

## Role of Nanoparticles in Cancer Treatment

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### **Abstract**

Cancer is a disease with complex pathological process. Current chemotherapy faces problems such as lack of specificity, cytotoxicity, induction of multi-drug resistance and stem-like cells growth. Nanomaterials are materials in the nano-range 1–100 nm which possess unique optical, magnetic, and electrical properties. Nanomaterials used in cancer therapy can be classified into several main categories. Targeting cancer cells, tumor microenvironment, and immune system, these nanomaterials have been modified for a wide range of cancer therapies to overcome toxicity and lack of specificity, enhance drug capacity as well as bioavailability. Although the number of studies has been increasing, the number of approved nano-drugs has not increased much over the years. To better improve clinical translation, further research is needed for targeted drug delivery by nano-carriers to reduce toxicity, enhance permeability and retention effects, and minimize the shielding effect of protein corona. This review summarizes novel nanomaterials fabricated in research and clinical use, discusses current limitations and obstacles that hinder the translation from research to clinical use, and provides suggestions for more efficient adoption of nanomaterials in cancer therapy.

**Keywords:** Cancer, Nanoparticles , Nanotechnology , Cancer treatment , Drug delivery

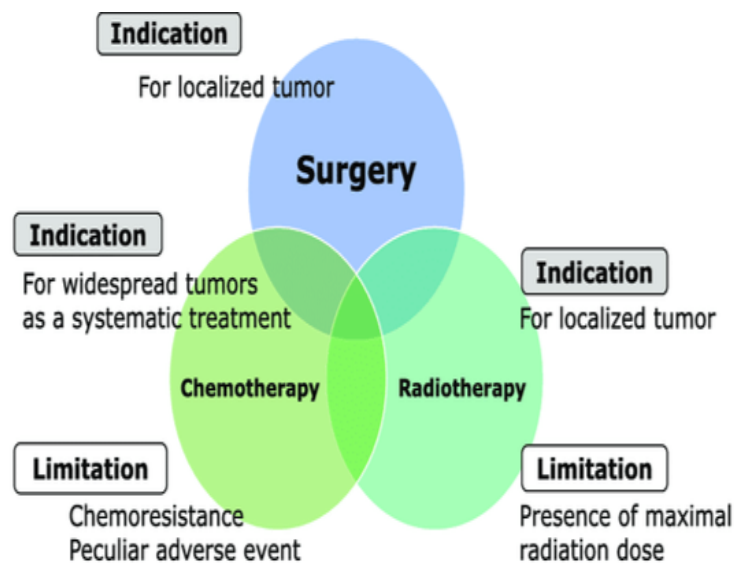
### **1. Introduction**

In recent times, nanotechnology playing important role in targeted drug delivery treatment in medicinal field [1,16]. Nanomaterial's are specific and may change their physical, chemical and biological properties with respect to surface: volume. However, the nanoprticles are still used as a therapeutic and diagnostic method. In the modern field of medicinal development like drug delivery ,anticancer agents and has increased the dependency on tumor attack for developing anticancer drugs .NP's , lipid or polymer can be planned or calculated to improve the pharmacological action and helpful properties of medicaments[1,16] . Cancer remains one of the world's most devastating diseases, with more than 10 million new cases every year [2,17] . However, death rate has

decreased in the past 2 years because of understanding between the tumor biology and enhanced or modern diagnostic devices or method and treatments [2,18]. Cancer is a common or general term for a set of diseases identify by uncontrolled, irregular cell division and invasiveness. Huge efforts are taken over several years to concentrate on detecting various risk factors for cancer. For some cancers, environmental (acquired factors) such as radiations, pollution etc can also dominantly connected with the etiology of cancer. However, another reasons is an unhealthy lifestyle like poorly balanced diet, smoking, tobacco consumption, lack of physical activity and stress strongly influence the determination of cancer risk [3,19, 20] . Latest cancer treatments consists surgical interruption,

radiation and chemotherapeutic drugs etc which frequently kill healthy cells and cause toxicity to the patients. Traditional or normally chemotherapeutic drugs also do not show targeted action and are dispersed inaccurately in the body where they affect both cancerous and normal cells. To overcome the lack of

specificity of traditional chemotherapeutic agents the molecular targeting therapy has emerged [1, 21]. Nanomedicine refers to the medicinal appeal of nanotechnologies. It ranges from biological nanomaterial's medical application to nano - electronic biosensors [4, 22, 23].



**Figure 1: Indication and limitations of three major cancer treatment modalities**

Nanotechnology influences a great probable and potential health maintenance and medical management. It has various advantages for example, it successfully delivers the drug, detection or identification of diseases is more rapidly and sensitively & finally it delivers vaccines through the patches and aerosols [4,24]. Nanotechnology has generated several favorable or hopeful results with its applications in the diagnosis and treatment of cancer, including drug [5, 25], gene therapy, detection and diagnosis drug carriage, biomarker mapping, targeted therapy and molecular imaging. Nanotechnology has been registered or put in the development of nanomaterials [5,26] such as gold nanoparticles and quantum dots, which are used for cancer diagnosis at the molecular level. Nanoparticles, by using both passive and active targeting strategies, can enhance the intracellular concentration of drugs in cancer cells while avoiding toxicity in normal cells [6,27,28].

## 2. Types of Nanoparticles in Cancer Therapy

NPS used extensively in drug delivery systems include organic NPS, inorganic NPS and hybrid NPS.

### 2.1 Polymeric Nanoparticles

Polymeric nanoparticles [PNPS] are well described as "colloidal macromolecules" with certain structural planning formed by different monomers [3,29]. The drug is either entrapped or attached to the NPS surface, producing a nanosphere or a nanocapsule to achieve controlled drug release in the target [3, 30].

Initially, PNPS are made up of non-biodegradable polymers such as polyacrylamide, polymethylmethacrylate [PMMA] and polystyrene [3,31] although the aggregation of these led to toxicity due to difficulty in removing them from the system. Biodegradable polymers such as polylactic acid, poly [amino acids], chitosan, alginate and albumin are now being used and are known to reduce toxicity and increase drug release and biocompatibility [3,32]. Research has been proven that by coating PNPS with polysorbates and by using polysorbates surfactant effect. External coating increases NPS interactions with the endothelial cell membrane of the blood brain barrier [BBB] [3, 33].

A study showed that nanocapsules filled with indomethacin involved a considerable decrease

in the size of tumor and enhanced survival in a xenograft glioma model in rats. [3,34] This is a growing field with more than ten polymeric NPS containing anticancer drugs are clinical development [3,35]. Polymers such as albumin, chitosan, and heparin occur naturally and have been a matter of choice for the conveyance of oligonucleotides, DNA and protein as well as drugs.[6,36]. Beside metastatic breast cancer, Abraxane has been assess in clinical trials involving many other cancers as well as non small cell lung cancer [phase 2 trial] and modern no hematological malignancies [phase 1 and pharmacokinetics trials] [6,37,38]. Among

artificial polymer such as N-[2-hydroxypropyl]-methacrylamide copolymer [HPMA], polystyrene maleic anhydride copolymerize, polyethylene glycol [PEG] and poly-L-glutamic acid [PGA],PGA was the initial biodegradable polymer to be used for combine synthesis [6,39]. HPMA and PEG are the most broadly used nonbiodegradable synthetic polymers [6, 40]. PKJ which is a conjugate of HPMA with doxorubicin was the synthetic polymer drug conjugate to be evaluated in clinical trials as an anticancer agent. Prepared by either dissolving, entrapping or conjugating a drug to a polymer [6, 41].

**Table 1: Advantages and disadvantages of polymeric nanoparticles [Ref.7]**

| Advantages  | Disadvantages  |
|---|--|
| <ul style="list-style-type: none"> <li>. Water-soluble, biodegradable, non toxic.</li> <li>. Can specifically target cancer cells.</li> <li>. Long shelf life.</li> <li>. Stable during storage.</li> </ul> | <ul style="list-style-type: none"> <li>. Time and expensive.</li> <li>. Highly equipment is required to manufacture these particles</li> </ul> |

## 2.2 Dendrimers

Dendrimers are round polymeric macromolecules with designated hyper branched architecture. Highly branched structures are the attribute feature of dendrimers. Generally, the synthesis of dendrimers is beginning by reacting with ammonia core with acrylic acid. After this reaction a 'tri-acid' molecule is formed which further reacts with ethylene diamine to form 'tri-amine'; a GO product. This product further react with acrylic acid to yield or give rise to hexa acid, which further produce 'hexa amine' product and so on [3,42]. Usually, the size of the dendrimers ranges from 1 -10 nm [3, 43].

Given their certain structure like defined molecular weight, variable branches, bioavailability, charge, etc and these defined structures are used to target nucleic acid. Some dendrimers that are broadly used are polyamidoamine [PAMAM], PEG [polyethylene glycol], PPI [polypropylene imine] and TEA [ triethanolamine] [3,44]. A PAMAM dendrimer was initially originate to achieve or to obtain MDR management. DNA assembled PAMAM dendrimer have been report significantly. In comparison with animals treated with single agent chemotherapy, the synthesized dendrimers extensively delayed the growth of epithelial cancer xenografts [3, 45].

**Table 2 : Advantages and disadvantages of dendrimers [Ref. 7]**

| Advantages   | Disadvantages  |
|--|--|
| <ul style="list-style-type: none"> <li>. Easy to functionalize due to structure</li> <li>. Molecular weight and size can be controlled</li> <li>. Degradation can be controlled</li> <li>. Biocompatible</li> <li>. Withstands physiology conditions</li> <li>. Can selectively target cancer cells</li> </ul> | <ul style="list-style-type: none"> <li>. Difficult to synthesize large quantities pure enough for clinical trials</li> </ul> |

## 2.3 Liposomes

These are spherical cells consisting phospholipids that may be either made up of

uni-lamellar or multi-lamellar to enclose drug molecules [3, 46]. Recently, there are more than 11 formulations which are accepted or approved for clinical use, with many more in clinical and

preclinical growth [3, 47]. Liposomes are special and unique for having characteristics such as low intrinsic toxicity, weak immunogenicity, and biological inertness or inactive [3, 48]. In 1965, liposomes are approved as a first nanoscale drug [3, 49]. A typical liposome structure is consisting of a 'hydrophilic core' and a 'hydrophobic phospholipids bilayer'. This unique design makes it possible for them to capture or entrap both hydrophilic and hydrophobic drug to successfully protect the captured drug from

surrounding breakdown in circulation [3,50]. To enhance their stability and circulation half life, the liposomes can be coated with polymers such as PEG [polyethylene glycol] [2]. Liposome gives an excellent surface for drug delivery such as doxorubicin, paclitaxel, and nucleic acid as well as illustrating higher anti tumor efficacy and enhanced bioavailability [3, 51]. Doxil and Myocet are approved liposome based formulation of daunorubicin used to treat MBC [3,52,53].

**Table 3: Advantages and disadvantages of liposomes [Ref.7]**

| Advantages  | Disadvantages   |
|---|---|
| <ul style="list-style-type: none"> <li>. Amphiphilic</li> <li>. Biocompatible</li> <li>. Easily modified and functionalized</li> <li>. Selectively target cancer cells</li> <li>. Carry both lipid and water soluble drugs</li> </ul> | <ul style="list-style-type: none"> <li>. Rapidly cleared from circulation due to primary uptake by the liver</li> </ul> |

#### 2.4 Solid – lipid Nano particles [SLN]

They are colloidal nanocarriers [1-100 nm] along with a phospholipids monolayer, emulsifier, and water [3, 54]. They are well known as zero dimensional nanomaterials. The lipid element may be containing triglycerides, fatty acids, waxes, steroids, and PEGylated lipids [3, 55]. Unlike standard liposomes, SLNs have a 'micelle-like structure' inside the drug is

entrapped in a non-aqueous core. Examples contain mitoxantrone loaded SLN, which has shown reduced or decrease toxicity and improve bioavailability [3,56]. Increased effectiveness of doxorubicin and idarubicin existence comprise in SLNs determine or indicates better results to treat leukemia cells and murine leukemia in mice models [8, 57,58].

**Table 4 : Advantages and disadvantages of solid lipid nanoparticles [Ref. 9]**

| Advantages   | Disadvantages   |
|--|---|
| <ul style="list-style-type: none"> <li>. High stability</li> <li>. Reduced toxicity</li> <li>. Enhanced bioavailability of poorly soluble drug molecules and targeted drug delivery</li> </ul> | <ul style="list-style-type: none"> <li>. Microbial growth upon storage</li> <li>. Active targeting is difficult to achieve</li> <li>. High manufacturing cost and CMC regulation for each material</li> </ul> |

#### 2.5 Carbon Nanoparticles

Carbon NPs as the name indicates that they are establish on the element carbon. They have been used in medical areas due to their optical, mechanical, and electronic properties. These properties are merge with biocompatibility [3, 59]. Due to their intrinsic hydrophobic nature or properties carbon NPs can encapsulate or entrapped drugs through  $\pi$ - $\pi$  stacking [3, 60]. Carbon nanoparticles are further classified into graphene, carbon nanotubes, fullerenes, carbon nanohorns and graphyne. However, all these

are carbon – based, they alter in their structure, morphology, construction, etiology, and properties.

Graphene 'is 2D crystal with sp<sup>2</sup> hybridized carbon sheet that holds remarkable mechanical, electrochemical, and high drug charging properties. Further, dependent on composition and properties graphene are divided into; [3,61]

1. Single – layer graphene
2. Graphene oxide [GO]
3. Reduced graphene oxide [rGO]

#### 4. Multi – layer graphene

Fullerenes –They are big carbon –caged molecules usually known as Bucky balls. Fullerenes are the most favorable anticancer carriers because of their special physical, chemical, electrical, and structural (hollow sphere) properties [7, 62]. Their stability creates a very best applicant for effective, potent, efficacious and safe drug distribution to the tumor cells. Comparatively, the reality or presence of  $\pi$ - conjugation, they can consume or absorb light, high triplet yield, and give rise to the susceptible oxygen species upon illumination. These photo characteristics or properties make them applicable for photodynamic treatment of cancer [7, 63].

#### 2.6 Quantum Dots

Quantum dots [QD] are semiconductor particles having sizes of a few nm. QD emit light of a certain wavelength when a current is put in or exposed to light. The discharged wave length can be adjusted by changing or altering the size, shape, material or disable the QDs. Smaller or minor QDs [2-3 nm] release or discharge light at short wavelengths [ orange , red , or IR ] . Additionally, it has been reveal or conveys that their fluorescence lifespan is also bind to particles size. The lifespan is longer in the larger dots, because the energy levels are more closely arranged in which the electron – hole pair can be trapped. Nanoparticles [NPs] are

also very minor structures but larger than QDs, generally ranging from 8 to 100 nm. Due to these, NPs shows conduct behaviors between the bulk matter and atoms or molecules. NPs frequently have unexpected optical properties as their size allows for quantum enclosurement effects .Further , the interfacial layer surrounding nanoparticles play an key role in all of their physical properties . The interfacial layer naturally consists of ions, inorganic material, or organic material [10]. They have exceptional optical properties as well as high brightness, resistance to photo bleaching and tuneful wavelength. The latest developments in surface modification of QDs permit their potential application in cancer visualizing. Fusion of QDs with bio molecules, including peptides and antibodies, could be used to target tumors in vivo [11]. Based on carbon, the Quantum dots divided into;

1. Graphene quantum dots
2. Nanodiamond quantum dots
3. Carbon quantum dots

Other than biological imaging, quantum dots are being actively examined in cancer treatment. The graphene quantum dots are commonly used due to their intrinsic or innate biocompatibility and rapid excretion .For example, quantum dots aptamer – doxorubicin conjugate targets prostate cancer cell [3, 64].

**Table 5 : Advantages and disadvantages of quantum dots [Ref : 12]**

| Advantages   | Disadvantages   |
|--|---|
| <ul style="list-style-type: none"> <li>. High quantum yield</li> <li>. Broadband excitation</li> <li>. Multiplexing</li> <li>. Size – tunable fluorescence</li> <li>. High photo bleaching threshold</li> <li>. Fluorescence of high quality and energy</li> </ul> | <ul style="list-style-type: none"> <li>. Toxicity</li> <li>. Blinking effect</li> </ul> |



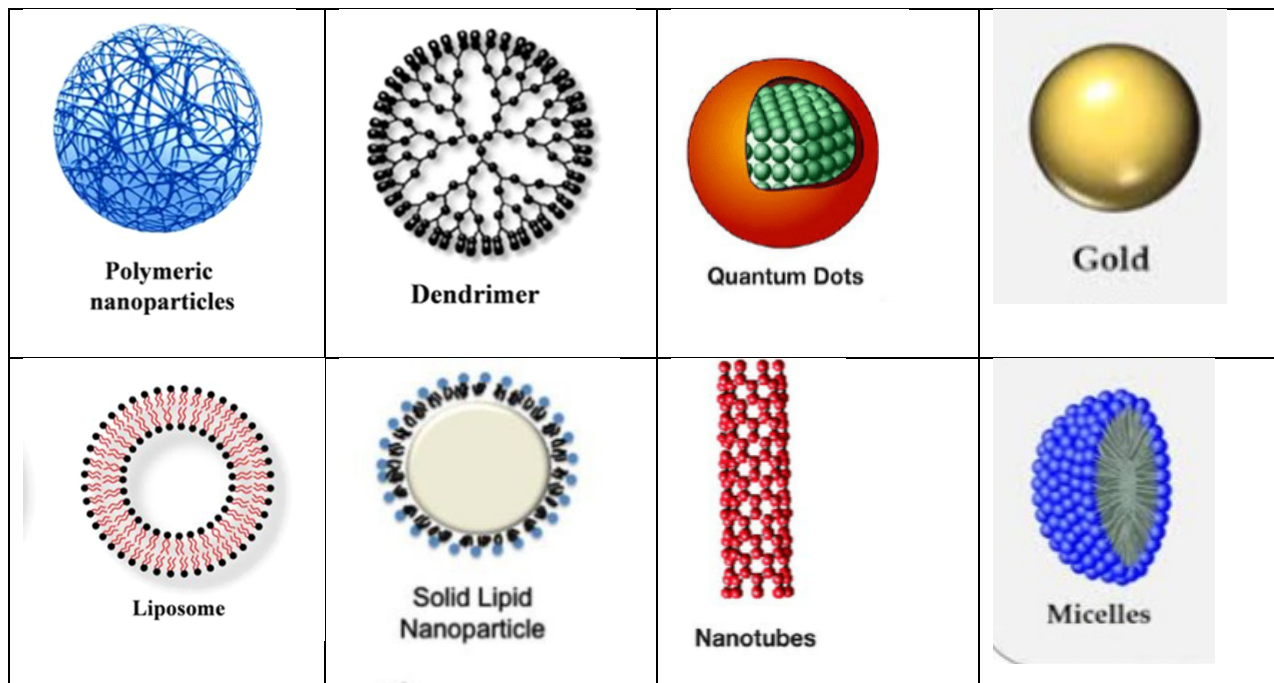


Figure 2: Type of Nanoparticles

2.7 Gold Nanoparticles

Gold nanoparticles [GNPs] are present in wine red solution with antioxidant capacity or power, whereas gold is present in a yellow solid that is inert in nature [13,65]. GNPs characteristics vary from bulk gold. Gold nanoparticles come in a various of sizes and forms which are ranging from 1nm to 8µm, and also contain

nanospheres, nanorods, nanoshells, nanotubes, nanocages and branched [13,66,67]. Gold nanoparticles have a different or unique combination of physical, chemical, optical and electrical capacity and they can be used as novel platform in a variety of sectors including medicine.

Table 6 : Advantages and disadvantages of gold nanoparticles

| Advantages  | Disadvantages  |
|---|--|
| <ul style="list-style-type: none"> <li>. Increased contrast</li> <li>. Less invasive</li> <li>. No photo bleaching</li> </ul> | <ul style="list-style-type: none"> <li>.Biocompatibility</li> <li>. Optical signal not strong</li> <li>. Toxicity</li> <li>. Tumor targeting efficacy low</li> </ul> |

3. Synthesis of Nanoparticles

In nanoparticle the various different shapes, sizes and structure are seen. So various methods are include. It is distributed In 2 groups.

3.1 Approach of lower to upper

In this approach include constructive method. Constructive Method: It includes the building up of material from atom to clusters to nanoparticles [3,68]. It includes follow as:

|                                 |
|---------------------------------|
| Spinning                        |
| Sot gel synthesis               |
| Chemical vapor deposition (CVD) |
| Plasma                          |

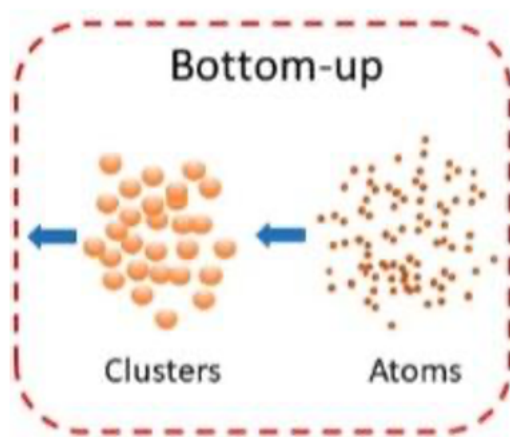


Figure 3: Bottom –Up synthesis [Ref : 3]

Tiny atoms and molecules are combined in bottom – up methods to create nano-structured particles. These include chemical and biological approaches;

1 .Chemical Vapor Deposition (CVD) \_ Chemical vapor deposition includes a vapor phase precursors. They are precursors Considered particular for CVD [83, 84]. IF they contain variability high chemical purity, stability, inexpensive, safe nature, long durability [83, 85] . For producing high quality

nanomaterials CVD is a best method [83, 86]. It is also famous for creating two dimensional nanoparticle [83, 87] .

2 .Sol gel process \_ Sol gel method is a also called as a wet chemical approach used to for the creating nanomaterial [83, 87].

3.2Approach of upper to lower In this involved a huge substance divided into pieces or in smaller decomposed which are convert into nanoparticles [3, 69].

Destructive Method: It includes follow as;

|                        |
|------------------------|
| Mechanical milling     |
| Nanolithograpy         |
| Chemical etching       |
| Laser ablation         |
| Sputtering             |
| Electro explosion      |
| Thermal decomposition. |

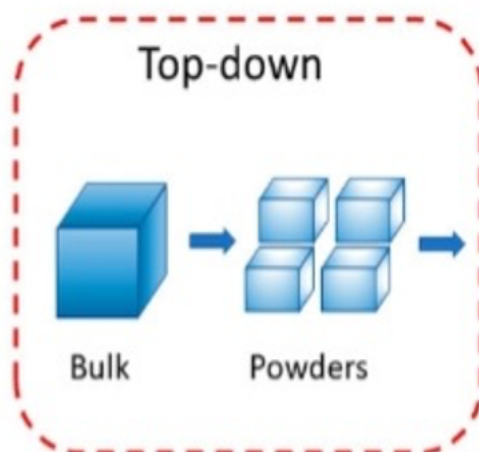


Figure 4: Top – Down Synthesis [Ref : 3]

The following techniques can achieve a top – down approach;

1. Mechanical Milling\_ It uses the balls inside the container by mechanical milling method and it is overcome by typically planetary and shakers mills, which is an effective method with high power. [83,89] .

A particular class of nanomaterials acknowledged as a ball milled carbon nanomaterials have capacity to acquire need for power storage, power conversion and denoxing [83,90] .

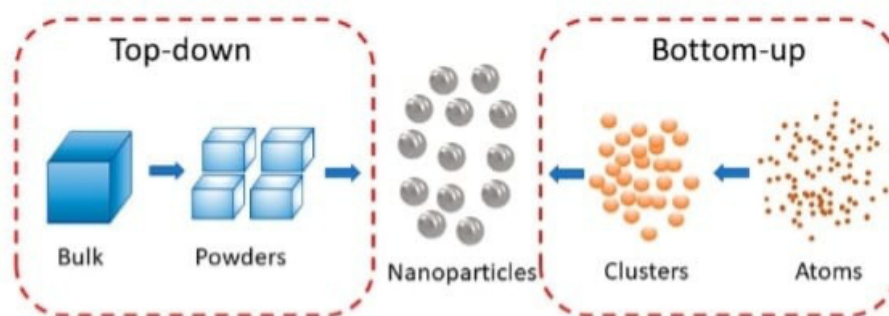
2. Electrospinning\_ Electro spinning method of advantages is a production of nanofibres from

various materials most of often semi-synthetic [83, 91].

This technique developed the core shell and hollow power, inorganic and organic and hybrid materials [83, 92].

3. Laser ablation\_ for producing the noble metal nanoparticles laser ablation is best technique. It is an environment friendly for production nanoparticle [83, 87].

4. Sputtering\_ It is a fascinating because it is economical than electronic beam lithography. It contain the sputtered nanomaterials which as like as target material [83, 87].



**Figure 5: Synthesis of Nanoparticles; Top-down and Bottom-up [Ref : 93]**

#### 4. Mechanism of action of Nanoparticles

##### 4.1 Passive targeting by nanoparticles

\*Enhanced permeability and retention effect –

The individual path physiology distinctive of neoplasm vessel facilitate macromolecule contain nanoparticle to the particular assemble in tumor tissue.

Rapid development of tumor cell desire /dictate the neovascularisation or for supply of oxygen and nutrients that existing vessel near the vessel.

\*Environment Tumor –

Other patron you passive targeting is the unique microenvironment surrounding tumor cell that's distinctive from normal cell rapid growing hyper generation cancer cell show a high metabolic rate, and usually provide of oxygen and nutrients is not sufficient for to maintain

this, therefore for obtaining extra energy tumor use glycolysis for obtaining extra energy tumor use glycolysis so it affect seen in acidic environment [6,70].

For the stable, PH sensitive liposomes are designed at a physiologic pH of 7.4, but corruption to liberate active drugs in target tissue in which the pH is not greater than physiologic values, such as tumor cell of in acidic nature [6,71].

Matrix metalloproteins [cancer cell shows and librates a specific enzyme] which are imply in the action and continuity mechanism [6,72]. Doxorubicin is an albumin bound form which is including matrix metalloproteins -2. Specific octapeptide sequence between the drug and carrier. They are cleaved by matrix metalloproteins [6,73].

- Examples of passive targeting ;

**Table 7 : Examples of passive targeting**

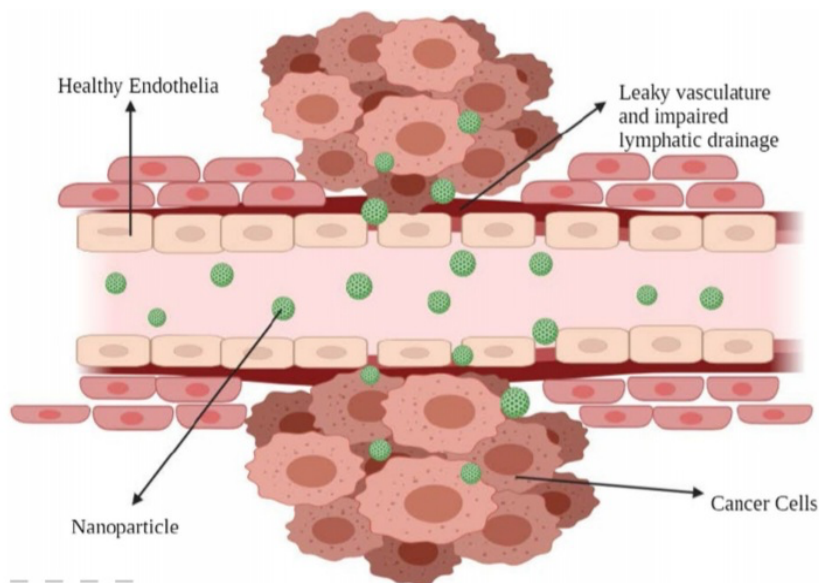
|            |               |
|------------|---------------|
| 1.Taxens   | 2. Paclitaxel |
| 3.Abraxane | 4.Daunoxome   |



- 1) Taxens: In cancer treatment taxanes is the one of the most successful drug group.
- 2) Paclitaxel: It is a great potency against broad spectrum range of cancer.
- 3) Abraxane: It is an Antimicrobial drug. Abraxane prevent the depolymerization (converting a polymer into monomer or mix of monomer) by the stabilizing the micro tubular.

Cytotoxic agent of combinations is abraxane [3, 74].

- 4) Daunoxome :Daunoxome prevent the growth of tumour cell . It is an anticancer medicine. It contain daunorubicin as a active substance. It is used in kaposi sarcoma (which related to skin cancer ) [3,75].



**Figure 6: Pictoral representation of Passive cellular targeting [Ref : 3]**

#### 4.2 Active targeting by nanoparticles

The factor depend on passive targeting mechanism that's system of drug delivery comprising binary conjugate which are inevitably faces intrinsic limitation to its specificity.

one appeal recommend to control conditions is the covalent or non covalent attachments of targeting ligand on the surface of nanoparticle enables them to recognize on the surface of nanoparticle enables them to recognize the specific antigen on receptor on target cells which is subsequently engulf the particle through endocytosis [6,76].

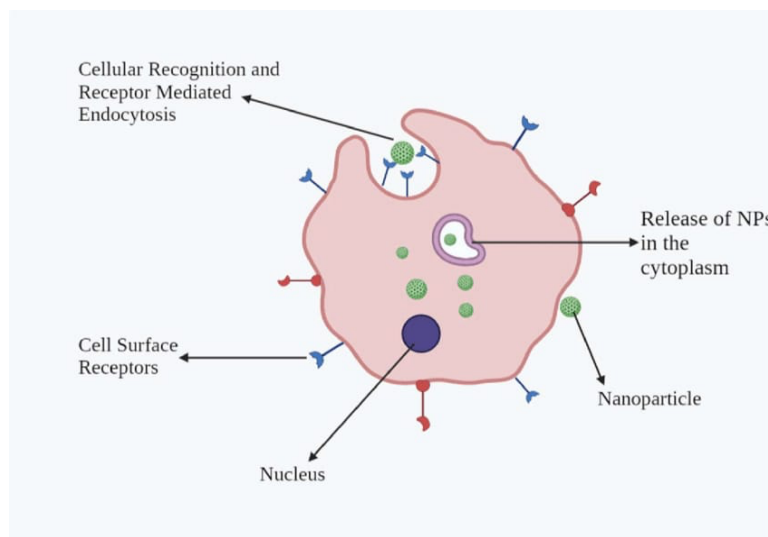
An antibody to a drug was attempted by direct conjugation. Though in clinical trials organized for promptly antibody drug conjugated have unsuccessful to be reveal supremacy as a for treatment of cancer by targeted delivery.

Antigen or receptor expression -The characteristics should for cell surface and receptor for specific tumor targets [6,77]. So it's include in expressive and non expressive factor

on tumor cell and non expressive factor normal cells .It should not be shed like last cell surface antigen and receptor into blood circulation.

\*Conjugate of target internalization - From the conjugate folate receptor are released to the cell membrane for to start transformation second round for new folate conjugate by binding method [6,78].

- Example of Active targeting ; The targeting human EGF receptor-2 (HE2) there is a therapeutic drug i.e Herceptin , a breast cancer cell surfaces are over exposed. For preventative cardio toxicity HER2 targeted PEG gylated liposomal doxorubicin was developed [3, 79]. CAM-1 is a vasulation cell adhesion molecule -1. It is a cancer of of endothelium revealed a glycoprotein involved in a development of new blood vessel. It's potential role is indicate that NPs that target VCAM -1 is the breast cancer model [3, 80] . For the cancer treatment nanoparticle are targeting folate receptor [3, 81, and 82].



**Figure 7: Pictorial representation of Active cellular targeting [Ref : 94]**

### 5. Application of Nanotechnology

- ❖ Different types of Nanoparticles [1 to 100 nm] are used to treat various types of cancer due to their unique characteristics and advantages such as biocompatibility , reduced toxicity , more excellent stability , enhanced permeability , retention effect and specific or accurate targeting [3].
- ❖ Nanoparticles not only solve the limitations of traditional or regular cancer treatment but also overcome multidrug resistance [3].
- ❖ The conventional use of nanotechnology in cancer beneficial or remedial has been to improve the pharmacokinetics and decreased the systemic toxicities of chemotherapies through the selective targeting and delivery of these anticancer drugs to tumor tissues .
- ❖ Application of Nanotechnology or nanoparticles in healthcare; Gene therapy, cancer therapy, drug delivery, ocular diseases, genetic disorders, cardiovascular diseases, brain and CNS disorders [14].
- ❖ Others application of Nanotechnology includes ;[15]
  - Nanomedicine
  - Nano biotechnology
  - Green nanotechnology
  - Energy applications of nanotechnology
  - Potential applications of carbon nanotubes
  - Industrial applications of nanotechnology
  - Nanoart
- ❖ Innovative Application of Nanotechnology ;
  - Energy
  - Medicine & drugs

- Nanobiotechnology
- Nanodevice
- Optical Engineering
- Defense & Security
- Bio Engineering
- Cosmetics
- Nano Fabrics

### 6. Conclusion

We can conclude that the usefulness of nanoparticles for the purpose of drug transportation to the cancer cells has importance as an great and acute value of upcoming or approaching novel method into field of therapeutics and has a scope and opportunity of grave and important and chief developments that have capacity and volume of changing the way or path of the treatment and therapeutics well organized history , the upcoming changes and evolution into the techniques research discovery involving targeted safe treatment method and cure .

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