AN OVERVIEW OF EMERGING POLYMER USED IN CANCER IMMUNOTHERAPY & FUTURE PROSPECTS

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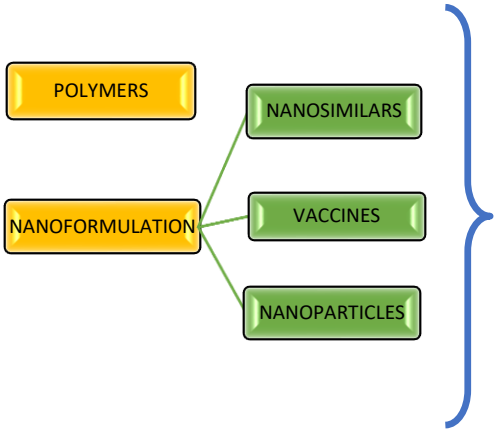
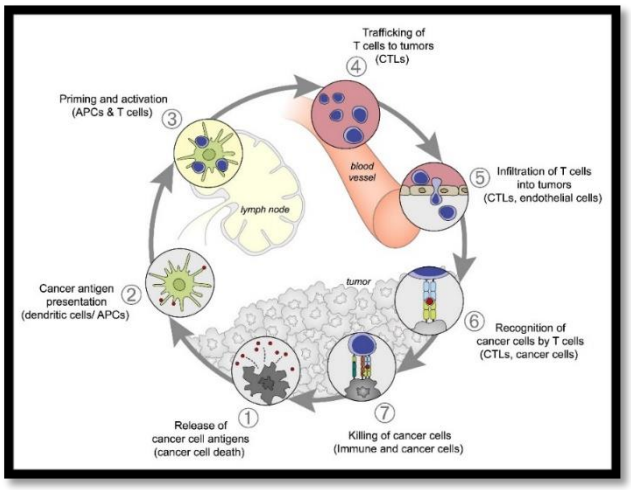
ABSTRACT
Cancer immunotherapy is one of the promising approaches in the treatment of the cancer. Various nanomaterials and nano formulations are used to treat cancer and are beneficial as they have an ability to overcome poor solubility and toxicity. This study mainly focuses on the polymers used in the treatment of the cancer immunotherapy. There are numerous polymers used in the treatment of the cancer: Block co-polymers conjugates, Thermo-sensitive polymers, pH-sensitive, Redox etc. Nanomaterials have great biocompatibility and absorption. The combination of the immunotherapies results in the increased therapeutic effect as compared to alone treatment. Vaccine prepared by nano formulations have great effect in the treatment. Patents of the cancer immunotherapy and future prospects are also presented. This review focuses mainly on the polymer used in cancer immunotherapy and also on the recent trends and future perspectives of the polymers used.

Keywords: Cancer immunotherapy, Nano formulations, vaccines, polymers.

Graphical abstract:

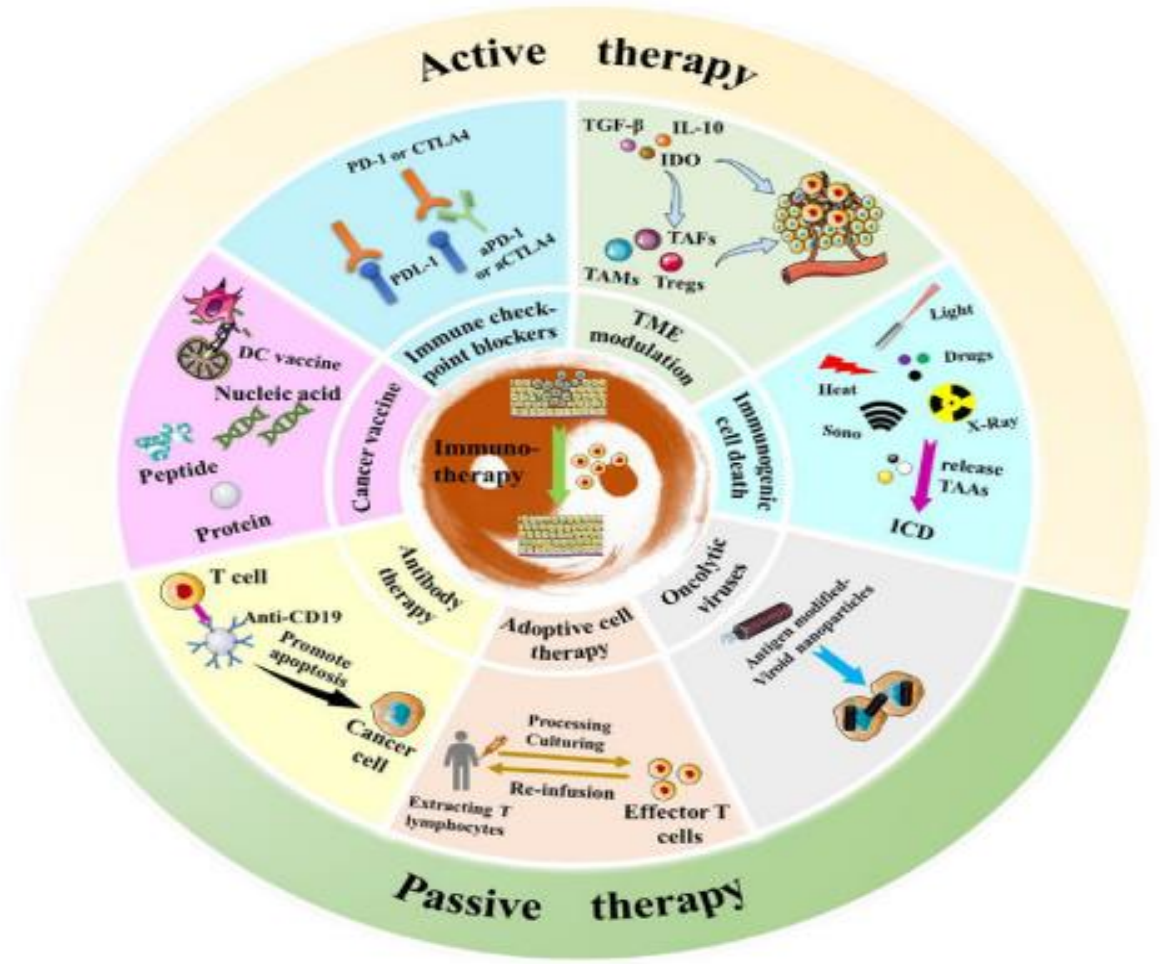




1. INTRODUCTION

Immunotherapy is a one way to deal with the treat disease hence it shows powerful therapeutic viability without the adverse results, experienced by ordinary remedial methodologies, for example chemotherapy, surgery, and the radiation [1]. The current treatment approaches of cancer immunotherapy and the corresponding mechanism of each immunotherapeutic approach mention in figure 1[2].

Figure 1: The current treatment approaches of cancer immunotherapy and the corresponding mechanism of each immunotherapeutic approach. [2]



Polymers play an essential function in the drug application, particularly in the field of drugdelivery. There are numerous polymers used in the cancer treatment such as Block co-polymer conjugates, Thermo-sensitive polymers, pH- sensitive polymers, Redox-polymers etc. The main principle of combining the polymers to chemotherapies is to accomplish the synergistic impact to improve their pharmacological actions [3].

Nanomaterials have several advantages including great biocompatibility, mucosal adsorption, and biodegradability. Other extraordinary physicochemical properties of nanomaterials as non-viral vectors incorporate a simplicity of handling and adjustment, controllable surface properties, the advancement of utilitarian particles into cells, and the assurance of DNA and proteins from degradation. Numerous nanomaterials have been created, including iron oxide nanoparticles, gold nanoparticles, cerium oxide nanoparticles, carbon-based nanomaterials and polymeric nanoparticles have displayed incredible potential in the uses of antibodies and medications. Furthermore, nanomaterials themselves have antigenic or restorative movement, and can inspire a solid insusceptible reaction; nanomaterials can hinder or even execute pathogeniccells by utilizing their cell poisonousness or autoimmunity [4].

Polymeric nano formulations have increased expanding acknowledgement for malignancy immunotherapy since they can possibly improve the immunotherapeutic adequacy and overcome limitations of IRAEs. For instance, polymeric nanomedicines permit for focused conveyance of malignancy antigens to antigen-introducing cells (For e.g. macrophages and dendritic cells) by which the immature T-cell can be successfully prepared. As in recent years, polymeric nanomedicines such as medications stacked micelles and polymer-drug forms have gotten expanding consideration for malignant growth treatment since they can viably convey anticancer operators to tumours by passive or dynamic focusing on mechanisms. Polymeric nanomedicines have been applied to different intractable illness, including diabetes, stroke, rheumatoid joint inflammation, furthermore myocardial localized necrosis. Vaccines are used to control or eradicate various diseases. Many new vaccines have been developed with modern advancement such as recombinant vaccines, synthetic vaccines, DNA vaccines and nanomedicines. As the era passes, the development in vaccine is also been seen as in improving the immunity, enhancement in design of vaccine, minimizing toxicity, adverse effect or side effects and improvement in its effect. Polymer and their roles in cancer drug delivery are mention in figure 2 and different nano formulation are mention in figure 3 [5].

Figure 2: Role of nanoparticle in cancer immunotherapy [5]

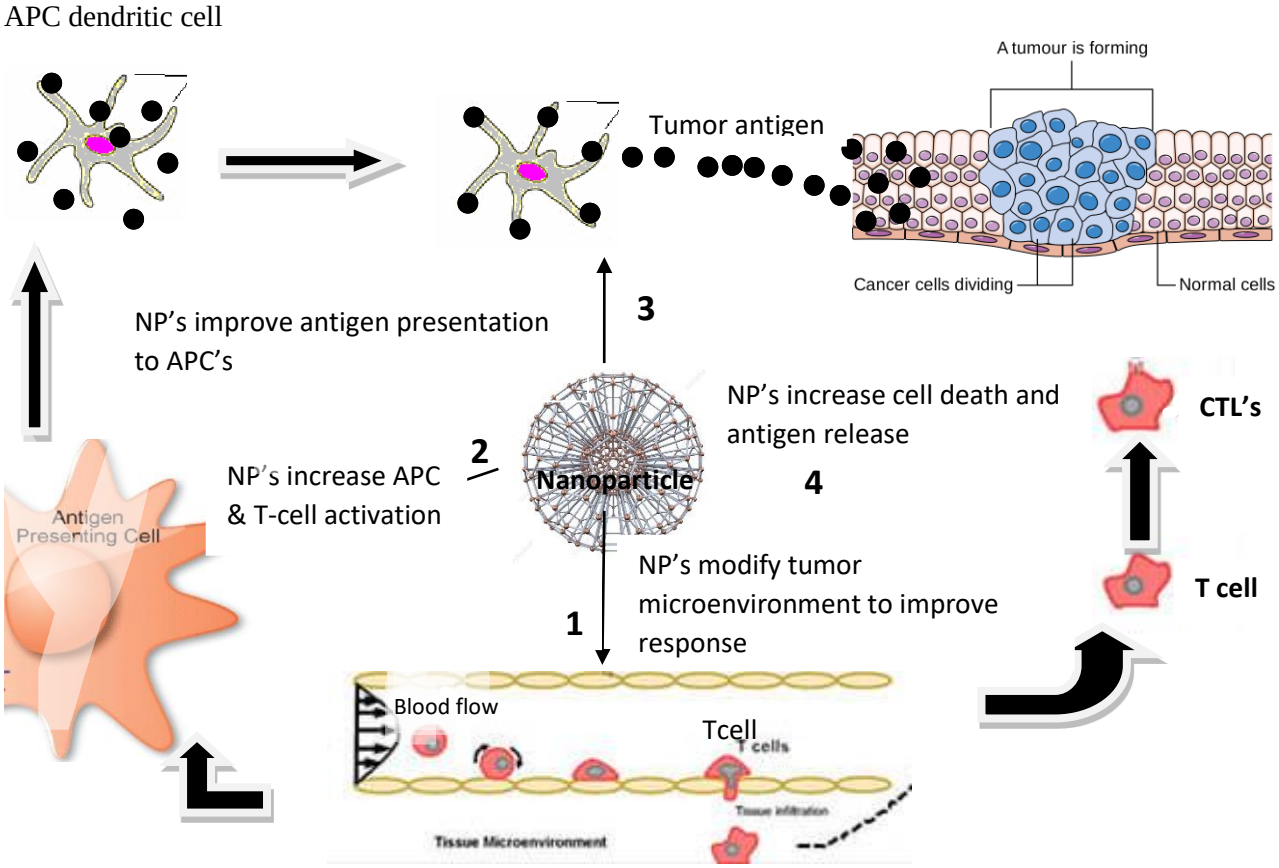
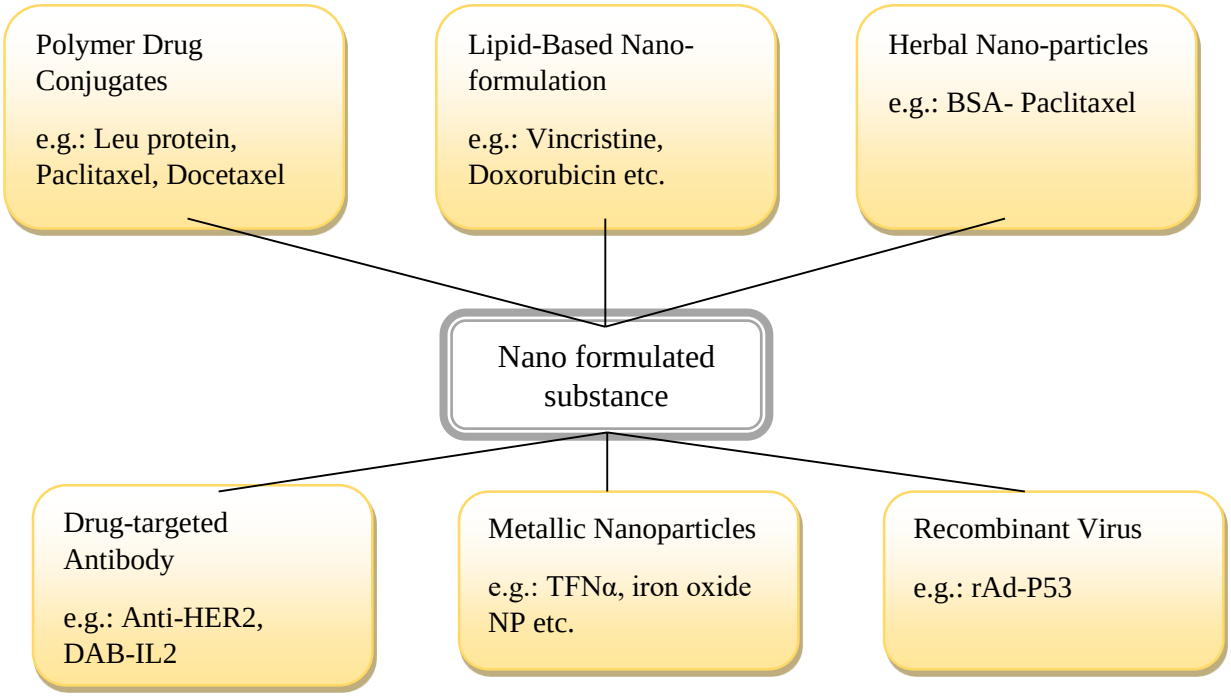


Figure 3: Nano-Formulated Drugs [5]



The different Nano-formulated Drugs used are as follows:
Polymers mainly are classified as: Natural polymers, biosynthesized polymers and chemically synthesized polymers.

1.1 Natural Polymer

Natural polymer is a sustainable asset that can be gotten from an assortment of sources, it can be debased into water, carbon dioxide and inorganic atoms. These can be created by physical and compound strategies, or through adjustment to turn into another material utilizing developing nanotechnologies. At present, regularly utilized common polymer materials incorporate chitosan, starch, alginate, cellulose, hyaluronic corrosive, chondroitin sulfate and so forth (Mention in Table 1) [6-9].

1.2 Biosynthesized Polymers

Biosynthesized polymers are acquired through catalyst hydrolysis (utilizing microbial chemicals). These mixes contain microbial polyesters and microbial polysaccharides. Delegate items are poly-β-hydroxybutyrate (PHB), poly (3-hydroxybutyrate-co-3- hydroxy valerate), biofibre group, polyamine corrosive and so forth (Mention in Table 2) [12-14].

1.3 Chemically Synthesized Polymer

Artificially orchestrated polymer materials, including PLA, PLGA, Polyurethane (PU), Poly(methyl methacrylate) (PMMA), polyester, polyvinylpyrrolidone (PVP), silicon elastic,polyvinyl liquor, and so forth, (Mention in Table 3) that are utilized in clinical materials are created through strategies [15-17].

Table 1: Natural Polymers [10-11]

Nano materials	Role	limitations	Structure	Melting Point

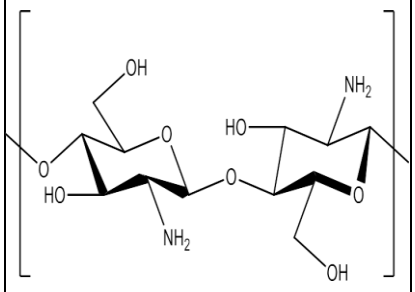
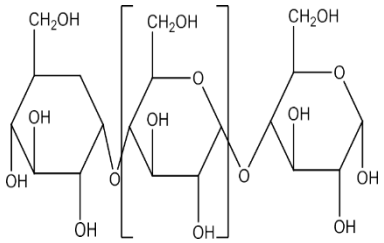
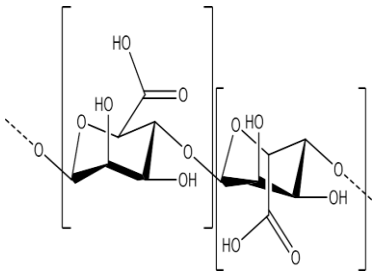
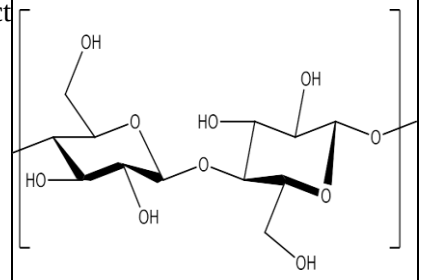
Chitosan	Biocompatibility, harmless, anti-microbial, easy to degrade, adsorbability, film formation, moisture retention	Poor spinnability, low strength, and less water soluble.		88ºC
Starch	Extensive source, co steffective, safe and non-toxic, non-antigenic	Less mechanical properties, resist to water, bad blocking performance		256-258ºC
Alginate	Less toxic, degraded safe and no toxic, non-antigenic	Low biodegradability, poor cell attachment.		99 °C
Cellulose	Extensive source, Cost - effective	Rare adverse effect are seen		260–270 °C

Table 2: Biosynthesized Polymers [10-11]

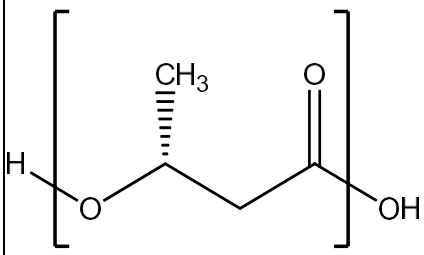
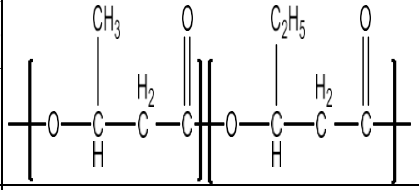
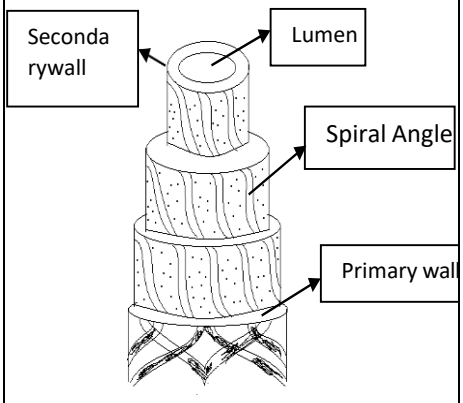
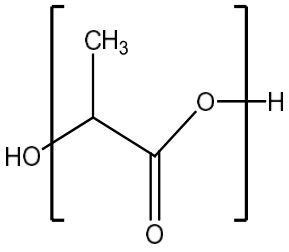
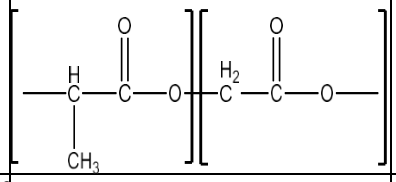
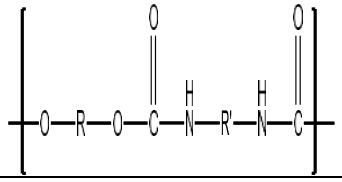
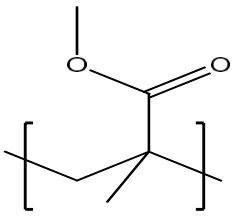
Nanomaterial	Role	Limitations	Structure	Melting point
Poly- β-hydroxybutyrate	Biodegradable effective, non-toxic, good physiochemical properties	Highly crystalline, low thermal stability		175 °C
poly (3-hydroxybutyrate-co- 3-hydroxyvalerate)	Easily biodegraded, non-toxic, biocompatible	Expensive, less thermal stable, brittle, difficult in processing.		153 °C
Biofiber	Cost effective, recyclable, less density, high mechanical properties, thermally stable	Hydrophilic, variability		165 – 195 °C

Table 3: Chemically Synthesized Polymers [10-11]

Nanomaterial	Role	Limitations	Structure	Melting point
PLA	Biocompatible, high mechanical property, non-Toxic.	Low toughness, easily degradable, hydrophobic,		130-180 °C

PLGA	Controlled biodegraded, biocompatibility	High cost, low stability		156.6 ± 0.2°C.
Polyurethane	Cost effective, rich source, high mechanical resistance	Low speed of degradation		56°C.
PMMA	Easily operable, high biocompatibility	Cytotoxic, easily oxidized		160°C

2. CANCER IMMUNOTHERAPY CYCLE AND Cis

Cancer immunotherapy is one of the promising approaches in the clinical practice to eradicate cancerous cells at primary stage. In comparison to radiotherapy, chemotherapy orthe surgery, immunotherapy shows one of the advantages in anti-tumour response and also reduces metastasis [18]. Till now around 3000 immunotherapeutic drugs have been approved by USFDA. Cancer vaccine regulates dendritic cells, immune checkpoint blockade which strengthens the T cells by blocking activity of tumour microenvironment (TME) [19].

Advantages in cancer immunotherapy are:
It results in superior therapeutic effects which potentiate patient's immune system. Generates memory T- cells, B-cells which cause long lasting immune memory. Its universal application is it overcomes the limitations of conventional cancertherapies.

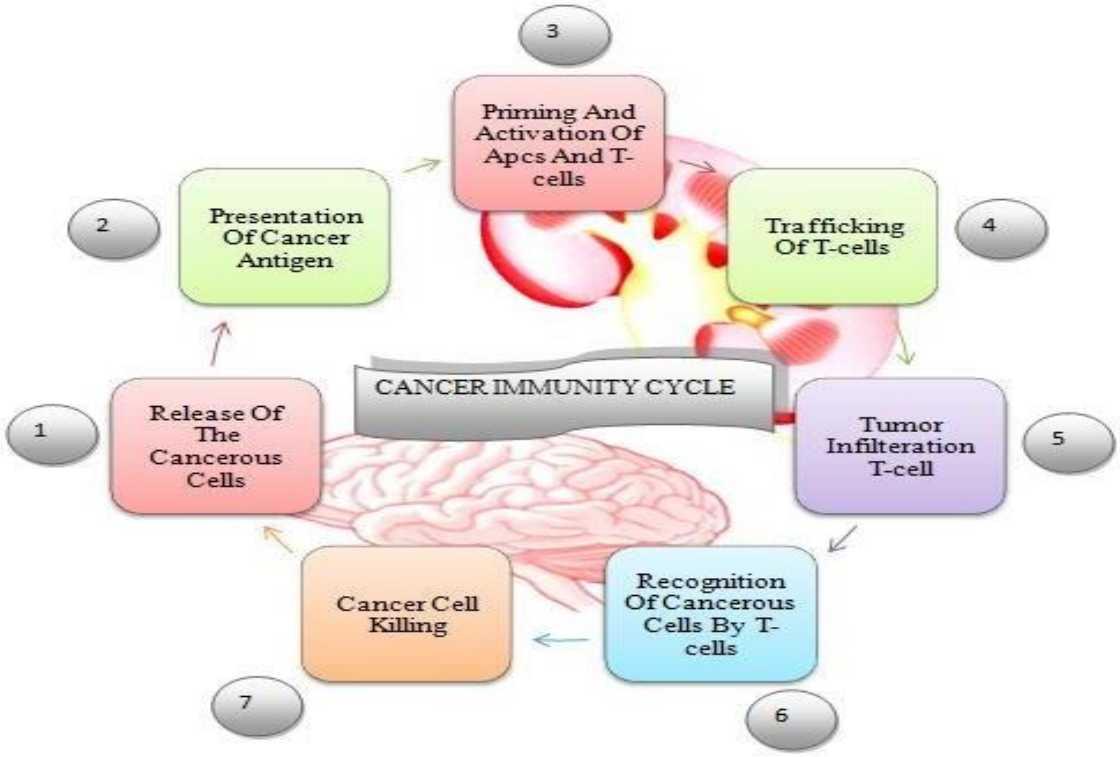
The **limitations** in cancer immunotherapy are:
Low reaction rate restricts the adequacy of immunotherapy. Systemic administration prompts unavoidable irAEs, as dermatologic harmfulness, toxicity in gastrointestinal, pneumonitis and some uncommon adverse effect related to immunity. Clinical interpretation is another issue. Immune evasion is also one of the reasons which results in low antitumor response rate that activates immune system. Various mechanisms make the treatment ineffective such as the defective antigenpresentation [20]. The schematic illustration of the process of the Cancer immunity cycle (Mention in figure 4).This process was developed by Daniel Chen & Ira Mellman in 2013.
This process was developed by Daniel Chen & Ira Mellman in 2013.
This process involves basic 7 steps: They are:

1. The cancer immunity cycle starts with the condition in which the cancer cells are present. When this cancer cells die, they release their content. This is the 1st step in Cancer Immunity cycle i.e. Release of cancer antigen cell into the surrounding micro- environment.
2. These released antigens are then taken up by the antigen presenting cell such as dendritic cells, like

other antigens the dendritic cells passes the antigen and present them on their surface.

3. The dendritic cell then migrates to nearby lymphatic organ such as lymph node where they present the antigens to the T-cells. If a cytotoxic T-cell passes an antigen presenting dendritic cell that has correct T-cell receptor for antigen recognition. This results in binding to one another. The interaction between the T-cells and dendritic cell is guided by several positive and negative factors. The most important factor in activation is the connection between the T-cell receptor and antigen, which is presented by MHC Class II molecule. This induces the positive signal inside T-cells thereby activating it. An e.g. of negative modulator is the binding CD80/CD86 to CTLA-4. The connection between thesecreates the negative signals inside the T-cell, inhibiting activation. In simple terms if the positive signals exceed the negative signals, T-cell is activated and starts to multiply.
4. The T-cell tries to control body. They eventually reach the organ containing tumor. This is facilitated by cytokines directing T-cell especially if the information is present in the effective tissue.
5. Activated cytotoxic T-cell infiltrate the tumor.
6. With the receptors the T-cell recognizing antigens express on the surface of the cancer cells and bind to them i.e. recognition of the cancer cells.
7. This step involves the interaction between the cancer cell and the T-cell, which results in the killing of the cancer cells and signifies the completion of the single round of the cancer immunity cycle. Upon binding, the cytotoxic T-cells aims to induce apoptosis in the cancer cells, this interaction is regulated by the positive and the negative signals in the T-cell. The positive signal is the interaction between the T-cell receptor and the antigen bound to MHC Class I on the cancer cell. A negative signal is the link between the PD-1 receptor and its ligand PD-L1. The negative signal can prevent T-cell mediated killing of cancer cells which leaves the cancer immunity cycle uncompleted [21-22].

Figure 4: Cancer Immunotherapy Cycle [20-22]



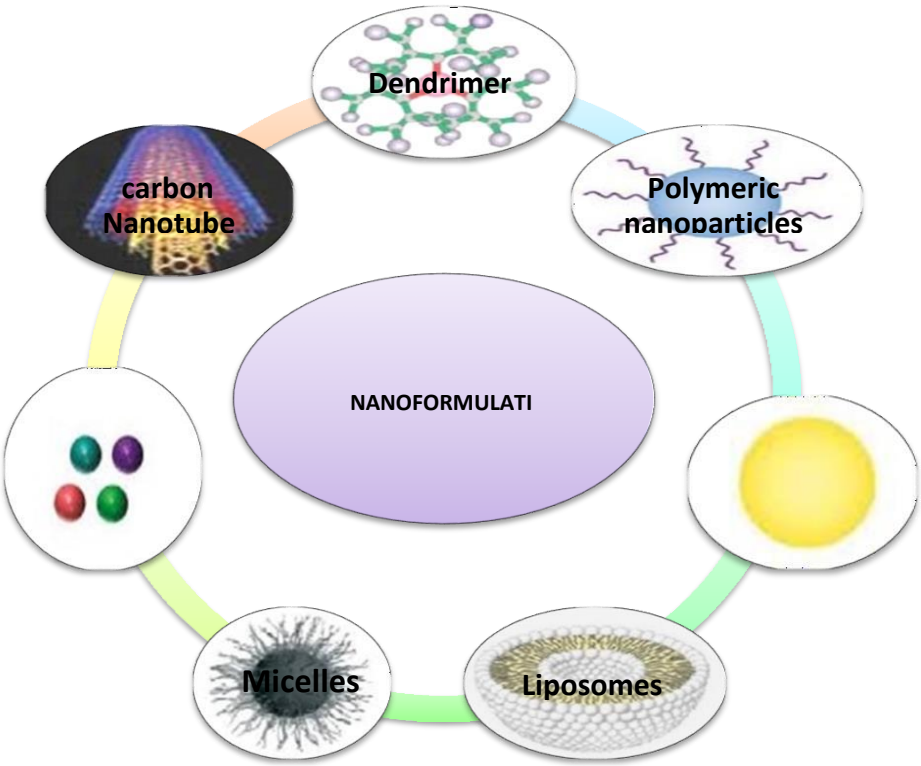
3. NANO FORMULATION EXPLORED IN CANCER IMMUNOTHERAPY

Nano formulation are defined as materials that have at least a dimension between 1 & 100nm, but practically they are usually from 1-200nm. In diagnosis and therapy of cancer there hasbeen tremendous success in this field. It is accepted that nanomaterial with a size 10- 200nm avoids kidney clearance while penetrating tumour tissues. Due to this reason, drugs that are loaded inside the nano formulation have long blood retention time and enhancement of tumour distribution and decreased toxicity that results in high tolerated dose. Nano formulation are easy to modify and the ligands pre-loaded on the surface helps Nano formulations taken up by specific cells. Nano formulation can be used for cancer vaccine design as well as in TME modulation (Mention in Table 4 & Figure 5) [21].

Table 4: Uses of Nano formulation in cancer vaccine and TME [21]

Nano formulation for cancer vaccine design	Nano formulation TME modulation
Co-encapsulation	Immune checkpoints
Adjuvant effect	Soluble mediators
Lymph node drainage	Targeting TAMs
DC uptake	Targeting MDSCs
DC targeting	Targeting Tregs
Antigen presentation	Targeting TAFs
Peptide/DNA/mRNA/whole cell antigen	

Figure 5: Nano formulations used in treatment of cancer [21]



4. ENHANCEMENT OF IMMNOGENICITY

Immunogenic cell death of the tumor improves the identification of APCs, which results in autoimmunity. Thus, in order to get an effective response against tumor it is frequently needed to destroy tumor totally from ordinary medicines [23]. One of the most challenging factors in immunology is to induce the strong and continued adaptive response post- ordinary treatment for the destruction of the tumor cells and metastasis. Chemotherapy induced DNA often initiates STING and cGAS pathway, which results in increase immunogenicity. There are few chemotherapeutic agents that kill the cancerous cell and trigger ICD and results in activation of immunity. The immune responses are usually weak when chemotherapeutic drug is given alone and are counteracted by tumor inhibitory micro-environment [24-25].

Comparatively, a combined treatment of PTT and CpG results in the superior effect of the immune system, rather than giving PTT or immunotherapy alone. This combination of medicine with immunotherapy results in potential therapeutic effect against tumor.

Faisal et. al. report a phase III trial non-small cell lung cancers with less PDL1 illustrated that Pembrolizumab-Chemo drug shows the superior effect whereas alone chemotherapy and immunotherapy does not show such superior effect. This combination provides a model forthose patients who have less expression towards PD-L1.

In other phase III trial, when patient with metastatic triple negative breast cancer received antibody inhibition Atezolizumab + Albumin-bound-Paclitaxel results in enhancement of anti-cancer activity of Atezolizumab. This combination results in greater therapeutic effect in metastatic small lung cancer, metastatic gastroesophageal adenocarcinoma and metastatic melanoma [26].

4.1 Targeting Antigen Presenting Cells

On exposure of tumor-specific antigens, the next step is recognized by the APCs.\ to T cells in lymphatic organ to activate CTLs. DC plays a vital role in activating immune between humoral and cellular immunity. Upon recognizing tumor antigens by DC, it gets displayed on the surface of the cells by MHC. In lymph node, there occurs interaction between MHC and T cells via T-cell receptors. This interaction evokes a progression of T- cell mediated immune response. Nanocarriers not only exclusively convey adjuvant and antigen both to APCs and lymph, but it results in increasing the efficacy of uptake of DC and antigen presenting cell, as nanocarriers are also used as immunogenic or as vaccine to activate DC. For e.g.: polysaccharides, inorganic nanoparticles, liposomes, polymers etc. Wu C et. al. (2019) report that by integrating the Polydopamine-stabilized graphene quantum dots with poly-cationic polymer/CpG oligodeoxynucleotide immunoadjuvant is by dendritic cells activation. On laser irradiation, this complex results in highly capability of photothermal therapy. In return, this activated DCs forms more CD8+ cells which infiltrate into tumor and conquer the tumour growth. Another novel DCs activation was previously developed byin-situ gold nanoparticle in melanoma, where AU3+ ions where decreased to metallic nanoparticle by interaction with redox enzyme and carbohydrates of the cell membrane as well as cytoplasm. Thus, the in-vivo study has proved that the DCs stimulating based immunotherapy can successfully eradicate tumour or inhibits the tumour recurrence [27].

4.2 Targeting T-Cells

The subsequent steps in cancer immunity cycle are summed up as follows:

APC present MHC antigen and immunogenicity sign to T-cell. This T-cell separates into CD8+ CTLs. Hence, the effector CD8+ T-cells relocate to the tumor site, where they applytheir antitumor impact. On the one hand, CD8+ T-cell recognize the antigens present on MHC I molecule and kills them. On the other hand, the cytokines (IFN-γ, TNF-α, IL-2) which are secreted by CD8+ recruit more immunogenic cell towards tumor site. Another important effector T-cell ie. CD4+, maintains the CD8+ activity by producing cytokines. At the point when tumor executing action is close to an end, the CD8+ T cell are immediately consumed, and less proportion of T cell differentiate into memory T-cell to prevent the re-irruption of cancer cell [28-32].

Wilson DS et. al (2017). report that CAR-T cell therapy increases the proportion of CD8+ T cells by activating and increasing T cells in-vitro and infusing them back to patient's body. These T cells can actively target specific tissue and achieve success in malignant cancers. Thus, this T cell manufacturing

process is lengthy, high costly and low response rate of immune. Nanomaterials can be used to activate DCs to shorten them and thus signifies the processof amplification. Chemically, TCR stimulation and co-stimulatory signals bind to the material surface of DCs. For e.g. a plan was presented to stimulate ACT T-cells by ACT- target PEGylated liposomes using fragments against antigens or cytokinin II molecule.

Other study showed that a synthetic DNA nanoparticle method by circulating T-cell with tumour, thus results in time consuming process, and low response rate. The Nanomaterials loads cytokines and controls their release to maintain T cell and promote their proliferation. The cytokine interleukin-2 was encapsulated by biodegradable PLGA, which gets conjugated by avidin palmitate through emulsion technique to promote the presentation of avidin on particle surface. This shell nanoparticle gets attached by anti- CD3, antiCD28, and peptide MHC complex [33].

5. NANO FORMULATIONS FOR CANCER IMMUNOTHERAPY AND ROLE OF POLYMERS

Nanotechnology is a vast branch and is broadly used to improve the efficiency of chemotherapy. Nano formulations of various drugs show advantages in therapeutic windows. Firstly, the increase in size of the nano formulations does not allow quick elimination. A nanoparticle enhances the accumulation of the drug within tumor by passiveand active targeting. Nanoparticles target the cancerous cells by either ligand or receptor and binds to the cell surface that has tumor cells. As conventional medicines targets cancer cells, the nanomedicines not only target cancerous cell but also lymphocytes or APCs in lymphatic tissue and blood. The nanoparticles that carries T cells, concentrate drug in tumors more as compared to nanoparticles alone, which results in more efficiency of the anti-cancer drug to tumor using nanoparticles [34].

Various natural-based nano formulations can be used to treat cancer such as Chitosan, Hyaluronic Acid-based nanoparticle, Alginate based nanoparticles, Dextran-based nanoparticles, Albumin based nanoparticles, Gelatin based nanoparticles. Other natural ingredients are: Polymeric gel, Polymeric micelles, Liposomes, Cell membrane-based drug delivery system, Cyclodextrin Inclusion Complex [35].

In comparison to conventional medicine, natural material-based drug delivery shows beneficial result. It offers high benefit such as biocompatible, biodegradable, non-toxic. There are various natural polymers that have different electronic charge, which is associated with the encapsulation of therapeutic agents. The electronic charge can be adjusted by polyamines with various natural materials.

Mechanical properties focusing on capacity and medication discharge way can likewise be constrained by adjusting the structure of common materials with polyamines and focusing on ligands.

There may be some biological issues, but apart from that there may be few challenges as well. It is not easy to scale up the industrial production to laboratory. This production requires equipment's and that may be costly. The stability of nanoparticles is also one of thebiggest concerns. Sometimes, the result of in-vivo and in-vitro may also result in contraindications. On evaluating the therapeutic efficacy, there is a wide difference between the patient and animal model, and so complete testing and evaluations in needed [36-37].

6. APPLICATION

Application of nanoparticle mention in below figure 6. In all this Surgery is one of the oldest methods for treating cancer. Initially, it was very crucial but as time passed, radiotherapy, chemotherapy, immunotherapy has played a tremendous role in the treatment of cancer. The current progress on surgical is such that the evaluation of disease extent using latest studies on imaging, less invasive surgery, short hospital stay andfast recovery rate. To prevent the tissue damage many surgeons are resort to robotic and image guided surgery. Recently, nanotechnology plays important role in treatment. The main contribution is nano endoscopy, real time tumor imaging, lymphatic mapping and use of nanotechnological based equipment's or instruments. It is expected in future, that combination of radiation therapy and chemotherapy can increase the effect [37-39].

There are numerous studies on animal model that gives a new concept of incorporation in

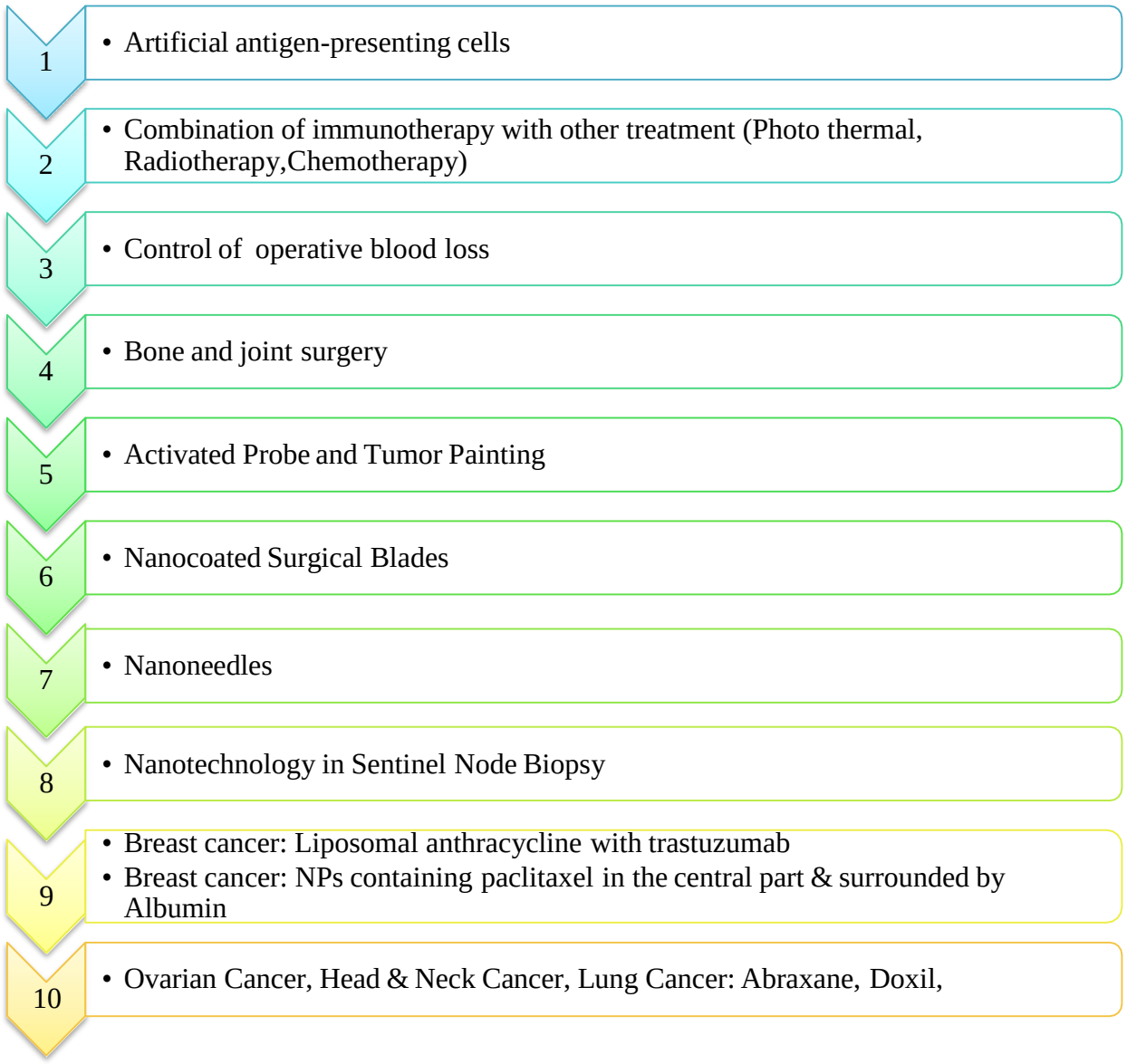
nanotechnology in surgery. Infrared Quantum dots nanoparticles are injected to skin of animals having cancer foe early localization. The same study is extrapolated to other lymphatic regions of body. In colorectal cancer, nanotechnology is used in cancer imaging by guanylyl cyclase C (GCC) in intestinal mucosa [40].

Nanoparticles can also apply in diagnosis and treatment of brain tumor. The only limitation involves is of blood brain barrier (BBB). Water, carbon dioxide, oxygen and fat-soluble substance such as alcohol can easily penetrate BBB. The main treatment involves is invasive operations, physiological approaches, and drug treatments. Researchers use drugs and physiological methods to increase the treatment efficiency of brain tumor. Those limitations mentioned above can be overcome by nanoparticle treatment. The first nanoparticles which were used were a type of Fe_3O_4, known as monocrystalline Fe_3O_4.

Gold, organics, polymers, liposomes, dendrimers and hydrogels can also be used as a nanoparticle for treatment of cancer.

In comparison with theragnostic Nanoparticles, Quantum dots, Fe_2O_3, Au and polymers have higher success in treatment comparatively [41-42].

Figure 6: Applications of Nanotechnology [37-39]



6.1 Polymers and their role in Vaccines for Cancer Immunotherapy

Cancer vaccine refers to either vaccine given to patient to prevent cancer or to a therapeutic vaccine given to eradicate tumor existing. For e.g., Gardasil® and Cervarix® is used to prevent cervical cancer, while Sipuleucel-T is used as a therapeutic vaccine for metastatic prostate cancer. A vaccine consists of tumor antigen and an adjuvant capable of producing immune response. Adjuvants stimulates the maturation of DCs. DCs then presents tumor antigens from vaccine on MHC surface molecules and stimulates anti- cancer T cell response.
Tumor antigens may be classified as tumor associated antigens (TAA) or tumor specific antigens (TSA) or can be expressed as proteins known as cancer-testis antigens (CTA).
TAAs are proteins that are expressed at high level in tumor cell as compared to normal cells.
TSAs are expressed by tumor cells. Non-cancerous cells lack the genetic materials that reduce off-target effects. These antigens arise from somatic mutations and evade immunological tolerance.
CTAs is the group of protein that are expressed in fetal ovaries, but may also be expressed in several types of the cancers. CTAs are also attractive substrates for cancer vaccine design [43].

6.2 Oncolytic Virus Therapy

Oncolytic infection treatment depends on specific disease and replication of hereditarily designed infectious inside malignancy cells, prompting immunogenic disease cell death.
After getting exposure to disease, these oncolytic infections can make malignant cells burst by killing the cancerous cells and delivering malignant antigens. These antigens results in stimulation of the immune and eliminates the remaining cancerous cells and possibly anywhere else in the body [44-46].
Clinical trials are been carried out in combination with other therapies i.e. immune checkpoint inhibitors or chemotherapy.
Results may differ as per the kind of oncolytic infection, what it targets and can also be influenced by the location as well as patients health. Sometimes, the oncolytic cells attacksthe normal cells of the body and results in risk for infection.
Other side effects may include: Fatigue, Flu, pain, nausea, vomiting and fever [47-48].

6.3 Monoclonal Antibodies

Monoclonal antibodies were developed by hybridoma technique in 1975. The characteristic of mAbs are antibody-dependent cellular cytotoxicity, antibody dependent cell phagocytosis. mAbs are used in 3 ways:

1. mAbs mark the cancer cells by which they are easily identified and destroys the immune system.
2. It can inhibit the action of the abnormal protein towards cancers.
3. The antibodies release the mechanism of immune system, which kills the cancerous cells [47].

6.4 Adoptive T cell Therapy

This therapy is one of the promising approaches in cancer immunotherapy which provides anti-tumor properties to eliminate tumor cells. In this, firstly the lymphocytes are stimulated, and then activated by T cells into patients. For adoptive therapy, large number of T cells is utilized that benefit from the combination of antibody to TCR. The most effective therapy involves Adoptive cell therapy using autologous TILs with anti-tumor activity [50-51].

6.5 Tumor-Infiltrating Lymphocytes (TIL) Therapy

The killer T cells are powerful immune cells and have the ability to recognize and eliminate the cancerous cells. For the effectiveness of the T cell, they have to be firstly been activated and so they can effectively kill the cancerous cells and can able to maintain their activity for a longer time.
This therapy firstly eliminates the T cells that have been placed in patient's tumor and thenactivate them, thereafter expands them. Thus, large numbers of T cells are infused in patient and then the cancerous cell gets destroy.

6.6 Engineered T cell Receptor (TCR) Therapy

Not all the patients T cell are being recognized by the tumors, for those patients TCR therapy is been approached. In this approach, the T cell are taken up from the patient, instead of activating and expanding them, it is been equipped with new T cell which targets and kills the cancerous cells

6.7 Chimeric Antigen Receptor (CAR) Therapy

To overcome the limitation of TIL & TCR, which targets and eliminate the cancerous cells, scientists have equipped T cell of patient with synthetic receptor known as CAR i.e. chimeric antigen receptor. The main advantage of CARs is even if the antigens are not present on the surface, they bind with cancer cells. As CAR T cell recognize antigens that are expressed on the surface of the cells, so antigen targets is lesser than with TCRs.

6.8 Natural killer (NK) cell Therapy

NK cells have the ability to detect as well as destroy the transformed cell by release of cytotoxic granules. This therapy shows better outcomes in cell lung cancer, gastric, colorectal carcinoma and melanoma associated with NK cell infiltration. NK cells has one application being investigated in the centre includes furnishing NK cells with disease focusing on CARs [52-53].
Different advantages and Limitation of polymers are mention in table 5.

Table 5: Advantages & Drawbacks [54-55]

CONTENT	ADVANTAGES	LIMITATIONS
Solid-Liquid Nanoparticles	Good solubility, bioavailability, control of drug release	Low drug loading capacity, contains colloids and has complex physical state
Liposomes	Wide range, increase drug load& minimize undesired activity of drug, low toxicity	Rapid degradation, requires special storage condition, limited permeation to skin
Polymeric	Versatile	Degradable
Magnetic Nanoparticles	Influenced by external magnetic field	Potential material toxicity
Quantum Dots	Fluorescent property	Potential material toxicity
Carbon Nanotubes	Able to penetrate and localize at cellular level for the delivery of chemotherapeutic agent	Potential material toxicity
Polymeric Nanoparticles	Controlled and sustained drug release, reproducible data are produced, highly stable	Scale-up difficulty, toxicological assessment is insufficient
Polymeric Micelles	Highly soluble for lipophilic drugs, controlled drug release	Only used for lipophilic drug, Low drug loading capacity

Dendrimers	Highly soluble for lipophilic drugs, multiple functional groupfor target drug delivery, solubility enhancers	Not good candidate for hydrophilic drug, cellular toxicity, costly
Lipid based Nanocarriers	Large scale production, less toxic, low cost	Low drug loading for SLNs

7. REGULATORY CHALLENGES FOR POLYMERS USED IN CANCER IMMUNOTHERAPY

Throughout the most recent years, nanomedicines have been effectively presented in the clinical practice and the persistent advancement in drug research is making more advanced ones which are entering in the facility preliminaries. In European Union, nanomedicines market is created by nanoparticle, liposomes, nanocrystals, nano emulsions, polymeric- protein forms, and nanocomplexes [56].

Nanomedicines were presented under the conventional structure of the benefit/risk ratio. Another challenge is evaluation of the follow-on nanomedicines at the time of patent expiration of the reference medicine [57].

Specific challenges are getting clear in two distinct areas. To start with, corresponding to the evaluation of those follow-on nanomedicines items presently starting to emerge as first-generation product come off patent. Such products are portrayed as 'comparative nanomedicine' (nano similar). These are new nanomedicines that are professed to be 'similar' to reference nanomedicine that has been permitted a marketing authorization license. To demonstrate similarity, there is a need of comparability study in relation to quality, safety, and efficacy of nano similar product and chosen reference nanomedicine. As nanomedicine contrast fundamentally in their complexity and nature, there might be necessity of product class specific approach. Before granting the permission, the drug development must be comparable with reference patented drug in terms of quality, safety, and efficacy. Given the degree of multifaceted nature of numerous nanomedicines products,uncommon logical contemplations might be expected to guarantee the equivalence of performance [58].

To introduce the generic in market, several parameters are to be involved. A complete analysis is needed for biological and non-biological, nanomedicines that goes far off concentration of plasma concentration. A comparison of bioequivalence, quality, safety, and efficacy with respect to reference medicine, leads to therapeutic equivalence and correspondence interchangeability is also required [59]. Different drugs approved by FDA in immunotherapy was mention in table 6.

The ongoing advances in nanoscience are bringing novel opportunities to ace issue at nanoscale sizes and this is prompting the formation of considerably more unpredictable, crossover structures by both new top-down fabrication and base up assembling strategies.

This is preparing for an influx of new pharmaceutical, imaging agents and combinational products that require the regulatory approval prior to approval of market authorization. Individual nanomedicines present challenge during development and regulatory evaluations. Robust methodology is to ensure long benefit-risk ratio and to ensure product characterization and manufacturing control specific tools are required.

Table 6: FDA Approved Immunotherapeutic Drugs [44, 60-62]

Sr. No.	Drug	Target	Patent No.	FDA approval	Antibody Class
1	Nivolumab	PD-1	US7595048	2014	IgG4
2	Ipilimumab	CTLA4	US10196445	2011	IgG1

3	Pembrolizumab	PD-1	US8952136	2014	IgG4
4	Avelumab	PD-L1	US2014341917	2017	IgG1
5	Atezolizumab	PD-L1	US8217149	2016	IgG1
6	Durvaluamb	PD-L1	US8779108	2017	IgG1
7	Spartalizumab	PD-1	US9683048B2	2009	IgG4K
8	Cemiplimab	PD-1	US20150203579	2018	IgG4
9	Camrelizumab	PD-1	US20160376367A1	2019	IgG4
10	Tislelizumab	PD-1	US8735553B1	2017	IgG4
11	Dostarlimab	PD-1	US9815897B2	-	IgG4
12	MEDI-0680	PD-1	US8609089B2	-	IgG4
13	SSI-361	PD-1	US20180346569A1	-	IgG4
14	AMP-224	PD-1	US20130017199	2014	PD-L2 IgG2a fusion protein
15	CX-072	PD-L1	US20160311903A1	-	Protease activable prodrug
16	BMS-936559	PD-L1	US7943743	2015	IgG4
17	KN035	PD-L1	US20180327494A1	-	Fusion proteinssof humanized anti-PD-L1 single domain antibody and human IgG1

Specific security issues identifying with novel Nanomaterials have been generally audited. Definition of nanomedicine safety is unmistaken from the more extensive issues identifying with nanomaterial toxicology as the product is intended for use at particular dose, with frequency of administration and in context of patient population. Environmentalimpact, safety and efficacy must be established. It is important to determine pharmacokinetic and Pharmacodynamic profile of nanomedicine. In determining safety and efficacy, the nature and stability of nanomedicine product is essential. Non-clinical studies of nanomedicines with respect to acute and long-term safety can be challenging. The proportion determining for the selection of dose administration is used to assess long term safety in clinical studies and during development [63].

EMA have released papers regarding nanomedicines. These papers are applied to nanomedicines and nano similar to provide guidance in marketing authorization application. They mainly outline issues

related to complexity and provides basic information on development of pharmaceutical, clinical and non-clinical studies.

In order to assess need for regulatory requirements for evaluation of nanomedicine, in 2006, the European Medicines Agency (EMA) created- Nanomedicine Expert Group. It was the further expanded by establishment of International Regulators Subgroup, an initiative launched jointly by medical regulatory agency of EU, USA, Japan and Canada. Experts were gathered from various countries and attended the workshop which was held in London in Sept 2010. More than 200 participants have attended. The main aim of the workshop was to share global experience, review of the existing and emerging nanomedicines, and discuss particular issues related to nanomedicines [64-65].

8. Future Trends

Recent studies have shown a new modification in nanomaterial-based modulation of immune cells. Nanomaterials are used mainly because they overcome poor solubility, low selectivity, as well as high toxicity of drugs [66]. Various nanomaterial such as lipid-based nanoparticles, polymers nano formulations and inorganic nanoparticles are formed as carriers. There may be many issues, but safety is the first concern. It is important to study toxicity data that should be performed for both long and short terms. The modulation of immune cells evokes toxicity due to interaction between drug loaded with nanomaterial and immune cells. Future studies should also include the direct targeting of nanomaterial with immune cells. Most of the studies have used tumor inhibition as major end point of cell-targeted Nanomaterials. There is usually the lack of known ligand molecules that are used to differentiate immune cells of normal tissues and tumor tissues. Further study is needed to identify specific ligand molecules or biomarkers and other immune cells [67].

Another issue is related to time for evaluating efficacy of immunotherapy in models. Unlike conventional therapy, immunotherapy requires greater time for study of clinical data due to delay activity of immune system. After several months from start of treatment,a benefit to immunotherapy can be observed. Tumor model should be selected carefully. As each tumor have different type of characteristic cell profile. It is shown in clinical data that the combined application of CTLA-4 & PD-1 that affects two different immune checkpoints, could improve the overall survival of melanoma patients. Many studies have utilized combinational strategies involved in checkpoint inhibitors and therapeutic drug- loaded nanocarrier. These combinational treatments have shown a synergistic outcome of immunotherapy on models of metastasis. For the enhanced clinical outcome, the nanomaterial based immune cells might be combined with immune checkpoint therapy [68-69].

9. Conclusion

This review focuses mainly on the polymer used in cancer immunotherapy. It also focuses on the recent trends and future perspectives of the polymers used. This review highlights different types of polymers explored for making nanoparticles intended for cancer immunotherapy. This review highlights vaccines used for cancer immunotherapy, preparedfrom the polymers. In recent advances, it is shown than combination therapy shows greatereffect as compared to alone therapy. Nanoparticles are mainly used in immunotherapy as they are highly stable, less toxic and provide good biocompatibility and bioavailability. As compared to conventional drug, nanoparticles have better pharmacokinetic and Pharmacodynamic action as well as biocompatibility and stability. These nanoparticles are applied widely to chemotherapy, radiotherapy, gene therapy. Nano vaccines and artificial APCs have results in increased efficacy as compared to conventional treatment.

References

1. Lee ES, Shin JM, Son S, Ko H, Um W, Song SH, (2019). Recent Advances in Polymeric Nanomedicines for Cancer Immunotherapy, pp.1–44.
2. Le Q, Yang G, Wu Y, Won H (2019). Nanomaterials for modulating innate immune cells incancer immunotherapy. Asian J Pharm Sci14(1), pp.16–29.
3. Jiayi Pan, Kobra R, Nina F Effect R (2019). Polymeric Co-Delivery Systems in CancerTreatment : An Overview on Component Drugs' Dosage, pp.1-32.
4. Guo X, Wang L, Wei X, Zhou S (2016). Polymer-Based Drug Delivery Systems for Cancer

Treatment Polymer-Based Drug Delivery Systems for Cancer Treatment. Pp.1-27.
5. Jinyu H, Dandan Z, Dan L,Wang X,Jin Z, Kai Z (2019) Polymer-Based Nanomaterials and Applications for Vaccines and Drugs. Pp.1–14.
6. Mohammed MA, Syeda JTM, Wasan KM, Wasan EK (2017). An Overview of Chitosan Nanoparticles and Its Application in Non-Parenteral Drug Delivery. Pharmaceutics, 9(4).
7. Cornejo-Ramírez YI, Martínez-Cruz O, Toro-Sánchez CL Del, Wong-Corral FJ, Borboa-Flores J, Cinco-Moroyoqui FJ (2018). The structural characteristics of starches and their functional properties. CYTA - J Food16(1); pp. 1003-1017.
8. Lee KY, Mooney DJ (2011). Alginate: Properties and biomedical applications. Prog Polym Sci.37(1); pp. 106-126.
9. Gupta PK, Raghunath SS, Prasanna DV (2019).An Update on Overview of Cellulose, Its Structure and Applications. Cellulose.
10. Alphandéry E, Grand-dewyse P, Lefèvre R, Durand-dubief M, Alphande E, Lefe R (2015).Expert Review of Anticancer Therapy scientific , regulatory and financial aspects Cancer therapy using nanoformulated substances : scientific , regulatory and financial aspects; pp.140
11. Célino A, Fréour S, Jacquemin F, Casari P (2013). The hygroscopic behavior of plantfibers : a review.1-13.
12. Reusch RN, Hiske TW, Sadoff HL (1986). Poly-beta-hydroxybutyrate membrane structure and its relationship to genetic transformability in Escherichia coli. J Bacteriol 168(2): pp. 553.
13. Makadia HK, Siegel SJ (2011). Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier. Polymers (Basel) 3(3); pp.1377.
14. Roccia M, França K, Castillo D, (2018). Artificial Hair: By the Dawn to Automatic Biofibre® Hair Implant. Open Access Maced J Med Sci. 6(1); pp. 156.
15. Luz CM, Boyles MSP, Falagan-Lotsch P (2017). Poly-lactic acid nanoparticles (PLA-NP) promote physiological modifications in lung epithelial cells and are internalized by clathrin-coated pits and lipid rafts. J Nanobiotechnology2017; pp. 15(1).
16. Akindoyo JO, Beg MDH, Ghazali S, Islam MR, Jeyaratnam N, Yuvaraj AR (2016). Polyurethane types, synthesis and applications-a review. RSC Adv 6(115); 114453-114482.
17. Shah E V, Patel CM, Roy DR (2018). Structure, electronic, optical and thermodynamic behavior on the polymerization of PMMA: A DFT investigation. Comput Biol Chem 72: pp.192-198.
18. Yang J, Wang C, Shi S, Dong C (2020). Nanotechnologies for enhancing cancerimmunotherapy 13(10); pp.2595–616.
19. Yang J (2020). Regulation of cancer-immunity cycle and tumor microenvironment by nanobiomaterials to enhance tumor immunotherapy; pp.1–24.
20. Tyzzer E (2018). Personalized vaccines for cancer immunotherapy; pp. 1355–60.
21. Song W, Musetti SN, Huang L (2017). Nanomaterials for Cancer Immunotherapy.Biomaterials; pp. 1-49.
22. Martin JD (2015). Opportunities and challenges. Nat Rev Clin Oncol
23. Ase C (2018). First Report of Dramatic Tumor Responses with Ramucirumab andPaclitaxel After Progression on Pembrolizumab in Two Cases of Metastatic Gastroesophageal Adenocarcinoma; pp. 1–4.
24. Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG (2018). Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer; pp.1-15
25. Shafique M, Tanvetyanon T. ce pt us cr t (2019). Expert Opin Biol Ther; 1(1).
26. Kasi PM (2019). Dramatic response to modified docetaxel , cisplatin , and fluorouracil chemotherapy after immunotherapy in a patient with refractory metastatic anal cancer; pp. 729–34.
27. Wu C, Guan X, Xu J, Zhang Y, Liu Q, Tian Y (2019). Biomaterials Highly e ffi cient cascading synergy of cancer photo-immunotherapy enabled by engineered graphene quantum dots / photosensitizer / CpG oligonucleotides hybrid nanotheranostics. Biomaterials; pp.106–19.
28. Stephan SB, Hutchinson F, Moffett HF, Hutchinson F, Mcknight L (2017). HHS PublicAccess.
29. Zheng Y, Stephan MT, Gai SA, Abraham W, Shearer A, Irvine DJ. In vivo targetingof adoptively transferred T-cells with antibody- and cytokine-conjugated liposomes.
30. J Control Release [Internet]. 2013;172(2):426–35.
31. Jackson HJ, Rafiq S, Brentjens RJ (2016). Driving CAR T - cells forward. Nat Publication 13(6);

pp.370–83.
32. Kuai R, Ochyl LJ, Bahjat KS, Schwendeman A, Moon JJ (2016). cancer immunotherapy 1; pp. 1-10.
33. Li AW, Sobral MC, Badrinath S, Choi Y, Graveline A, Stafford AG (2018) A facileapproach to enhance antigen response for personalized cancer vaccination.
34. Wilson DS, Hirosue S, Raczy MM, Bonilla-ramirez L, Jeanbart L, Wang R(2017). cellular immunity. Nat Mater
35. Jin J, Zhao Q (2020). Engineering nanoparticles to reprogram radiotherapy and immunotherapy: recent advances and future challenges. J Nanobiotechnology; pp.1–17.
36. Journal AI, Pethe AM, Yadav KS, Group F (2019). Polymers , responsiveness and cancertherapy. Artif Cells, Nanomedicine, Biotechnol 47(1); pp. 395–405.
37. Galateanu B, Tsatsakis A (2017). Poly (HydroxyButyrate-co- HydroxyValerate) (PHBHV) Nanocarriers for Silymarin Release as Adjuvant Therapy in Colo-rectalCancer. Pp.1-12.
38. Avramovi N, Savi A. Polymeric Nanocarriers of Drug Delivery Systems in CancerTherapy. :1–17.
39. Maleki AA, Fotouhi A (2019). Nanoparticles and cancer therapy: Perspectives forapplication of nanoparticles in the treatment of cancers.
40. Verma M (2008), Ph D. Application Of Nanotechnology in Cancer 7(2); pp.1-6.
41. Biswal BM, Yusoff Z (2017). Application of Nanotechnology in Cancer Treatment 1-43.
42. Misra R, Acharya S, Sahoo SK (2010). Cancer nanotechnology: application of nanotechnology in cancer therapy. Drug Discov Today15(19–20): pp.842–850.
43. Gmeiner WH, Ghosh S (2015). HHS Public Access. Nanotechnology for cancer treatment3(2): pp. 111–22.
44. Taefehshokr N, Baradaran B, Baghbanzadeh A, Taefehshokr S (2019). Jo ur na l P of. Immunobiology.
45. Pandey S (2010). Hybridoma technology for production of monoclonal antibodies.1(2): pp. 1-7.
46. Kimiz I, Sultan G, Iz G, Avci CB (2018). Monoclonal antibodies in cancer immunotherapy.Mol Biol Rep 45(6); pp. 2935–40.
47. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic Cell Death in CancerTherapy.
48. Pol J, Kroemer G, Galluzzi L (2016). First oncolytic virus approved for melanoma immunotherapy First oncolytic virus approved for melanoma immunotherapy.
49. Wang P, Li X, Wang J, Gao D, Li Y, Li H, et al. agent. Nat Commun [Internet]. :1–15.
50. Sathyanarayanan V, Neelapu SS (2015). ScienceDirect Cancer immunotherapy: Strategies for personalization and combinatorial approaches 5.9; p. 1-11.
51. Chambers CA, Allison JP. Co-stimulation in T cell responses. :396–404.
52. Hinrichs CS, Rosenberg SA (2014). Exploiting the curative potential of adoptive T-celltherapy for cancer 257; pp. 56–71.
53. Dexter A, Jr P, August B (2018). CAR T Cells in Solid Tumors : Blueprints for Buildingeffective Therapies; pp. 1–20.
54. Kahraman E (2017). Potential enhancement and targeting strategies of polymeric and lipid-based nanocarriers in dermal drug delivery; pp. 967–85.
55. Lee JJ, Che CA (2017). A review on current nanomaterials and their drug conjugate fortargeted breast cancer treatment; pp. 2373–84.
56. Sikder S, Gote V, Alshamrani M, Sicotte J, Pal D. ce pt us cr t (2019). Expert Opin DrugDeliv [Internet]. Pp. 1-15
57. Astier A, Pai AB, Bissig M, Crommelin DJA, Hecq J, Knoeff J (2017). How to selecta nanosimilar; pp.1–13.
58. Hee Y, Hyo C, Han K (2018). Nanomedicines : current status and future perspectives in aspect of drug delivery and pharmacokinetics. J Pharm Investig 48(1); pp.43–60.
59. Sakai-kato K, Duncan R, Papaluca M (2013). Next-generation nanomedicines and nanosimilars : EU regulators' initiatives relating to the development and evaluationof nanomedicines S pecial R eport 8; pp.849–56.
60. Lee JJ, Che CA (2017). A review on current nanomaterials and their drug conjugate fortargeted breast cancer treatment. 2017; 2373–84. doi: https://dx.doi.org/10.2147%2FIJN.S127329
61. Products THE, This IN, Have L, Approved B. APPROVED DRUG PRODUCTS.2020;

62. Guo L, Wei R, Lin Y, Kwok HF (2020). Clinical and Recent Patents Applications of PD-1 /PD-L1 Targeting Immunotherapy in Cancer Treatment — Current Progress, Strategy, and Future Perspective; pp. 1–19.
63. Soares S, Sousa J, Pais A, Vitorino C (2018). Nanomedicine : Principles, Properties, andRegulatory Issues; pp. 1–15.
64. Bawa R, Borchard G (2014). Nanomedicines : Addressing the scientific and regulatory gap Nanomedicines : addressing the scientific.
65. Hafner A, Lovrić J (2014). Nanotherapeutics in the EU : an overview on current state andfuture directions; pp. 1005–23.
66. Wicki A, Witzigmann D, Balasubramanian V, Huwyler J (2015). Nanomedicine in cancertherapy : Challenges, opportunities, and clinical applications. J Control Release 200; pp. 138–57.
67. Mundry CS, Eberle KC, Singh PK, Hollingsworth MA (2020). BBA - Reviews on CancerLocal and systemic immunosuppression in pancreatic cancer : Targeting the stalwarts in tumor's arsenal. BBA -Rev Cancer 1874(1); pp. 188-387.
68. Pucci C (2019). Innovative approaches for cancer treatment : current perspectives and new challenges; pp. 1–26.
69. Song W, Das M, Xu Y, Si X, Zhang Y, Tang Z (2019). Materials Today Nano Leveraging biomaterials for cancer immunotherapy : targeting pattern recognitionreceptors 5; pp. 1–15.