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Paper Authors

Devireddy.Samyuktha,Kakani Anil Kumar, Manne. A. Anupama, Kakumanu.BalaVinod, Sahithi Kamepalli,Gullapalli Revanth, Jaladi Bhagavan,Anisette Sai Manikanta, Kanaka Durga Devi.Nelluri

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The Essence of All Cancer Immunotherapy is Therapeutic Vaccination

Devireddy.Samyuktha[1],Kakani Anil Kumar[1], Manne. A. Anupama [2], Kakumanu.BalaVinod[1], Sahithi Kamepalli[1],Gullapalli Revanth[1], Jaladi Bhagavan[1],Anisette Sai Manikanta[1], Kanaka Durga Devi.Nelluri[1*]

[1]KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh, India.
[2]Department of Civil Engineering, PVP Siddhartha Institute of Technology, Vijayawada, Andhra Pradesh, India
nelluriss@rediffmail.com, nellurikvsr22@gmail.com

Abstract
With a high incidence and high mortality rate, cancer can be called a spring tide in the ocean of deadly diseases that enfeebles the patient not only physically but also mentally, As Traditional therapies cause release of additional antigens from tumor cells, they do not effectively treat malignancies which is a further threat to life. Therefore, to stem the tide of cancer and heal the sick, a distinctive therapeutic invention which can effectively aim at and eliminate tumor cells while avoiding any ADRs is needed. Current studies have shown that a common route for a competent and dynamic anticancer immune response exists between the recognition of tumor neoantigens and the aiming of cancer cells by utilizing the T cells. Cancer immunotherapy reduces side effects while boosting the ability of immune system's to covertly aim and eradicate tumor cells. In addition to being important targets for checkpoint blockade therapy, tumor-specific mutant antigens can also be utilized to develop individualized cancer-specific vaccines and explore the underlying molecular principles of various checkpoint blockade therapies. This mechanism, which also eradicates cancers, creates the phenotypes that are immunogenic of tumors that sooner or later develop in immunosuppressed hosts. Additionally, different nanoparticles with strong structures which can deliver medicaments to the site of action while maintaining their capabilities and standards must be integrated while they are being formed. Additionally, it may be preferable to use combination treatments so that the drawbacks of a therapy can be offset by another.

Keywords: Neoantigens, Tumour Cells, Cancer Immunotherapy, Immunosuppressed

Introduction

One of the most common fatal diseases, cancer has a high incidence and mortality rate. The immune system is made up of innate and adaptive immunity that is required to combat infections and cancers, acting as both an intrinsic tumour promoter and an extrinsic tumour suppressor by either destroying emerging tumours or playing a key role in controlling the course of cancers. Our immune system does more than only inhibit their growth.[1,2,3]. Normal bodily cells give rise to cancer cells. Every time there is an imbalance between T regulatory and T stimulatory cells, it prevents T cells from activating, which suppresses the immune system, promotes the development of cancerous tumours, and allows them to metastasize to healthy tissues.[4]

Radiation, chemotherapy, and tumour removal surgery are the three conventional methods for treating cancer.[5,6,7]However, these conventional therapies increase the amount of antigens released from the tumour cells and are ineffective against malignancies. Hence, an distinctive therapeutic that can efficiently aim at and eliminate tumour cells while avoiding any ADRs is required. This approach benefited a lot from current advances in cancer biology and anticancer immunity and revolutionized the treatment of cancer.

In contradiction to chemotherapy and other therapies which aim at directly killing the

tumor cells, immunotherapy stimulates and/or promotes the immune system ability to invade and kill tumor cells in a indirect way, while reducing off-target effects.Active and passive approaches are used in cancer immunotherapy. Immune cells (T cells and NK cells) or antibodies are given to the patients using the passive technique. This prolongs the time that immune cells are in their active state. Because to its negative autoimmunity and toxic effects, it does not trigger an immune response specific to an antigen and is therefore restricted. Active cellular immunotherapy, on the other hand, guides the immune system of the host to the tumor-associated antigens on the tumour surface.

Vaccines with antigens alone induce poor immunogenicity. For example, soluble peptide and protein vaccines induce immune tolerance, where there is downregulation of the immune response against the tumor which is an undesirable outcome. So they need to be co-administered with adjuvants for strong immune responses. Adjuvants are substances that boost immunogenicity by improving antigen presentation and by identifying and activating particular cell receptors that start innate immunity and provide long-lasting protection from infections.[6,8,9]

Additionally, a variety of synthetic methods, including carriers and delivery systems, have been expanded for the effective delivery of immunotherapeutic agents in order to address issues with invivo drug transportation, such as preventing drug degradation, extending systemic circulation, regulating drug distribution at the lesion site, promoting drug passage through physiological barriers, facilitating drug penetration through biological membranes, and managing drug concentration. Examples include delivery systems based on micro- and nanoparticles and dendritic cells.

Beyond these developments in the development of cancer immunotherapy, concerns need to be raised about its drawbacks and dangers. A better knowledge of the tumour microenvironment (TME) and immunosuppressive processes over the past two decades has revealed a number of new routes that need to be investigated for the creation of new cancer treatments.

IMMUNE SYSYTEM AND ITS ROLE IN CANCER

The immune system being the body's instinctive defense system plays a pivotal role in cancer pathogenesis. Within the immune system different types of cells (like helper T cells, Killer T cells, B cells, macrophages, dendritic cells, etc.), molecules (like Antibodies, cytokines), and organs (like bone marrow, lymph nodes, spleen, skin) with identifying, marking and destroying functions work together to fight with infections and diseases.

The development of a tumor depends on the surrounding tumor microenvironment. When the tumor starts growing various cells including T cells, B cells, NK cells, vascular endothelial cells, adipocytes, and fibroblast surrounds it and secretes signals responses against immunogenic cancer cells which controls tumor progression.[10,11] Some of the selected cancer cells which survive adopt two main strategies i.e avoiding immune recognition by losing the expression of tumor antigen on the cell surface and provoking immunosuppressive tumor microenvironment by expression of checkpoint molecules (CTLA4) on T regulator cells. These cells escape the immune selection and enter a phase of outgrowth resulting in the downregulation of T cells activity leading to the inhibition of the T cells anti-tumor activities. These changes cause the immune system to lose its capability to fight the tumor cell and lead to tumor cell proliferation and progression to the metastatic stage finally resulting in a worse prognosis.

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IMMUNOMODULATION

Several immune evasive techniques have been created by tumours to manipulate innate, adaptive, and regulatory immunity. Immunomodulation relies on the immune system's ability to recognise and eliminate tumour cells in order to combat these tumour cells' tactics.Agents with either of the two techniques for immune activation—non-specific immunological activation or tumour antigen-specific immune activation—make up immunotherapy.[12]

Non-specific immune activators work to suppress the tumour microenvironment, but tumor-specific immune activators direct the immune system to precisely target and eradicate tumour cells. By boosting tumour antigen presentation, producing targeted CTL activity, directing T cells to the tumour, and suppressing tumour T regulator cells, these techniques can be combined to kill tumour cells. **Table.1** shows various agents that utilizes these two strategies to produce immunomodulation.

Table 1.Agents with immunotherapeutic strategies

Non-specific immune activators	Anti CTLA-4 antibodies Anti PD-1 / PDL-1 antibodies Cytokines
Tumor antigen specific immune activators	Peptide/ protein based vaccines DNA vaccines RNA Vaccines

Depending on the components of the vaccine like the type of tumor-specific antigen, carrier or delivery system, adjuvants, and those which target the tumor microenvironment the immunotherapeutic vaccines could be of various types. Once the target or target antigen was chosen carrier or delivery systems act as a source vehicle to deliver antigen to the relevant immune cells or target sites.

Antigen Specific Vaccines

Tumor specific antigen are those whichusually comes from the cancer cell (glycoproteins, carbohydrates, proteins, DNA, RNA) which is encoded with cancer associated antigen.Sovaccines which are intended to target specific antigen rely on proteins/ peptides, DNA, RNA as shown in **Fig1.**

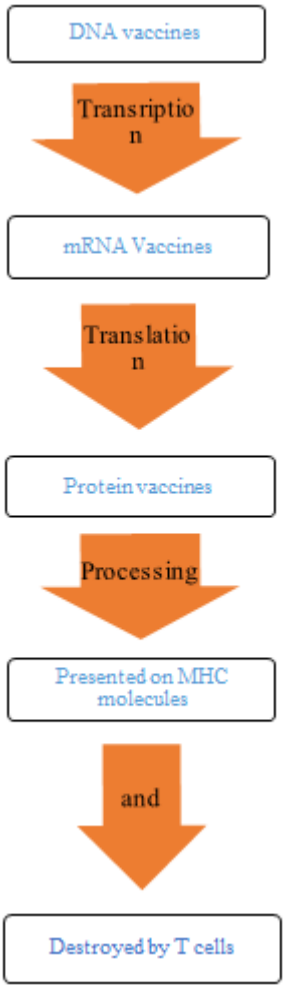

Figure1: Various Antigen Specific Vaccines

Peptide/ protein based vaccines:

Antigen-presenting cells (APCs) of the innate immune system must be triggered for the adaptive immune system to function. Antigen binding to the MHC is the first step in antigen presentation, which is followed by delivery of the complex to the

cell surface where a T cell receptor may recognise it (TCR). MHC class I and class II associate with cytosolic intracellular peptides and, after internalisation, with proteins or peptides in endosomes or lysosomes. Immature CD8 T cells are stimulated to create cytotoxic T cells by the MHC-I/peptide complex. When antigen proteins are processed, HLAs present peptides on MHC-I, which are subsequently eliminated by CTL cells. whereas CD4 T cells are exposed to MHC class II antigens. Th1 and Th2 cell subtype differentiation occurs in proliferating CD4 T cellsB cells, T cells, dendritic cells, and antibodies that recognise antigens are released when the adaptive immune system is engaged.[12,13,14]

Antigen presentation of the tumor cells is different from that of the normal cells. On determining tumor-specific or associated antigen (TSA or TAA) to be targeted an appropriate protein sequence was designed such that they are loaded on the carrier, processed, and presented on MHC class I and class II molecules.[14] These peptide epitopes bind to the HLA class I and II and stimulate CD8 and CD4 T cells respectively and aid in the destroying tumor cells.

Peptide vaccines were cost-effective when compared to various other approaches. So it had been the general interest for vaccine designs in cancer therapeutic trials. However, these peptide vaccines have low immunogenicity. Combining with the adjuvants or cytokines or with immune checkpoint inhibitors has shown to enhance the immunogenicity of peptide vaccines.

DNA Vaccines:

DNA vaccines utilize the plasmid DNA. Plasmid DNA consists of a DNA sequence of tumor antigens and a promoter for gene expression. These DNA vaccines can be injected as naked DNA without any use of viral vectors or formulations and can sustain the expression for longer periods compared to protein or RNA-based vaccines. On injecting the DNA vaccine it presents the antigen on the APC it then enters the nucleus where it is transcribed and then translated. It then produces antigens as proteins for processing which are presented to the CD8 cells for destruction.[12,15] They also have the ability to induce antibody responses. They have good stability and solubility when compared with RNA vaccines.[16]

RNA Vaccines:

RNA vaccine therapy including therapeutic ribozymes, aptamers, and siRNAs has the potential to target cells that escaped immune recognition or evolved as resistant forms. RNA vaccines are similar to that of peptide vaccines. On administration of RNA vaccine, they get translated and processed to long peptides by APCs and are expressed on the cell surface to activate the T cells. As the host genome is made up of DNA these RNA vaccines have the advantage that they cannot be integrated with it.[16] Nanoparticles are used to administer these RNA vaccines as it is susceptible to degradation by RNases. Unlike DNA vaccines, RNA vaccines don't require to be transcribed in the nucleus.[15]The mechanism of action of antigen specific vaccines was described in Table 2.

TABLE 2: Antigen-specific vaccines - Mechanism of action

DNA Vaccines	DNA vaccines work by injecting a genetically altered plasmid with the DNA sequence encoded with the antigen(s) against which an immune response is required . This causes the cells to produce the antigen directly and starts an immune response that is protective.
mRNA vaccines	In order to trigger an immunological response, an mRNA vaccine uses a copy of the messenger RNA (mRNA) molecule.
Protein vaccines	An efficient anti-tumor T-cell response is induced using peptides from tumor-associated antigens.

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Tumor microenvironment modulators:
Extracellular matrix (ECM), Cancer-associated fibroblasts (CAFs), and signalling molecules are nonimmune components of the tumour microenvironment that support the integrity of tumours and emit various cytokines and chemokines. These immune cells include NK Cells, T cells, B cells, and macrophages. They create ECM building blocks like collagen, fibronectin, and matrix metalloproteinases, which can help make the ECM stiffer and thwart T cell invasion. During tumor development these cells surrounds the tumor and release signals necessary to control tumor progression which is called as immune surveillance.T cell activation depends on the expression of CD28 and checkpoint molecules (CTLA-4, PD1).[17,18]. Checkpoint molecules are the negative regulators of T cells where they prevent the over-activation of T cells by getting expressed on T regulator cells and produce cytokines that cause immunosuppressive TME. The tumor cells which escape the immune surveillance modify or activate these checkpoint molecules and reduce the T cell activation by competing with CD28 and rendering defense to the tumor cells.

All these together contribute to the immunosuppression of tumor microenvironment. So monoclonal antibodies which target these checkpoints either block their co-inhibitory responses or activate the co-stimulatory pathways. Together with these effects, the TME's cytokines and chemokines can even cause an immune-suppressive TME and lessen T cell responses. Moreover, these checkpoint molecules can be combined with other forms of immunotherapeutic vaccines to increase their immunogenicity and efficacy. The overview of the Tumor micro environment is shown in **Fig 2.**Shows the overview of tumour micro environment

Figure 2: Overview of tumor microenvironment

Anti CTLA-4 antibodies:
In order to bind with its ligands B7-1 (CD80) and B7-2 (CD86) on APCs, CTLA-4 must outcompete CD28, which then produces an obstructive signal that prevents a T-cell response. IpilimumabandTremelimumab are the anti CTLA-4 antibodiesthat are used as first line agents. They are shown to be effective against some advanced cancers. Ipilimumab is a human Immunoglobulin G1k (IgG1k) anti CTLA-4 monoclonal antibody.[18,19]It was given FDA approval. A CTLA4-blocking antibody with a human Immunoglobulin G2 (IgG2) isotype is called tremelimumab. 20 The ability of these two to produce antibody-dependent cell-mediated cytotoxicity and their binding kinetics are different. The CD28-mediated co-stimulative pathways required for T cell activation are prevented from being competed with by them by binding to CTLA4 on the surface of the Treg cell. These antibodies induce antibody-dependent cellular cytotoxicity when they bind to an APC's Fc receptor (ADCC). Regulatory T cells that are CD4+CD25+ express more CTLA4 than other types of T cells, making them more vulnerable to -CTLA4-induced ADCC. Moreover, they encourage T cell responses by inhibiting CTLA4 on the surface of activated conventional T cells.[19]

Anti PD1/PDL1 antibodies:

Programmed cell death 1 (PD1) is a second inhibitory immune checkpoint pathway found on the surface of B lymphocytes, T lymphocytes, and monocytes.Activated T cells express PD1 that binds to its ligand (PDL-1) and interferes with T cell activation.[19]

Nivolumab, a human immunoglobulin G4 (IgG4) monoclonal antibody was the first clinically evaluated anti PD1 antibody.Pembrolizumab and pidilizumab are the other anti PD1 monoclonal antibodies.Atezolizumab is an example of anti PDL1 antibodies.[18]These antibodies prevent the PD1 from binding to PDL1 and increase the T cell activation further regaining the antitumoral T cell activity. Consequently, more T cells bind to tumor antigen enhancing tumor killing.[19]These anti PD1 antibodies have fewer adverse effects when compared to anti CTLA-4 antibodies.[21]

Cytokines:

Cytokines are soluble proteins that delivers inflammatory or anti-inflammatory signals in response to immune cells.[5]Cytokines such as interferons and interleukins are known to induce maturation, activation, and migration of inflammatory cells that can initiate the immune system to fight against tumor cells.[22] Studies state that systemic administration of cytokines promotes the immune responses against tumors. But its use is limited due to its toxicity and rapid degradation and elimination. These drawbacks can be controlled with local delivery as their biological activity arises from paracrine actions.Recent advances utilise the introduction of cytokine genes into tumor cells, through ex vivo gene therapy. This approach allows the sustained and local release of cytokines capable of secreting interleukins, interferons, TNF alpha that causes tumor destruction by specific and non-specific mechanisms.

Interleukin:

IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, and IL-13, IL-18, IL-21 are examples of interleukins which showed tumoricidal effects.IL-2,a pro-inflammatory cytokine is the positive regulator of Treg cells which enhances proliferation and cytotoxic effects of effector immune cells.[12,23] It summates the pre-existing immune response against tumor cells. More than 60%of cytokine supported cancer clinical gene therapy trials use IL-2. However, it is important to manage the toxicity of IL-2 because it affects most of the organs in the body. There is some evidence that the low/ intermediate doses can reduce the toxicity of IL-2 while augmenting the antitumor responses.

Other interleukins which are used instead of IL-2, activate the effector cells but not the Treg cells. For example, IL-21 activates the effector cells (like T cells, B cells) but suppresses the Treg cells.Another example is the immunostimulatory cytokine IL-18, which has lately come into being. It can promote anti-tumor therapy by inducing IFN-, IL-2, TNF-, GM-CSF, and IL-1, activating effector T cells, and enhancing NK cell cytotoxicity, but it suppresses Treg cells. IL-10 is an immunosuppressive cytokine that inhibits NK and T cell activation and cytokine production while decreasing the expression of APCs.[5]

Interferons:

Type I interferons include INFα and β and type II includes INFγ.In the clinical trials, type I interferon has shown the efficacy for the treatments of leukemia, melanoma and renal-cell carcinoma. They enhance the activity of NK-cell by increasing the expression of Fcγ receptors and thus inhibit the generation of allospecific suppressor T-cells.

Contrarily, Type II are released by effector T cells and NK cells, and they have antiangiogenic actions, induce apoptosis, upregulate HLA-I and HLA-II, and promote antigen expression in cancer cells. It has been shown that IFN expression is correlated with markers of prognostic variables and cancer survival.[12]

Adjuvants:

Adjuvants are important elements for improving the efficiency of vaccines. Adjuvants are heterogeneous groupings of chemicals that increase immunological responsiveness by either boosting antigen presentation or by inducing the innate immune response by recognising and

initiating particular cell receptors, which may lead to long-term protection against infections. [7]Vaccines with antigens alone were shown to have a poor immune response when compared to the combined antigen and adjuvant vaccine administration.[15] Different types of adjuvants have been developed. Some of them are emulsions, virosomes, microbial derivatives like CpG oligonucleotides, liposomes, mineral salts like aluminum hydroxide, aluminum phosphate. Currently licensed vaccines are alum salts, emulsions and liposomes.[12]

As adjuvants, water-in-oil emulsions like Montanide are frequently utilised. It holds the soluble antigens there, preventing the nearby lymph nodes from absorbing them. This causes swelling, a slow release of the antigen, and immunological reactions.[15]Virosomes are the unilamellar lipid envelopes which are derived from viruses that adopt with the viral antigenic properties but lack the viral genome. Only virosomes are licensed up to date. They are influenza virosomes (IRIVs) (Epaxal®) or influenza (Inflexal®) which protect against hepatitis A and Sendai virosomes reconstituted from Sendai viral envelope.[24]They have a fusion protein that causes the virosome and plasma membrane to fuse, releasing the contents of the virosome into the cytoplasm. The co-stimulatory molecules CD80 and CD86 are also upregulated on the surface of dendritic cells. Their ability to load antigenic peptides is however constrained.

Cytosine-phosphate Guanine (CpG), which is regarded as an immunostimulatory adjuvant, activates a range of immune cells to initiate adaptive and innate immunological responses. A phosphodiester link ("p") separates the cytosine triphosphate deoxynucleotide ("C") from the guanine triphosphate deoxynucleotide ("G") in the sequence of the synthetic short ssDNA known as CpG ODN. Water soluble CpG is phagocytosed by lymphocytes, enters the endosome, and is recognised by the pattern recognition receptor (PRR), Toll-like receptor 9 (TLR9), which in turn triggers innate and adaptive responses, whereas unmethylatedCpG motifs are recognised as pathogen-related molecular patterns (PAMPs).

With intratumoral injection, cyclic dinucleotides (CDNs), another potent immunostimulatory adjuvant, triggers the stimulator of interferon genes (STING receptors) in APCs.[23,25,26]. Alum salts (Aluminium hydroxide, Aluminium phosphate) adjuvants initially act to enhance antibody production and are suitable for vaccines targeting pathogens killed by antibodies. They are mostly used as adjuvants for vaccine development. However, they were incompatible with some of the antigens and has the inability to induce cell-mediated immune responses. Via PRRs, liposomes with the right targeting ligands stimulate and activate cells, maturing APCs (co-stimulatory chemicals and cytokine signals), and processing and presenting antigens. To ensure that T and B cells respond effectively to the pathogen, these APC signals control T and B cell polarisation. One such instance of a liposome-based vaccination adjuvant system is AS01, which contains the saponin and monophosphoryl lipid A (MPL), two immunostimulants. QS-21.[9]

Carriers or delivery systems:
The two most APCs of the immune system that have the capacity to digest and deliver antigen for the triggering T cells against cancer and other infectious illnesses are dendritic cells and macrophages.

APCs deliver antigen to T cells by either presenting MHC I to CD8+ T cells or MHC II to CD4+ T cells. APCs also emit a costimulatory signal, in which positive signals encourage T cells to attack antigenic cells and negative signals cause effector T cells to be suppressed.

Dendritic cells:
DCs are thought of as expert antigen-presenting cells. They are crucial for triggering anti-tumor responses. They

originate from modified dendritic cells taken from patients that display tumor-associated antigens, which in turn trigger T lymphocytes to attack cancer cells.

Immature DCs take up the antigen via endocytosis, phagocytosis, micropinocytosis, and receptors. When it comes to inflammatory mediators they develop as mature DCs. These mDCs travel to DLNs and present antigens to T cells. The MHC I and II molecules in DC can be physically loaded with antigenic proteins, peptides, tumour lysate from radioactively treated tumour cells, or transfecting DCs with tumour antigens encoded DNA or RNA that can be carried by themselves by either ex vivo or in vivo. Injecting the patient with the loaded DCs boosts the patient's immunogenicity against the tumour.[12]

Example includes: Sipuleucel-T is an "immune cell"-based cancer vaccine and the first therapeutic cancer vaccine ever approved by the US FDA for the treatment of asymptomatic metastatic castrate-resistant prostate cancer (mCRPC).[12,27] It targets prostate cancer consisting of autologous whole immune cells incubated with PA2024 which contains prostatic acid phosphatase (PAP) fused to GMCSF.

Delivery of immunomodulators with nanomaterials

Nanoparticles acts as a delivery systems or carriers to target the tumor cells and to prevent the drugs from premature inactivation during delivery. They act as a vehicle for delivering drugs that has pharmacokinetic limitations like short half-life, poor solubility, and poor bioavailability. Nano-formulations provide means to modify the pharmacokinetics and pharmacodynamics properties of drugs without altering their anti-tumor responses. Nanoparticles have a better capability of activating dendritic cells and T cells via multiple co-stimulating signalling pathways.

Nanoparticle deliversbio-therapeutic encoded withtumor antigens directly into APCs such as dendritic cells. On recognition of antigen by DC it promotes differentiation of T cells to effector T cell and presents the antigen to T cells that attacks and eliminates the cell expressing the antigen.

Polymeric nanoparticles, micelles, liposomes, carbon nanotubes, mesoporous silica nanoparticles, gold nanoparticles, and virus nanoparticles are just a few of the many nanoparticles that have been identified as delivery methods. They can all be utilised separately or in combination. Popular nanoparticle-based delivery systems include those made of polymeric and lipid materials.[15]

Anticancer medications can be embodied into the inner cores of nano-formulations made utilising various material compositions. Targeting moieties like antibodies, peptides, or recombinant proteins can be docked onto the surface of nanoparticles to help with the further selective accumulation of medicines inside tumour tissues.[28]

Example for Polymeric Nanoparticles include PLGA-Based Polymeric Nanoparticles. PLGA is usually synthesized by ring-open polymerization. PLGA nanoparticles have been mostly used as an effective carrier in cancer drug delivery and in tissue engineering. These nanoparticles can carry and deliver proteins in an active form and can elevate the cellular and humoral immune responses. They are phagocytized by DC and enhance the surface expression of MHC molecules.[5,24,29]

Liposomes are self-assembling, closed entities with an aqueous interior made of lipid bilayers. Protein and DNA are encapsulated in liposomes for delivery in vitro and in vivo.[5,12,29] ·DNA and proteins can bind to the outside surface, can be enclosed in the inside space, or can do both. They are adaptable and may be built with a range of various features by altering the lipid content, size, charge, and surface characteristics. These lipid-based nanoparticles encapsulated with nucleic acids encoded with the target antigen can

be designed to present antigen-presenting cells such as dendritic cells which induces antitumor T cell responses. On introduction into the host, they are delivered to APCs for the presentation of antigen on MHC molecules for tumoricidal activity.

The hydrophilic nanocarriers known as nanogels exhibit remarkable biocompatibility and flexibility. These can be created using synthetic polymers like PEG or PNIPAM as well as their composites, as well as natural biomaterials including polysaccharides, peptides, and nucleic acids[25-32].

However, there are toxicity characteristics associated with nanoparticle based delivery systems that need to be addressed. The cost and complexity of manufacturing these nano-formulations are also high. Some of the nanoparticles that have been used in regulation of TME were shown in **Fig 3**.

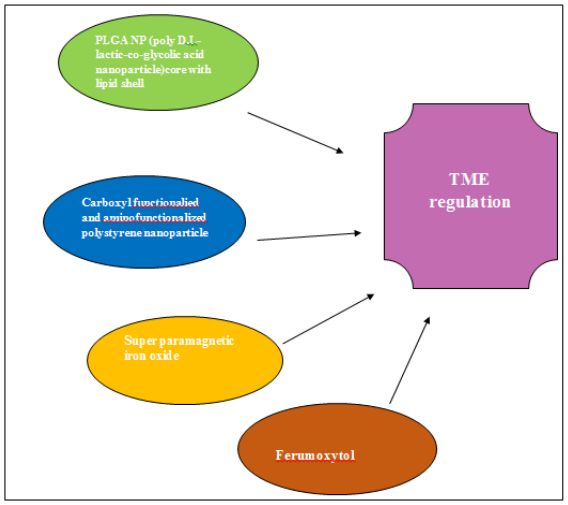

Figure 3: Various nanoparticles implicated in the control of tme

Conclusions and future directions:

Although standard cancer therapies are still clinically evident, malignant tumors, offer a newer approach to cancer treatment surmounting these standard therapies like chemotherapy, surgery, and radiotherapy. This could be due to tumors own mechanisms of immune evasion including immune escape by losing antigen, MHC loss, the presence of immunosuppressive cells or soluble factors in the tumor microenvironment and lack of anti-tumor immune responses.

With its success, cancer immunotherapy has opened up new avenues for research into developing antitumor immune responses. Immunotherapy still confronts several difficulties, though, including immunological biomarker deficiencies and off-target effects, all of which point to potential future areas for advancement.

Moreover, the delivery method for cancer immunotherapy is still in its budding stage. We can assume that as time goes on, these cutting-edge delivery systems that enhance immunotherapy will gradually gain acceptance. The vaccine platform and the delivery systems have undergone a lot of improvements in the last decades.

It is essential to have smart drug delivery approaches that can integrate with the human body and its mechanisms. Nanomedicines and Nano-formulations are such advancements that are gaining a lot of attention nowadays. Moreover, pharmaceutical companies are already involved in utilizing nanotechnology to enhance the extensive efficacy of immunomodulatory therapeutics.

Considering the mechanisms of immunomodulators it is necessary to improve and consider nanomaterials from different perspectives like formulations, physicochemical properties, release behaviours, manufacturing processes, etc. which could improve the immune responses that can be foreseeable in the future.

Additionally, different nanoparticles with strong estimation structures which can deliver drugs at the site of action and protect their effectiveness and properties are to be consolidated while developing them.

Two other factors can be improved in the future. One is to research cutting-edge delivery methods. Another is the need for the development of biological materials to promote T cell ex vivo growth.

In addition to the therapeutic advantages, it is important to take into account other aspects including biocompatibility, manufacturing costs, and storage in light of design elements and administration routes. In order to expand the use of cancer immunotherapy, new developments in medication delivery must be made.

Another important concern that needs to be considered is about developing vaccines that could target non-self or mutated antigens when delivered with appropriate adjuvants and delivery systems. Adjuvants are the other important elements that have emerged or are presently being investigated that will enhance the immune response and improve the vaccine's effectiveness.

Moreover, choosing combination therapies can be considered so that the deficiency of a therapy can be resolved by another. But before considering second therapy the potential interactions and effects need to be studied and optimized to produce maximum efficacy and decrease toxicity has to be the point for future considerations.

Apart from all these flaws and concerns about immunotherapy, it is considered to be one of the most effective and efficient cancer therapies which has to be developed and improved in the future for better advancements in immune responses against tumor-related factors.

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Abbreviations:

NK Cells	Natural Killer cells
TME	Tumor Microenvironment
CTLA-4	Cytotoxic T lymphocyte associated antigen - 4
CTL	Cytotoxic T lymphocyte
PD-1	Programmed cell death protein - 1
PDL-1	Programmed Death Ligand – 1
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
APC	Antigen Presenting Cells
TCR	T- cell Receptor
MHC	Major Histocompatibility Complex
HLA	Human Leucocyte Antigen
TSA	Tumor Specific Antigen
TAA	Tumor Associated Antigen
CAF	Cancer Associated Fibroblast
ECM	Extracellular Matrix
FDA	Food and Drug Administration
ADCC	Antibody Dependent Cellular Cytotoxicity
IL	Interleukin
INF	Interferon
GM- CSF	Granulocyte Macrophage Colony Stimulating Factor
CPG ODN	Cytosine Phosphate Guanine Oligodeoxynucleotide
IRIV	ImmunopotentiatingReconstityted Influenza Virosomes
PAMPs	Pathogen related Molecular Patterns
PRR	Pattern Recognition Receptor
TLR - 9	Toll Like Receptor – 9
CDN	Cyclic Dinucleotide
STING	Stimulator of Interferon Genes
DC	Dendritic Cells
mCRPC	Metastatic Castrate-Resistant Prostate Cancer
PAP	Prostatic Acid Phosphatase
PLGA	Poly D,L – Lactic co glycolic acid
PEG	Polyethylene Glycol
PNIPAM	Poly (N-isopropylacrylamide)

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