

CURRENT UPDATES ON IMMUNOTHERAPY AND THE SCOPE OF NANOMEDICINE IN CANCER THERAPY

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ABSTRACT

A brief history Cancer immunotherapy has brought significant improvements in survival and quality of life. It has established itself as a pillar of cancer care. We highlight how the history of cancer immunotherapy paved the way for discoveries. We also highlight the current pitfalls and limitations of checkpoint immunotherapy. Immune infiltrates in the tumor microenvironment have been shown to play a key role in tumor development. Extensive research and discussion against tumor-infiltrating immune cells would throw some light on the mechanisms of cancer-immune evasion. We outline the recent progress in cancer immunotherapy, Monoclonal Antibody therapy, Dendritic Cell Cancer Therapy, checkpoint inhibition, CAR T cell therapy, and Oncolytic virus therapy, and in the field of nanomedicine is regarded as an innovational field with potential for improving cancer treatment. The application of nanotechnology in medicine is still in its infancy, but it is expected to have a revolutionary impact on healthcare. Nanomedicine has the potential to offer many benefits, including improved efficacy, bioavailability, dose-response, targeting ability, customization, and safety compared to traditional drugs. The most rousing concept in nanomedicine research may be multifunctional nanoparticle design and development. (NP) complexes that can at the same time deliver diagnostic and therapeutic agents to target sites. These properties are unparalleled and represent a huge advance in improving patient diagnosis, treatment and monitoring.

KEYWORDS- Cellular therapy, immunotherapy, treatment, nanomedicine, CART T therapy, cancer vaccines and Drugs design.

1. INTRODUCTION

Cancer is classified as the leading cause of death worldwide in the 21st century. According to the World Health Organization (WHO), cancer was the first or second leading cause of death before age 2015 marked 70 years in most countries, while new cancer cases and cancer deaths. By 2030, it is expected to reach 21.4 and 13.2 million per year. In general, the incidence and mortality from cancer are increasing rapidly worldwide. The reasons for the increase in cancer cases are complex but mainly reflect aging, population growth and changes in important cancer risk factors, several of which are which is related to socioeconomic development.

Cancer is a group of diseases that involve the abnormal growth of cells that can invade or spread to other parts of the body. Thus, for the treatment of cancer immunotherapy has become an entrenched pillar by refining the prediction of many patients with a wide variety of hematological and solid malignancies. Cancer immunotherapy has enlarged and is directed toward generating fruitful therapeutic procedures to magnify the precision and power of the immune system to battle against tumors. Contemporary efforts in cancer immunotherapy descend into three main proceed therapies. One is by block off of immune checkpoints, another is by adoptive cellular therapy, last is through vaccination. The aim of immunotherapy is to stabilize the immune system to remove the cancer cells and the field of nanomedicine is generating a new scale drug delivery strategy embracing trend the of functionalization that enhances site-specific delivery and tailored release in cancer. In this review article, we will provide a complete overview of nanomedicine- liposomes and drug delivery mechanism, advanced therapies – immunotherapy, Monoclonal Antibodies therapy, Dendritic Cell Cancer Therapy, checkpoint inhibition, CAR T cell therapy, Oncolytic virus therapy

2. IMMUNOTHERAPY

Immunotherapy works by helping the body's immune system work better against cancer. Immunotherapy is a form of cancer treatment that strengthens the immune system and helps the body find and destroy cancer cells. It is a biological therapy that can treat many types of cancer. The immune system detects and destroys abnormal cells and is believed to prevent or slow the growth of many cancers. However, cancer cells have ways to evade destruction by the immune system. Immunotherapy helps the immune system to better act against cancer by blocking immune checkpoints, boosting T cells, or using monoclonal antibodies. Immunotherapy can be administered in several ways, including intravenous (IV), oral, topical, and intravesically. Cells involved in the immune system responses are used as our t cells, B cells, cytokines, interferon and NK cells, etc [2].

Immunotherapy can be classified into three forms on basis mode of action:

Active Immunotherapy: Active immunotherapy has been effective against agents that cause acute infections. Active immunotherapy targets the body's cells and elicits an immune response. Active immunotherapy is used for the treatment of neurodegenerative disorders person's prion disease multiple sclerosis, Alzheimer's disease, etc [1]. The categories of active immunotherapy are:

- **Non-specific activity active immunotherapy** It generates immune response using cytokines and other cell signaling molecules Examples: cytokines, and BCG vaccines [4].
- **Specific active immunotherapy:** It uses specific antigens as its therapy allowing the host to create antigen-specific response development against antibodies by helping in the recognition of cytotoxic t lymphocytes or malignant tumor cells in the case of Cancer Therapy [2].

Effective immunotherapy: Is used for chronic infectious disease or in Cancer for appropriate target antigens the optimization of the interaction between antigenic peptides antigen-presenting cells and t cells that block negative regulator mechanism that suppresses the immunotherapeutic effect [1].

Passive immunotherapy: It was developed in (1888, Emil Roux and Alexandre Yerson) isolated the toxin from diphtheria bacteria they injected small doses of diphtheria toxin into animals to gain serum containing antibodies (antitoxin) that provide passive to treat diphtheria. It is also called serum therapy; it uses monoclonal activities or receptor FC fusion proteins and has shown clinical success. Immunotherapy is used in the treatment of Bladder cancer, Brain cancer, Breast cancer, Leukemia, liver cancer, lung cancer, lymphoma, melanoma, ovarian cancer, stomach cancer, etc [1].

Immunotherapy can be classified into two major categories on basis of site of action: Non **target immunotherapy** and **Targeted immunotherapy**.

3.TARGETED THERAPIES:

Targeted therapy is a cancer treatment method. By the use of drugs to target specific genes and proteins that help cancer cells survive and grow. it can affect the tissue environment and cells involved in cancer growth such as blood vessel cells. Targeted therapy can treat many different cancers. It can also be used with other cancer treatments, such as chemotherapy. Currently, targeted therapies are not available for all cancers, but this is a rapidly growing area of research and many new targeted therapies are being investigated in clinical trials.

A. MONOCLONAL ANTIBODIES THERAPY

The development of monoclonal antibodies by Köhler and Milstein captured the imagination of the medical community in 1975. Monoclonal Antibodies are antibodies that are made up of identical immune cells that are clones of their parent cell. Monoclonal antibodies have monovalent affinity, in that they bind to the same epitope [3].

Monoclonal antibodies are used in diagnosing and treating various human disorders, including cancer and infectious diseases, by modulating immune responses. Recent advances include targeting cell-surface structures, genetic engineering, and using toxins or radionuclides to enhance their effectiveness. Recent advances in monoclonal

antibodies (mAbs) have led to the approval of bevacizumab and cetuximab, which have shown significant benefits in oncology, Further drugs approved by FDA are mentioned in Table-1 [1]. Combined with standard chemotherapy, these antibodies prolong survival in metastatic cancers, produce clinically meaningful anti-tumor responses, and reduce relapses in breast cancer patients. However, progress in radioimmunoconjugates remains hindered by administration complexity, toxicity concerns, and insufficient tumor targeting [3].

Table 1: Monoclonal Antibodies Approved by The Us Food and Drug Administration [1]

| Sno. | PRODUCT | TYPE | TARGET ACTION | OF | CONDITION | YEAR |
|------|----------------------------------|------------------------------|--|----|---------------------------------------|------|
| 1 | Muronomab-CD3 (Orthoclone OKT3) | Mouse | CD3 antigen on T cells | | Transplant allograft rejection | 1986 |
| 2 | Abciximac (ReoPro) | Chimeric | Glycoproteins IIb and IIIa on activated lymphocytes | | Cardiovascular disease | 1994 |
| 3 | Rituximab (Rituxan) | Chimeric | CD20 on lymphocytes | B | Non-Hodgkin lymphoma | 1997 |
| 4 | Daclizumab (Zenapax) | Humanized | CD25 (IL-2R α , Tac) on activated lymphocytes | | Transplant allograft rejection | 1997 |
| 5 | Infliximab (Remicade) | Chimeric | TNF-alpha | | Rheumatoid arthritis, Crohn's disease | 1998 |
| 6 | Palivizumab (Synagis) | Humanized | F protein on respiratory syncytial virus | | Respiratory syncytial virus | 1998 |
| 7 | Trastuzumab (Herceptin) | Humanized | HER2 oncoprotein | | Metastatic breast cancer | 1998 |
| 8 | Gemtuzumab ozogamicin (Mylotarg) | Humanized toxin-linked | CD33 on leukemic blasts | | Acute myelogenous leukaemia | 2000 |
| 9 | Alezmtumab (Campath 1H) | Humanized | CD52 on B, T, and NK cells and monocytes | | Chronic lymphocytic leukemia | 2001 |
| 10 | Ibritumomab tiuxetan (Zevalin) | Chimeric radionuclide-linked | CD20 on lymphocytes | B | Non-Hodgkin lymphoma | 2002 |

B. SMALL MOLECULE DRUG

These are Small-molecule drugs. Medicines called small molecule drugs can block a process that helps cancer cells multiply and spread. Some drugs mentioned are given in Table 2 given below.

TABLE 2. Approved some of the selective small molecule kinase inhibitors.

| Sno. | CLASS | DRUG NAME | FIRST APPROVED |
|-------------|--------------|------------------------------|-----------------------|
| 1 | ABL | Asciminib (scemblix) | 2021 |
| 2 | KIT | Avapritnib (ayvakit) | 2020 |
| 3 | HER | Tucatinib (tukysa) | 2020 |
| 4 | ALK | Lorlatinib (lorviqua) | 2018 |

4. CELLULAR THERAPIES

A. Dendritic Cell Therapy

Dendritic cells (DCs) are considered professional antigen-presenting cells (APCs), which include different subsets that can reside in organs or travel between lymphoid and other organs. In the normal steady state, DCs simultaneously process and present major histocompatibility complex (MHC) class I and II antigens. However, they are still activated after exposure to antigens. Recently, several approaches have been used to improve the efficiency of antigen presentation to elicit robust immune responses against tumor cells [19]. In DC-based cancer immunotherapy, DCs are obtained from the patient and modulated *ex vivo* to attract the immune system towards tumor elimination. Several approaches have been used to assess the long-term antitumor immune responses of DCs. On the other hand, the combination of DC vaccines with other cancer drugs such as chemotherapy and monoclonal antibodies can provide effective anticancer treatment [19].

B. CHECKPOINT INHIBITION

Checkpoint inhibitors are a type of immunotherapy. They block proteins that prevent the immune system from attacking cancer cells. Cancer drugs are not always suitable for certain types of treatment. Checkpoint inhibitors are also described as a type of monoclonal antibody or targeted therapy. Our immune system protects us from disease and kills bacteria and viruses. One of the main types of immune cells that do this is called T cells [9]. T cells have proteins that start the immune response and other proteins that turn it off. These are termed as checkpoint proteins. Some checkpoint proteins help T cells to activate, for example, when an infection occurs. But if T cells are active for too long a period, they destroy healthy tissue and cells. So, the other checkpoints help the T cells turn off. Some cancer cells produce large amounts of proteins. These can turn off T cells when they should actually be attacking cancer cells. In this way, cancer cells press the stop button of the immune system. And T cells can no longer recognize and kill cancer cells. Drugs used to block checkpoint proteins are termed checkpoint inhibitors. Some drugs are mentioned below in Table 3. They prevent proteins in cancer cells from hitting the stop button. This kicks the immune system back and the T cells can find and attack the cancer cells [9].

Table 3: Drugs for checkpoint inhibition

| Sno. | DRUGS | BLOCKS | CHECKPOINT INHIBITOR | TREATMENT |
|------|---|---|--|--|
| 1 | PD-1 (programmed cell death protein 1). | Checkpoint inhibitors that block PD-1 include | nivolumab (Opdivo) pembrolizumab (Keytruda) | melanoma skin cancer, Hodgkin lymphoma, non-small cell lung cancer. cancers of the urinary tract. |
| 2 | CTLA-4 (cytotoxic T lymphocyte-associated protein 4) | checkpoint inhibitor drug that blocks CTLA-4 | Ipilimumab (Yervoy) | advanced melanoma and advanced renal cell cancer |
| 3 | PD-L1 (Programmed cell death ligand 1) | Checkpoint inhibitors that block PD-L1 | atezolizumab avelumab Durvalumab | lung cancer, some liver cancers, some breast cancers skin cancer called merkel cell carcinoma (MCC) non-small cell lung cancer (NSCLC) |

C.CAR (Chimeric Antigen Receptor) T CELL THERAPY:

Chimeric antigen receptor (CAR) T cell therapy treats certain cancers by making your T lymphocytes, or T cells, more effective cancer-fighting machines. Although researchers are still collecting long-term data, CAR T-cell therapy has proven to be a very effective way to treat certain blood cancers. Your T cells are the white blood cells of your immune system. Your immune system checks your body for invaders, including cancer (and also infected or other abnormal cells), by looking for proteins called antigens. Antigens are located on the surface of invading cells. Your T cells have their proteins called receptors. When your T-cell defense team detects invading antigens, they use their receptors to capture and block the invaders. In addition, your T cells can kill invading cells. But the intruder genes have their form of defense. They can camouflage themselves to hide from your T cells. CAR T cell therapy ensures that your T cells get through the masking or shielding of the invading antigen [21].

It is used in treatment of B cell acute lymphoblastic leukemia it affects white blood cells and immature b lymphocytes growing in bone marrow treated by chemotherapy and bone marrow transplant, Mantle cell lymphoma, Multiple myeloma etc [23].

5. ONCOLYTIC VIRUS THERAPY

This type of therapy uses a non-pathogenic genetically modified virus that helps the immune system destroy cancer cells without harming healthy cells. The virus is injected directly into the tumor, where it can invade cancer cells and

multiply uncontrollably until the cancer cell explodes and dies. when the cancer cell explodes during apoptosis, cancer cells release antigens that trigger the immune system to mount a targeted response against all cancer cells that share the same antigens.

Example of an oncology vaccine therapy approved for the treatment of advanced melanoma skin cancer is Talimogene laherparepvec (T-VEC). It comes from a genetically engineered herpes virus and is injected directly into melanoma cells, where it continuously replicates, causing the tumor cells to burst and die [30].

6. CANCER VACCINES

Cancer vaccines are a type of immunotherapy that can help recognize and eliminate cancerous cell.

A. Protein or peptide vaccines

These vaccines are made from special proteins found in cancer cells. Or made bits of protein (peptides). Their purpose is to stimulate your immune system to attack the cancer. Scientists have engineered the genetic codes for many proteins in cancer cells so they can make them in large quantities in the laboratory.

B. DNA and RNA vaccines

These vaccines are made from pieces of DNA or RNA that are usually found in cancer cells. They can be injected into the body to make the cells of the immune system better respond to and destroy cancer cells.

C. Whole cell vaccines

A whole cell vaccine uses the entire cancer cell to make the vaccine, not just a specific cell antigen. Cancer cells are altered in a laboratory to make them easier for the immune system to find, vaccine is made from your own cancer cells, from another person's cancer cells, or from cancer cells grown in a laboratory.

D. Dendritic cell vaccines

Dendritic cells help the immune system recognize and attack abnormal cells, such as cancer cells. To make the vaccine, researchers grow dendritic cells in the laboratory along with cancer cells.

vaccine stimulates immune system to attack the cancer.

E. Viral vaccines

Scientists can modify the viruses in the laboratory and use them to carry cancer antigens into the body. They modify viruses so that they cannot cause serious disease. A modified virus is called a viral vector. Some vaccines use a viral vector to carry cancer antigens into the body. Your immune system reacts to the viral vector. This helps your immune system recognize and respond to the cancer antigen. A treatment called T-VEC (talimogene laherparepvec), also known as Imlygic, is similar to viral vaccines. It uses a strain of the cold virus (herpes simplex virus). The virus was modified by changing the genes that tell the virus how it should behave. This tells the virus to destroy cancer cells and ignore healthy cells. This process appears to help the immune system find and destroy other cancer cells. T-VEC is now available to treat some people with melanoma skin cancer whose cancer cannot be removed with surgery. It is also being studied in head and neck cancer research. You injected T-VEC directly into melanoma or head and neck cancer [32].

7. NON -TARGETED THERAPY

A. CYTOKINE THERAPY

The mixture of cytokines produced in the tumor microenvironment plays an important role in the pathogenesis of cancer. Cytokines released in response to infection, inflammation and immunity can inhibit tumor development and progression. IFN α regulates MHC class I surface molecules, promotes caspase-dependent apoptosis in certain cancer types, has anti-angiogenic effects on tumor vasculature, polarizes immune responses against Th1, increases cytotoxicity and survival of NK cells, stimulates generation and survival of CTL cells, and memory CD8. T cells and promotes dendritic cell (DC) maturation. Alternatively, cancer cells may respond to host-derived cytokines that promote growth, impair apoptosis, and facilitate invasion and metastasis. A more detailed understanding of cytokine-tumor-cell interactions offers new opportunities to improve cancer immunotherapy. Examples -are INTERFERONS, INTERLEUKINS etc [31].

B. BACILLUS CALMETTE GUERIN (BCG):

BCG immunotherapy is the standard therapy for non-muscle invasive bladder cancer with a high risk of recurrence or progression. Preclinical and clinical studies have shown that the strong inflammatory response to BCG involves several steps: fixation of BCG; internalization of BCG by established immune cells, normal cells, and tumor urothelial cells; BCG-mediated induction of innate immunity arranged by the cellular and cytokine environment; and induction of BCG-mediated tumor-specific immunity [20]. Adding to the complexity, differences between clinical BCG strains can influence the development of tumor immunity. A better understanding of the mechanisms underlying BCG-mediated tumor immunity can improve efficacy, improve tolerability of therapy, and identify new immune-based therapies. Indeed, eagerness for bladder cancer immunotherapy and the possibility of combining BCG with other therapies is increasing as targeted immunotherapies, including checkpoint inhibitors, become available. Great progress has been made in understanding the mechanism of action of BCG immunotherapy, but many questions remain and more basic and clinical research is needed to develop new treatment strategies for patients with bladder cancer [20].

8. CANCER STEM CELLS

CSCs can continuously divide & give rise to identical daughter cells, leading to the expansion of the CSC population within the tumor. CSCs can differentiate into various cell types present within the tumor, contributing to cellular heterogeneity and tumor plasticity CSCs can be isolated and identified on the expression of specific cell surface markers, such as CD44, CD133, ALDH1[6].

A. Rationale for targeting cancer stem cells and tumor microenvironment in cancer therapy-

Tumor Heterogeneity - Cancer Stem Cells (CSCs) contribute to tumor Heterogeneity by giving rise to different cell types within the tumor. Targeting CSCs allows for more effective elimination of cells responsible for tumor initiation, growth, and therapeutic resistance.

Tumor Initiation & Recurrence - CSCs possess self-renewal and differentiation capabilities.

Metastasis & Invasion - CSCs play a key role in Tumor metastasis and invasion by initiating the formation of pre-metastatic niches and promoting epithelial-mesenchymal transition (EMT). Targeting CSCs may prevent or inhibit these processes, limiting tumor spread [7].

Angiogenesis and Nutrient Supply- Targeting TME can disrupt angiogenic processes, leading to tumor degeneration.

Synergistic Effects- Simultaneous targeting of CSCs and TME can result in Synergistic Effects, as the interaction and crosstalk between these components greatly contribute to tumor progression and therapy resistance.

9. HYPOXIA- TARGET THERAPY

Hypoxia, or low oxygen levels, is a common feature of solid tumors and plays a remarkable role in tumor progression and therapy resistance. These therapies can improve the efficacy of cancer treatments by increasing tumor oxygenation and reducing therapy resistance. ER α and the hypoxia-inducible factor HIF-1 α uniformly modulate a group of genes. HIF-1 α overexpression in MCF-7 xenografts induced resistance to antiestrogen treatment and a hypoxia gene signature associated with poor response to endocrine therapy in ER breast cancers and HIF-1 α -concordant hypoxia confers radio resistance and chemoresistance in colorectal cancer (CRC), hypoxia mediates self-renewal of glioblastoma stem cells (GSCs) [27] maintaining their phenotype and is likely related to the HIF-2 α factor [28]. Targeting and selecting the hypoxia-induced amino acid transporter SNAT2 may sensitize hypoxic breast cancer cells to antiestrogen treatment

A. Advancement in TME Characterization Techniques-

Improvement in TME characterization techniques is crucial for better understanding the complex interactions between tumor cells, stromal cells, and extracellular matrix. Novel imaging technologies, such as Multiplex Immunohistochemistry, and Multiphoton Microscopy, enable high-resolution visualization of the TME components. Single-cell sequencing techniques allow to identification of various cell types within the TME and their gene expression patterns [29].

B. CSC Inhibitors and Significance -

CSCs emerged from studies of Acute Myeloid Leukemia (AML) due to the isolation of hematopoietic cell surface antigens by flow cytometry. CD44 is a significant marker of cancer stem cells and it's a cell surface glycoprotein that is characterized by its numerous isoforms it acts as a sticking molecule that has a key role in signaling and migration.

C. Therapeutic Approaches -:

- The most specific Treg marker is Forkhead box P3 (FOX P3).
- An FDA-approved monoclonal antibody Daclizumab is raised against the CD25 receptor which is effective for decreasing circulating T cells.

D. Preclinical & Clinical Trails Assessing the CSC Targeted Therapeutics -

Preclinical trials are carried out in the laboratory using animal models, or cell lines for the assessment of the potential of novel drugs. Advancement In the Characterization Techniques- Multiplex immuno-chemistry and Multiphoton Microscopy are novel imaging techniques that enable high visualization and high resolution of TME components.

E. Cancer Stem Cell Markers in Common Cancers & Its Therapeutic Implications - Recently, the hyaluronan receptor and stem cell markers such as CD44 and MDR-1 tend to possess molecular link which was reported in breast and ovarian cells. Clinical Implications & Future Trends - Drug – Bevacizumab, Target - Antibody against vascular endothelial growth factor and Cancer type - Breast, Lung & Colon cancer and Drug- Sorafenib Target - Tyrosine Kinase

Receptors Inhibition, Cancer type - Kidney cancer, renal cell carcinoma

10. NANOMEDICINE

Nanomedicine is one of the fastest growing areas in nanotechnology and is composed to revolutionize healthcare and medicine. Nanomedicine heralds a new opportunity for drug delivery to improve treatment indicators. Many biological hurdles affect drug delivery in cancer like renal, hepatic, etc. Nanoparticles loaded with drugs can be designed to overcome these hurdles [26].

A. Nanoparticles

Nanoparticles are defined as particles with one dimension less than 100 nm with different properties commonly not found in large samples of the same material.

B. Types of nanoparticles

- Polymeric nanoparticles (polymer-drug conjugates):
These drugs are conjugated to the side chain of linear polymer with the help of a linker. They are water-soluble and biodegradable. ex- Abraxane (specific targeting on cancerous cells)
- Polymeric micelles: -
Amphiphilic copolymer joins together and forms a micelle with a hydrophilic shell and hydrophobic core. They are carriers for water-insoluble drugs. ex- PEG Pluronic DOX (targeting ability) [16].

- Dendrimers: --Spiral appearing highly branched synthetic polymer with regular design and repeated unit. ex- PAMAM- MTX (multifunctional, controlled degradation) [17].
- Liposomes: --Self-build closed colloidal structure consisting of the lipid bilayer. ex- Pegylated liposomal DOX (targeting potential) [15].
- Viral nanoparticles: - Protein cage with polyvalent, self-assembled structure. Surface modified by mutagenesis. ex-HSP-DX (specific tumor targeting)
- Carbon nanotubes: - These are carbon cylinder collections of benzene rings. Organic functionalization. ex- CNT-MTX [1].
- Gold nanoparticles: - Safer cancer agent. Excellent drug and anti-cancer agent carrier in cancer therapy [25].

C. Liposomes

They are spherical bilayer vesicle which has one or more lipid layer, known as liposomes. That can be used to insert both hydrophobic and hydrophilic drugs. Liposomes have been considered accomplished drug vesicles. Liposomes display great features like site targeting, lower toxic side effects, sustained or controlled release, high therapeutic effect, and protection of the drug from decay [15].

D. Structure and main components of liposomes

The main components of liposomes are phospholipids and cholesterol.

Liposomes can be categorized into 3 types

- Unilamellar vesical (ULVs)
- Oligolamellar vesicle (OLVs)
- Multilamellar vesicles (MLVs) [15]

E. The process of drug delivery by liposomes includes:

The preparation of MLVs or ULVs depends upon methods

- Film hydration method: It is beneficial for the loading of the hydrophilic drug.
- Double emulsification method: this method leads to the formation of water-in-oil emulsion, water-in-oil-in-water emulsion, solvent extraction, and microfiltration.
- Solvent injection technique: lipid material and hydrophilic substance are mixed in water– miscible organic solvent and injected in the aqueous buffer.
- In–situ preparation of liposomes: In situ is considered as liposomes that are formed before clinical use.
- Size reduction: Several methods are there for the size reduction of liposomes like sonication by bath or probe, extrusion, and French press. The highly used technique is extrusion and high-pressure homogenization (HPH) [14].

F. Drug targeting

Drug loading: high drug loading is required to minimize the number of additives to reach a therapeutic agent. The two drug targeting methods are active and passive targeting [13].

a. Active targeting

Active targeting targets the cancerous cell by direct interaction between receptor and ligand. The ligand on the nanoparticles is chosen to target the molecule that is highly expressed in the cancerous cell, which differentiates between Targeted cell from the healthy cell [13].

b. passive targeting

Passive targeting is designed to differentiate tumor and normal tissue. The drug is reached to the target site to act as a therapeutic. A high increase of cancerous cells prevails upon neovascularization and huge pores in vascular wall led to bad imbibition of tumor vessels in comparison to normal vessels [13]

- Buffer exchange and concentration
- Therapeutic molecule is loaded in liposomes to tumor cells
- Particle size and size distribution
- Surface modification
- Lyophilization if needed packaging.

11. CONCLUSION

As the field of cancer immunotherapy has evolved, the focus of treatment has changed from the treatment of the hospital to the specific biological characteristics of the tumor and its treatment interaction with the patient's innate immunological capacity, or "cancer-immune arrangement". fight the disease. Because the immune system can remember and Immunotherapy is always used to detect and destroy tumor variants when they appear inherent advantages over other treatments that lack these two key features. Specifically, to make it effective, cancer immunotherapy must find ways to manipulate the immune system in (probably most) patients who little or no immune response to their tumors, even down to the tumor the microenvironment is an "immune desert" lacking tumor-infiltrating T cell. Breakthrough discoveries are needed to continuously strengthen in immune system of cancer patients and restore MHC class I antigens in those tumors that downregulate them. Immunotherapy is a growing field for research and development in regard to cancer treatment.

AUTHORS CONTRIBUTION

The authors confirm their contribution to the paper as fellow: A.R., A.M., R., A.M., DATA collection and manuscript preparation; D.D. DEAN: study conception and design, and critical analysis. All authors reviewed the result and approved the final version of the manuscript.

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