

# Enhancing Cancer Immunotherapy Treatment Goals by Using Nanoparticle Delivery System

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**Abstract:** Recently, there has been an incredible increase in research about the abnormal growth of cells (neoplasm), focusing on the management, treatment and preventing reoccurrence. It has been understood that the natural defense system, composed of a variety of immune defensive cells, does not just limit its function in eliminating neoplastic cells, but also controls the growth and spread of tumor cells of different kinds to other parts of the body. Cancer immunotherapy, is a cancer treatment plan that educates the body's defensive system to forestall, control, and eliminate tumor cells. The effectiveness of immunotherapy is achieved, to its highest efficacy, by the use of nanoparticles (NPs) for precise and timely delivery of immunotherapies to specific targeted neoplasms, with less or no harm to the healthy cells. Immunotherapies have been affirmed in clinical trials as a cancer regimen for various types of cancers, the side effects resulting from imprecise and non-targeted conveyance is well managed with the use of nanoparticles. Nonetheless, we will concentrate on enhancing cancer immunotherapy approaches by the use of nanoparticles for the productivity of antitumor immunity. Nanoparticles will be presented and utilized as an objective immunotherapy delivery system for high exactness and are thus a promising methodology for cancer treatment.

**Keywords:** tumor immunotherapy, immune system, nanoparticles, drug delivery, drug release

## Introduction

Cancer immunotherapy was founded around the late phase of 1890s by a famous cancer specialist Dr. William B. Coley (1862–1936) who was also a surgeon.<sup>1</sup> During a patient's treatment process, he realized that when some specific bacteria were administered to patients who were suffering from neoplasm, there was a great effect to the growth tissues which could even lead to total disappearance, which serves as a foundation for lots of immunotherapy research nowadays.<sup>2</sup> Many researchers have come to demonstrate that when patients are exposed to the bacteria-toxin, there is an activation which boosts the immune system to assault the neoplastic cells which could possibly improve the patient's situation as well as set them free from malignancy.<sup>3</sup> Immunotherapy upgrades the immune defense system's capacity to perceive, target, and set free from neoplastic cells thereby not modifying or hurting the healthy cells, which makes it a better option for the management and treatment of all kinds of cancer.<sup>4</sup> Engaging the immune system is a better approach to battle tumors because of the following realistic views as shown in Table 1.

Immunotherapy has been affirmed clinically as the primary line of treatment and management for most malignancies,<sup>9</sup> and may likewise be a powerful therapy for

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**Table 1** The Immunity Affiliation with the Immunotherapy

Natural Immunity	Responses to Foreign Invaders and Neoplasm	Ref
The immune system	The body's defensive mechanism is exact, which makes it feasible for locating unwanted growth cells for destruction without harming non-neoplastic cells.	[5,6]
	The body's defensive mechanism can adjust ceaselessly as well as powerfully, much the same as neoplastic cells do, so if a tumor figures out how to get away, the defensive cells can rethink and dispatch a fresh assault to the tumor.	[6,7]
	The body's defensive mechanism's "memory" makes it possible to recall the nature of neoplastic cells and eliminates them in case of reoccurrence.	[5,8]

**Note:** Immunotherapy has a remarkable relationship with the immune system being able to instruct the immune system to perceive and assault explicit neoplastic cells, empowering immune cells to take out tumor cells and improving the immune reaction.

patients with specific tumors that are impervious to treatment.<sup>10</sup> Irrespective of the fact that immunotherapy can be given to patients in many ways, conveyance of small-particle medications to their malignant growth target destinations of activity generally presents perhaps the greatest problem in view of the cancer's homogeneous tissue dispersion, renal freedom, and absence of target specificity.<sup>11</sup> In order to better manage the above challenges, nanotherapeutics is fast giving hope for the treatment of cancer to both researchers and clinicians.<sup>12</sup> Its molecular size measuring approximately 1–100 nm makes it an ideal means by which drug delivery for treating and preventing tumor cells gain more effectiveness and are more precise as well.<sup>13</sup>

Nanoparticles are typically synthesized from a top-down or bottom-up approach.<sup>14</sup> A bottom-up approach relies on nucleating atomic-sized materials into the eventual nanoparticles. While the exact synthesis method depends on the material being generated, some common methods include the Turkevich method (citrate reduction), gas phase synthesis, block copolymer synthesis, and more recently, microbial synthesis. Top-down methods, where a bulk material is physically broken down to make smaller molecules, include milling, laser ablation and spark ablation.<sup>14,15</sup>

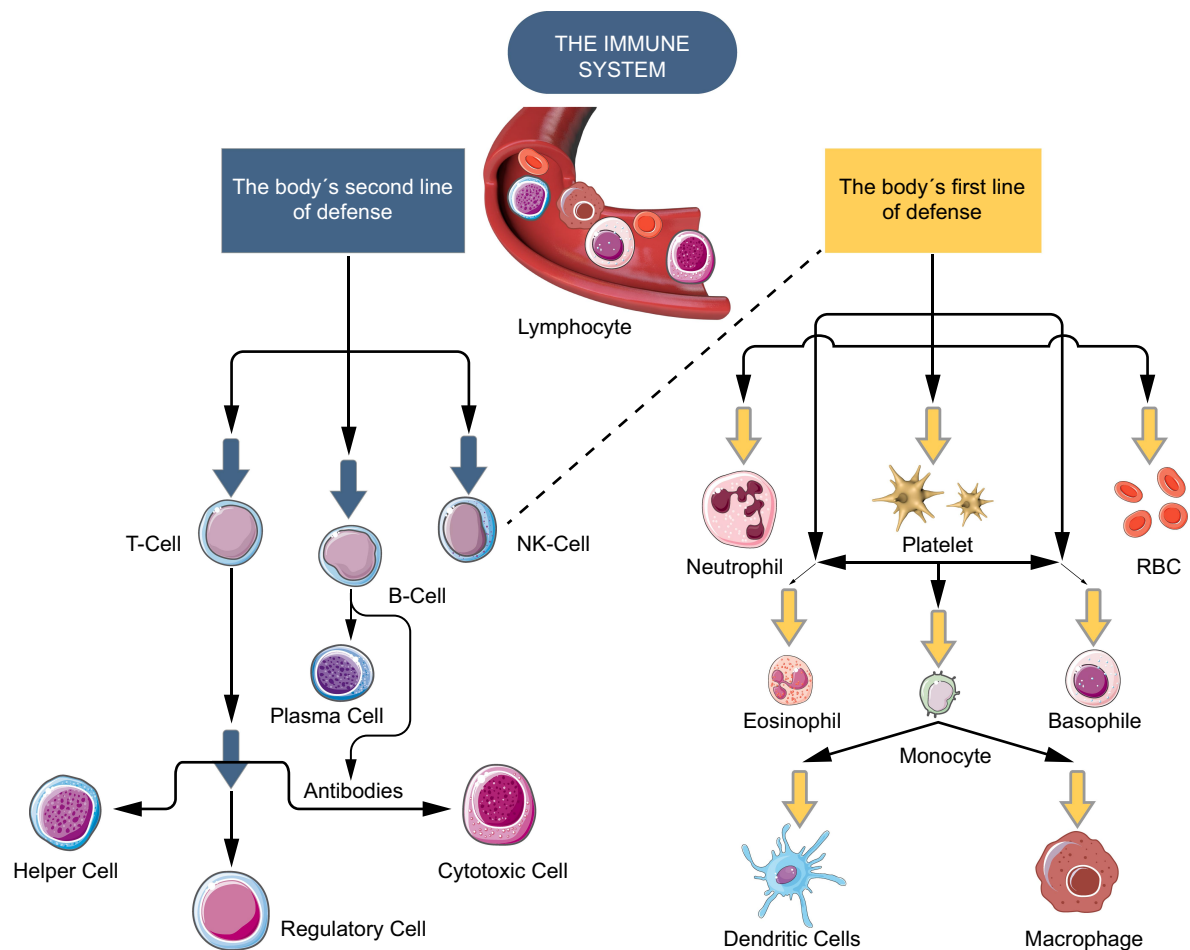
NPs possess an ideal pharmacokinetics with delayed dissemination time, particular endothelial porosity at a few objective tissues, and high explicitness for biological targets are the beautiful nature of nanotherapeutics that

drive the scientists to zero in on the utilization of nanoparticles for the medication delivery system.<sup>16</sup> The disclosure and utilization of nanoparticles for clinical application has been grasped enthusiastically for the headway of remedial apparatuses which productively prompts the accomplishment of cancer immunotherapy's objective.<sup>17</sup> Nanoparticles are best for focusing on explicit delivery, with a noteworthy lessening in side effects and a decrease in systemic toxicity.<sup>18</sup> NPs contain an assortment of molecular bonding sites and shielding the molecules from degradation and controlling their delivery kinetics.<sup>19</sup> Nanoparticles assume a significant part in cancer immunotherapy since they have tweaked size, shape, charge and surface properties bringing about better viability.<sup>13,20</sup> NP-based immunotherapy drug conveyance systems have considerable abilities for tumor treatment. The critical central purposes of nanoparticles utilized as medication transporters includes high sufficiency, high transporter limit, practicality incorporation of both hydrophilic and hydrophobic substances and probability of variable ways of administration such as oral and inhalant.<sup>21</sup> These properties of nanoparticles empowered drug bioavailabilities and efficacy and decrease the unwanted targeting which are significant snags in tumor management.<sup>22</sup>

## Tumor Cells and Body's Defensive Mechanism Cells

The body's defensive mechanism relays the functions of the innate and adaptive immunity, which are the focal segments that provide the medium for which microbe diseases are targeted and eliminated,<sup>23</sup> the innate immune cells are liable for sure-fire insurance while the adaptive immune cells are answerable for long-haul assurance.<sup>24</sup> The cells of the immune system can be seen in [Figure 1](#).

The innate immunity, made up of immune cells ranging from dendritic-cells (DCs), macrophages, and natural-killer-cells (NK-cells), brings about the prior defense system by perceiving rationed pathogen associated molecular patterns (PAMPs) following the mechanism of pattern recognition receptors (PRRs), which are made up of toll-like receptors (TLRs) bound to the membrane.<sup>5,25</sup> Antigen presenting cells (APCs) are responsible for capturing pathogens, including macrophages, as well as dendrite-cells, proceeds fractioned into peptide fragments then exposed to the major-histocompatibility-complex (MHC) which are noticeable with the aid of T-cell-receptors (TCR).<sup>23,26</sup> In a not shell, NK-cells are capable of



**Figure 1** Adaptive and active immunity in cancer immunotherapy: T-cells control the activity of the defensive system; B-cells synthesize antibodies which gives signal to the T-cells; NK-cells are signalled by T-cells to eliminate compromised cells; phagocytes which include; helper-cells are responsible for targeting the malignancy; neutrophils are a sort of phagocyte which function in eliminating bacteria; monocytes are the largest type and have several roles; macrophages survey the immunity to eliminate wasted cells. **Note:** The body's defensive mechanism works in such a way that the immunity is set free from all sorts of danger.

eliminating low functional host cells instead of targeting foreign pathogen for minimal presentation of the MHC-1 on malignant cells. NK-cells have the capacity to suddenly murder virally contaminated and a wide assortment of tumor cells yet save most healthy cells,<sup>27</sup> NK-cells are fit for intervening the executing of tumor cells by a few unmistakable instruments including the emission of an expansive range of cytokines, extravasating just as entering tissue districts, shifting from premalignant to dangerous tissues.<sup>2</sup> Also, NK-cells are likewise known to be exceptionally receptive to numerous organic agents, including cytokines, for example, interleukin (IL)-2 or IL-12 and interferons (IFNs), and quickly to expand their cytolytic, secretory, proliferative, and other capacities upon incitement with these agents.

The adaptive defensive immunity continues the innate defensive immunity that has enacted T- and B-cells specific

pathogenicity. Just like the defensive ability of the PRRs of the innate immunity,<sup>28</sup> T- and B-cells are the immunity foundations of a broad variety ligation of pathogenic-receptors leading to the formation of numerous antigen-receptors.<sup>29</sup> The marker present of the molecular surfaces of T-cells can characterize the differentiation into various small entities ranging from cytotoxic-T-lymphocyte (CTL) likewise referred to as CD8+ T-cells, having a function in prompt killing of foreign pathogens or harmed and broken malignant-cells.<sup>30,31</sup> To actuate CTLs, it's fundamental to invigorate T-cells with solid MHC signals or extra signals delivered by "helper" T-cells (TH) cells. TH-cells (CD4+ T-cells) assume significant parts in adaptive immune guideline though they don't straightforwardly include microbe phagocytosis or annihilation.<sup>32</sup> Additionally, significant adaptive defensive cells such as B-cells are responsible for providing antibodies associated with pathogen inactivation.

## “Immunosurveillance” and “Immunoediting” Relation with the Tumor

While a considerable number of our cells grow and divide normally, the process is firmly monitored by lots of factors, including the gene qualities inside the cells, change in shape of cells, change in position, the cell-cell adhesion, the quantity of a particular protein present in a cell and the quantity of enzyme tryptophan pyrrolase in the liver. The effectiveness of tumor immunotherapy is based on the “tumor immunosurveillance”.<sup>12</sup> At the point when no more growth is required, cells are advised to quit growing. Tragically, malignant growth cells gain deserts that cause them to disregard these stop signs, and then develop wildly.<sup>33</sup> However, notwithstanding the ability of the immune system to react in opposition to most tumor cells, the appearance of tumor signals allow the growing tumor to escape detection or to avoid the immune response.<sup>34</sup> The “immunoediting” concept, tries to shed the mechanism of evasion through describing tumor development as a system following three stages which can be seen in Table 2 and Figure 2. During the “immunoediting”, the immune defensive system shapes tumor movement into two contrary directions which secure the host against malignancy and mold tumor immunogenicity through three stages, namely; elimination, equilibrium and escape. In the elimination stage, tumor cells initiate the inborn immune defensive system because of the mechanical interruption of sound tissues. IFN-gamma emissions from macrophages and dendritic cells (DCs) cause direct cell demise and initiate angiostatin chemokine articulation in tumor cells. The antigen-presenting cells (APCs), for example, dendritic cells and macrophages pick up the dying tumor cells along with antigens and are conveyed to depleting lymph nodes to enact CD4<sup>+</sup> T-cells and thus

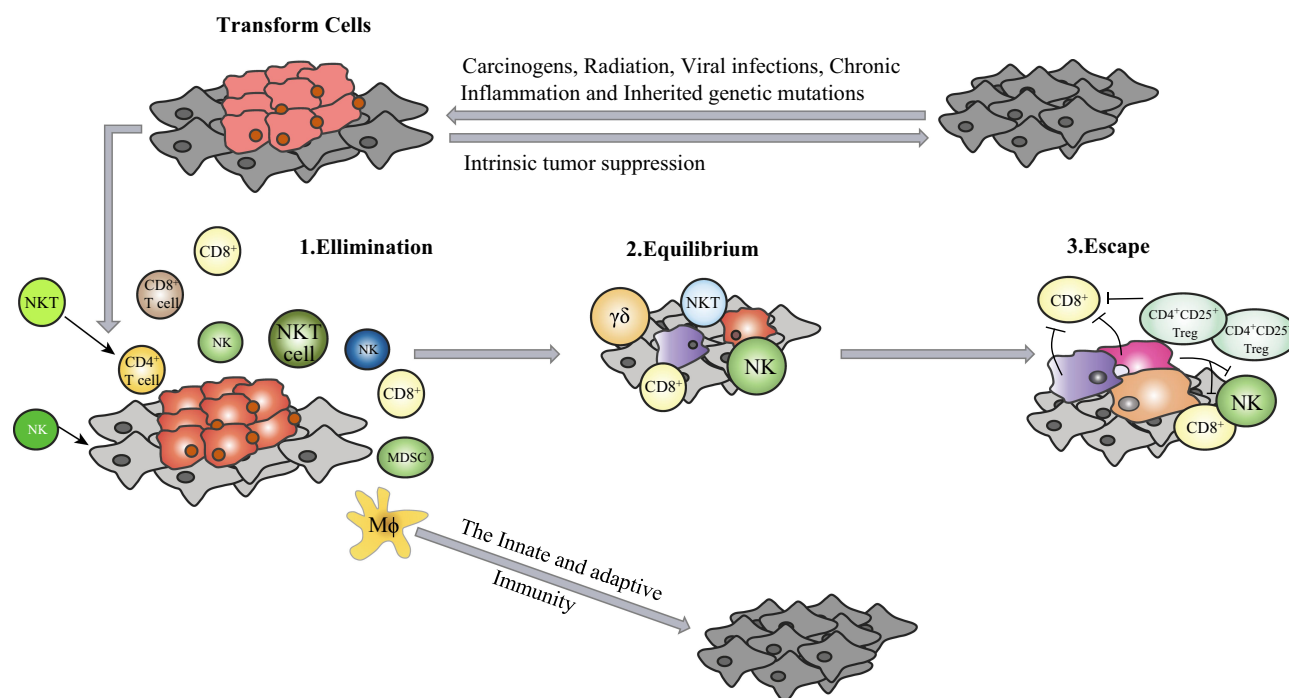
CD8<sup>+</sup> T-cells.<sup>35</sup> Tumor-associated antigen (TAA) actuated T-cells course to the tumor microenvironment and initiate cell demise by delivering cytotoxic proteins including perforin or granzyme, or by the Fas/FasL pathway. The IFN-gamma-initiated proinflammatory tumor microenvironment upgrades apoptosis through a criticism circle of creation of more IFN-gamma and IL-12. Hereditarily changing immune tumor cells that endure the elimination stage then proceeds to the equilibrium phase. Now, tumor cells go into a peaceful stage and there is a harmony between invulnerable assault and malignant growth cell expansion that forestalls tumor outgrowth. As the immune defensive system hinders multiplication of insusceptible delicate variations, tumor cells which stay safe gain changes that shield them from discovery and make an immunosuppressive tumor microenvironment.<sup>36</sup> Two notable break components are diminishing TAA introduction and deficiency of MHC1 articulation which ties to T-cell receptors (TCRs) on CD8<sup>+</sup> T-cells. Additionally, malignancy cells produce suppressive cytokines, for example, TGF-beta and IL-10 just as inhibitory costimulatory molecules, for example, CTLA-4, PD-1, and PD-L1.<sup>35,37</sup> Regulatory T-cells, myeloid-determined dendritic cells, and tumor-related macrophages add to tumor endurance and extension.

## Nanoparticles in Cancer Immunotherapy

In recent years, remarkable advances and attempts have revealed the ability of nanoparticle production and application for high efficacy and great potency in the field of medicine, especially as a conveyance medium for immunotherapy.<sup>41</sup> The promising results are realized because of the physiochemical properties of the nanoparticle consisting of a precise and consistent immunotherapeutic drug conveyance strategy.<sup>42</sup> The nanoparticle’s size, nature and the immunotherapeutic conveyance are a few remarkable features that make it a perfect model for enhancing cancer immunotherapy.<sup>43</sup> Furthermore, NPs possess a few similarities in feature like malignant cells which lead to an advancement of the permeability and retention effect. NPs normally are composed of metals, organic compounds as well as polymers. They can be manufactured for the conveyance of precise immunotherapy including those of less soluble and absorbability.<sup>44</sup> Most commercially manufactured NPs use liabilities that focus on strategies that are entirely localized on the impact of permeability and retention effect (EPR).<sup>21</sup> Nevertheless,

**Table 2** Tumor Development Stages and Characteristics

Stages	Characteristics	Ref
Elimination	Components of innate and adaptive immunity may eradicate the growing tumor and protect the cells from growing out of control to become cancerous	[38]
Equilibrium	The immune cells known as the “editor” will control further production of tumor cells	[39]
Escape	These tumor cells may promote the recruitment of regulatory cells of the innate and the adaptive defensive cells.	[40]



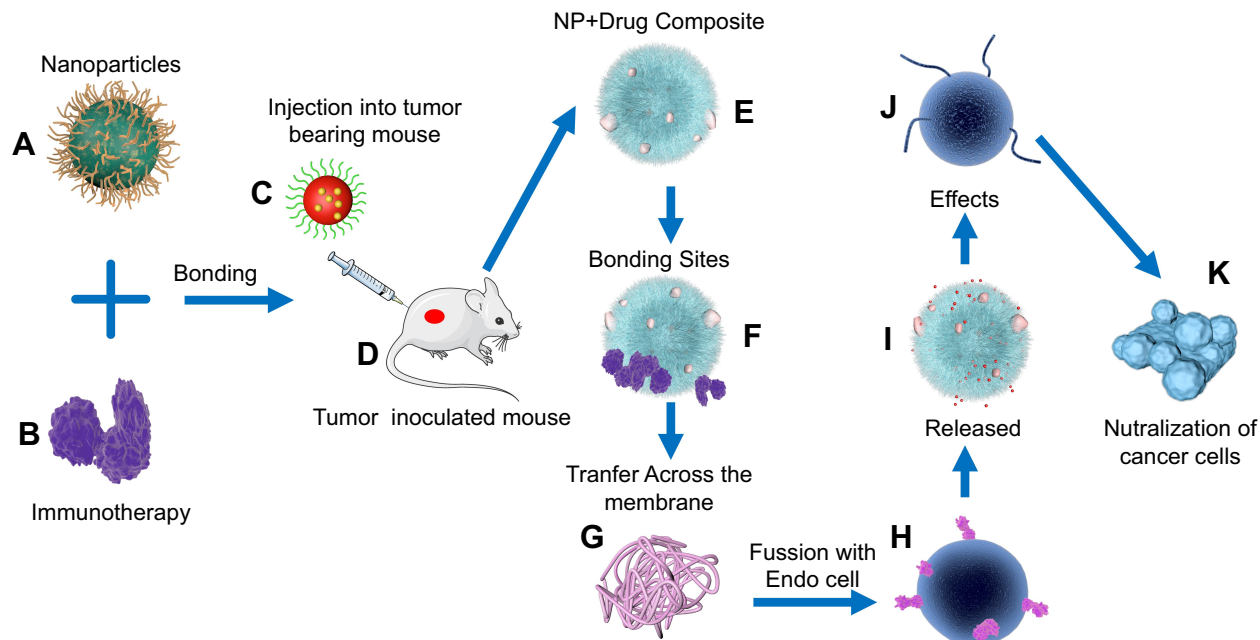
**Figure 2** The three phases of the cancer immunoeediting process: normal cells exposed to oncogenic stimuli eventually undergo transformation and become tumor cells. The transformation process gives a signal which can either act to alert the body immunity to eliminate tumor cells or initiate the tumor immunoeediting process. (1) The immune elimination phase of cancer immunoeediting is the beginning stage of the immunosurveillance measure. It visualizes the obliteration or annihilation of malignancy by the host defensive system. It visualizes the obliteration or annihilation of malignancy by the host defensive system and is acknowledged to happen when the cells got changed by vanquishing its inborn tumor silencer protocol, prior to having the alternative to develop into an all-out tumor. (2) During the equilibrium stage, the tumor and the defensive system both concur without permitting each other to overpower. The defensive system cannot dispense with the malignancy during this stage. Nonetheless, it does not permit it to extend or metastasize. The tumor thusly is etched by the defensive system, subsequently prompting the rise of variations impervious to the immunological assault. (3) Finally, the escape phase which has formed the purpose for the advancement of various therapeutics intending to defer the neoplastic formation. On account of growing genomic frailty, tumor cells acquire various credits engaging them to maintain a strategic distance from the defensive system or to adjust it in such a manner which is valuable to tumor cells.

technology which bring into use the ability of nanoparticle active targeting during which immunotherapy can precisely adhere to the nanoparticles and effectively convey at the malignant cells site where tumor cells are neutralized while sparing healthy cells.<sup>45</sup> See Figure 3.

## Nanoparticles Enhancing Cancer Immunotherapy

Lots of NPs have been discovered as immunotherapy carriers to convey antitumor immunotherapeutics specifically to tumor cells. These NPs have the capability of offering stability, increasing solubility and causing less toxicity to healthy cells.<sup>46</sup> NPs have the potential to supply immunotherapeutics directly at malignancy sites which can be accounted for by the improved duration within the blood stream without altering physiochemical properties of the body.<sup>47</sup> The lymphoid node secures the NPs preceding their drug conveyance priority and elimination of the toxic waste products. There is a great decrease in cellular cytotoxicity and reasonable outcome when NPs-immunotherapy are

passively used for aiming malignancy.<sup>48</sup> Here, we have to understand that there is a variation in patients and several forms of neoplasm exist so how can we better understand the enhancement of immunotherapy considering a single form of neoplasm? These can be achieved based on the morphological structure, dimension, the positive or negative nature of the NPs which are the prior features that play the focal role regarding the duration in circulation, migration into neoplasm sites for tumor targeting and its firmness to immunotherapy preventing untargeted dispatches,<sup>49</sup> see Figure 3. Renal clearance and phagocytosis are the two major ways by which NPs are clear from the body based on their sizes respectively. The covalent attachment nature of polyethylene glycation to the NPs can successfully block the liquidation of the NPs and hence enforce their planned drift.<sup>50</sup> Irrespective of the fact that these adjustments can effectively block the liquidation of NPs, they as well influence the rate at which immunotherapies are conveyed to the neoplastic tissues.<sup>51</sup> Ligation of precise tumor attracted ligands to the NPs is the best way to avoid dispatches of immunotherapy to untargeted



**Figure 3** The above figure shows the latest progress in research whereby NPs actively or passively bind immunotherapy and release within the cells for targeting cancer cells. (A) Synergized NPs, (B) immunotherapy, (C) immunotherapy-NPs composite, (D) cancer cells are cultured and inoculated into the mouse, (E and F) NPs are modified and loaded with immunotherapy, (G) the NPs can be attached to the cancer cell and get carried into the cell. (H) The drug-loaded NPs only attack the cancer cells and spare healthy cells. The cancer bonded NPs are transported into the cells through a pit found on the surface of the cell. (I) Inside the cell, the NPs fuses with the end cell compartment which digests the incoming NPs hence releasing the immunotherapy. (J) The drug assault cancer cells. (K) NPs delivery system provides a way for killing tumor cells and not harming healthy cells.

and non-precise cells which can be toxic, so the traits of NPs give a quintessential function in toxicity, pharmaco-kinetics, remedy potential, and bio-distribution of immunotherapy against neoplasm.<sup>52</sup> With most malignant's immunotherapy drugs, the introduction of NPs as a means for delivering the immunotherapies offers several workable outcomes over ordinary cure tactics. The healthcare department are plying the utilization of nano-materials such as NPs in various ways including the conveyance of immunotherapy to tumor districts and also for diagnostic purposes.<sup>22</sup> The successful transport of the immunotherapeutic drug encompasses the covalent bonding which exists between the immunotherapy and the NPs. Also, the means by which the NPs convey the drugs to the tumor fields.<sup>53</sup> In addition, more hope comes as a result of the periodic migration of the immunotherapy within the blood flow to the precise tumor tissues.<sup>54</sup> The defensive surveyance molecules can be provoked by NPs which causes phagocytosis of cells and in regards awaken the surveyance response against neoplasm.<sup>55</sup> In evaluation, NPs have been evacuated and are successfully used for the conveyance of vaccines clinically, which relay on

MHC-I and MHC-II in dendrite cells.<sup>56</sup> Immunotherapeutic vaccines that focus on dendrite-cells in most tumor regiments are classified specifically into different techniques including those with a bacteria-vector and a non-bacteria vector as well as those based on the cellular line for the conveyance system.<sup>57</sup> Because the malignant tissues shelter incorporates molecules which can suppress the defensive system component, this bothers the rate at which the defensive system assaults malignant cells to a greater extent.<sup>21</sup> NPs demonstrate beyond reasonable doubt to beautify the ability of the molecules that make up the defensive system by means of calling to action the dendrite cells.<sup>58</sup> NPs also can engineer DCs through specific attachments which produce the signals that activate the defensive mechanism to play and eliminate malignancy.

## Nanoparticles as Immunotherapy Delivery Vehicle

Nanoparticle immunotherapy drug conveyance is an emerging significant department of medicine whereby

nanoparticles drug delivery system is helping in the realization of cancer treatment. Nanoscale edifices have at present been created to comprise of two principle segments which include the NPs main component responsible for adhesion and immunotherapeutic drug itself as in Figure 3.<sup>59</sup> The immunotherapy is conveyed to neoplasm fields through absorption or surface adhesion. The nano-system immunotherapeutic conveyance strategy is of maximum efficacy to cancer regiments which provide satisfactory results with minimal abnormalities.<sup>60</sup> The outstanding performance of the nanoparticles-immunotherapy conveyance system with high preciseness is completely dependent on a few principles that have to be obeyed. Such principles include: the conveyance system should possess the effective and firmly adhesive nature for bonding the immunotherapy<sup>61</sup> also, the firmly adhesive complex should be maintained within the circulation and only dispatch at the tumor tissue regions.<sup>62</sup> The NP-immunotherapy adhesive molecule should prevent unwanted dispatches of the immunotherapy which can be toxic in the cytoplasm and finally the immunotherapy's precise dispatch should be able to educate the immune defensive system to recognize and eradicate neoplastic cells in the case of reoccurrence.<sup>63</sup> The immunotherapy adhesive molecule should be produced from live synthesized molecules which can easily be neutralized by the system and reduce the risk of healthy cell's toxicity.<sup>64</sup>

Within the previous decade, a range of immunotherapy conveyance systems have been put in play for high precision in clinic and as a therapeutic medium of transport. The NPs that are used to stack immunotherapies possess a surface with bonding sites which are capable of entrapping, engulfing and releasing the immunotherapy, hence preventing degradation and denaturation.<sup>65</sup> Therefore, NPs promote increasing and developing interests in the field of cancer immunotherapy treatments.

## Transport of Nanoparticle-Immunotherapy Complex to Malignant Cells

When nanoparticles are administrated into the general circulatory system, they will be conveyed to the malignant site by active or passive means. Considering passive conveyance, NPs can make the maximum transport of immunotherapy to the malignant cells because of the understanding of the EPR-impart of malignancy by NPs.<sup>22</sup> The nature of the circulatory medium in terms of blood volume and variation in thickness hinders the equilibrium distribution so NPs

bonding sites are modified in such a way that they can be easily localized and engulf malignant cells,<sup>66</sup> Figure 3F. The malignant cells which have been marked for eradication should have surface properties which can easily be recognized by the NPs engulfing the immunotherapy for precise delivery.<sup>67</sup> Paying more attention to malignant cells, the NPs can successfully achieve a substantial delivery of immunotherapy to the malignant cells with a sharp drop in toxicity of non-malignant cells.<sup>68</sup> Additionally, findings have likewise demonstrated that various bonding sites (receptors) at the same time can result in nanoparticles showing multi-valent qualities and henceforth more grounded cooperation for bonding and conveying of immunotherapy at the tumor cells sites.<sup>69</sup> Once conveyed the immunotherapy should be able to completely dissociate from the NPs by erosion as well as degradation or disintegration, Figure 3I. The dispatched immunotherapies struggle for optimal function in eradicating the tumor cells.<sup>70</sup> Consequently, there may be a competition among how speedy the immunotherapy gets to the intracellular space, via each energetic (active) delivery system, likewise the talent of the receptor interceded endocytosis, and the way rapidly it will proceed to malignant cells.<sup>71</sup> Thus, for an effective outcome to be achieved, the delivery system has to be modified in such a way that the immunotherapeutic carrier gets into the intracellular space before dispatching the immunotherapy.

## Specific Delivery of Immunotherapies from the Nanoparticle-Immunotherapy Composite

The outstanding performance of NPs for delivering immunotherapy to precise tumor cells has influenced researchers to work on the mechanism by which the drugs are adhered to the various types of NPs, transported and precisely delivered to targeted tumor cells.<sup>69</sup> Several types of NP (Table 3) exist ranging from carbon-based NPs, ceramic NPs, metal NPs, semiconductor NPs, polymeric NPs and lipid-based NPs and have been used for drug delivery. They are classified into different types focusing on the size, morphology, physical and chemical properties of the NPs.<sup>72</sup> An outline of NPs for drug conveyancing in malignant tumor cells includes; liposome NPs composing of hydrophilic and hydrophobic which can convey hydrophilic immunotherapies inside the fluid center zone while hydrophobic immunotherapies are inside the hydrophobic district of the bilayer; polymeric

**Table 3** Most Commonly Used Clinical Nanoparticles

Nanoparticles (NPs)	Properties	Ref.
Liposome-NP	Acts as an activator for T-cells and can respond in a variety of pH. The integration of the engulfing molecule (antigen) at the inner membrane of the cell causes disintegration.	[75]
Gold-NP	Potable physiochemical properties with low cytotoxicity potential. Possesses the influencing factors to immune responses and induces a systemic antigen specific immune response.	[76]
Poly(propylene) sulfide (PPS)	CD4+ and CD8+ T-cell inducer, passive targeting of the lymph node. In the presence of ipsilateral, the PPS aims at TDLNs. Promotes CD4+ and CD8+ T-cells integrating malignancy.	[12,38]
PLGA-NP	Governs the release of antigen, endosomal or lysosomal escape. Lengthens the lifespan of CD8+ T-cells, has the ability to deliver to DC-cells.	[21,77]
Artificial exosomes	Easy to produce with potable physiochemical properties and released influential factors. They have a nature which is attracted to malignant cells, making them good immunotherapy carriers.	[72,78]
Exosomes-NP	Contains antigens that go for MHC-II, capable of inducing cytotoxic CD8+ T-cell response through MHC-I. The optimal function relies on pH, and supports the MHC-I pathway for transportation.	[26,79]
Dendrimers-NP	Sufficient bonding sites and a changeable size and shape. Promotes the ligation of bioactive molecules and transportation of molecules with high resemblance, such as proteins, and possess a malignant effect.	[30,80]

NPs are made of polymers and can exemplify hydrophilic and hydrophobic molecules; micelles are made of a hydrophobic monolayer of amphiphilic lipids encasing a hydrophobic center, which can convey hydrophobic anticancer immunotherapies; dendrimers are tediously spread particles comprising of radially symmetric atoms of tree-like arms or branches which can embody hydrophilic and hydrophobic substances; polymersomes are fake

vesicles made of a bilayer of engineered amphiphilic block copolymers encasing a hydrophilic center, which convey hydrophilic and hydrophobic immunotherapies; lastly, inorganic NPs are particles shaped by the crystallization of inorganic salts, framing a tridimensional course of action with connected iotas, which can epitomize hydrophilic and hydrophobic and are vesicles made of a hydrophobic bilayer of amphiphilic lipids.<sup>53,69,73,74</sup>

## The Encapsulation Efficiency, Loading Capacity, Stability and Release of Nanoparticle-Immunotherapy Composite

Encapsulation efficiency is the degree of drug that is effectively entangled into the NPs. Encapsulation efficiency (EE%) is determined by (absolute medication added – free non-ensnared drug) divided by the complete medication added.<sup>81</sup> Loading capacity is the proportion of drug stacked per unit weight of the NPs, demonstrating the level of mass of the NPs that is due to the embodied drug.<sup>82</sup> Loading capacity (LC%) can be determined by the measure of absolute captured drug partitioned by the all-out NP weight. In drug conveyance, yield (given as a percent) is an impression of the measure of drug conveyed per sum epitomized. The incomparable EE%, LC% and stability of NPs engaged them to be used for immunotherapy drug conveyance.<sup>83,84</sup>

The clearance rate of immunotherapies in the system is solely dependent on the blood circulation and the clearance rate is driven by the renal excretion and the interaction with the reticuloendothelial system of intracellular delivery and release. Once the nanotherapeutics are conveyed to malignant sites, the NPs-immunotherapy-drug composite must dissociate to release the immunotherapy.<sup>85</sup> NPs do not only limit the transport of immunotherapy into the cells, they also act as a medium for transporting amino acids and nucleotides into the intercellular space.<sup>82</sup> The variation in surface morphology and nature of the NP could help them to actively or passively bind the molecule and transport to the targeted malignant cells. The charge nature of NPs varies which is also an advantage for easy adhesion-dissociation.<sup>86</sup> Nevertheless, surface modification of the nanoparticles provides it with stealth-like characteristics, enabling them to have an increased circulation time by limiting the NP's immunogenicity and inhibiting their recognition and phagocytosis by mononuclear phagocytic cells.<sup>87</sup> The used of NPs as a means of delivery comes as a solution for precise



delivery which brings about fewer side-effects commonly noticed in chemotherapy. The adhesiveness of immunotherapy to the NPs at a specific recognitive site and dissociation at the malignant sites reduced unwanted targeting and promoted the immunotherapy outcome.<sup>88</sup> Thus, smaller nanoparticles are easily cleared through the kidney and larger particles by the reticuloendothelial system. Once the nanoparticles are intracellularly delivered and released, the larger and smaller molecules undergo phagocytosis and endocytosis for their uptake respectively.<sup>73,89</sup> The nature and physiochemical traits of the NPs as well as the various integration sites available for bonding contributes greatly to the cellular migration.

## Factors Involved in Immunotherapy Release from Nanoparticles

Despite the fact that new approaches for delivering immunotherapy to tumor cells holds a promising future, there are several factors, as elaborated in Table 4, which influence the release of immunotherapy from the NPs into the intracellular space at the precise tumor site.

## Important Characteristics and Application of Nanoparticles for Vaccine Delivery

The biological nature of NPs characterize them as good delivery agents of immunotherapy to tumor cells. The overwarming nature and the less or no harmful side-effects to the human system provides additional advantages suitable for vaccine delivery.<sup>100</sup> The success of vaccines has been highly improved with the used of a variety of NPs and many more are still in the research process.<sup>47</sup> The immunotherapeutic regiment system is made up of the immune response initiators, known as antigen, which can either be in the form of peptide or the nucleotide DNA that codes for the tumor associated antigens.<sup>101</sup> The activator, known as the adjuvant, alerts the defensive mechanism if there is an invader or unwanted cell growth and finally the transporter which is highly precise and timely, releases the immunotherapy to evade the invader or neoplasm.<sup>102,103</sup> The application of NPs as a transport medium for vaccines is based on their potential such as, preservation of the immunotherapy, the

**Table 4** Influencing Factors for Immunotherapy Drug Release

Factors	Immunotherapy Released Influential Properties	Ref
Enzyme	The adhesion of immunotherapy onto the ligation site present on the surfaces of NPs is highly influenced by enzymatic activities. So, when the immunotherapies are transported to their site of action there is an enzymatic reaction that triggers the breakage of bonds that keeps the composite together thereby releasing the immunotherapy.	[74,90,91]
pH	The pH of the NPs is not constant, the variation is closely related to that of the cellular system which effectively influences the dissociation of immunotherapy from the NPs. If immunotherapy was to be administered orally, the malignant cellular activities lead to a variation in pH as compared to healthy cells so, it's easier to design NPs with precision for targeting and releasing the immunotherapy.	[92-94]
Redox potential	The redox potential difference across the plasma membrane of a normal cell makes the extracellular and intracellular regions oxidative and reductive respectively. Poor vasculature in tumor tissues results in the formation of hypoxic areas that are environmentally reductive owing to the presence and action of reductases, the bad vasculature in tumor tissues leads to the formation of hypoxic areas which might be environmentally reductive owing to the presence and mechanism of reductases which influenced the breakage of bonds, leading to immunotherapeutic release.	[95]
Thermoresponsive	Temperature variation lead to hydrophilic or hydrophobic imbalance, the hydration state of a thermoresponsive NP which might lead to disruption of the delivery system so affecting the efficiency of the NP. Thermoresponsive NPs are then required to release immunotherapy to malignant cell sites with a high temperature.	[90,96]
Photo responsive	UV-radiation, infrared frequency can be used to promote the bond adjustment thereby promoting the lysis of bonds and release of the immunotherapy.	[97,98]
Dual-responsive nanocarriers	Dual-responsive NPs can release immunotherapy responding to two different stimuli often related to the mixture of pH and ionic strength as well as pH and thermoresponsiveness.	[99]

antigen and adjuvants for optimal function in relation to the protection and enabling maximum absorption by the dendrite cells over traditional cancer regimens.<sup>104</sup> The NP-delivery system is programmed to influence the defense system positively by activating immunogenic-cells elimination and setting in place the control mechanism that ignites the protective and monitoring system.<sup>105</sup> In conclusion, NPs possess flexible properties which can be modified and used based of the requirement of the molecules to be transported.

## Improvement of DC-Based Cancer Immunotherapy by NPs

The conveyance immunotherapy by NPs to DCs has been a point of focus for most cancer immunotherapy researchers. The tumor immunity reaction to immunotherapy is solely based on the availability of the drug at the cancer site and it is effective with the use of NPs to present the vaccine for DCs uptake.<sup>102,105</sup> When the immunotherapeutic vaccine is conveyed to the dendritic cells in vivo, they are accompanied by antigens/adjuvants which have a similarity to those intracellular cells, thus improving the efficacy as compared to ex vivo with prolonged functional time.<sup>106</sup> Furthermore, the physiochemical and biological properties of vaccines focusing on DCs in vivo along with the NPs delivery system and its beautiful nature makes dendritic cell-based immunotherapy a dream come true.

## The Challenges and Solution of the NP-Immunotherapy Delivery System

Irrespective of the promising features of the NPs-immunotherapy conveyance system, some demanding situations focusing on in vivo targeting conveyancing of the immunotherapy to malignant cells slows down the full potential of NPs.<sup>107</sup> Lots of NPs generally used in the clinic by oncologists are now determined on EPR effect and passive malignant growth aiming for the improvement of immunotherapy efficacy.<sup>108</sup> Several side-effects of EPR in xenograft experiments which are more severe than those found in cancer raise a conflict on the usage of EPR and passive targeting.<sup>109</sup> The malignant stoma is poorly developed in tumor xenografts hence the limitation in diffusion boundary and patients suffering from malignancy might present low susceptibility to passive tumor concentrated on with the aid of the EPR effect than formerly anticipated in preclinical models. The rate of immunotherapy released,

cellular migration and durability do not attend its goals as shown in the xenograft model.<sup>110</sup> A good quantity of immunotherapy is expelled without arriving at their targeted point. Therefore, the use of NPs for the conveyance of immunotherapies facilitates the delivery of immunotherapeutic molecules including those insoluble in water and too easily diffused through the cellular membrane for precise delivery.<sup>111</sup> Nevertheless, molecules with sustainable sizes ranging from peptides to nucleic acids require a barrier transport mediator for effective uptake and efficacy which is sometimes limited by cellular clearance and by means of phagocytosis.<sup>112</sup> When proinflammatory cytokine are conveyed to a portion of APCs, the is a stimulation of a variety of responses which function as organizing and initiating the immune defensive cells to precisely target the malignant cells and evade them out of the body.<sup>113</sup> However, the goal of immunotherapy is not limited to malignant cells only but also to activate the defensive cells at the level of the tumor microenvironment (TME). The malignant cells residing at the TME level are reachable with the aid of NPs as the immunotherapy transport medium.<sup>114</sup> The phagocytic cells function best for the ability to ingest, and sometimes digest tumor cells. Furthermore, the encapsulation of tumor cells affects TAM functionality, as apoptotic cell uptake promotes macrophage anti-inflammatory functions. Both phagocytosis and efferocytosis affect TAM functionality and how these mechanisms impact on antitumor immunity is being researched.<sup>115</sup> A better understanding of NP delivery systems enables researchers to forecast and elaborate on the consequences of cancer immunotherapies on the immune status of the TME. Future cancer immunotherapy treatment can thereby be designed to not only impact directly on tumor cells, but also to favorably modulate TAM phagocytic activity to benefit from the potential of this central immune player to achieve more potent therapeutic efficacy.<sup>116</sup>

The utilization of numerous drugs in combination has become the essential technique to treat drug resistant tumors. Nonetheless, the organization of combinatorial therapy is restricted by the changing pharmacokinetics of various medications, which brings about conflicting medication take-up and imperfect medication blend at the tumor destinations.<sup>117</sup> Customary blend techniques in plan to amplify helpful adequacy dependents on greatest endured portion does not represent the remedial synergism that is delicate to both dosing and booking of different medications. To overcome this, nanoparticle-based blend

methodologies against malignant growth drug obstructions including co-encapsulation of drugs with different physicochemical properties, ratiometric control over drug loading, precise delivery, and temporal sequencing on drug release.<sup>118</sup> Nanoparticles composed absolutely by three clinically affirmed parts can be utilized for close infrared laser-set off photothermal removal of essential tumors, creating tumor-related antigens, which, within the sight of R837-containing nanoparticles as the adjuvant, can show immunization like capacities.<sup>119</sup> NPs can be used for examination or remedial purposes. In examination, they can be used as fluorescent imprints for the disclosure of biomolecules and microorganisms contrast agents in magnetic resonance and other studies. Likewise, NPs can be used for the centered conveyance of drugs, including protein and polynucleotide substances; in photodynamic treatment and warm destruction of tumors, and in prosthetic maintenance.<sup>120</sup>

## Toxicity of Different Types of Nanoparticle Delivery System

The use of NPs in the field of medicine comes with side-effects which can be harmful. The toxicity of the NPs is one of the major challenges. The toxicity of most NPs is based on how they are transported within the fluid circulatory system, the lymphoid flow and the manner by which they are taken into cells and tissues.<sup>54</sup> Most of the cells and organs undergo cell and morphology alteration in the presence of the NPs since the NP's shape, size and surface charger are the principle factors that determine the cellular uptake, disintegration and degradation. If the NPs are not completely degraded, there is a subsequent pile-up at the tissular and organelle level which will eventually become toxic.<sup>121</sup> Nevertheless, scientists continue to investigate different techniques of synthesis NPs with low toxicity and less harmful as compared to the tradition tumor immunotherapies. The focus of the routes and ways by which the NPs are managed within the body. The mechanisms by which the human body functions best is well understood and the NPs are produced similarly to those biological molecules within the body which prevent the accumulation since they can easily get degraded.<sup>122</sup> So, NPs can be synthesised with minimal toxicity by considering the physicochemical properties and relevant experimental model trials to evaluate and manage the effects on the biological system. Hence, the application of NPs clinically

still has a long way to go since lots of researchers are still working on the physicochemical properties of NPs.

## Associated Human Health Effects Related to NPs Immunotherapy Delivery System

When the immunotherapy drugs are loaded into the NPs, the carrier-drug composite needs to get into the cell through the membrane by transcytosis or be simply diffused. In summary, the cell membrane needs to be penetrated by the NPs for effective delivery hence causing damage to the membrane; NPs have the ability of altering the process of cell division which is dependent on the constituent and components of the cytoskeleton as well as the transport system affected by the NP delivery system. NPs create an unbalanced energy flow by destroying the mitochondria and altering the cellular metabolism; NPs alter the interface with the formation of lysosomes, thereby hampering autophagy and degradation of macromolecules and triggering cell apoptosis; NPs caused structural changes in membrane proteins thereby disturbing the flow of substances into and out of cells, including inter-cellular transport and, finally, NPs activate the synthesis of inflammatory mediators by disturbing the normal mechanisms of cell metabolism, tissue and organ metabolism.<sup>123-125</sup> The size of NPs permits them to infiltrate through epithelial and endothelial obstructions into the lymph and blood to be conveyed by the circulatory system and lymph stream to various organs and tissues, including the cerebrum, heart, liver, kidneys, spleen, bone marrow and sensory system.<sup>126</sup> Nevertheless, the development and application of NPs as immunotherapeutic tools in targeting neoplasm in preclinical has been demonstrated, beyond reasonable doubt, as a strategic approach that holds top notch potential. The *in vivo* biodistribution, size as well as the pharmacokinetics of the NPs influence the freely lymphatic circulation and also timely and precise delivery to malignant cells.<sup>127</sup> Despite the fact that the mechanism ensuring optimal functioning, including dispatches of adjuvants, surface properties and cytotoxicity to healthy cells, are still under study. NPs which might be biocompatible and possess immunotherapeutic adhesive potential needs to be investigated for its ability to stimulate immune defensive cells which includes DCs, T-cells as well as macrophages. The immunological interest and healing efficacy of such NPs and targeting tumor cells with immunotherapy, completely studied would contribute greatly in cancer prevention, vaccines and cancer

treatment.<sup>128</sup> Combining cancer therapies, such as immuno-chemo therapy as well as other treatment strategies, has proven a favorable synergistic effect on anti-tumor reaction, more efforts are still put in research to further elucidate the connection between NPs enhance immunotherapy and every other remedy routine.<sup>129</sup> Also, for NPs enhanced cancer immunotherapy to be effectively translated into the clinic, a variety of types of malignancy need to be evaluated and the potential of NPs and immunotherapy to the tumor type. The defects of other pathways as a results of cancer vaccines have to be causally evaluated.<sup>130</sup> Nanoparticle enhancing immunotherapy for the treatment of tumors has an extended way to go for it to be clinically applicable.

## Conclusion and Future Perspectives

Enhancing cancer immunotherapy treatment goals by using NP delivery systems is not just a means of treating cancer but also a way by which the immune defensive cells can be educated in such a way that the immune defensive cells possess a memory that can recognize and eradicate malignancy if in any case there is a reoccurrence. The precise and timely delivery of immunotherapy by NPs helps the body to develop a special “immunomemory” which offers protection by recognizing and eliminating reoccurred malignancy or abnormal growth cells for several years after treatment. NPs enhanced cancer immunotherapy has limited toxicity and side-effects unlike chemotherapy that might damage other fast-growing cells, radiotherapy which has a high possibility of damaging other healthy cells within the locality, surgery which removes cells and photothermal therapy (PTT) which is preferred for breast and prostate regimens, because it does not involve the cutting of the skin but has the negativity of killing healthy surrounding cells and failed to prevent a reoccurrence.

Although traditional cancer therapy such as chemotherapy, radiotherapy and surgery are still the most clinically applicable, immunotherapy remains a priority in the days ahead. The advancement of the nanoparticle-based conveyance frameworks as at present utilized may address a monetarily canny and promising alternative treatment method in future. As earlier discussed, we can realize that NP mediated immunotherapy has a great affirmation for neoplasm management. Their significant focal points, for instance, improvement of medication bioavailability and a decrease of the dosing recurrence brings a reason for better administration of the drugs making straightforward

means for lasting protection against reoccurrence and effective therapy.<sup>131</sup>

Another significantly favorable position of the nanoparticles is the reasonableness of the versatile ways of therapy administration such as oral and inhalation. Furthermore, a high strength of the nanoparticles recommends a long timeframe of realistic usability. It tends to the fact that future research will zero in on the improvement of the vectorized conveyance systems combining the focal points of the colloidal transporters, for instance enormous payloads of a medication, with dynamic focusing to the tumor districts.<sup>132</sup> Additionally, advancement of imaginative plan advances recommends that nanoparticles can be consolidated into different strong estimation structures which can convey the drugs at the site of activity, protecting their unique properties. These techniques would moreover improve feasibility and practicability of the nanoparticle-based formulations.

Finally, the achievement of this innovation will doubtlessly depend upon the toxicologic issues related with comprehension of the predetermination of nanocarriers and their polymeric constituents in the body, similarly as removal of the peril of the extra regular solvents.

In this regard, the chance of utilizing drug transporters produced using regular polymers such as chitosan or alginate, addresses an appealing viewpoint.

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## Author Contributions

All authors contributed to data analysis, drafting or revision of this article, have agreed on the journal to which the article will be submitted, given final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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The authors declare no conflicts of interest for this work.

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