

Chapter 16

Synthesis and Application of Nanomaterials for Biomedical Anticancer Therapy



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16.1 Introduction

The nanomaterials, can be grouped into nanoparticles, nanorods, nanosphere, nanoshells, and nanostars according to their structure and these have been usually employed in various medical purposes like biomedical imaging and treatment of cancer. These nanomaterials are considered to be good carriers for drug molecules. The technology using nanomaterials have developed in such a way that these are employed in the fields of functional imaging, tumor therapies, and synergistic combinational platforms. In this chapter, we will about numerous purposes of nanomaterials in the fields of biomedical imaging and tumor therapies. The clinical imaging modalities incorporate attractive reverberation imaging, imaging by using any kind of penetrating wave, antielectron discharge penetrating wave, single antielectron outflow automated penetrating wave and optoacoustic imaging. Different disease restorative techniques will likewise be incorporated, with photothermal treatment, PDT, cancer treatment, and biological therapy. This survey likewise covers both therapeutics and diagnostics, which utilize a similar specialist in analysis and treatment. This remembers ongoing advances for multimodality imaging, picture guided treatment, and mix treatment. We establish that the ceaseless advance of union and plan of new nanoparticles will improve the future improvement of clinical imaging and malignant growth treatment. Notwithstanding, more assets ought to be accessible to inspect results and cell harmfulness when utilizing nanomaterials in people (Siddique & Chow, 2020).

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The utilization of nanoparticles has upgraded practically all significant imaging methods, especially MRI, PET, etc. A portion of the significant achievements are the utilization of Fe₃O₄ nanoparticles in T1 weighted as well as T2-weighted MRI, the plan of radioisotope fluorescent free antielectron discharge penetrating wave, and the improvement of fluorescent nanoparticles (Rosado-De-Castro, Morales, Pimentel-Coelho, Mendez-Otero, & Herranz, 2018). Then again, novel sorts of optical nanoprobe, for example, determined glow nanoparticles (PLNPs), are being created to exploit enduring close infrared (NIR) radiance capacity (Lecuyer et al., 2016). This permits optical imaging without steady excitation and auto fluorescence (Liu et al., 2019). The most recent examination and progression in nanotechnology direct to the advancement of different nanoparticles for symptomatic and helpful application. Despite the fact that clinically, the quantity of utilizations of nanomaterials is restricted by the mind boggling requests on their pharmaceutical features, nanodiagnostics boost the comprehension of significant physiological standards of different illnesses and medicines. Then again, NPs are broadly utilized in the center for remedial purposes. Restorative nanoparticles boost the aggregation and arrival of pharmacologically dynamic operators at the obsessive site, which generally speaking, expands remedial viability and diminishes the frequency and power of the results. NPs hold extraordinary guarantee for incorporating symptomatic and restorative operators into a solitary nanoparticle for various medical applications. A genuine model would screen biodistribution and target site collection, evaluating and envisioning discharge of the drug, and longitudinally surveying helpful adequacy. These nanoparticles are utilized for customized nanomedicine-based treatments (Baetke, Lammers, & Kiessling, 2015). Nanoparticles' natural extraordinary attractive or optical parameters help in making them perfect for using in different bioimaging purposes. Nanoparticles make incredible differentiation specialists because of their high affectability, little size, and piece. Nanoparticles are regularly formed with reasonable focusing on ligands on the outside of the particles. Nanoparticles with various functions can be created by joining different useful materials, and this empowers multimodal imaging and treatment at the same time, otherwise called theranostics (Kim, Lee, & Hyeon, 2017). Albeit every one of the imaging and treatment modalities has improved essentially in the course of there are admonitions in nanoparticle properties that are hindering its uses. For instance, no sole atomic imaging methodology can proffer all the necessary information completely portraying the properties of a regulated operator. Each imaging methodology has a significant weakness, for example, MRI has great-goal yet less affectability, optical strategies have restricted infiltration and procedures have generally helpless goal yet high affectability. Consolidating different imaging procedures can empower these applications to supplement each other, and a multimodal imaging operator turns into the way to upgrading those imaging frameworks (Burke, Cawthorne, & Archibald, 2017).

This section investigated the various functions of nanomaterials, for example, contrast specialist and portion enhancer, in biomedical imaging and disease treatment. Additionally, the section examined the fundamental instruments of nanoparticles including physical, compound, and natural frameworks. Some new employments of nanoparticles as theranostic pros are discovered.

16.2 Synthesis of Nanoparticles for Anticancer Therapy

16.2.1 *Gold Nanoparticles*

16.2.1.1 Synthesis Through Ultrasound Irradiation

This method is rapid and the synthesis is carried out under appropriate situation without the use of more reducing agents. The heating in ultrasound is produced from the acoustic cavitation. Usually, water is employed in the production using ultrasound. The acoustic cavitation develops through the sonolysis of water which will result in the production of numerous huge number of H^{\cdot} radicals, the combinations of which results in the production of hydrogen (Bang & Suslick, 2010; Duan, Wang, & Li, 2015).

16.2.1.2 Synthesis Through Microwave Irradiation

The effectiveness of microwave irradiation is due to high dielectric solvents induced by localized superheating and pressure effect, which has capacity of higher heating rate when compared with the usual heating which will result in the decrease in the time period. One of the major drawbacks of microwave irradiation synthesis is that microwave irradiation pose difficulty in penetrating fluid in huge reactors and thus difficult to use for industrial purpose (Duan et al., 2015).

16.2.1.3 Synthesis by Arc-Discharge Method

This is another method for nanoparticles production, where we employ two electrodes made of gold to produce gold nanomaterials. These gold electrodes are made to be in contact with an arc and separated as soon as possible to maintain the arc inside the salt solution. These two electrodes can be subjected to high temperature and can be melted and this can result in the plasma discharge and now it can be changed into gold nanomaterials (Ashkarran, 2012).

16.2.1.4 Seed-mediated Synthesis

Seed-mediated synthesis of nanoparticles is yet another and most widely adopted method to synthesize gold nanoparticles for the particles other than spherical shape. The very general principle of the seeded growth method is, first these particles formed by the reduction of the gold salts. Then to the solution the seed particles are added which contains metal salts which is done usually in the presence of a weak reducing agent which prevents nucleation and will speed up the growth of the Au NPs (Shah et al., 2014).

16.2.1.5 Synthesis Through Chemicals

Au NPs synthesis utilizing chemical, is a cruel way to obtain nanoparticles of various types. Lessening specialists, for example, sodium tetrahydridoborate, caustic soda, ascorbic corrosive, $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7$ and H_2O_2 are utilized in the decrease of Au(III) particles to Au(0). The union happens within the sight of at least one water-dissolvable polymers, surfactants, or covering specialists with the inclusion of outside energy like warmth, photograph light, and ultrasound illumination. The advantage of this method is mono-dispersed materials and the figure and dimension of the nanomaterial can be inhibited through this method (Brown & Brown, 1962; Chandra et al., 2013; Schlesinger et al., 1953; Xiao, Shlyahovsky, Popov, Pavlov, & Willner, 2005).

16.2.1.6 Biological Synthesis

This biological method includes the use of prokaryotic cells to eukaryotic fungus and complex plants. Biological synthesis methods have been suggested as safe, inexpensive, possible environment friendly ways and alternate options to chemical and physical kind of synthesis (Manikprabhu et al., 2016). Generally, plant adds its therapeutic properties to the nanoparticles, thereby enhancing its activities (Muthukumar et al., 2016).

These microbes result in the production of inorganic materials either inside their cells or outside their cells which synthesize the nanoparticles. In the intracellular methodology, it needs a unique ion transportation in the microbial cell. There are several proteins which are resident on the cell wall and these can decrease the ions. Once these particles are synthesized they can get diffused out. These microorganisms are well known for their ability to produce cofactors and enzymes.

16.2.2 Gold Nanoparticles for Cancer Therapy

Gold nanoparticles found great advantage in cancer therapy based on: (1) It's non-toxic nature (2) the specific physical parameters and (3) their potential to interact only with cancer cells and tumor masses which are damaged. Gold nanoparticles for killing tumor in vivo have to overcome many obstacles (Kodiha, Wang, Hutter, Maysinger, & Stochaj, 2015). Gold nanoparticles destroy cancer cells, either by mechanical damage or due to hyperthermia (Kodiha et al., 2015).

Destroying the cancer cells via hyperthermia depends on the heating sensitivity of the tissues leading to cell death. First the nanoparticles are directed to the cancerous tissue. These particles can get accumulated in the tumor mass. Using an external source these particles can be heated up and the temperature or heat around the cancerous cells increases and thereby these cancerous cells will be selectively killed.

16.2.3 *Silver Nanoparticles*

16.2.3.1 **Production of Silver Nanomaterials Through Physical and Chemical Methodologies**

In the physical methodology, nanoparticles are developed with the evaporation–condensation technique (Gurav, Kodas, Wang, Kauppinen, & Joutsensaari, 1994; Kruijs, Fissan, & Rellinghaus, 2000). In olden days other kinds of physical methodologies were employed for the preparation of silver nanoparticles (Pluym et al., 1993; Tien et al., 2008). Physical methods are considered to be better because of these methods are rapid, and the radiation is done using reducing agents. Another advantage in physical method is that these methods do not involve any poisonous chemicals. Limitations of physical method is that the yield will be less and so much energy is consumed for the methodology, the solvent gets contaminated, and at times it is not uniformly distributed (Elsupikhe, Shameli, Ahmad, Ibrahim, & Zainudin, 2015; Shameli et al., 2010).

In the chemical methodology, water or organic solvents are employed for the synthesis of the AgNPs (Tao, Sinsermsuksakul, & Yang, 2006). This chemical method involves three major compounds, which are metal precursors, reducing agents, and stabilizing agents. Usually, these silver nanomaterials can be produced by two mechanisms, which are grouped as “top-down” and “bottom-up” (Deepak et al., 2011). In the first mechanism that is “top-down” method, it involves the mechanical grinding of the heavy metals simultaneously will stabilize with the help of colloidal protecting agents (Amulyavichus, Daugvila, Davidonis, & Sipavichus, 1998). In the second method that is the “bottom-up” method, it involves a chemical reduction, electrochemical methods, and sono-decomposition. Chemical methods have more preference because this method gives higher yield, in comparison with the physical methods, which have shown to give low yield.

Different researchers around the globe are keen on delivering nanomaterials as an elective device to make details that can target explicit dangerous masses as it were. Gopinath et al. in one of the examinations took care of the subatomic system of silver nanoparticles. That examination bunch saw that customized cell passing was fixation subordinate under different conditions. In these investigations, the analysts found that silver nanoparticles actuate apoptosis as well as sharpen malignancy cells (Gopinath, Gogoi, Chattopadhyay, & Ghosh, 2008). Silver nanoparticles actuated changes in cell structure, diminished cell suitability and biological movement, and expanded pressure related to oxidation prompting mitochondrial harm and expanded creation of ROS, finishing with issues in cells.

Silver nanoparticles are employed in both diagnosis and therapies of cancer. Various clinical testing have shown the application of silver nanoparticles as nano-carriers for target site delivery of drugs. These nanoparticles are also employed as agents which has therapeutic effects and also as enhancers for radiation and photodynamic therapy.

16.2.4 *Titanium Oxide Nanoparticles*

Titanium dioxide photocatalyst is a notable and well-informed photocatalyst because of its intriguing properties which incorporate strength, non-harmfulness, compatibility and other parameters. The ongoing advancement of nanotechnology has demonstrated that nanomaterials, can have high movement in the photodegradation of a wide scope of natural and inorganic pollutants present in water bodies. It is fit for corrupting poisons (Beydoun, Amal, & Low, 1999). For it to be extremely compelling, it ought to have certain properties, for example, reasonable molecule size, shape, crystallinity, and a decent proportion of anatase to rutile. This is the motivation behind why most analysts have been attempting to utilize various techniques to get particles with reasonable attributes for natural remediation or for different uses of interest. As of late, packages and varieties of titanium dioxide nanotubes (TNTs) with various characteristics have been blended by a wide range of strategies, for example, layout helped, sol-gel, aqueous, electro-anodization, compound fume affidavit and actual fume statement (Macák, 2008). There are different procedures for getting ready titanium dioxide (TiO_2) nanoparticles and these incorporate converse micelles, the sol-gel measure, the metal-natural compound fume affidavit (MOCVD) (Pratsinis, 2011), gas stage (airborne) blend (Chen & Mao, 2007), wet-substance union by precipitation of hydroxides from salts, microemulsion-interceded techniques (Chabra, Pillai, Mishra, Morrone, & Shah, 1995) and electrochemical amalgamation. These strategies can be isolated into five general gatherings to be specific sol-gel, affidavit techniques, sonochemical, and microwave-helped strategies, hydro/solvothermal strategies and oxidation strategies.

These nanomaterials were explored as an upgrade operator for processed tomography imaging (CT) and radiation treatment. In radiation treatment, ionizing radiation targets tumor and makes the harm DNA of tumor cells which brings about cell demise. Double mode picture differentiation and improvement treatment is another territory wherein nanoparticles are utilized. Harada et al. arranged in vivo examinations to assess conveyance of micelles through tissues and ultrasound effectiveness in hindering development of tumors (Harada, Ono, & Yuba, 2013). In the examination with CT26 cells, it was discovered that TiO_2 nanoparticles have created oxidative pressure without UV. TiO_2 NPs incite creation of responsive oxygen species (ROS), this is another anticancer component of these nanoparticles (Fujiwara, Luo, & Sasaki, 2015).

16.2.5 *Iron Oxide Nanoparticles*

Basically there are two methods by which these nanoparticles can be produced: The first method is known as the “top-down” method. In this particular method large pieces are broken down in order to produce these nanomaterials (Harris & Chess, 2003; Veisoh, Gunn, & Zhang, 2010). 15 base up combination systems for IONPs

including coprecipitation, warm deterioration, microemulsion, aqueous, and solvo-thermal union. The IONPS incorporated with these techniques permit the control of their size and shape, expanding their strength, dissolvability, and biocompatibility (Tombácz, Turcu, Socoliuc, & Vékás, 2015; Wu, He, & Jiang, 2008).

The metabolism of iron in tumorous mass is altered. Tumor cells have an increased need for iron to facilitate their high proliferating rate (Buss, Torti, & Torti, 2003; Terman & Kurz, 2012). The iron uptake into cancer cells is increased by the elevation of iron regulatory proteins such as transferrin receptors (Bystrom, Guzman, & Rivella, 2014). The need of iron is important for various cellular processors such as cell division, synthesis of genetic material and mitochondrial electron transport. Iron is important for the function of ribonucleotide reductase, which is an enzyme that reduces ribonucleotides to deoxyribonucleotides for DNA synthesis and repair. This is the rate-controlling stage of genetic material biosynthesis. This enzyme is closely correlated with cellular replication in the G1-S phase of the cell cycle. Since deoxyribonucleoside triphosphates are in low concentrations in cells, it would be a good strategy to inhibit the enzyme, ribonucleotide reductase. This, in turn, causes embarrassment of cellular production in tumor tissues (Rao et al., 2009).

Manipulating the iron content in the cancer cells could be a good strategy to destroy cancer cells. This can be done by the use of iron chelators. Iron chelators will have a double impact: Firstly, they will be depleting iron through chelation and inhibiting ribonucleotide reductase, thus inhibiting cell proliferation. The second method is that iron chelators can be used to bind to intrasomal iron to form redox active chelators to produce cytotoxic reactive oxygen species through the Fenton reaction promoting programmed cell death (apoptosis) in tumor masses (Foy & Labhasetwar, 2011; Liu, Lin, & Sartorelli, 1992).

16.2.6 Silica Nanoparticles

Silica NPs can likewise be delivered during maximum heat fire decay of metal-natural forerunners. This cycle is additionally alluded to as compound fume buildup (CVC) (Silva, 2004). In a regular Central venous pressure measure, silica NPs are created by responding tetrachlorosilane with H_2 and O_2 (Vansant, Voort, & Vrancken, 1995). Trouble in controlling the molecule dimension, shape, and stage structure is the fundamental impediment of the fire union (Klabunde, 2001). In any case, this is the conspicuous technique that has been utilized to economically create silica NPs in fine powder structure.

Enormous Si compounds with a normal size of 2.2 m for the most part have bigger polarization than NPs. Notwithstanding, an ongoing report indicated that a lot more modest silicon molecule. For magnetic resonance imaging application, a Si-based difference specialist can be delivered by consolidating progress metal particles into a molecule's body. This differentiation operator abbreviates the atomic turn grid unwinding time (T1) of the protons of close by tissues, and at last, intensifies the sign in T1 imaging. Direct recognition of the Si signal is preposterous

because of its low affectability of Si cores, which prompts long obtaining occasions. Be that as it may, this impediment can be illuminated through hyperpolarization. Using this strategy, the imaging window length keeps going around 50–130 s, which permits fast responses and digestion without oxygen to be examined and additionally be utilized to describe the diagnosis of disease. Upside of utilizing a Si-based differentiation specialist is its adaptability of science; the connection of utilitarian natural atoms on the outside of the compounds doesn't altogether lessen any of the ideal atomic attractive reverberation properties (Kwiatkowski et al., 2017).

16.2.7 Polymeric Nanomaterials

These nanomaterials can be set up by scattering performed polymers utilizing various techniques as dissolvable dissipation, nanoprecipitation, salting-out, dialysis and supercritical liquid innovation. These systems have comparative properties that they include a natural stage containing the nanoparticle segments and a water stage containing stabilizers. The other comparability is the helpless epitome of halfway water solvent and uninhibitedly water-dissolvable medications (involving proteins and peptides), which escape from the natural stage to the watery stage (Quintanar-Guerrero, 1998).

To defeat the constraints of chemotherapy like the off objective medication conveyance it was important to locate another option. Polymeric nanoparticles have been seen to be better medication carriers as they can convey the medications to the objective site and furthermore considers have announced their capacity to perform both finding and treatment of tumor (Parveen and Sahoo, 2008). These polymeric nanomaterials have different focal points like soundness, biocompatibility, biodegradability, can be changed, and are economical.

16.3 Influence of Physicochemical Properties on Nanocarriers

16.3.1 Dimension and Nature of the NPs

For the determination of nanocarriers one significant boundary is the dimension of the NPs. The size of nanoparticles can impact the cell take-up, and because of the inclination to frame groups in the arrangement, the size of nanoparticles can likewise expand (Benne, van Duijn, Kuiper, Jiskoot, & Slutter, 2016; Silva, Soema, Slutter, Ossendorp, & Jiskoot, 2016). The perception and investigation of three sorts of attractive NPs by Ge et al. showed that NPs with various dimensions and surface properties can result in diverse reactions, particularly in total of MNPs, and the

bigger particles would create higher cell takes-up (Ge, Zhang, Xia, et al., 2009; Kyrychenko, Pasko, & Kalugin, 2017; Limbach, Li, & Grass, 2005). A comparable report on the connection among the dimension of ceria NPs and cell take-up demonstrated a straight relationship inside a specific reach. The cell take-up of bigger compounds was fundamentally larger than that of more modest compounds in a similar focus. The dimension of the nanoparticles will likewise influence their leeway from the flow (Longmire, Choyke, & Kobayashi, 2008). Compounds with 200 nm or bigger are generally taken out by the macrophage system framework, interceded by cells in different body organs (Moghimi, Hunter, & Murray, 2001). At 100 nm, NPs include helpless dispersion inside the thick collagen framework of the interstitial space, subsequently bringing about helpless entrance into the tumor tissue and limited NP collection about tumor veins (Moghimi et al., 2001).

The state of the nanomaterial is likewise an unmistakable boundary that influences the action of the molecule (Culver et al., 2016; Rampersaud, Fang, & Wei, 2016). Reports have indicated to pathways by which compounds go through the tissues, duration for cycling, focusing on impact, capacity to beat natural boundary, and different properties rely generally upon molecule shape and size, on the grounds that these attributes are probably going to impact the compounds in the blood carrying, particularly in little nerves and cancer cell associated nerves, and how cells see and react (Moghimi et al., 2001).

16.3.2 *Surface Charge of Nanoparticles*

Surface charges are firmly identified with different natural exhibitions of the nanoparticles, such as solvency, bio distribution, security, cell take-up, cytotoxicity (Peng, Lu, Wang, Li, & Chen, 2017; Mou, Xing, & Ren, 2017), for example, solvency, bio distribution, security, cell take-up, cytotoxicity, and such. The charge reaction among particles and cells is a significant reason for these natural exhibitions (Pittella, Zhang, & Lee, 2011). The exploratory after effects of Tang et al. demonstrated that the NPs are scattered in the way of life means, just decidedly stimulating compounds can be ingested by the tissues; if the compounds are associated with the protein, among the emphatically and adversely stimulating compounds can be totally wiped out (Tang et al., 2015). Despite the fact that protein-covered compounds may help distinguish receptors (Holgate, 2010; Mou et al., 2017) principally in light of the fact that the cell layer is adversely charged, now and again with a limited quantity of the fix, consequently, the decidedly charged compounds are added effectively than contrarily unbiased compounds by cell layer adsorption. Graf et al., in view of the investigation of Si NPs, found that maximum sure charge compounds can instigate viable cell disguise, while contrarily charged compounds and the PEG functionalized compounds express diminished cell take-up (Leonenko, Finot, & Amrein, 2007).

16.3.3 Cytotoxic Impacts

The toxic level will depend on the reactions which are between the nanomaterials and the surrounding where the nanoparticles get into inside the body of humans. The structure of the nanomaterial has a great role in deciding the toxic property, especially the core material. The mechanism of toxicity is such that the toxic molecules get leaked from these nanomaterials when they decompose and these molecules gets deposited (Pelaz, Charron, & Pfeiffer, 2013). This decomposition process of the nanomaterials can be avoided with the help of an inorganic core or a shell. When it is coated with such coatings it can prevent the nanoparticle decomposition and these can stay on the surface or can be embedded in a cross-shaped polymer and thereby these coatings can stay stable.

These numerous properties of nanomaterials are prominent parameters that help in the determination of the nanomaterial's characteristics, which are proved by the strong outcomes in both theories and in practicals. These outcomes have proved their application in the area of medical fields. The various parameters of nanomaterials can be modified accordingly and can be used as the nanodrugs to treat tumor, which means, these kind of treatments can be used to cure the cancerous cells accordingly to the patients conditions.

16.4 Cancer Therapy

Cancer therapy is used to get rid of the tumor cells or to stop the growth of such cancerous cell masses. There are numerous methods which are available and each one of them is comparatively better than the other therapies. Application of nanoparticles have enhanced most of the cancer treatments and these therapies are discussed in the below section:

16.4.1 Photothermal Therapy

This type of treatment is a hyperthermia-dependent treatment. Mechanism of photothermal treatment is to destruct the cancer masses meanwhile the healthy tissues are not heated and protected. The tissue cells do not have NIR-absorbing chromophores. When the lasers are used they have a "tissue optical window" which is around 700–1000 nm and thereby it reduces the tissue heating, whereas the silver nanoparticles highly absorb the heat in the NIR region. This is the main mechanism to achieve selective heating of the cancerous cells (Hirschberg & Madsen, 2019). Another advantage of the gold nanomaterials is that these particles can be altered with numerous functional groups. The colloidal gold showcase localized plasmon surface resonance. This helps the gold to take in light at various frequencies or

wavelengths. This property helps them to be applied for the hyperthermic tumor therapy application. The plasmon surface resonance can be altered by changing the gold nanoparticle's structure shape and size. This modification can result in the change of other characteristics like its photothermal and photoacoustic parameters, which will then help these particles to utilize various range of wavelengths. Due to size in nanometer scale, these particles can get localized in the cancerous cells and can be excreted through the urine (Vines, Yoon, Ryu, Lim, & Park, 2019). One of limitations of this photothermal therapy is that heat which is generated by the nanoparticles are heterogeneous in the cancer cells, that is only a part of the cell mass which gets heated and will be treated whereas some portion of tumor gets untreated. Researchers came up with a new proposal which involved the application of silica gold nanoshells for photothermal therapy (Simón, Norregaard, Jørgensen, Oddershede, & Kjaer, 2019).

Usually nanoparticles which are gold based are used in the therapy due to the reasons that these gold nanoparticles are very compatible bioparticles, are very efficient in converting light to heat energy and also they can NIR light which penetrates tissue more deeply. Another highlight using nanoparticles is that due to their small diameter, they can easily go inside or penetrate to cancerous cells and due to bioconjugation any functional groups can be attached to these nanoparticles. Usually Nanoshells, nanocages, nanorods, and nanostars are employed as photothermal transducers. Most of the gold nanoparticles have been developed to take in maximum within the first NIR window, which has been reported to be about 2–3 cm of the tissue (Riley & Day, 2017).

It was recently reported that PET are reliable to be used with photothermal therapy (Jørgensen et al., 2016). In this method the temperature was increased to 42 °C and due to this high temperature the tumor cells were destroyed. To make it more efficient an agent capable of absorbing light or materials with photothermal affect can also be put inside the cancer tissues (Estelrich & Antònia Busquets, 2018).

16.4.2 Photodynamic Therapy

In this therapy, light therapy is used and it can produce molecular oxygen, visible light, and photosensitizers (PS) which will result in the destruction of the tumor cells and pathogenic bacteria. This therapy is noninvasive mode of therapy. The advantage of this therapy is that it can selectively kill the malignant cells. When light is used the molecules are produced and these can directly cause damage. The photosensitizer is present throughout the cancer tissue. When light at a specific wavelength is given, due to the oxygen present in the molecular form that is as reactive oxygen species (ROS) will be produced and this will lead to oxidative damage of the components inside the tissue or cell and thereby leads to death of the tissue or cells. Thereby the tumor cells get damaged. Commonly gold nanomaterials are employed in photodynamic therapy (Mokoena, George, & Abrahamse, 2019). Porphyrins are reported to be effective in treating tumor tissues in photodynamic

therapy (Bretin et al., 2019). The mechanism of photodynamic therapy is by the deposition of the photosensitizers in the cancer cells. Structure like bacteriochlorins, porphyrins, and phthalocyanines which are modified with functional groups are employed in photodynamic therapies. Most of these compounds have passed various clinical trials. In photodynamic therapy, photosensitizers are designed in such a way that these are conjugated with various functional groups. One of the main purposes of nanotechnology is target-based delivery of drug (Abrahamse & Hamblin, 2016). When the supply of nutrients is inhibited it would lead to starvation therapy and the hydrogen peroxide can be employed to improve the photodynamic therapy (Yu, Zhou, Pan, Li, & Tang, 2018).

16.4.3 Chemotherapy

One of the drugs DOX comes under the division of anthracycline. Studies have shown that they are widely used in various cancer therapies. It has been reported that these drugs are widely used in treating tumor in breast. One of the other common drugs applied in breast cancer is paclitaxel. Some of the other drugs include cisplatin, tamoxifen, trastuzumab, and docetaxel. It is fact that if the drug molecule reaches the exact target site then the drug can be very effective at the site of delivery. As nanotechnology progressed drug were enclosed in nanoparticle-based carriers and later reaches the target site. Few of the nanomaterials which are used in therapy of breast tumor are nanoparticles based on polymers, liposome nanoparticles, metal-based nanoparticles based on gold, nanoparticles made of carbon atoms, mesoporous silica nanoparticles, and nanoparticles with proteins (Liyange et al., 2019).

New developments have occurred in the field of nanomaterial vehicles and clinicians are currently using these and also few of these vehicles are under clinical trials for treating tumor. These consist of dendrimers, liposomes, and polymeric micelles. Researchers are doing various trial levels for the development of new nano-based drug formulations, and most of these include activation when a particular stimulus comes in contact with the particles.

Various nanoparticle combinations are accepted by the FDA and EMA for the treating numerous cancers (Lee, Dees, & Wang, 2017). Numerous kinds of proteins molecules or short peptides are added on to the outer area of the nanomaterials to enhance the efficiency of the drugs. This helps in the action of drugs only at various specific parts. One such example is of serum glycoprotein, which is applied along with the nanoparticles for the delivery of drugs (Press, 2018). The drug chloroquine can help in reducing the immunological clearance of nanoparticles by macrophages which are present in the liver, which will result in the accumulation of the drug at that site (Pelt et al., 2018).

DOX-BLM-PEG gold nanomaterials and EpCAM-RP gold nanomaterials are two nanoparticles of gold which have been reported to have high efficiency in various therapies (Singh et al., 2018). Cisplatin is a genotoxic agent which can be employed along with radiation or can be applied alone in various chemotherapies. This has been reported to be used in various kinds of cancers. The limitation is that

the resistance which are both acquired and intrinsic and dose to normal tissue. Chemotherapy can lead to toxicity because it can also affect the healthy normal cells along with the cancerous tumor cells or tissues. So to overcome this problem, these nanomaterials can be employed which helps in delivering the drugs such as cisplatin to the exact target site unlike the normal conventional drugs. Few organic nanomaterials can be employed to transport drugs like cisplatin. Few inorganic nanoparticles are gold nanomaterials, ferromagnetic nanoparticles, and mesoporous silica nanoparticles. Few of the hybrid nanoparticles are carbon nanotubes, nanoscale coordination polymers, and polysilsesquioxane nanoparticles (Duan, He, Kron, & Lin, 2016). For delivering drug molecules usually organic nanoparticles or organic nanomaterials are commonly and popularly used. It is because of the reason that they have higher time period of life and gets accumulated in the cancer cells in comparison with other nanoparticles. Therapy involves a combination of various drugs used in treating tumors (Meng, Han, & Yeo, 2017). Nanoparticles can be loaded with numerous drugs which belong to various classes. Literature tells that the preclinical models are in the final trials. One such trial is going on for DOX and mitomycin C drugs which are encapsulated inside the nanoparticles. It was observed that these kind of drug delivery have better efficiency and also it can act on the cells which have become resistant to these drugs. For the trials with nanoparticles encapsulated with various drugs, the main drugs used were: paclitaxel, 17-AAG (Triolinimus), and rapamycin. The study was conducted on MDA-MB-231 cancer containing animal model (Fisusi & Akala, 2019). Hypoxia promotes the invasiveness of cancer masses and resistance to particular drugs. Recently a nanocarrier have been designed which has a combination of curcumin and baicalin. It was observed that these can overcome the resistance developed by the cancer cells against the usual drugs. Mannose will get bound to the receptors which are present on the outer portion of the macrophages which are associated with the cancer tissues. To boost the cellular uptake by the cancer cells, oligomeric hyaluronic acid can also be employed. These will act as targeting molecules. Nanodandelions are small molecules which can get inside the cancer cells or tissues easily. The outcomes showed better anticancer activity and it was also observed that side effects were less and these anticancer experiments were conducted and confirmed in A549 mouse which had cancer cells (Wang et al., 2019).

These nanoparticles helps in sustaining the amount of drug at the site of cancer and this can make the treatment more effective. These particles can also enhance the penetration of drug inside the cancer tissues or cells. This comparatively had better anticancer activity with respect to the conventional drugs (Mangal, Gao, Li, & Zhou, 2017).

16.4.4 Immunotherapy

As time went by, the field of nanotechnology improved and this had promised a favorable promise in the area of tumor immune therapy. Immunotherapy is a technique through which the immune system of the patient will be stimulated or

activated. This activation will help in the destruction of the tumor mass (Saleh & Shojaosadati, 2016). The five divisions of this therapy includes: growth factors trigger the production of white blood cells, agonistic Ab which acted beside various proteins, cancer immunotherapy, immune cells, and vaccines for cancer. To target the T cells nanomaterials are employed. Nanoparticles are also employed in the transportation of RNA to the tumor masses, or for the transportation of various vaccines in this therapy (Riley, June, Langer, & Mitchell, 2019). Studies have shown that nanoparticle systems are efficient in delivering the antigens at particular site.

It can be seen that these nanoparticles have various roles in modern immunotherapy (Wen, Umeano, Kou, Xu, & Farooqi, 2019). It has been reported that this therapy is one of the most efficient method for treating tumors. It is because in this therapy, the tumor sites are treated along with the combination of immunology (Park, Heo, & Han, 2018). Very recently cancer immunotherapy was proposed employing plant virus-based nanoparticles. In this for the production of vaccine, the virus particles which infect plant were employed (Sau et al., 2018).

Metallic nanoparticles also have great roles in this therapy. Various metallic nanoparticles like gold nanoparticles are employed in such therapies and can be used in combination with the therapeutic agents like ovalbumin (OVA). Metallic nanoparticles have been reported to enhance anticancer cytotoxic T cell response (Evans, Bugga, Asthana, & Drezek, 2018).

16.4.5 Metalloid Boron as an Enzyme Inhibitor

This is one of the most common proteins or peptides which are produce proteolysis effect in human prostate cells and it is a well-known biomarker of prostate tumor (Emanet Ciofani, Şen, & Culha, 2020). PSA is thought to cleave insulin-like growth factor-binding protein-3 (IGFBP 3) (Emanet Ciofani et al., 2020; Gallardo-Williams et al., 2004). In addition foods rich in boron can prevent several cancers due to their role in inhibition (Scorei & Popa, 2012). All these studies have actually developed a novel path to treat cancer cells or tissues by developing boron based nanoparticles. Most of the studies related to boron based nanoparticles and cancer cells suggest that these cells are being arrested by the boron compounds (Tian et al., 2019). In nature of hydrogen borate and BN are the common forms. These can be a very fine supply of boron compounds and can be used for such therapeutic applications (Li et al., 2017; Mateti et al., 2017). The researcher suggests that the biocompatibility solely based on their dimension, outline, formation, chemical nature and that apoptosis is affected by the unsaturated boron atoms. In addition replacing the rest of the atoms with boron atoms can be a good method to block the cancer growth as mentioned before.

16.4.6 Oxygen Capturing Approach

The cancer cells can develop to a size of about 1–2 mm³ when it is given the proper nutrients and oxygen. These are supplied by diffusion. But later the tumor cells will need new vessels to grow beyond this size. This process of forming blood vessels is known as vascularization (Orme & Chaplain, 1997). When the cancer cells become angiogenic in nature, the mass of cells will attract the blood vessels (Hillen & Griffioen, 2007). This process of attracting the blood vessels is taken care by various stimulators and inhibitors. The stimulator do up regulation of the genes required for the angiogenesis and the inhibitors help in down regulation (Nishida, Yano, Nishida, Kamura, & Kojiro, 2006). Anti-angiogenic plans only cannot stop or inhibit the cancer cells growth because these cancer cells can find new mechanisms to form the blood vessels (Abunahla et al., 2019; Kerbel & Kamen, 2004). But reports signifies that most of these drugs which inhibits angiogenesis can create a toxic environment and there is a need for novel plans to deliver these drugs at the target site (Yoncheva & Momekov, 2011). Nanoparticles can also make the membranes of the cancer cells more leaky and therefore nanomedicine plays a very prominent role in cancer therapies (Desai, 2012; Ma et al., 2001). The production of various compatible nanoparticles has become very demanding in the field of therapies and medicine. Any method in order to produce nanoparticles is very worthy given that the starting materials are compatible or if it can safely release from the body (Zhang et al., 2017).

16.4.7 Self-therapeutic Organic Nanomaterials

These are like peptide-based nanomaterials and are employed in therapies for various medical uses. One of the greatest advantage using peptide-based therapeutic systems is that they can act only on the tumor cells and remain stable in the healthy normal tissues without leaving a toxic trail in the healthy normal tissues (Wu et al., 2014). The (KLAKLAK)₂ (KLAK) amphiphilic peptide is a good anticancer amino acid commonly utilized in tumor treatment and that repress the development of severe cancer forms by break the cell organelles (Qi, Gao, Wang, & Wang, 2018). Wang et al. created a library of KLAK-based NPs for tumor therapy by in situ polymerization and optimized the NPs with different formulations and concentrations of compounds (Qiao et al., 2016). The beclin1 peptide is a different tumor inhibits peptide; (Wang et al., 2015). For restoring p53 cancer cell inhibition effect, the disruption of interactions between the MDM2 and p53 axis is a promising strategy. However, due to its low proteolytic constancy and poor cell-membrane penetration, the cancer-suppressing effect of PMI is severely controlled (Frappier, Duran, & Keating, 2018; Yan et al., 2017).

16.5 Nanomaterial as Drug Delivery Agents

16.5.1 Advantages of Nanomaterials as Drug Carrier

During times when chemotherapeutic drugs were mostly used. All together it was observed that such drugs can reduce the therapeutic efficiency when compared to the nano drugs. The Nanocarrier-based platforms are systems in which nanoparticles can be employed for the target site specific drug delivery. The size of these nano carriers are around 500 nm. It has been seen that these nanostructured carriers have great efficiency in delivering a drug in the diseased area which makes these nanocarriers efficient drug carriers. The drugs enclosed can be even anticancer drugs.

The nanoparticles systems can be grouped into two namely *organic* and *inorganic* nanocarriers. These particles characteristics change according to their compositions such as organic, inorganic, or hybrid, various parameters which include size, shapes, and their outer layer parameters. These nanocarriers have been tested for various clinical trials and many of them are also in the clinical phase of testing (Tran, DeGiovanni, Piel, & Rai, 2017; Ventola, 2017). Some of the characteristics of nanocarriers are discussed below. With the help of nanotechnology drug delivery can get the following advantages:

1. It helps in delivery of drugs which are hydrophobic.
2. It is a target site drug delivery there by protecting the healthy cells.
3. It will help in retaining the drug or chemical molecules with in the body for longer time thereby increasing the efficiency of the therapy.
4. The drug must be protected from the surrounding biological stimuli.
5. It can help the drug molecules to reach various tissues by helping them cross the epithelial and endothelial barriers.
6. Nanotechnology helps in combining both diagnosis and the therapy for a particular disease.

16.5.2 Inorganic Nanoparticles

The Inorganic nanomaterials involve silver, gold, iron oxide, and silica nanomaterials. Much of the reports based on these are not there but still few reports discuss about their potential uses. For the clinical use only few of these nanomaterials are only used and some of the other nanoparticles are still on different phases of clinical study. Metal nanoparticles, silver and gold, have specific characteristics such as surface plasmon resonance, that various other nanoparticles don't have. These nanoparticles show various benefits like their biocompatibility and the property of modification which helps in attaching various functional groups.

The reports on the drug delivery related activities are not clear but the mechanism of action has been proposed (Choi, Lee, Jeong, & Choy, 2013). The particular drugs for a particular disease can be conjugated to the surface of the gold nanomaterial. The basic force between the drug and nanomaterial is ionic or covalent bonding and physical absorption. This helps in proper delivery of the drug molecule to the desired target site. Then the drug release can be controlled when there is a proper biological stimuli or it can be activated in a particular wavelength of the light (Kong et al., 2017). Silver nanomaterials have been reported for their antimicrobial properties. But much reports the role as drug carriers are not been conducted, for example, Prusty and Swain (2018), produced a conjugated and soft PAM/D nano-hydrogels (Prusty & Swain, 2018). In one of the studies, the iron oxide nanoparticles were produced with the help of laser pyrolysis method (Marcu et al., 2013).

16.5.2.1 Metal Nanoparticle and Metal Oxides

It has been few years, that researchers started focusing on the metallic nanoparticles and various applications in the field of medicine (McNamara & Tofail, 2015; McNamara & Tofail, 2017). The basic concept is that, these synthesized nanoparticles can be adapted or various functional groups can be linked to the nanoparticles. These groups can help these nanoparticles bind to the antibodies, drugs and other ligands. This property makes the nanoparticles very promising agent in the field of medicine (Kudr et al., 2017).

16.5.2.2 Carbon-based Materials

These carbon-based nanoparticles are also involved in drug delivery and thereby release the drug at the target site. This is possible by attaching the functional groups to the surface or the outside of these nanomaterials. The drug which is entrapped inside can be released by various methods like thermal or enzymatic disengagement. Both these two mechanisms i.e., in thermal and enzymatic mechanism, there will be a damage for the drug molecules, so it is said that a better mechanism is by filling the hollow region of the carbon nanotube with the desired drug molecules. The nanotubes can be filled with metals (Huang et al., 2004; Kumar, Ramesh, Lin, & Fey, 2004). This technique can only be suitable for the metals but it cannot be used for other chemotherapeutic agents to the inside portion of the tubes. The most common and simple method used to fill the interior of the nanotubes is by capillary action (Monthieux, 2002). By oxidation reaction, nanotubes can be opened and it can help in forming holes along the wall of the tube and this can lead to the enhancement of the permeability for filling the drug inside the nanotubes (Sitharaman et al., 2005). Opened nanotubes without any functional groups commonly will have carboxyl groups to make the drugs soluble (Ajima et al., 2005; Matsumura, Ajima, Yudasaka, Iijima, & Shiba, 2007).

16.5.3 *Organic Nanomaterials*

16.5.3.1 **Liposomes**

In the year 1960, liposomes were discovered by Alec Bangham. These are employed in the pharma industries for the delivery of molecules and are learned the most. These were developed for improving the drug to be delivered properly. They are reported to be very efficient in drug delivery (Bozzuto & Molinari, 2015). Problems have been reported with the use of liposomes for the purpose of transporting drugs (Sercombe et al., 2015). Dimov, Kastner, Hussain, Perrie, and Szita (2017), have submitted works on the work plan of synthesis, functionalization and cleansing of these materials. It is prominent because the expense of production have a major role in the determination of commercialization. These are now accepted by the FDA (Sapsford et al., 2013; Zhang et al., 2008; Zylberberg & Matosevic, 2016).

16.5.3.2 **Polymeric Nanoparticles**

These particles are in the nano dimensions and these nanoparticles are constituted with copolymers which are amphiphilic in nature. These come together to create a shield like configuration when kept in a liquid environment. The interior portion will be hydrophobic in nature and the interior portion can be filled with drugs which are hydrophobic in nature for example camptothecin. Meanwhile the outside portion will be hydrophilic and stabilize the whole structure. These particles are under 100 nm in size (Miyata, Christie, & Kataoka, 2011; Xu et al., 2017).

The drugs are entrapped within these polymers of micelles usually by three methodologies. These strategies incorporate right off the bat direct disintegration measure, at that point dissolvable vanishing measure, lastly by the dialysis cycle. As of the immediate disintegration measure, the copolymer and the medications join with one another without anyone else in the water medium and structures a medication stacked with the aggregate of surfactant molecules. While on account of dissolvable dissipation procedure, the copolymer and the medication that must be consolidated are broken down utilizing an unstable natural dissolvable lastly, if there should be an occurrence of the dialysis cycle, both the medication in arrangement and the copolymer in the natural dissolvable are joined in the dialysis pack and afterward dialyzed with the development of the aggregate of surfactant molecules (Xu, Ling, & Zhang, 2013). The focusing of the medications utilizing distinctive polymeric micelles as set up by different component of activity including the helped vulnerability and the holding impact improvements; complexing of an unmistakable pointing ligand atom to the outside of the aggregate of surfactant molecules (Wakaskar, 2017). Polymeric micelles are accounted for to be pertinent for both medication conveyance against disease (Kulthe, Choudhari, Inamdar, & Mourya, 2012) and furthermore for visual medication conveyance (Mandal, Bisht, Rupenthal, & Mitra, 2017).

16.5.3.3 Dendrimers

These are branched or bifurcated, colloid, definite and 3D forms. These dendrimers are shaped in the form of globules and the outer portion is attached with functional groups and these can make them very potent in delivering drugs (Kesharwani et al., 2015; Madaan, Kumar, Poonia, Lather, & Pandita, 2014; Zhu & Shi, 2013). These nanoparticles can be prepared by two methods. Firstly, dendrimer synthesis begins from the inner region and then it is extensive outwards. The other method is the combined one, which begins from the outer of the dendrimer (Cheng, Xu, Ma, & Xu, 2008). Depending on the functional groups attached the dendrimers are classified into: Poly(amidoamine), Proton-pump inhibitors, LCs, core-shell, chirality effect, amino acids, architectures of dendrimers and Poly(amidoamine-organosilicon). Most of study reports are on PAMAM, for the oral delivery of the drugs due to their solubility of the drugs and also these can pass through the epithelial cells (Noriega-Luna et al., 2014). Due to the amine functional groups present on these nanoparticles these dendrimers are not used much in clinical studies. The amine groups are charged positive and due to this charge it makes them toxic, so these nanoparticles are altered to make it less toxic or to remove the particles from the body. The drug is encapsulated in these nanoparticles through various methods (Tripathy & Das, 2013). The drug which is encapsulated in these dendrimers are delivered by various mechanisms, initially by the in vivo corruption of medication cascade molecules' covalent holding based on accessibility of reasonable chemicals or positive climate that could separate the securities and furthermore by release of the medication because of changes in the actual climate like pH, temperature, and so on, and cascade molecules have been created for systemic distribution, oral, visual, aspiratory and in focused medication conveyance (Kesharwani, Jain, & Jain, 2014). Jain, Gupta, and Jain (2014) have reported one of the studies with folate conjugated with poly-L-lysine dendrimers and they have shown to prevent tumor using the drug encapsulated in them.

16.6 Nanomaterials for Targeted Delivery

16.6.1 *Passive Targeting*

It has been reported that under several states of conditions such as in inflammation or hypoxia, which is usually seen in association with cancer, the endothelium of blood vessels will become leaky in comparison with the healthy vessels (Torchilin, 2011). During condition like hypoxia, the growing masses of cancer cells will start making new vessels or the cells will engulf existing blood vessels. These vessels which are leaky and new can help in the entry of various nanoparticles and molecules to the cancer sites.

It means that when the membranes become leaky the nanoparticles can enter easily into these cancer cells and also these particles will get retained inside these cancer tissues in comparison with the normal healthy tissues. This special property, in any case, isn't pertinent to small particle drugs which have practically short

course time and quick waste of time from the cancer cells. Along these lines, the embodiment of small-molecule tranquilizers in small size drug transporters improves their pharmacokinetics, gives some tumor selectivity and diminishes results. This sort of cancer focusing on named “aloof” depends on transporter qualities and cancer science, however doesn't have a functional group for explicit tissue or organ authoritative (Fang, 2011; Maeda, 2001).

However, EPR effect provides rather modest tumor specificity with 20–30% in delivery increase compared to normal organs. The EPR effect is highly dependent on the intrinsic tumor biology (Kobayashi, 2013). All of these factors, together with the physical and chemical properties of nanocarriers, will determine its drug delivery effectiveness.

Be that as it may, it is conceivable to regulate enhanced permeability and retention impact synthetically or precisely to accomplish vascular standardization prompting higher amassing of nanocarriers. Among synthetic enhanced permeability and retention enhancers, one could discover $C_{50}H_{73}N_{15}O_{11}$, NO, NO_3 , group of lipids, VPF, VEGF, and different growth factors (Fang, 2011; Maeda, 2001). These atoms prompt hypertension or vascular standardization, which could impermanent upgrade cancer perfusion. Different methodologies use ultrasound, radiation, high body temperature, or PI to weak cancer cells and increment nano systems penetration. In any case, all depicted techniques have restrictions and contra-indications and consequently require cautious thought (Arap, 1998; Huynh & Zheng, 2015).

16.6.2 Active Targeting

In this kind of targeting, it has been seen that drug can be delivered to the exact target site when compared to the other modes of drug delivery.

Once the nanoparticle reaches the target site then the efficiency of the drug can be improved with the method called as active targeting. The cancer tissues or the cells will have particular biomarkers on the membranes which can bind to the functional groups present on the surface of the nanocarriers. When this binding happens the nanoparticles gets activated and also this interaction improves the strength of association and there by helps in better diffusion. The main proof of this wonder was proposed in 1980 with antibodies united in the outside of liposomes, (Leserman, 1980) trailed by different sorts of functional groups (Kamaly, 2012; Wang, 2014).

Numerous numbers of receptors have been identified as well as their antibodies have been identified. These can be produced and investigated both in vitro and in vivo. Initiating solid receptor, subsequently filling in as possible models to advance dynamic focusing on innovation. It has been discovered that arginine-glycine-aspartate peptide ties to $\alpha V\beta 3$ principal receptors. These receptors are exceptionally introduced on both the brain cancer cells and on the cellular arrangement of tumor microenvironment (Bello, 2001). F3 peptide was found to tie to nucleolar protein communicated on formation of new blood vessels endothelial cells in the tumor microenvironment (Christian, 2003). In like manner, enzymes has been

distinguished as expected receptor in the tumor microenvironment (Pasqualini, 2000) and has been demonstrated to be focused by a peptide derived from three amino acids (Arap, 1998). Among the old style instances of functional groups, we can refer to the folic corrosive that explicitly ties to the B-vitamin receptor just as present in TME. All things considered, various methodologies have been accounted for, through blend of FA-drug forms and through FA-grafting onto nanocarriers advancing their actively transporting molecules in malignancy cells.

16.6.3 *siRNA Nanomedicine for Cancer Therapy*

siRNA are reported to be very efficient in treating viral diseases as well as cancer by inhibiting the disease-causing genes (Farrow et al., 2003). The discovery was in nematode *Caenorhabditis elegans*. In the mammalian cells, scientists have reported that constructed siRNAs were also able to promote RNAi and thereby it can block the expression of the changed proteins (Fire et al., 1998; Schwarz, Hutvagner, Haley, & Zamore, 2002).

The RNAi for in vivo uses have been modified through numerous chemicals and it has been observed that this can increase the efficacy and potency (Behlke, 2008). In such manner, normal compound plans have permitted siRNA traveler strands to be bound to adjustment than siRNA manage strands. These engineered systems have empowered to supplant either non-crossing over oxygen on the phosphate linkage with a sulfur molecule, the 2'-hydroxyl bunch change of the sugar ring with a methyl gathering and ethyl gathering, among others (Chiu & Rana, 2003; Watts, Deleavey, & Damha, 2008). Moreover, different methodologies have been created to convey siRNAs securely in the cytoplasm. While most stripped siRNAs have been successful for a decent number of tumor cells in vitro, these siRNAs have sadly bombed when have infused in vivo by foundational organizations (Xu & Wang, 2015).

Immunotherapy have been focused too much these days due to their potency in activating the host immune system. The mechanism of activation is through by simply introducing cytokines, or using antigen-presenting cells (APC) (Ghafouri-Fard & Ghafouri-Fard, 2012). Dendritic cells (DCs) are considered to be the strongest antigen exhibiting cells (Banchereau & Steinman, 1998; Klippstein & Pozo, 2010).

16.7 Drug Release Strategy

16.7.1 *Redox-Activated Drug Release*

The unique feature with tumor tissues is that they have a reducing environment inside the cells. This environment will act as a biological stimuli for the redox-responsive nanocarriers and thereby the cancerous tissues or cells will be degraded and release the drug with in these carriers. These type of nanocarriers have three

basic advantages when compared to the other nanocarriers. Firstly, these redox-activated drugs are stable in normal tissues, which can protect the cells from the toxic effects of the drugs. Second, they show a brief reaction to high Glutathione focus in tumor cells to deliver cargoes (typically a couple of moments to hours). At last, contrasted with other possible locales of freight discharge, the delivery in cytoplasm is regularly expected to have better remedial impacts (Meng, Cheng, Deng, & Zhong, 2012; Meng, Hennink, & Zhong, 2009). In this survey, we summed up presently existing DDSs transporters into the accompanying classifications dependent on their disparities in structure. For example, DDSs conveyance frameworks with disulfide bonds and DDSs conveyance frameworks with diselane bonds.

16.7.2 pH-Mediated Drug Release

When the polymeric micelles are used in delivering a drug, various parameters are taken into consideration. These include the rate of diffusion of the drugs, partition coefficient, micelle stability, and rate of biodegradation of the copolymers. For cancer chemotherapy, it is very important to take note on the amount of the drug which is released at the cancer tissues and also minimal release rate is advised during its movement in the blood or through the healthy normal tissues or cells (Felber, Dufresne, & Leroux, 2012).

For the purpose of developing new treatments for cancer therapy, the cancer microenvironment has to be well observed. In the case where the drugs will be released during in response to a stimuli, the drug which is can be encapsulated in the nanoparticles and can be given a particular stimuli like the temperature or pH difference. In comparison with all the stimuli, acidic pH is considered to be a perfect trigger for releasing the drug because of the reason that the cancer tissues will have a comparatively lower pH with respect to the normal healthy cells. This implies that pH based approach is better than the use of traditional drugs (Manchun, Dass, & Sriamornsak, 2012).

pH-sensitive polymeric micelles are employed and these are used for target site drug delivery to cancerous tissues. These micelles are stable at physiological pH, but once they encounter acidic conditions then these micelles will be deformed and this deformation is responsible for the release of the drug which was entrapped. The cancerous cells are under mild acidic conditions outside or inside, as a consequence the cancerous cells will be treated with minimum effects on the surrounding healthy cells or tissue. These polymeric micelles are pH-sensitive, that is these micelles will release the drugs when there is a change in the pH level. In comparison with the healthy tissues, the cancer cells will have comparatively lower pH, thereby these micelles releases the drug only in the tumor cells rather than releasing in the healthy tissues (Zhang, Lin, & Gillies, 2010).

16.8 Nanomaterials in Diagnosis of Cancer

16.8.1 Magnetic Resonance Imaging

It is one form a noninvasive technique which helps in creating or forming images (Yousaf, Dervenoulas, & Politis, 2018). It was in the 1980s, this technique developed and it altered the medical and clinical imaging technology (Hemond & Bakshi, 2018). The contrast agent will help in enhancement of the image and plays a prominent role in magnetic resonance imaging (Behzadi, Farooq, Newhouse, & Prince, 2018). In the recent years of advancement in nanotechnology it can be seen that these nanoparticles can be used as contrast agent in magnetic resonance imaging.

16.8.2 Computed Tomography

In this technique we use one X-ray source and a detector array which can detect and later convert it to images. During all these times computed tomography had been employed for imaging purposes in clinics. They can create an image with better spatial and temporal resolution. One limitation with CT is that its sensitivity toward contrast agents. Still this technique is a promising technique (Dong et al., 2019).

16.8.3 Positron Emission Tomography

This is a technique for nuclear biomedical imaging. PET is a noninvasive method. In this technique, radiotracers are used to create images. The tracers used in positron emission tomography can give us an idea on the biological pathways (Santos & Ferreira, 2019).

16.8.4 Single Photon Emission Computerized Tomography

This technique for nuclear imaging and employs gamma radiations to report the biochemical alterations. All these years, this technique has been the nuclear imaging technique (Chakravarty, Hong, & Cai, 2015).

16.8.5 Optical Imaging

Using this technique one can observe numerous types of structures which are involved in autophagy at both macro and micro levels. This technique involves fluorescence, chemiluminescence, and Raman imaging. This helps in getting a two

dimensional or 3D image at microscopic and macroscopic dynamic levels. Fluorescence imaging provides intuitive outcomes, takes much lesser time and the image formed can be understood better when compared with the various other techniques. This is the sole reason why scientists prefer optical imaging for getting images (Wang, Li, Wei, & Duan, 2017).

16.8.6 Ultrasound

This technique is a noninvasive imaging method which helps in observing the structure, morphology, direction, and limitations (Guo, Lu, Qin, & Fei, 2018). In the recent years, nanobubbles (NBs) have developed to be a promising agent. These are basically composed of gas cores and shells which are stabilized. Chitosan is a compound derived from chitin and it is reported to be one of the major materials on the earth. Nanobubbles have been created using chitosan and they have been proved to be potential in treating tumors since they are biocompatible and can carry the drug within. In one of the recent studies DOX-loaded chitosan nanobubbles were made. Later in the year of 2016 new kind of ultrasound imaging contrast agent was developed.

16.8.7 Photoacoustic Imaging

In this technique it utilizes the photoacoustic effect. It creates images from the signals captured from the materials (Choi, Park, Jeon, & Kim, 2018). This method is also known as optoacoustic imaging (Steinberg et al., 2019).

16.8.8 Multimodality Imaging

SPIONs, (Feraheme, FH) and $[^{89}\text{Zr}]\text{Zr}$ was utilized as a nanoplatform for PET and MRI. PET-MRI coordinates the phenomenal affectability of PET with the spatial goal and differentiation of delicate tissue by MRI. Feraheme can abbreviate the cross over unwinding time, T2, and is commonly utilized for dull differentiation improvement. Nonetheless, dull differentiation is frequently difficult to execute in clinical settings for applications, for example, identification and determination of metastases in the lymph hubs. FH radiolabelled with OET tracer can exploit exceptionally delicate brilliant signs from PET. It can distinguish the presence of FH in districts, where the MRI contrast is excessively low or loud. Test results demonstrated that FH is a truly appropriate SPION for without chelate marking of PET tracers, and can be utilized in half and half PET-MRI (Yuan et al., 2020). For consolidated magnetomotive ultrasound PET/CT and MRI for sentinel lymph hubs, ^{68}Ga -marked SPIONs were proposed.

16.8.9 *Image-Guided Therapy*

A semiconducting plasmonic nanovesicle was proposed; this contained both semiconducting poly and PEG which were joined together to a gold nanoparticle (Au@PPDI/PEG). The electromagnetic field increased the efficiency of absorbing the light. It can produce photothermal effect. These can also produce high photoacoustic signal. All together due to their various characteristics, these complexes have great importance as theranostic agents (Yang et al., 2017). Au nanorods in photoacoustic imaging and photothermal therapy have been examined. The beneficial properties of Au NPs, for example, behavior of biomaterials, tunable surface plasmonic reverberation, and controlled combination settle on them an incredible decision for theranostic applications. Photoacoustic imaging guided photothermal therapy is conceivable when the beat is utilized to crush the malignant growth cells. The nanotubes can be employed as tools in various therapies in PTT and PAI (Siregar, Oktamuliani, & Saijo, 2018).

The atomic number of gold nanoparticles is high. Due to this very high atomic number these nanoparticles, absorb low and medium energy X-rays very strongly (He & Chow, 2016). One limitation is when the electrons are released and these can cause damage (Wang et al., 2016). One of studies showed their capacity of active targeting and these can be used in CT imaging for enhancing the technique and can also be used as tools in medicine and therapies.

16.8.10 *Combination Therapy*

This therapy cures various malignancies and there by improve the test outcomes. Usually these have synergistic drug action and have been reported to be successful in cases when there is a problem of drug resistance. Liposomes are generally employed in these kind of therapies. Numerous liposomal formulation of DOX include DaunoXome and ONCO-TCS. These are very popularly employed in delivering drugs at various sites. Few other nanoparticles that are employed in these therapies are polymeric nanoparticles. These polymeric nanoparticles have high thermodynamic and kinetic characteristics which help in target based anticancer drug delivery to the specific cancer cells (Gurunathan, Kang, Qasim, & Kim, 2018). In recent studies it has been reported that studies conducted both in in vivo and in vitro, and outcomes showed the nanoprobe had great efficiency in targeting cancer tissues, the drug was retained for longer period of time, and appropriate therapy effect was there on the cancer cells (Zhang et al., 2019). These can get highly accumulated in the cancer cells because of their very small size, around 60 nm and modified outer surface. All of these characters make it a great agent to be applied in image-guided photodynamic therapy or photothermal therapy (Miao et al., 2016).

Conventionally cancer is treated with the help of chemotherapy but it has many limitations like it kills other neighboring healthy cells too. The recent theranostic

nanoparticles are a combination of both detecting if there is a disorder and also treat the same disorder using the drug entrapped within the nanoparticle and there by increases the target site delivery thereby only the tumor cells gets treated with the drug and along with that helps in detecting and monitoring of the cancerous cells.

16.9 Summary

The very recent advancements in the field of nanotechnology have shown a prominent development, which have great benefits from the modifications of numerous nanoparticles. Another advantage with these materials is that they can be used in target delivery of various drugs. Otherwise these kind of target site based drug delivery would not have been possible and clinical results have shown that these nanomaterials provide a fundamental basis for some tumor treatments. Researchers believe that since there are continuous discoveries in the field of nanotechnology, there will be a great impact of nanotechnology in the fields of tumor therapies and medical imaging. There are some limitations like cytotoxicity and non-biodegradability. These have to be observed more to understand the side effects on human health. But still barriers like the nanomaterials' characteristics, metabolism of the drug, the effect on cells and their compatibility, still remain. Another limitation is that the mechanisms of action are not reported so far. Based on the above challenges, it is recommended to study the further optimizations and mechanisms between the cell and nanomaterials are also to be understood, this can lead to a better imaging and therapeutic effects.

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