tumor-specific ligands. This process has also the benefit of being delivered even after surgery, chemotherapy, radiotherapy without producing immunosuppressive adverse effects [52].

5.3 Radiotherapy and Radio-frequency Therapy using Advanced Nanotechnology

It has been studied high atomic number (Z) materials might increase the radiation exposure. According to some states, packing high atomic number may cause the tumor to absorb more photons than the surrounding tissues, increasing the radiation dose that is given to the tumor. In cell tests and in a murine model, gold (Au: Z=79) or nanogold shown dose-enhancing effects. Because of their biocompatibility and simplicity in conjugating to biomolecules, gold nanoparticles have been intensively researched in a wide range of biomedical applications [53]. Radiofrequency ablation is most frequently utilised in cancer therapy, while it has also been used to treat cardiac conduction problems, neurological disorders, and cancer. The most frequent tumor treated with this method are inoperable malignant liver tumors. Nanotechnology is enabling the development of non-invasive radiofrequency ablation of tumors, a well-established method for eliminating tumors that formerly required the insertion of probes into tumors. Gold nanoparticles may be used to specifically target cancer cells. They have successfully thermally ablated tissue and cancer cells in both in vitro and in vivo systems by utilising an innovative, non-invasive radio wave device paired with gold nanoparticle enhancer solutions [54]. Different ways of providing drugs for cancer treatments are shown in Table.1

Table 1. Different ways of providing drugs for cancer treatment

Sl. N	Drug Delivery Vehicle	Description of Nano	Drug Used	Application	References
1.	Nanoparticle	Albumin-bound nanoparticle	Paclitaxel	Metastatic breast cancer	[55]
2.	Liposome	Liposome	Doxorubicin	Solid tumor	[56]
3.	Nanoparticle	Gold nanoparticle loaded with tumor necrosis factor	-	Solid tumors	[57]
4.	Nanoparticle	Gold nanoparticle	-	Lung cancer, head and neck cancer	[58]
5.	Nanoparticle	Near-infrared irradiation with gold nano shells	-	Head and neck cancers	[59]

		(Localized thermal ablation)			
6.	Liposome	Liposome proapoptotic	Bik gene (Bikdd)	Pancreatic cancer	[60]
7.	Conjugates	Polymer matrix	Docetaxel	Prostate cancer	[61]
8.	Liposome	PEGylated matrix	Doxorubicin	Metastatic breast and ovarian cancer, Kaposi sarcoma	[62]
9.	Conjugates	Cyclodextrin-containing polymer	siRNA	Solid tumor	[63]
10.	-	PEG-Coated SiO	-	Melanoma	[64]
11.	Micelle	Cyclodextrin-containing polymer	Camptothecin	Ovarian/tubal/peritoneal cancer, rectal cancer	[65]
12.	-	Cyclodextrin-based polymer	Docetaxel	Solid tumor	[66]
13.	Nanoparticle	Gold nanoparticle	Tumor necrosis factor	Pancreatic cancer, melanoma, ovarian, breast cancer	[67]
14.	Liposome	Liposome	Daunorubicin	Kaposi sarcoma	[68]
15.	Liposome	Liposome	Cytarabine	Lymphoma	[69]
16.	-	Dendrimer	Docetaxel	Breast,prostate,lung,and ovarian cancer	[70]
17.	-	Polymeric nanoparticle	Docetaxel	Advanced solid malignancies	[71]
18.	Micelle	Liposome	Doxorubicin	Kaposi sarcoma	[72]
19.	Micelle	Polymeric micellar nanoparticle	Paclitaxel	Breast cancer	[73]
20.	Liposome	Liposome	Annamycin	Acute lymphoblastic leukemia, acute myelogenous leukemia	[74]

21.	Liposome	Liposome	Vincristine sulfate	Lymphoblastic leukemia	[75]
22.	Liposome	Human antibody fragment-targeted liposomal doxorubicin	Doxorubicin	Metastatic stomach cancer	[76]
23.	Liposome	Liposome	Doxorubicin	Metastatic breast cancer	[77]
24.	Micelle	Micellar nanoparticle	Paclitaxel	Breast cancer	[78]

6. Future Outlook

Multiple research teams have employed nanotechnology extensively in various cancer treatment and diagnosis. It may be the next big thing in the fight against cancer. Although a lot of research work has been done so far in the area of cancer nanotechnology but much more is still to come. The future of DNA-based nanomaterial in cancer therapy is indisputable, despite its inherent disadvantages. It will still continue to develop in the field of DNA nanomaterial, which causes a significance improvement in cancer detection and treatment methods. In addition, it is essential to highlight synthesis of a multi modal nanoparticle that might deal an additional hit to cancer through rapid detection and successful treatment. Therefore, it is evident that in the upcoming future cancer nanotechnology will undoubtedly provide an effective, safe cancer detection and therapeutic approach.

7. Conclusion

Over the past few decades have seen a huge increases in the use of nanomaterials in many different branches of science, engineering, and technology. Nanoparticles are widely used in biomedical research as a method of delivering medicines for cancer treatment. Consistent with this fact, usage of nanotechnology in cancer diagnostics and therapy has created the possibility for a completely novel field of research called as Nano oncology. Modern developments in nanotechnology have driven various research efforts in the field of nano-oncology over the years. It helps to establish nano-oncology as a feasible cancer therapy approach. However, researchers have created a huge number of unique anticancer drugs and diagnostic molecules which may easily detect and treat cancer cells, there are some drawbacks also present. It becomes a major challenge to deliver anticancer drugs at the targeted cancer cells during therapy. Due to their specificities, nanoparticles enable targeted drugs administration in affected cells with low toxicity. But as with other therapeutic options, this technology is not completely devoid of toxicities. It comes with few challenges with its use including systemic. Different nano polymers have been developed as drug carriers. We can evaluate their properties and also can be to design new molecules which are more effective and compatible with a biological system. Overall, we can conclude that nano-oncology has created numerous possibilities for drug delivery and delivery system development in the prevention of cancer. In the upcoming future, ongoing and in-depth research in Nano-oncology will make an established cancer treatment method.

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