

Review Article

Recent Advancements in Development of Vaccines for the Treatment of Cancer: A Review

Rama Shukla^{a*}, Fauziya Husaini^a, Nisha Thakre^a, Manu Singhai^b, A.K. Singhai^a, Laxmi Tripathi^c

^aDepartment of Pharmaceutics, Lakshmi Narain College of Pharmacy, Bhopal, India.

^bISF College of Pharmacy, Moga, Punjab, India.

^cDepartment of Pharmaceutical Chemistry, Agra Public Pharmacy College, Delhi–Agra National Highway-2, Agra, Uttar Pradesh, India.

* **Corresponding Author:** Tel.: +91 9827335444, E-mail: shukla.pharma15@gmail.com

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ABSTRACT

The human immune system is one of the essential responses for survival. It has evolved to protect the individual from the surrounding pathogenic substances. Immune system acts like a warrior to attack and eliminate infectious organisms from the body. Our immune system consists of special cells, proteins, tissues and organs which defend human against micro-organisms and pathogens. Both innate and adaptive mechanisms have ability to distinguish our tissues to foreign tissues i.e. allergens and toxic substances. Dead or defected cells are also recognized and cleared by immune system. Cancer is one of the most common destructive disease in the World. Various treatments for cancer are available like chemotherapy, surgery, radiation therapy and immunotherapy. Among all the treatments, immunotherapy has the potential to treat cancer effectively and with less toxicity than chemotherapy and radiation therapy. In this review we discuss about the type of immune system along with the examples of immune mechanism and recent advancements in vaccine development against cancer.

1. INTRODUCTION

The biological immune system is a robust, complex, adaptive system that defends the body from foreign pathogens. It is able to categorize all cells (or molecules) within the body as self-cells or non-self cells. It does this with the help of a distributed task force that has the intelligence to take action from a local and also a global perspective using its network of chemical messengers for communication. There are two major branches of the immune system. The innate immune system is an unchanging mechanism that detects and destroys certain invading organisms, whilst the adaptive immune system responds to previously unknown foreign cells and builds a response to them that can remain in the body over a long period of time. This remarkable

information processing biological system has caught the attention of computer science in recent years [1]. The link between the immune system and cancer has been widely appreciated for over a century and was first highlighted by Rudolph Virchow over 150 years ago [2]. The underlying basis for this relationship between cancer and immunity involves three basic principles of how the immune system acts to defend and protect an individual: it detects “nonself” antigens from pathogens or infected/malignant cells; it encompasses effector functions to specifically target and destroy the pathogen or infected/malignant cells while protecting the host; and it develops immunological memory via the adaptive immune responses for subsequent defense mechanisms following an injury or an attack against the host[3]. Interestingly, this ability of cancer to evade or escape

the immune response is now recognized to be one of the most distinguished cancer hallmarks, which provides the platform for treatments within the context of immunotherapies. Although the initial utilization of immunotherapy for cancer treatments dates back to the early nineteenth century, suggestive of work done by William B. Coley and colleagues [1, 4], it was the more recent scientific advance that have helped to elucidate innovative approaches for implementing immunotherapies to eradicate and/or treat various type of cancers. These advances have made the concept of immunooncology and cancer immunotherapy more clinically relevant.

Cancer is one of the main health problem of mankind. In spite of extensive research being conducted over many years, effective cures have been developed only for some forms of cancer, so that the hazard is not substantially reduced. There are several techniques that are used in the diagnosis and treatment of cancer, this includes: Chemotherapy, Surgery, Immunotherapy, Hormone therapy and Radiation therapy. From long time and majorly used technique for treatment of cancer patients is surgery. According to the American Cancer Society, out of people diagnosed with cancer, sixty percent will undergo surgery, before metastasis of cancer cell it have the another option to remove entire tumor.

But it is not the stand alone option, it is usually combination of radiation or chemotherapy [5, 6].

2. ROLE OF THERAPIES IN CANCER [7]

- In **Radiation therapy**, the particular organ of the body will expose to various radiations to reduce reproducing cancer cells which results in various side effects like dryness, fatigue and nausea, peeling of skin and vomiting. Radiation therapy leads to shrinkage of cancer cells and also used to prevent reoccurrence of cancer cells after surgery.
- **Chemotherapy** is treatment of cancer by the use of various medicines. It is the most effective method in case of failure of other method or used in combination with other therapies. Similar to radiation therapy it is also used to cure, prevent spread and modify the symptoms.
- **Immunotherapy** is one of the most recently used treatments for cancer. These involves the change in or controls the balance of hormonal level for cancer treatment, it also includes the surgical removal of affected hormonal glands. Although these treatments are only life extending for many patients, those are rarely curative for spread cancers in body.

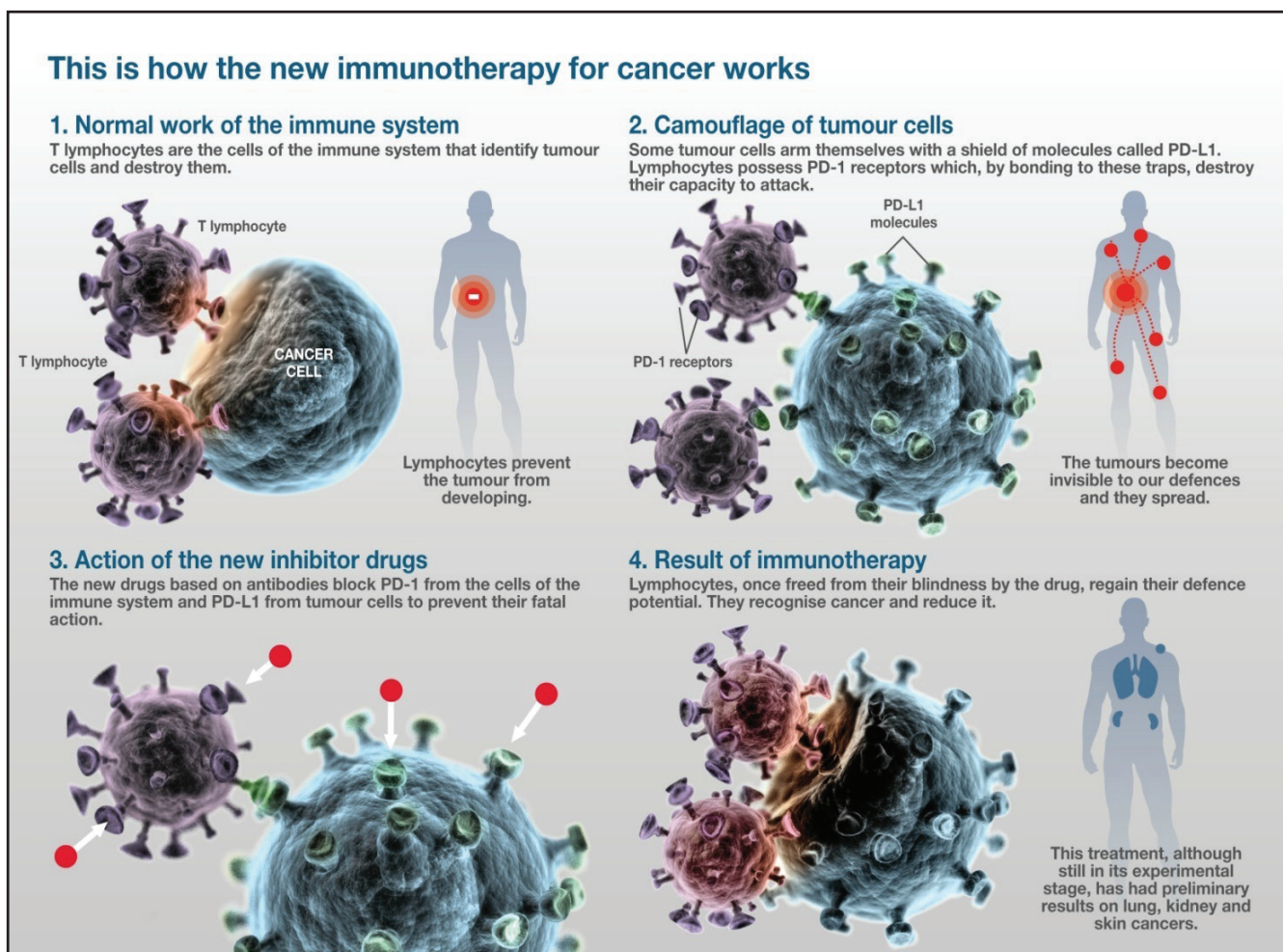


Fig. 1 schematic for working of Immunotherapy in cancer [8]

Immune cells at the primary tumor site influence metastatic behaviour of cancer cells. The infiltration of immune cells into the primary tumor can have positive or negative effects on the patient's prognosis [9]. Tumors not only actively escape from the immune system; they can also co-opt certain immune processes. A major mediator of this co-opting process by the tumor is through modification of the tumor stroma. The stroma consists of several cell types that contribute to tissue homeostasis, including fibroblasts, endothelial cells, nerve cells, immune cells and the extracellular matrix (ECM). Normally, it provides tissue haemostasis by controlling the balance between cell proliferation and cell death through interactions with the extracellular matrix (ECM) and fibroblasts [10]. However in cancer, fibroblasts often induce tumor progression by stimulating the proliferation and invasive phenotype of cancer cells, increasing their metastatic potential [11]. In pancreatic cancer, the dense fibrosis (desmoplasia) has been postulated to play either an inhibitory role constraining tumor growth or a protective role by providing survival signals and possibly impeding drug delivery to the cancer cells [12-14]. Tumor stroma can also promote the formation of new blood vessels, a process called angiogenesis. Without angiogenesis, a solid tumor will be limited in size and in its ability to access the blood stream for dissemination, an essential aspect to metastasis.

3. IMMUNOTHERAPY

Immunotherapy, also called biologic therapy, is a type of cancer treatment that boosts the body's natural defense to fight cancer. It uses substances made by the body or in a laboratory to improve or restore immune system function. Immunotherapy may work by:

- Stopping or slowing the growth of cancer cells.
- Stopping cancer from spreading to other parts of the body.
- Helping the immune system work better at destroying cancer cells.

There are several types of immunotherapy, including:

3.1 Monoclonal antibodies

When the body's immune system detects something harmful, it produces antibodies. Antibodies are proteins that fight infection. Monoclonal antibodies are a specific type of therapy made in a laboratory. They may be used in a variety of ways. For example, monoclonal antibodies can be used as a targeted therapy to block an abnormal protein in a cancer cell.

Monoclonal antibodies can also be used as an immunotherapy. For example, some monoclonal antibodies attach to specific proteins on cancer cells. This flags the cells so the immune system can find and destroy those cells.

Other types of antibodies work by releasing the brakes on the immune system so it can destroy cancer cells. PD-1/PD-L1 and CTLA-4 pathways are critical to the immune system's ability to control cancer growth. These pathways are often called immune checkpoints. Many cancers use these pathways to escape the immune system. The immune system responds to the cancer by blocking these pathways with specific antibodies called immune

checkpoint inhibitors. Once the immune system is able to find and respond to the cancer, it can stop or slow cancer growth.

The following are examples of immune checkpoint inhibitors:

- Ipilimumab (Yervoy)
- Nivolumab (Opdivo)
- Pembrolizumab (Keytruda)
- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Durvalumab (Imfinzi)

Clinical trials of monoclonal antibodies are ongoing for several types of cancers. The side effects of monoclonal antibody treatment depend on the purpose of the drug. For example, the side effects of monoclonal antibodies used for targeted therapy are different than those used for immunotherapy. The side effects of immune checkpoint inhibitors may include side effects similar to an allergic reaction.

3.2 Non-specific Immunotherapies

Like monoclonal antibodies, non-specific immunotherapies also help the immune system to destroy cancer cells. Most non-specific immunotherapies are given after or at the same time as another cancer treatment, such as chemotherapy or radiation therapy. However, some non-specific immunotherapies are given as the main cancer treatment.

Two common non-specific immunotherapies are:

- **Interferons:** Interferons help the immune system fight cancer and may slow the growth of cancer cells. A type of interferon made in a laboratory is called interferon alpha (Roferon-A [2a], Intron A [2b], Alferon [2a]). This is the most common type of interferon used in cancer treatment. Side effects of interferon treatment may include flu-like symptoms, an increased risk of infection, rashes, and thinning hair.
- **Interleukins:** Interleukins help the immune system produce cells that destroy cancer. An interleukin made in a laboratory is called interleukin-2, IL-2, or aldesleukin (Proleukin). It is used to treat kidney cancer and skin cancer, including melanoma. Common side effects of IL-2 treatment include weight gain and low blood pressure. Some people may also experience flu-like symptoms.

3.3 Oncolytic virus therapy

Oncolytic virus therapy uses genetically modified viruses to kill cancer cells. First, the doctor injects a virus into the tumor. The virus then enters the cancer cells and makes copies of itself. As a result, the cells burst and die. As the cells die, they release specific substances called antigens. This triggers the patient's immune system to target all the cancer cells in the body that have those same antigens. The virus does not enter healthy cells.

In 2015, the U.S. Food and Drug Administration approved the first oncolytic virus therapy to treat melanoma. The virus used in the treatment is called talimogene laherparepvec (Imlygic),

or T-VEC. The virus is a genetically modified version of the herpes simplex virus that causes cold sores. The doctor can inject T-VEC directly into areas of melanoma that a surgeon cannot remove. People receive a series of injections until there are no areas of melanoma left. Side effects can include: Fatigue, Fever, Chills, Nausea, Flu-like symptoms and Pain at the injection site. Researchers are testing other oncolytic viruses for different types of cancer in clinical trials. They are also testing the viruses in combination with other treatments, such as chemotherapy.

3.4 T-cell therapy

T-cells are immune cells that fight infection. In T-cell therapy, some T-cells are removed from a patient's blood. Then, the cells are changed in a laboratory so they have specific proteins called receptors. The receptors allow those T-cells to recognize the cancer cells. The changed T-cells are grown in large numbers in the laboratory and returned to the patient's body. Once there, they seek out and destroy cancer cells. This type of therapy is called chimeric antigen receptor (CAR) T-cell therapy. The use of T-cells for CAR therapy has been very effective in treating certain blood cancers. Researchers are still studying this and other ways of modifying T-cells to treat cancer.

3.5 Cancer vaccines

A cancer vaccine is another method used to help the body fight disease. A vaccine exposes the immune system to an antigen. This triggers the immune system to recognize and destroy that antigen or related materials.

There are 2 types of cancer vaccines:

- Prevention vaccines
- Treatment vaccines.

Cancer treatment vaccines boost the immune system's ability to recognize and destroy antigens. Often, cancer cells have certain molecules called cancer-specific antigens on their surface that healthy cells do not have. When these molecules are given to a person, the molecules act as antigens. They stimulate the immune system to recognize and destroy cancer cells that have these molecules on their surface. Most cancer vaccines also contain adjuvant, which are substances that may help strengthen the immune response. The aim of cancer vaccines is to stimulate the immune system to be able to recognize cancer cells as abnormal and destroy them some vaccines for particular cancers have been developed and are being tested to see whether they can treat a cancer, or help to stop it from coming back after cancer treatment.

Some cancer vaccines are made for individual patients. These types of vaccines are produced from the patient's tumor sample. This means that surgery is needed to get a large enough sample of the tumor to create the vaccine. Other cancer vaccines target specific cancer antigens and are given to people whose tumors have those antigens on the surface of the tumor cells [14].

3.5.1 Types of Cancer Vaccines

Probably the most promising form of cancer treatment is immunotherapy, where scientists are developing several

experimental cancer vaccines that could lead to the eradication of cancer in this century. There are two major categories that cancer vaccines fit into:

- Specific cancer vaccine
- Universal cancer vaccine

As the name suggests, specific cancer vaccines are designed to treat specific types of cancers. In other words, a vaccine could be developed for lung cancer, another vaccine could be used to treat colon cancer and yet another vaccine could treat skin cancer and so on. A more appealing cancer vaccine would be one that could fight cancer cells regardless of cancer type [15].

3.6 Stem Cell Immunotherapy

Immunotherapy through the use of stem cells remains in its infancy and has yet to become as focused as other forms of immunotherapy. The pluripotent characteristics allow stem cells to become virtually any kind of cell. Some stem cell therapies include inducing stem cells to produce dendritic cells, natural killer cells, and antigen specific T-cells. These dendritic cells were functional but had limited ability for cross presentation of antigens to CD8+ T-cells MHC. Differentiation of ES cells to form antigen specific T-cells has been produced by a combination of transcription factors and the introduction of fetal thymus organ culture in order to provide an environment conducive for the formation of diverse CD4+ and CD8+. There have also been reports of successfully differentiated induced pluripotent stem cells to form antigen specific T-cells that can recognize the epitope of melanoma antigen MART-1[16-18].

3.7 Tumor Infiltrating Lymphocyte Immunotherapy

Tumor infiltrating lymphocytes (TIL) are a heterogeneous mixture of lymphocytes that are found growing within a tumor. TILs are predominately ineffective for killing the cancer cells within the tumor for a number of reasons including a high number of immunosuppressive T regulatory cells, a low number of anti-tumor cells, or anti-tumor cells that have become deactivated or anergic. Immunotherapy using TIL involves the removal of the TILs from the tumor microenvironment before inducing the growth of these cells *in vitro* and then delivering them back into the body to combat the cancer. Lymphodepletion is thought to increase the activity of the TILs in addition to removing immunosuppressive T-reg cells in order to create an environment that is more conducive for the TILs to combat cancer. This process may even reduce the competition of IL-7 and IL-25 and create space for the proliferation of TILs including NK cells. Treatment involving TIL therapy has shown itself to be one of the most effective forms of immunotherapy [19-21].

3.8 Neoantigens

Immunotherapies which are boosting the ability of endogenous T-cells to destroy cancer cells have showed therapeutic efficacy in a variety of human malignancies. Until now, evidence that the endogenous T-cell compartment could help control tumor growth was in big part restricted to preclinical mouse tumor

models and to human melanoma [22]. With respect to human studies, effects of the T-cell cytokine IL-2 in a small subset of melanoma patients provided early clinical evidence of the potential of immunotherapy in the said disease. A randomized clinical trial was performed in 2010 showed that Ipilimumab, an antibody targets T-cell checkpoint protein CTLA-4 could improve patient survival, even with metastatic melanoma [23].

With recent technology, we can check the uplevel of neoantigens as a tumor-specific mutation consequence, and emerging data suggest that this neoantigen play a role in the activity of clinical immunotherapies, thus this load may be used as cancer immunotherapy biomarker and an incentive development of novel therapeutic approaches can be provided [24]. In cancer, so-called neopeptide peptides are derived from proteins encoded by mutated genes. Recent advances in next-generation DNA and RNA sequencing now enable rapid mapping of all expressed mutated genes in an individual tumor, and it is possible to predict epitopes that are efficiently presented on the surface of cancer cells [25].

3.9 Gold Nanoparticle Vaccine

Gold nanoparticles can specially accumulate within lymphocytes in addition to other tissues for delivering immune therapies like vaccines [26-29]. They come in a variety of sizes which have different properties with regard to absorption and localization of the nanoparticles [30]. The antigens and cytokines that are presented on the gold nanoparticles are protected from degradation. Modulation of dendritic cells and T-cell activation in addition to other humoral responses is a function of gold nanoparticle mediated adjuvant delivers [31-32]. Gold nanoparticles offer a persistent and strong immunological response and have been used to deliver large payloads of antigens to given sites associated with the size of the nanoparticles [33-37].

3.10 Immune checkpoint blockade

Human cancers carry a multitude of somatic gene mutations and epigenetically altered genes, the products of which are potentially recognizable as foreign antigens. Although an endogenous immune response to cancer is observed in preclinical models and patients, this response is not efficient because tumors induce tolerance among tumor-specific T-cells and by expressing ligands that bind inhibitory receptors and dampen T-cell functions within the tumor microenvironment [38-40]. One approach to trigger antitumor immune responses has been termed “checkpoint blockade”, referring to the blockade of immune-inhibitory pathways activated by cancer cells.

4. CONCLUSION

There are many aspects of commercializing cancer vaccines that will require developers, regulators and clinicians to collaborate on an unprecedented level to expedite the delivery of these new therapies to patients. Cancer immunotherapy is a promising and effective treatment modality for patients with cancers. Cytokine, anticytokine, and antibody therapies appear to be effective in

treating various forms of cancer [41]. Vaccines, either preventive or therapeutic, against tumor specific or associated antigens are a promising immunotherapeutic strategy, as well. Targeted therapy drugs attack a specific feature, or target, in cancer cells, and largely leave healthy cells alone. Immunotherapy was declared the breakthrough of the Year by *Science* in 2013. To ensure that immunotherapy realizes its full potential, much more must be learned about the immune system, cancer, and their interactions within the complex and ever-changing tumor environments of individual patients [42]. Combination therapy with cancer vaccines and other conventional treatments such as radiation therapy may result in significant tumor regression and serve as a potential treatment regimen for cancer patient's. Therefore, combination therapies will be superior choices for cancer immunotherapy in the future [43].

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